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Published in:
Journal of Electrocardiology

DOI (link to publication from Publisher):
[10.1016/j.jelectrocard.2018.05.015](https://doi.org/10.1016/j.jelectrocard.2018.05.015)

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Publication date:
2018

Document Version
Accepted author manuscript, peer reviewed version

[Link to publication from Aalborg University](#)

Citation for published version (APA):
Isaksen, J. L., Graff, C., Ellervik, C., Jensen, J. S., Andersen, H. U., Rossing, P., Kanters, J. K., & Jensen, M. T. (2018). Type 1 diabetes is associated with T-wave morphology changes: The Thousand & 1 Study. *Journal of Electrocardiology*, 51(6, Suppl.), S72-S77. <https://doi.org/10.1016/j.jelectrocard.2018.05.015>

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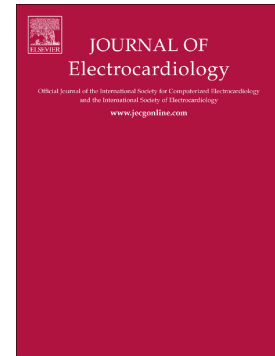
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Accepted Manuscript

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PII: S0022-0736(18)30148-1
DOI: doi:[10.1016/j.jelectrocard.2018.05.015](https://doi.org/10.1016/j.jelectrocard.2018.05.015)
Reference: YJELC 52634

To appear in:

Please cite this article as: Jonas L. Isaksen, Claus Graff, Christina Ellervik, Jan Skov Jensen, Henrik Ullits Andersen, Peter Rossing, Jorgen K. Kanter, Magnus T. Jensen , Type 1 diabetes is associated with T-wave morphology changes. The Thousand & 1 Study. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Yjelc(2017), doi:[10.1016/j.jelectrocard.2018.05.015](https://doi.org/10.1016/j.jelectrocard.2018.05.015)

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Type 1 Diabetes is associated with T-wave morphology changes. The Thousand & 1 Study

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Journal Subject Terms: Electrocardiology; Biomarkers; Diabetes, Type 1; Cardiovascular Disease;

Word Count Manuscript: 2622

Word Count Abstract: 148

Reference Count: 28

Tables count: 3

Figures count: 1

Abstract:

Background– Repolarization is impaired in patients with type 1 diabetes mellitus (T1DM), and repolarization disturbances are associated with an increased mortality. To study cardiac repolarization, we assessed T-wave morphology in patients with T1DM without known heart disease.

Methods– 855 T1DM patients without known heart disease were matched 1:2 with 1710 people from a background population. Rate-corrected T-wave morphology markers were obtained. Patients were stratified by albuminuria. Results are mean±standard deviation.

Results– T-waves were flatter (0.398 ± 0.059 vs. 0.382 ± 0.062 , $p<0.001$) and more asymmetric (0.082 ± 0.068 vs. 0.071 ± 0.084 , $p=0.001$) in T1DM. Patients with albuminuria had an increased heart rate (normoalbuminuria: 71 ± 13 bpm, microalbuminuria: 75 ± 12 bpm, $p<0.001$, macroalbuminuria: 78 ± 12 bpm, $p<0.001$) and more asymmetric T-waves (normoalbuminuria: 0.079 ± 0.060 , microalbuminuria: 0.094 ± 0.085 , $p<0.01$, macroalbuminuria: 0.101 ± 0.080 , $p<0.01$), but the QTc interval remained unchanged.

Conclusions– T1DM is associated with changes in T-wave morphology. T-wave asymmetry but not QTc interval is associated with albuminuria in T1DM and may be used for stratification.

Key Words: Type 1 diabetes mellitus, electrocardiography, T-wave morphology, albuminuria, repolarization

Introduction

T-wave morphologic markers describe the shape of the T-wave of the surface electrocardiogram (ECG). Using T-wave morphology, more detailed information beyond QT prolongation can be obtained about cardiac repolarization.¹⁻⁴ Specifically, blockage of the Kv11.1 channel (hERG) underlying the rapid delayed rectifier potassium current, can be detected using markers for the asymmetry, flatness, and presence of notches for T-waves.⁵ Changes in T-wave morphology has been linked to mortality in type 2 diabetes⁶ as well as the general population.^{1, 7}

Cardiovascular disease is the leading comorbidity in type 1 diabetes mellitus (T1DM),⁸ and the risk of cardiovascular death in young individuals with T1DM has been found to be up to 40-fold higher compared to the background population.⁹ A particular syndrome, termed the “dead in bed” syndrome, in which unexpected nocturnal death of young individuals with otherwise healthy T1DM subjects occurs, has gained interest, and disturbances in autonomous dysfunction and prolonged repolarization may play a role in the syndrome.¹⁰

We have previously described ECG changes in T1DM patients without known heart disease and with normal ejection fraction, which includes an increased heart rate of about 10 bpm, a prolonged QRS duration, and a prolonged repolarization in the young patients with T1DM.¹¹

This study aims to investigate differences in T-wave morphology in type 1 diabetes patients without known heart disease, with normal ejection fraction, and with various degrees of albuminuria – as a proxy for disease progression - compared to matched subjects from the background population to assess the early cardiac changes caused by type 1 diabetes.

Methods

Populations

The Thousand & 1 ECG Study is a cohort study of 855 patients with T1DM and without known heart disease.^{11, 12} The patients were included at Steno Diabetes Center Copenhagen from 2010 through 2012. The study was performed in accordance with the Second Helsinki Declaration and was approved by the Danish Data Protection Agency (00934-Geh-2010-003) and the regional ethics committee (H-3-2009-139).^{12, 13}

Exclusion criteria were known cardiac disease, electrical conduction abnormalities and ejection fraction <50%. Known cardiac disease was defined as registered heart failure, congenital heart disease, or coronary heart disease including stable angina, previous acute myocardial infarction, percutaneous coronary intervention, or coronary artery bypass. Electrical conduction abnormalities included atrial fibrillation, atrial flutter, and left bundle branch block, or the presence of a pacemaker or an implantable cardioverter defibrillator.

As a diabetes-free background population, two matched subjects per case were drawn from the Danish General Suburban Population Study (GESUS)¹⁴ and included in the Thousand & 1 ECG Study. The GESUS Study describes a population of individuals aged 20 years and up from the Naestved municipality 70 km south of Copenhagen between 2010 and 2013. The study was performed in accordance with the Declaration of Helsinki and was approved by the Danish Data Protection Agency and the regional ethics committee (SJ-113 and SJ-114).

Males and females were drawn independently and matched on age to the T1DM population as described previously.¹¹ In the GESUS cohort, subjects with diabetes mellitus were excluded, as well as subjects with known heart disease or electrical conduction abnormalities. Known heart disease included self-reported previous myocardial infarction, stable angina, ischemic heart disease, and pacemaker. Electrical conduction abnormalities disturbances included left bundle branch block, atrial fibrillation, and atrial flutter.

Electrocardiogram (ECG)

In both groups, resting 12-lead 10-second ECGs were recorded from the supine position after a few minutes of rest and stored digitally. The Marquette 12SL software (version 21, GE Healthcare, Milwaukee, WI, USA) was used for automatic measurements.

Heart rate, QRS duration, QT interval, and morphology combination score (MCS) including the sub-components asymmetry, flatness, and the presence of notches were obtained as previously described.¹⁵ The corrected QT interval was reported using the cubic root correction of Fridericia (QTcF) and the square root correction of Bazett (QTcB). All other continuous variables were corrected linearly with RR interval and reported with a subscript c for an expected heart rate of 60 bpm.

The MCS is based on measurements of flatness, asymmetry, and notching of the T-wave (figure 1).¹⁵ For all component measurements, the first principal component of the ST-T segment of the median beat is used. Flatness is calculated on the normalized T-wave similar to the way kurtosis of any distribution is calculated. Asymmetry is calculated as the average squared difference in slope on both sides of the top of the T-wave. Based on the first and the second derivatives of the T-wave, potential notches are identified. The depth of any notch in the T-wave gives rise to the third component of the score.

Measurements

In both populations, blood pressures were obtained after five minutes of rest in the supine position. The estimated Glomerular Filtration Rate (eGFR) was obtained for both groups using the CKD-EPI formula.¹⁶ Levels of glycated hemoglobin (HbA1c), plasma potassium, and total cholesterol were measured on the day of visit for the control group and within ± 4

months of the ECG for the T1DM group. Body mass index (BMI) was calculated as body weight per height squared as kg/m^2 .

Albuminuria was measured in the T1DM group in morning spot urine samples using immunoassay. Patients were categorized as normoalbuminuric if their albumin/creatinine ratio was within 3.4 mg/mmol creatinine. For those with elevated levels (>3.4 mg/mmol), 24-hour sterile urine collections were obtained. If two consecutive albumin measurements of three total measurements were between 30-300 mg/day the patient was categorized as microalbuminuric, and for the result of >300 mg albumin/day, the patient would be categorized as macroalbuminuric.

Statistics

The R statistical package (version 3.4.3) was used, and continuous and categorical variables were reported as mean \pm SD (standard deviation) and % (n), respectively. For continuous variables, linear regression was used to test for differences in means. For categorical variables, a χ^2 test was used, or Fisher's exact test if one entry contained less than 5 observations.

In the multivariate regression, the effects of T1DM and albuminuria were adjusted for clinical confounders by the inclusion of sex, age, BMI, systolic blood pressure, and plasma levels of potassium and cholesterol in the models. The sensitivity analysis for T1DM vs. background population included additional information on smoking (categorical as 'never', 'previous', or 'current') and alcohol consumption (categorical as 'less than 7 units per week', '7-21 units per week', or 'more than 21 units per week', one unit of alcohol corresponding to 12 gram). The sensitivity analysis for albuminuria in the T1DM group included information on smoking, alcohol consumption, physical activity (categorical as 'lightly active: less than 3 hours of physical activity per week', 'moderately active: 3-7 hours of physical activity per

week', or 'very active: more than 7 hours of physical activity per week'), and usage of betablockers, angiotensin converting enzyme inhibitors or angiotensin II antagonists, acetylsalicylic acid, and calcium antagonists. A p-value less than 0.05 was considered significant.

Results

The clinical characteristics of the T1DM population and their age- and gender matched controls are listed in table 1. The patients with T1DM had a lower BMI and blood pressure compared to the background population, and a lower P-cholesterol. More T1DM patients had impaired renal function and the patients with T1DM had higher levels of HbA1c and P-potassium compared to the background population.

With increasing degree of albuminuria in T1DM, T1DM duration, systolic blood pressure, and HbA1c, increased whereas eGFR decreased. P-potassium was higher in the microalbuminuric group compared to normoalbuminuria, the potassium level in the macroalbuminuric group was similar to that in the microalbuminuric group but did not reach statistically significant difference compared to the normoalbuminuric group ($p=0.09$). Age and BMI were higher in microalbuminuria compared to normoalbuminuria, diastolic blood pressure was increased in the macroalbuminuric group only.

T-wave morphology was altered in T1DM (table 2). The T-waves were more asymmetric and flattened, but the presence of notches in the T-waves was unchanged compared to the

background population. As a consequence, the combined score of MCS was higher in T1DM compared to control.

The T1DM patients were categorized by degree of albuminuria: 20% had microalbuminuria and 8% had macroalbuminuria (table 2). The value of the asymmetry marker of the T-wave increased significantly with increasing degree of albuminuria i.e. disease progression, but interestingly the QT interval did not. Heart rate was correlated with the degree of albuminuria, and patients with micro- and macroalbuminuria had an increased heart rate of 4 bpm and 7 bpm, respectively, compared to patients with normoalbuminuria. The QRS duration decreased with increasing degree of albuminuria, although the shorter duration in the microalbuminuric group was only borderline significant without additional adjustment ($p=0.06$).

When correcting these findings for clinical confounders, the results remained virtually the same for both T1DM vs. background population and in T1DM stratified by degree of albuminuria (table 3). For patients with micro- and macroalbuminuria, heart rate was increased by 4 and 5 bpm, respectively, and the asymmetry marker of the T-wave was increased by 23% and 42%, respectively. The decrease in rate-corrected QRS duration was statistically significant in both groups with a magnitude of 2 and 3 ms for micro- and macroalbuminuria, respectively.

For T1DM compared to the background population, there was no difference in smoking status ($p=0.19$), but alcohol consumption was higher in the T1DM group ($p<0.001$). In a

sensitivity analysis on the T1DM vs. background population, the inclusion of smoking status and alcohol consumption in the model did not change the results significantly.

4.1 % of patients with T1DM were treated with betablockers, 42.3 % took angiotensin converting enzyme inhibitors or angiotensin II receptor blockers to lower blood pressure, 26.1 % used medication containing acetylsalicylic acid, and 16.3 % took calcium channel blockers. The use of medication was more prevalent with increasing degree of albuminuria for all of these medications. A sensitivity analysis revealed that correcting for use of medication, physical activity, alcohol consumption, and smoking status in the multivariable model did not change the findings significantly.

Discussion

In the present study, we compared differences in T-wave morphology between patients with T1DM without known heart disease and normal left ventricular function compared to age and sex matched controls from the background population without diabetes mellitus. T-wave morphology was changed in T1DM compared to the background population. With increasing degree of albuminuria in the T1DM population, QTcF remained unchanged, but T-wave morphology markers identified subtle repolarization changes.

T-wave morphology

The T-waves of the T1DM population were more asymmetric and flat compared to the background population. The increase in MCS in the T1DM population suggests that patients

with T1DM have impaired hERG potassium channel function.⁵ Hyperglycemia is known to cause a reduction in hERG function,¹⁷ and it is possible that chronic hyperglycemia explains the increased asymmetry and flatness of the T-wave which was found in T1DM. In the rabbit, diabetes has been found to reduce I_{Kr} , an effect that was mediated by oxidative stress and reversible with insulin. On the other hand, in the dog, I_{Kr} function was unaffected eight weeks post diabetes induction, but I_{Ks} and I_{to} were decreased.¹⁸

Although both MCS and QTcF were unchanged with albuminuria, we found a significant increase in the asymmetry marker of the T-wave. Both flatness and asymmetry detect hERG blockade, but only asymmetry was associated with albuminuria. It is possible that the asymmetry marker is more sensitive to subtle hERG changes that do not affect the flatness of the T-wave. Logically, asymmetry must be affected by ST segment deviations,⁵ but the inclusion of J-point amplitude in the model did not change the asymmetry findings significantly. Similarly, HbA_{1c}, eGFR, and diabetes duration did not explain the increase in asymmetry with albuminuria. In contrast, an increase in systolic blood pressure was associated with a decrease in T-wave asymmetry (results not shown).

The QT interval was previously found to be related to albuminuria in patients with long term T1DM.¹⁹ In that study, however, the authors used the correction of Bazett (QTcB), which is known to have heavy residual heart rate dependence.²⁰ As albuminuria is associated with elevated heart rate, the reported association probably reflects an increased heart rate rather than a prolongation of the QT interval. Indeed, we find that the macroalbuminuric group has a slightly longer QTcB compared to the normoalbuminuric group whereas QTcF is unchanged between all groups of albuminuria.

Diabetic autonomic neuropathy is a known complication of T1DM that involves reduced heart rate variability and resting tachycardia.²¹ In the present study, the only marker for diabetic autonomic neuropathy was resting heart rate. All repolarization markers including T-wave morphology and QT interval have been appropriately corrected for heart rate.

Diabetic autonomic neuropathy and nephropathy are correlated,²² and it seems likely that the association between albuminuria and repolarization arises because both neuropathy and nephropathy have chronic hyperglycemia as the underlying cause.

The T1DM population in the present study were all without known heart disease and with ejection fraction >50%. Still, the T-wave morphology was significantly altered, suggesting impaired ionic current flow before the occurrence of clinical cardiac symptoms. The 12-lead ECG is an important tool for risk stratification and although the findings in this study suggest that asymmetry of the T-wave might be a predictor for the development of albuminuria in the T1DM population, intervention studies are needed to confirm the role of asymmetry in risk stratification.

The finding that repolarization is impaired in patients with T1DM could support the theory, that impaired repolarization is a mechanism in the “dead in bed” syndrome. By the means of advanced T-wave analysis, one can obtain detailed information about cardiac repolarization, and it seems possible that T-wave analysis could become a tool for risk stratification in the clinic for patients with T1DM. However, further studies are needed to assess whether T-wave morphology markers such as MCS can predict the occurrence of the “dead in bed” syndrome.

Heart rate and albuminuria

For the T1DM population, we found that albuminuria was associated with an increase in heart rate. Others have found that albuminuria is associated with an elevated heart rate in the general population as well,²³ and microalbuminuria increases the predictive power of ST-T wave abnormalities in the general population.²⁴

Compared to other studies, the T1DM group in the Thousand & 1 ECG Study seems to have a similar or lower prevalence of albuminuria relative to diabetes duration. In a previous Danish study with an average T1DM duration of 22 years, prevalences of 20% and 18% were found for microalbuminuria and macroalbuminuria, respectively.²⁵ In the EDIC study, 16 % had microalbuminuria after an average T1DM duration of 14 years.²⁶ In a Spanish study of asymptomatic patients with T1DM and without known coronary heart disease the mean diabetes duration was 20 years and microalbuminuria was found in only 9% of patients.²⁷ However, no patients above 50 were included in that study, which might in part explain the low prevalence. In the present study and the Spanish study, which both included patients with T1DM and without known heart disease, the inclusion criterion of no known heart disease likely represents a bias towards patients that are managing their diabetes better and therefore are less likely to develop albuminuria.

Limitations

Albuminuria was not assessed in the control group. Whereas plasma potassium was assessed and included in the full model, divalent cations such as calcium and magnesium were not. Although particularly calcium homeostasis may be disturbed in patients with diabetes, according to previous reports calcium affects primarily the duration of the ST segment but leaves the T-wave unaltered.²⁸ The T-wave morphology variables are therefore likely to be unaffected by physiological calcium level variations.

Conclusion

T-wave morphology, as a marker for repolarization disturbances, is altered in T1DM before the onset of clinical cardiac symptoms, possibly caused by a decrease in ventricular I_{Kr} function. Advanced T-wave morphology markers can provide additional information compared to the heart rate corrected QT interval, and asymmetry of the T-wave is associated with albuminuria in the T1DM population.

Funding Sources

Support for this work was given by The European Foundation for the Study of Diabetes/Pfizer European Programme 2010 for Research in Cardiovascular Risk Reduction in Patients with Diabetes, Düsseldorf, Germany, and the Danish Heart Foundation, Copenhagen, Denmark (12-04-R90-A3840-22725).

Disclosures

JKK and CG are the co-authors of a patent for the MCS. The remaining authors have no conflicts of interest to declare.

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Table 1. Demographics for T1DM vs. background and in T1DM stratified by degree of albuminuria.

Variable	Background	T1DM	T1DM stratified by albuminuria		
			Normo	Micro	Macro
n	1710	855	619	170	66
Age [years] (mean±SD)	49 ± 13	48 ± 15	46 ± 15	53 ± 14 ^{†††}	48 ± 11
T1DM duration [years] (mean±SD)	-	25.0 ± 13.7	22 ± 13	31 ± 14 ^{†††}	34 ± 11 ^{†††}
Sex [male] (%) (n)	51.7 (884)	51.7 (442)	52.2 (317)	53.5 (91)	51.5 (34)
BMI [kg/m ²] (mean±SD)	26.3 ± 4.4	25.6 ± 4.0 ^{***}	25.4 ± 3.9	26.1 ± 4.2 [†]	26.0 ± 4.5
Systolic BP [mmHg] (mean±SD)	135.4 ± 19.3	133.1 ± 16.6 ^{**}	131.3 ± 15.9	135.9 ± 16.3 ^{††}	142.9 ± 19.1 ^{†††}
Systolic BP>140mmHg (%) (n)	36.4 (621)	28.0 (237) ^{***}	23.7 (145)	34.9 (59) ^{††}	50.8 (33) ^{†††}
Diastolic BP [mmHg] (mean±SD)	84.0 ± 10.8	74.1 ± 9.7 ^{***}	73.8 ± 9.3	73.7 ± 10.5	77.3 ± 10.6 ^{††}
Diastolic BP>90mmHg (%) (n)	24.1 (411)	4.7 (40) ^{***}	3.8 (23)	6.5 (11)	9.2 (6)
eGFR [mL/min/1.73m ²] (mean±SD)	91.0 ± 16.3	94.0 ± 21.0 ^{***}	98.1 ± 16.9	88.3 ± 21.6 ^{†††}	69.9 ± 31.8 ^{†††}
eGFR<60mL/min/1.73m² (%) (n)	3.6 (61)	7.1 (61) ^{***}	1.9 (12)	12.4 (21) ^{†††}	42.4 (28) ^{†††}
HbA1c [%] (mean±SD)	5.4 ± 0.3	8.3 ± 1.3 ^{***}	8.1 ± 1.3	8.4 ± 1.1 [†]	9.0 ± 1.4 ^{†††}
HbA1c [mmol/mol] (mean±SD)	36 ± 3	67 ± 14 ^{***}	65 ± 14	68 ± 12 [†]	75 ± 16 ^{†††}
P-potassium [mM] (mean±SD)	3.87 ± 0.28	4.05 ± 0.34 ^{***}	4.03 ± 0.31	4.10 ± 0.40 [†]	4.11 ± 0.46
P-cholesterol [mM] (mean±SD)	5.28 ± 0.99	4.84 ± 0.91 ^{***}	4.86 ± 0.86	4.75 ± 0.85	4.92 ± 1.38

^{**}p<0.01 vs. control; ^{***}p<0.001 vs. control; [†]p<0.05 vs. normoalbuminuria; ^{††}p<0.01 vs. normoalbuminuria; ^{†††}p<0.001 vs. normoalbuminuria. BMI: Body Mass Index. BP: Blood pressure. eGFR: estimated Glomerular Filtration Rate. HbA1c: Glycated hemoglobin.

Table 2. ECG measurements. In albuminuria stratification, correction for age was applied due to age differences between the groups.

Variable	Background	T1DM	T1DM by albuminuria		
			Normo	Micro	Macro
n	1710	855	619	170	66
Heart rate [bpm] (mean±SD)	63 ± 11	72 ± 13 ^{***}	71 ± 13	75 ± 12 ^{†††}	78 ± 12 ^{†††}
RR interval [ms] (mean±SD)	974 ± 166	854 ± 153 ^{***}	870 ± 157	820 ± 133 ^{†††}	794 ± 134 ^{†††}
QRS_c duration [ms] (mean±SD)	95 ± 11	97 ± 11 ^{**}	98 ± 10	96 ± 12	95 ± 9 [†]
QTcB [ms] (mean±SD)	415 ± 23	430 ± 22 ^{***}	428 ± 22	431 ± 21	433 ± 21 [†]
QTcF [ms] (mean±SD)	412 ± 19	417 ± 17 ^{***}	417 ± 16	416 ± 17	417 ± 19
MCS_c (mean±SD)	0.69 ± 0.19	0.72 ± 0.15 ^{***}	0.72 ± 0.15	0.73 ± 0.20	0.73 ± 0.15
Asymmetry_c (mean±SD)	0.072±0.091	0.078±0.060 ^{**}	0.079±0.060	0.094±0.085 ^{††}	0.101±0.080 ^{††}
Flatness_c (mean±SD)	0.383±0.063	0.399±0.057 ^{***}	0.399±0.056	0.397±0.065	0.396±0.064
Notch					
None (%) (n)	99.4 (1700)	99.5 (851)	99.7 (617)	98.8 (168)	100 (66)
Subtle (%) (n)	0.1 (2)	0.2 (2)	0.2 (1)	0.6 (1)	0 (0)
Pronounced (%) (n)	0.5 (8)	0.2 (2)	0.2 (1)	0.6 (1)	0 (0)

*p<0.05 vs. control; **p<0.01 vs. control; ***p<0.001 vs. control; †p<0.05 vs.

normoalbuminuria; ††p<0.01 vs. normoalbuminuria; †††p<0.001 vs. normoalbuminuria. MCS:

Morphology Combination Score.

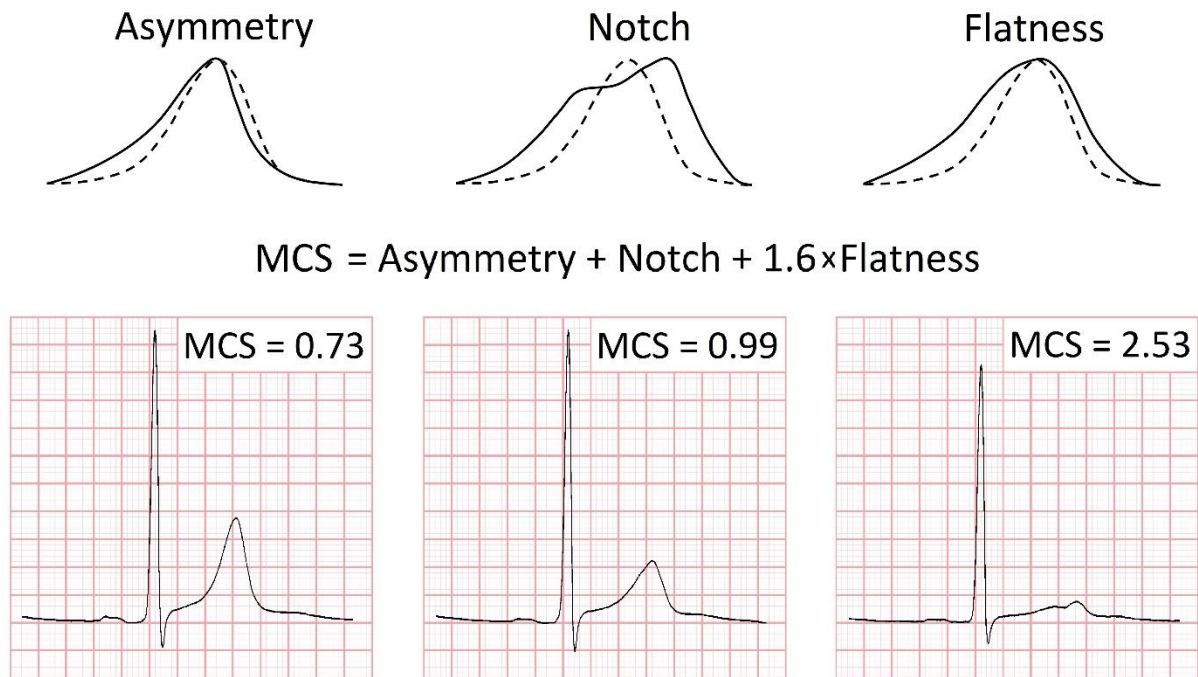
Table 3. T1DM and albuminuria effects on ECG measurements corrected for clinical confounders: sex, age, BMI, systolic blood pressure, P-potassium, and P-cholesterol.

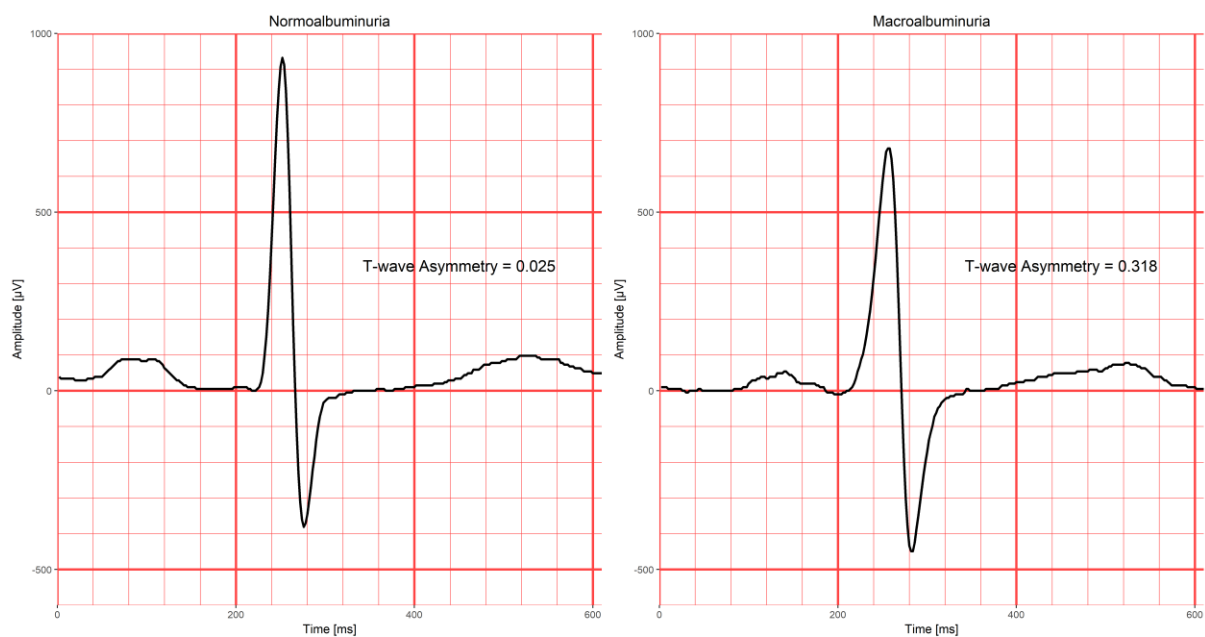
Variable	Background (mean±SD)	T1DM (delta±SE)	T1DM by albuminuria		
			Normo (mean±SD)	Micro vs. normo (delta±SE)	Macro vs. normo (delta±SE)
n	1710	855	619	170	66
Heart rate [bpm]	63 ± 11	10 ± 0.5 ^{***}	71 ± 13	4 ± 1.1 ^{†††}	6 ± 1.6 ^{†††}
RR interval [ms]	976 ± 166	-140 ± 7 ^{***}	870 ± 157	-50 ± 13 ^{†††}	-65 ± 20 ^{†††}
QRS_c duration [ms]	95 ± 11	2.5 ± 0.4 ^{***}	98 ± 10	-2.0 ± 0.9 [†]	-2.8 ± 1.3 [†]
QTcB [ms]	415 ± 23	17 ± 0.9 ^{***}	429 ± 22	2.6 ± 1.9	5.4 ± 2.8
QTcF [ms]	412 ± 19	6 ± 0.8 ^{***}	417 ± 16	-1.4 ± 1.5	0.0 ± 2.2
MCS_c	0.69 ± 0.18	0.04 ± 0.01 ^{***}	0.72 ± 0.15	0.02 ± 0.01	0.04 ± 0.02
Asymmetry_c	0.071±0.084	0.012±0.004 ^{**}	0.078±0.060	0.018±0.006 ^{††}	0.033±0.009 ^{†††}
Flatness_c	0.382±0.062	0.020±0.003 ^{***}	0.399±0.057	-0.001±0.005	0.002±0.008

*p<0.05 vs. control; ***p<0.001 vs. control; †p<0.05 vs. normoalbuminuria; ††p<0.01 vs. normoalbuminuria; †††p<0.001 vs. normoalbuminuria. BMI: Body Mass Index. MCS: Morphology Combination Score.

Fig. 1. **Morphology Combination Score (MCS).** MCS is a composite of the three measures of asymmetry, flatness, and notching of the T-wave. The lower panel represents left: a visually normal T-wave with a low MCS; center: a visually normal T-wave, but MCS reveals that it is slightly abnormal; and right: a visually abnormal T-wave with a corresponding high MCS. Reproduced with permission.¹⁵

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Figure 1:



Graphical abstract

Highlights

- T-wave morphology is changed in patients with type 1 diabetes
- Morphology changes precede known heart disease
- T-wave asymmetry is associated with albuminuria in patients with type 1 diabetes
- The QTc interval is not associated with albuminuria
- Heart rate correlates with albuminuria

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