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Electrocardiographic markers in patients with type 2 diabetes and the role of diabetes duration

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ABSTRACT

Background: The association between type 2 diabetes and electrocardiographic (ECG) markers are incompletely explored and the dependence on diabetes duration is largely unknown. We aimed to investigate the electrocardiographic (ECG) changes associated with type 2 diabetes over time.
Methods: In this cross-sectional study, we matched people with type 2 diabetes 1:1 on sex, age, and body mass index with people without diabetes from the general population. We regressed ECG markers with the presence of diabetes and the duration of clinical diabetes, respectively, adjusted for sex, age, body mass index, smoking, heart rate, diabetes medication, renal function, hypertension, and myocardial infarction.
Results: We matched 988 people with type 2 diabetes (332, 34% females) with as many controls. Heart rate was 8 bpm higher ($p < 0.001$) in people with vs. without type 2 diabetes, but the difference declined with increasing diabetes duration. For most depolarization markers, the difference between people with and without type 2 diabetes increased progressively with diabetes duration. On average, R-wave amplitude was 6 mm lower in lead V5 ($p < 0.001$), P-wave duration was 5 ms shorter ($p < 0.001$) and QRS duration was 3 ms ($p = 0.03$). Among repolarization markers, T-wave amplitude (measured in V5) was lower in patients with type 2 diabetes (1 mm lower, $p < 0.001$) and the QRS-T angle was 10 degrees wider ($p = 0.002$). We observed no association between diabetes duration and repolarization markers.
Conclusions: Type 2 diabetes was independently associated with electrocardiographic depolarization and repolarization changes. Differences in depolarization markers, but not repolarization markers, increased with increasing diabetes duration.

Introduction

The risks of cardiovascular diseases and death from cardiovascular causes are greatly increased among people with type 2 diabetes [1,2], making cardiovascular health important in the management of diabetes. Type 2 diabetes is associated with progressive diabetic autonomic neuropathy and diabetic cardiomyopathy, which involves remodeling processes in the myocardium such as fibrosis and cardiomyocyte hypertrophy driven by hyperglycemia [3]. All these diabetes-specific remodeling processes can manifest in overt electrocardiogram (ECG) changes. Increased heart rate and abnormal cardiac repolarization and depolarization have been associated with mortality among people with

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diabetes [4–7].

Importantly, the cardiac manifestations of diabetic end organ damage progress over time. Nevertheless, the relation between ECG markers and type 2 diabetes and particularly the relation with diabetes duration remains largely unexplored. The paucity of studies is surprising because it has been established that cardiac function decreases with diabetes duration [8] and that cardiovascular disease is the leading cause of death among people with diabetes [2]. Therefore we hypothesized that ECG markers were changed in people with diabetes in a disease duration-dependent manner.

In this study, we aimed to assess the changes in ECG markers in people with type 2 diabetes compared to well-matched controls and to assess the influence of diabetes duration on these ECG changes.

Participants and methods

Type 2 diabetes population

We included participants from the Thousand&2 study, a multicenter cross-sectional study on 1030 people with type 2 diabetes from 2011 to 2013. The participants were included at one of two high-volume, specialized diabetes clinics in the Copenhagen area and about 50% of the people invited at the center participated in the study after providing informed consent. The details of the population have been published elsewhere [9,10]. Standard 10-s, 12-lead ECGs were obtained using a Cardiosoft version 6.61 (GE Healthcare, Wauwatosa, WI, USA). In the present study we excluded participants without a digital ECG (4%, $n = 42$). We recorded use of anti-diabetic medication in five groups: insulin, metformin, sulfonylurea, dipeptidyl peptidase-4 (DPP-IV) inhibitors, and glucagon-like peptide 1 (GLP-1) agonists coded as yes/no.

Matched control population

As a control group, we included participants from the Danish General Suburban Population Study (GESUS) [11] with a digital ECG ($n = 8944$ available) from 2010 to 2013 matched 1:1 on sex, age, and body mass index (BMI). All participants provided informed consent. Matching was done using the MatchIt package [12] with nearest neighbor using Mahalanobis distance for continuous parameters and exactly on sex (i.e. males matched only to males and females to females). We excluded people with self-reported diabetes (of any type), self-reported use of insulin or other medication for the management of diabetes, or with a glycated hemoglobin (HbA_{1c}) level $\geq$ 48 mmol/L ($n = 775$). We also excluded people with missing values ($n = 319$). Standard 10-s, 12-lead ECGs were recorded on a MAC5500 versions 009C, 010 A, and 010 A.1 (GE Healthcare, Wauwatosa, WI, USA).

Electrocardiographic markers

We re-analyzed ECGs from both cohorts using the same version of the 12SL algorithm (version 2.43, GE Healthcare) to ensure that no bias arose from differences in analysis program or version. We used the 12SL algorithm to obtain the *global* measurements of heart rate (and average RR interval), P-wave axis, P-wave duration, PR interval, QRS axis, QRS duration, QT interval, QT_{cF} (QT corrected with the cubic root of the average RR interval, QT_c Fridericia), T-wave axis, and the following three markers of T-wave morphology: T-wave flatness, T-wave asymmetry, and T-wave notching (see details below). We also used 12SL to obtain *lead-specific* amplitude measurements of R waves and T waves.

To assess R-wave progression, we defined the transition zone as the first precordial lead where the R-peak amplitude exceeded the S-peak amplitude (measured by 12SL). We reported transition zone using groups V1-V2, V3, V4, and V5-V6 as done previously [13]. In the adjusted analyses, we dichotomized transition zone as late (V5-V6) or not late (V1-V4).

We calculated the spatial QRS-T angle as the angle between the mean vectorcardiographic (3D) QRS and T axes/vectors. We used the Kors transformation to obtain the vectorcardiogram as done previously [14].

The markers of T-wave morphology were developed to detect altered I_{Kr} (hERG) current inhibition [15,16] and previously identified repolarization abnormalities in people with type 1 diabetes [17].

Representative ECGs

We show one representative ECG of people with and without type 2 diabetes, respectively, calculated as the median value in each lead of all ECGs in that group. ECGs from all individuals were aligned similarly in time by the 12SL algorithm (Q-wave onset) allowing the group-specific median to be computed directly. The representative ECGs are thus averages of ECGs from all individuals within a group and not specific ECGs from any one individual.

Biochemical markers

The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula. HbA_{1c} values were reported in units of mmol/L and %. Total cholesterol was reported in mmol/L and mg/dL.

Statistics

The study was a cross-sectional study without follow-up. We analyzed differences in electrocardiographic markers between people with type 2 diabetes and age-, sex-, and BMI-matched controls using linear models for continuous variables and logistic regression for the categorical variables T-wave notching (yes/no) and late transition (yes/no). We report unadjusted values for type 2 diabetes and control, respectively, and adjusted differences with adjustment for matching variables (age, sex, and BMI), smoking (current/previous/never), anti-diabetic medication, heart rate as average RR interval (except for models on heart rate and the already rate-corrected QT_{cF}), hypertension, previous myocardial infarction, and eGFR.

To properly assess the effect of diabetes duration on ECG markers independent of aging, we used the control group as reference and categorized diabetes duration into 0–2 years, 2–5 years, 5–10 years, 10–15 years, 15–20 years, or 20 year or more. Age was categorized into $<$50 years, 50–55 years, 55–60 years, 60–65 years, 65–70 years, 70–80 years, or $>$ 80 years. We regressed continuous ECG markers on diabetes duration, adjusted for categorized age, sex, BMI, heart rate (except for heat rate and QT_{cF}), smoking, anti-diabetic medication, hypertension, previous myocardial infarction, and eGFR.

We conducted a separate analysis on the impact of medication on ECG markers in patients with diabetes. We regressed one ECG marker at a time against all five medications with adjustment for sex, age, BMI, smoking, heart rate as average RR interval, hypertension, previous myocardial infarction, and eGFR.

The first and last authors had full access to the data and resume responsibility for the integrity of the data and the analyses. All analyses were conducted using R (v. 4.1.2, R Foundation for Statistical Computing, Vienna, Austria) and p-values <0.05 were considered significant.

Results

Demographics and clinical descriptions

We matched 988 people with type 2 diabetes (332, 34% females) to 988 controls (also 332 females) without diabetes (Table 1). The matched populations both had a median age of 65 years and a mean BMI of 30 kg/m^2.

Compared to controls, people with type 2 diabetes had lower blood pressures and lower cholesterol levels, but a higher HbA_{1c} and more often impaired kidney function, hypertension, and prior myocardial

Table 1
Demographics and clinical characteristics of participants with and without type 2 diabetes.

Variable	Diabetes	Control	*p*
n	988	988	
Age, years	65.4 [58.8,71.3]	65.1 [58.5, 71.2]	
Female sex, *n* (%)	34% (332)	34% (332)	
Diabetes duration, years	12 [4;17]	N/A	
BMI, kg/m^2	30.3 ± 5.6	30.2 ± 5.4	
Systolic BP, mmHg	135 ± 17	148 ± 21	<0.001
Diastolic BP, mmHg	80 ± 11	88 ± 11	<0.001
Hypertension, *n* (%)	890 (90%)	366 (37%)	<0.001
Previous myocardial infarction, *n* (%)	114 (12%)	32 (3%)	<0.001
eGFR<60mLmin^{-1}1.73 m^{-2}, *n* (%)	22% (216)	12% (118)	<0.001
HbA_{1c}, mmol/mol	58 ± 15	38 ± 4	<0.001
HbA_{1c}, %	7.4 ± 1.4	5.7 ± 0.3	
Total cholesterol, mmol/L	4.2 ± 1.0	5.6 ± 1.0	<0.001
Total cholesterol, mg/dL	164 ± 38	217 ± 40	
Never smoker, *n* (%)	43% (421)	38% (376)	0.003
Previous smoker, *n* (%)	40% (394)	48% (469)	
Current smoker, *n* (%)	18% (173)	15% (143)	

BMI: Body Mass Index; BP: Blood Pressure; eGFR: Estimated Glomerular Filtration Rate; HbA_{1c}: Glycated hemoglobin; N/A: Not applicable.

infarction (all $p < 0.001$). More people with type 2 diabetes had never started smoking, and fewer of those who did start had stopped again ($p = 0.003$).

In this 2011–2013 cohort of patients with type 2 diabetes, the most commonly used anti-diabetic drug was metformin (71%) followed by insulin (47%). Most patients were treated with a single drug (38%) or a combination of two drugs (41%). Diabetes duration was 0–2 years for 11%, 2–5 years for 14%, 5–10 years for 23%, 10–15 years for 23%, 15–20 years for 14%, and 20 years or more for 16% of diabetes patients at time of examination.

Electrocardiographic differences in people with type 2 diabetes vs control

Depolarization markers were markedly and significantly changed in people with type 2 diabetes compared to controls (Table 2). We found a 6 mm lower R-wave amplitude in lead V5 in people with diabetes, and R-wave amplitudes were visually different in most precordial leads (Fig. 1). The transition zone was more often delayed in people with type 2 diabetes (38% vs 13%, adjusted odds-ratio: 4.1, $p < 0.001$). P-wave duration was 5 ms shorter ($p < 0.001$), but there was no change in the PR interval ($p = 0.3$). QRS duration was 3 ms longer ($p = 0.03$).

Heart rate was significantly higher (76 vs 67 bpm, adjusted difference 4 bpm, $p < 0.001$) in people with type 2 diabetes compared to controls. The unadjusted QT interval was shorter in people with type 2 diabetes (17 ms without adjustment, $p < 0.001$, visible in Fig. 1), but there was no significant difference after adjustment ($p = 0.3$).

Other repolarization markers were significantly different in people with type 2 diabetes: T-wave amplitudes were visibly reduced (1 mm in V5, $p < 0.001$) and the QRS-T angle was increased by 10 degrees ($p = 0.002$). The T-waves in patients with type 2 diabetes appeared flatter and more asymmetric compared to controls, but these differences disappeared with adjustment.

We found no difference in the QRS axis of people with type 2 diabetes compared to controls (matched on BMI), but we did find that higher BMI was overall associated with a decreased QRS axis (−1 degree pr. kg/m^2).

Diabetes duration and ECG changes (Fig. 2)

In this cross-sectional study, depolarization markers were highly associated with diabetes duration (Fig. 2). R-wave amplitude (measured in V5) was decreased by 5 mm at diagnosis, which increased to 7 mm after 20 years of diabetes. In an exploratory analysis, we regressed R-wave amplitude on HbA_{1c} among people with type 2 diabetes, adjusted for the same confounders as the primary model plus diabetes duration, and found a 0.3 mm R-wave amplitude decrease per 10 mmol/mol increase in HbA_{1c} ($p = 0.004$). Odds of a delayed transition zone (V5-V6) increased just after clinical diagnosis and reached a stable level after two years post diagnosis.

P-wave duration became relatively shorter compared to controls whereas PR interval became relatively longer with increasing diabetes duration.

Heart rate in people with type 2 diabetes at time of diagnosis was 5 bpm higher, but after 20 years or more this difference was diminished (1 bpm, $p > 0.05$). We found no association between heart rate and aging (all $p > 0.05$).

Table 2
ECG parameters for people with diabetes vs. controls. Unadjusted and adjusted results are shown for all ECG markers. Adjusted results for QT interval are presented as QT_{cF}.

Variable	Diabetes	Control	*p* (unadjusted)	Adjusted differences [diabetes-control (95% confidence interval)]*	*p* (adjusted)
n	988	988			
Heart rate, bpm	76 ± 13	67 ± 12	<0.001	4 (2, 7)	<0.001
P axis, deg	46 ± 25	45 ± 26	0.59	−4 (−9, 1)	0.09
P-wave duration, ms	108 ± 15	113 ± 14	<0.001	−5 (−7, −2)	<0.001
PR interval, ms	170 ± 32	168 ± 25	0.04	3 (−2, 8)	0.25
QRS axis, deg	12 ± 41	14 ± 35	0.13	−2 (−9, 5)	0.54
R-wave amplitude V5, mm	8 ± 4	14 ± 5	<0.001	−5.5 (−6.3, −4.6)	<0.001
Transition zone					
V1-V2, % (*n*)	14% (135)	20% (202)	<0.001	–	–
V3, % (*n*)	15% (148)	33% (329)		–	–
V4, % (*n*)	33% (327)	33% (325)		–	–
V5-V6, % (*n*)	38% (378)	13% (132)		4.1 (2.8, 6.1) †	<0.001
QRS duration, ms	98 ± 21	97 ± 16	0.33	3 (0, 6)	0.03
QT interval, ms	390 ± 33	407 ± 30	<0.001	–	–
QT_{cF} interval, ms	418 ± 24	419 ± 20	0.54	2 (−2, 6)	0.32
QRS-T angle, deg	76 ± 40	61 ± 33	<0.001	10 (3, 16)	0.002
T axis, deg	42 ± 38	36 ± 28	<0.001	2 (−3, 8)	0.42
T-wave amplitude V5, mm	2.2 ± 1.4	3.4 ± 1.8	<0.001	−0.7 (−1.0, −0.4)	<0.001
T-wave asymmetry	0.095 ± 0.105	0.062 ± 0.084	<0.001	0.014 (−0.003, 0.031)	0.10
T-wave flatness	0.357 ± 0.080	0.371 ± 0.076	<0.001	0.008 (−0.003, 0.020)	0.17
T-wave notch	1.6% (16)	1.0% (10)	0.32	0.4 (0.1, 2.4)†	0.34

Unadjusted results are shown as mean ± standard deviation or % (*n*). Adjusted results are predicted difference (95% confidence interval), or odds ratio (95% confidence interval). ECG: Electrocardiogram. QT_{cF}, Fridericia-corrected QT interval. *The models were adjusted for sex, age, BMI, smoking, heart rate as applicable, hypertension, previous myocardial infarction, and estimated glomerular filtration rate (eGFR). †Odds ratio.

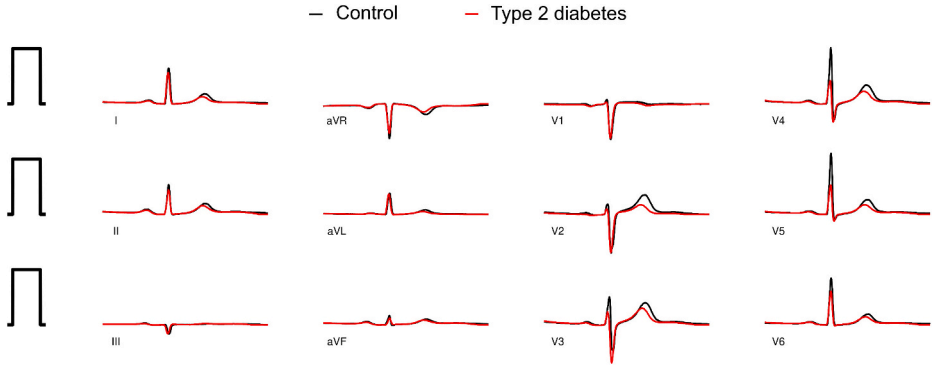

Fig. 1. Electrocardiograms in type 2 diabetes vs. age-, sex-, and BMI-matched controls. Median ECGs (representative beat) across both groups are shown in black (control) and red (diabetes). R-wave progression is markedly different. R-wave amplitude and T-wave amplitude are decreased in people with diabetes, and T waves are more flattened and asymmetric. The calibration pulse is 200 ms wide and 1 mV (10 mm) tall. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

None of the axes showed consistent changes with increasing diabetes duration, and the QRS-T angle was somewhat constantly increased at diagnosis and onwards. We found no association between repolarization markers and diabetes duration.

Effects of anti-diabetic drugs on ECG markers

Among patients with type 2 diabetes, multiple anti-diabetic drugs were significantly associated with ECG markers (Table 3). Heart rate was increased by 2–3.5 bpm among people using metformin, sulfonylurea, or GLP-1 agonists. Metformin was associated with decreased QRS duration, decreased QT_{cF} interval, and reduced T-wave amplitude even with adjustment for heart rate.

DPP-IV inhibitors were associated with a large 7 ms increase in PR interval. Insulin and sulfonylurea were associated with increased T-wave flatness and asymmetry, respectively. In addition to the effects on heart rate, the GLP-1 agonists were also associated with a 6 degree decrease in P axis.

Discussion

In the present study, we identified significant differences in ECG markers of depolarization and repolarization between people with and without type 2 diabetes matched on sex, age, and BMI. Most markedly, we found a significantly lower R-wave amplitude primarily in the precordial leads and delayed R-wave progression in people with type 2 diabetes. Most depolarization changes became more pronounced with increasing diabetes duration, whereas repolarization differences were independent of diabetes duration. All ECG markers, that were changed, were different already at 0–5 years post diagnosis.

Changes in markers with diabetes duration

Depolarization markers P-wave duration and R-peak amplitude (in V5) were both significantly changed at time of diagnosis and the difference grew with increasing diabetes duration. That raises the hypothesis – which future studies may test – that these markers may have been changes already before a clinical diagnosis of diabetes is made. More importantly, these markers may contain information about subclinical end organ damage i.e., disease progression at time of diagnosis. However, this type of personalized medicine probably requires a reference ECG because the disease effect appear smaller than or equal to the inter-individual variation. In other words, the observed effects of type 2 diabetes (2–7 ms for P-wave duration, 5–6 mm for R-peak amplitude) are not larger in amplitude than the natural variation in the population (standard deviations of 15 ms for P-wave duration and 5 mm for R-peak amplitude in V5).

Differences in depolarization markers and AV node conduction

Lower R-peak amplitude in primarily the precordial leads is a novel, overt, and important finding. As discussed already, the R-wave amplitude seems to decrease further with increasing diabetes duration. As we adjusted for BMI, an increased body mass probably did not drive the effect. Multiple studies have shown that type 2 diabetes is associated with increased left ventricular mass index [18] and left ventricular hypertrophy [9], which would lead to an increased R-wave amplitudes in V5 if the added mass is electrically active. A recent magnetic resonance imaging-based study on people from the UK Biobank revealed that prior to overt cardiac disease, cardiac chambers are smaller in people with type 2 diabetes and the mass-to-volume ratio is higher (total mass is similar) [19]. The mechanism may thus be remodeling which would explain the decreased electrical mass without a decreased total cardiac mass [3].

Other factors might also contribute to the effect. Hypertension, myocardial infarction, and renal disease were all associated with diabetes and may lead to ECG changes, but we controlled for these factors in the statistical analyses. The metabolic syndrome, which may lead to diabetes, was previously associated with a reduced QRS amplitude [20]. A glucose clamp study in people without diabetes showed an increased R-wave amplitude with hyperinsulinemia during euglycemia and hypoglycemia alike [21]. Here, we report a possible relationship between decreased R-wave amplitude and hyperglycemia, i.e. a state of relative insulin deficiency. Thus, the R-wave amplitude seems influenced by circulating insulin levels relative to the insulin resistance level. Numerous ion-channels are dysregulated in diabetes [22–24], and a part of the decreased R-wave amplitude may be caused by a decreased conduction velocity, possibly as a feature of decreased action potential upstroke velocity. This would be supported by the increased QRS duration reported in this study and in our previous study on people with type 1 diabetes [25].

We found a shorter P-wave duration in diabetes patients, a result that corresponds well with the finding by Jensen et al. that both atria are smaller in people with type 2 diabetes [19]. We were unable to find other human studies of P-wave duration in people with type 2 diabetes and consider this a novel finding.

Of note, others have associated diabetes not with a shortened but with a prolonged P-wave duration without atrial enlargement [26]. However, that model was created using a combination of diet and streptozotocin (selective beta-cell toxin), questioning whether the rat model represents type 1 or type 2 diabetes.

Type 2 diabetes was previously associated with heart block [27,28], however we found no effect of diabetes on the PR interval – only from use of DPP-IV inhibitors. This class of drugs acts on the dipeptidyl peptidase-4 enzyme to inhibit the degradation of GLP-1, and one DPP-IV

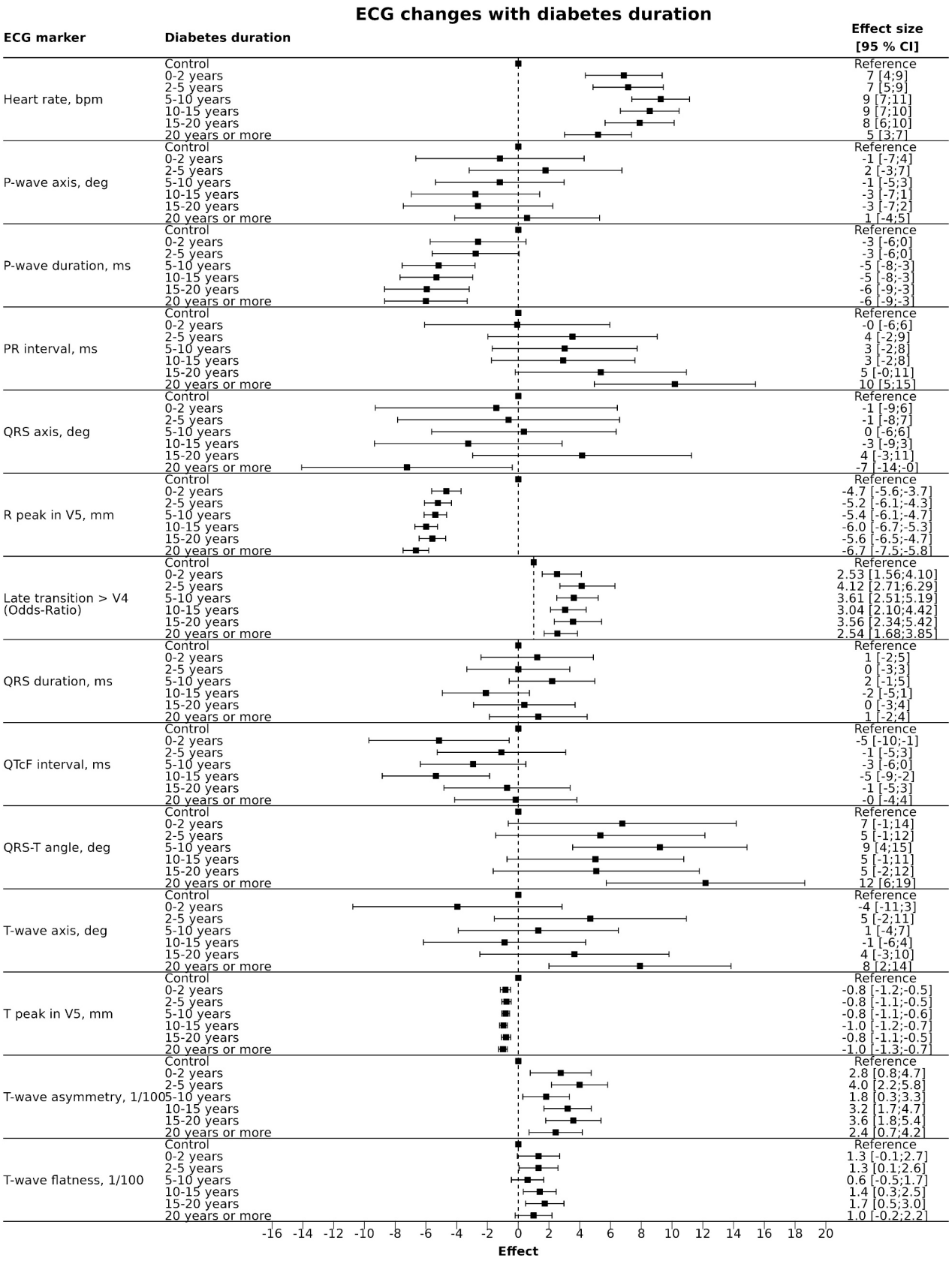

Fig. 2. Electrocardiographic effects of diabetes duration. Duration effects were adjusted for age, sex, body mass index, smoking, heart rate (where applicable), hypertension, myocardial infarction, and estimated glomerular filtration rate.

Table 3
Adjusted effect of antidiabetic medications on ECG markers with 95% confidence intervals. Adjustments as in Table 2.

Variable	Insulin	Metformin	Sulfonylurea	DPP-IV inhibitors	GLP-1 agonist
n (%)	461 (47%)	704 (71%)	160 (16%)	99 (10%)	233 (24%)
Heart rate, bpm	1.1 [−0.6;2.8]	**2.0* [0.1;3.9]**	**2.5* [0.3;4.7]**	1.1 [−1.6;3.8]	**3.5* [1.5;5.5]**
P axis, deg	1.2 [−2.3;4.7]	3.5 [−0.4;7.4]	2.0 [−2.6;6.6]	0.9 [−4.7;6.4]	**−5.5* [−9.5;−1.5]**
P-wave duration, ms	–1.5 [−3.6;0.7]	1.3 [−1.1;3.7]	−1.0 [−3.8;1.8]	2.1 [−1.3;5.6]	−1.6 [−4.0;0.9]
PR interval, ms	1.7 [−2.8;6.2]	−0.3 [−5.3;4.8]	−2.7 [−8.5;3.2]	**7.3* [0.3;14.3]**	2.6 [−2.7;7.8]
QRS axis, deg	3.8 [−1.7;9.3]	−2.1 [−8.2;4.0]	3.2 [−3.9;10.4]	4.1 [−4.5;12.8]	−3.1 [−9.6;3.3]
R-wave amplitude V5, mm	0.1 [−0.5;0.6]	−0.3 [−0.9;0.2]	0.2 [−0.5;0.8]	−0.5 [−1.3;0.3]	−0.6 [−1.2;0.0]
Transition zone > V4, OR	0.8 [0.6;1.1]	0.8 [0.6;1.1]	0.9 [0.6;1.4]	1.0 [0.7;1.6]	1.0 [0.7;1.4]
QRS duration, ms	−1.7 [−4.3;0.9]	**−3.2* [−6.1;–0.3]**	−2.2 [−5.6;1.3]	2.0 [−2.2;6.1]	2.1 [−1.0;5.1]
QT_{cF} interval, ms	−1.0 [−4.1;2.2]	**−5.2* [−8.7;–1.7]**	−3.6 [−7.7;0.5]	3.5 [−1.5;8.5]	−0.6 [−4.3;3.0]
QRS-T angle, deg	1.4 [−3.8;6.5]	−3.8 [−9.5;1.9]	1.3 [−5.4;8.0]	1.8 [−6.3;9.8]	−0.7 [−6.7;5.2]
T axis, deg	4.3 [−0.7;9.3]	−1.6 [−7.2;3.9]	2.3 [−4.3;8.8]	−3.2 [−11.2;4.7]	−3.3 [−9.1;2.6]
T-wave amplitude V5, mm	−0.2 [−0.3;0.0]	**−0.2* [−0.4;–0.0]**	−0.2 [−0.4;0.0]	0.1 [−0.2;0.3]	0.0 [−0.2;0.2]
T-wave asymmetry	0.01 [−0.00;0.03]	0.01 [−0.01;0.02]	**0.02* [0.00;0.04]**	0.00 [−0.02;0.02]	0.00 [−0.01;0.02]
T-wave flatness	**0.01* [0.00;0.02]**	0.01 [−0.00;0.01]	0.00 [−0.01;0.02]	−0.00 [−0.02;0.01]	−0.01 [−0.02;0.01]
T-wave notch, OR	1.2 [0.4;3.6]	1.9 [0.5;7.3]	2.3 [0.7;7.6]	1.1 [0.2;5.1]	0.9 [0.3;3.1]

OR: Odds ratio. Bold font and asterisk indicate significant difference $p < 0.05$.

inhibitor, vildagliptin, was in clinical studies associated with a higher incidence of first-degree AV block (PR > 200 ms) [29].

Ventricular repolarization

We found a markedly lower T-wave amplitude in precordial leads among people with type 2 diabetes, which remained after adjustment, and the combined depolarization and repolarization marker QRS-T angle was also changed in people with diabetes. However, the remaining repolarization markers were unchanged after full adjustment. A large part of the apparent (unadjusted) differences in repolarization was attributed to effects of anti-diabetic medication. We found a 5 ms QT_c-shortening effect of metformin, a drug whose mode of action is incompletely understood, and which exerts its effects on multiple organs including the liver and the gastrointestinal tract [30]. At least a part of the QT_c-shortening effect appears to be driven by metformin shortening the QRS duration by 3 ms. It is unclear how metformin targeting energy production at sites on mitochondria or lysosomes [30] may lead to a shortened QRS duration or the 0.2 mm decreased T-wave amplitude which we also observed. Metformin is used as first-in-line therapy and patients not on metformin are thus likely to be older and have more comorbidities, which may otherwise be associated with an increased QTc interval. To account for this potential confounding, we adjusted for age, eGFR and previous myocardial infarction, and despite the effect being driven largely by a QRS-shortening, we cannot rule out residual confounding.

The apparent more asymmetric T waves in patients with type 2 diabetes was in part driven by the use of sulfonylureas. This class of drugs has been reported to influence repolarization to prolong the QT interval and interactions with single nucleotide polymorphisms suggest a genetic predisposition to drug effects [31]. Sulfonylureas block the pancreatic $I_{K,ATP}$ potassium current to increase insulin release, and in circumstances where the cardiac $I_{K,ATP}$ potassium current is active [32], sulfonylureas may affect cardiac repolarization by blockage of this current.

Our data suggests that use of insulin might be associated with and increased T-wave flatness and thus altered cardiac repolarization. A recent genetic study found that several loci related to insulin and insulin receptors were associated with cardiac repolarization [33], making our findings biologically plausible. The QT interval itself was not associated with use of insulin, but since a previous study showed that T-wave morphology markers including T-wave flatness were more sensitive to detecting a history of torsade des pointes, they may in general be more sensitive to repolarization disturbances than the QT interval [34].

Although some repolarization markers were changed in patients with type 2 diabetes, we found no association between repolarization markers and diabetes duration. This finding is corroborated by a previous study on people with type 2 diabetes and T-wave axis and QRS-T angle [35]. Perhaps these repolarization changes are sensitive to a prediabetic setting (such as the metabolic syndrome [20]) and thus occur before diabetes diagnosis. That may explain why no further development is seen after diagnosis in the present study.

Heart rate

The 4 bpm increased heart rate in people with type 2 diabetes identified in the present study is probably necessary due to smaller stroke volumes and heart chambers [19], or it may be caused by autonomic neuropathy [36]. Interestingly, although the difference to controls was stable the first 15 years, it was reduced at longer diabetes durations. Perhaps this reduction is driven by the increased mortality with higher heart rates [37] (healthy survivor bias), because resting heart rate did not otherwise increase with age in this study or previous studies [38]. It is also possible that the normalization of heart rate is a treatment effect. The increased heart rate at the time of diagnosis in the present study is in line with a previous study, that established that increased heart rate was a predictor of incident diabetes within five years [39].

Strengths and limitations

The study has several strengths. First, the study is well-powered due to the inclusion of a high number of people with type 2 diabetes and controls. Second, controls were accurately matched on sex, age, and BMI, which are key confounders of most ECG markers. Third, the automated analysis employed in this study – using the same software for all ECGs – ensured reproducible and reliable measuring of ECG markers. Fourth, the use of cohort studies – compared to a register study – allowed better characterization of the population and adjustment for smoking status. Fifth, the detailed adjustment for use of anti-diabetic medication limits the risk of mistaking drug-induced effects for features of type 2 diabetes.

The study also has some limitations. The observational design and combination of two cohorts introduce the possibility of bias and residual confounding. The cross-sectional design limits inference about the temporal relationship between the exposure and outcome, and a study design with serial ECGs could presumably provide more precise information on ECG marker development over time. Inclusion of medications used exclusively in one group increases collinearity and thus widens confidence intervals pertaining to effect estimates. Lastly, as the Thousand&2 cohort consists of patients with less well-controlled type 2 diabetes [9], the effects described in the present report are likely more

pronounced than what is seen in patients with well-controlled type 2 diabetes.

In conclusion, we found significant electrophysiological differences in ventricular depolarization and repolarization in people with type 2 diabetes compared to controls matched on sex, age, and BMI. R-wave amplitude was markedly lower in the precordial leads and R-wave progression was delayed. Diabetes duration significantly impacted cardiac depolarization markers.

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Disclosures

JKK and CG are co-authors on a patent on T-wave morphology. CBS is an employee of Novo Nordisk. The remaining authors have nothing to declare.

CRediT authorship contribution statement

Jonas L. Isaksen: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Christian B Sivertsen:** Statement, Writing - original draft, Software, Investigation, Writing - review & editing. **Christian Zinck Jensen:** Writing – review & editing, Methodology, Conceptualization. **Claus Graff:** Writing – review & editing, Data curation. **Dominik Linz:** Writing – review & editing, Supervision, Methodology. **Christina Ellervik:** Writing – review & editing, Methodology, Funding acquisition, Data curation. **Magnus T. Jensen:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Peter G. Jørgensen:** Writing – review & editing, Methodology, Funding acquisition, Data curation, Conceptualization. **Jørgen K. Kanters:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jonas L. Isaksen reports financial support was provided by Danish Cardiovascular Academy. Christina Ellervik reports financial support was provided by Boston Children's Hospital. Jorgen K. Kanters reports financial support was provided by Independent Research Fund Denmark. Christian B. Sivertsen reports a relationship with Novo Nordisk that includes: employment. Jorgen K. Kanters, Claus Graff has patent licensed to GE Healthcare. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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