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Myocardial repolarization is affected in patients with diabetic retinopathy

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Diabetes Mellitus (DM), considered the equivalent of coronary artery disease, is one cause of ventricular repolarization (VR) dispersion. Retinopathy is one of the vascular consequences of diabetes. The association between myocardial repolarization dispersion and diabetic retinopathy is not fully elucidated. We aimed to evaluate ventricular repolarization using Tp-e interval and corrected (c) Tp-e/QT ratio in DM patients with and without retinopathy.
Methods: A total of 124 diabetic subjects were included in this retrospective cohort study**.** All medical data were obtained from the electronic database of our university hospital. The subjects were divided into the no diabetic retinopathy (NDR) group (n=45), and the diabetic retinopathy (DR) group (n=79), which were compared in terms of demographic features, clinic and laboratory findings, and electrocardiographic findings such as QT, QTc, Tp-e, Tp-e/QT, Tp-e/QTc.
Results: The groups were similar in terms of demographic features (P>0.05). Both Tp-e interval and Tp-e/QTc were significantly prolonged in the DR group compared to the NDR group. There were significant correlations between Tp-e, Tp-e/QTc, DM duration, and age. In multivariate logistic regression analysis, Tp-e (OR=6.01, %95 CI=4.17-7.52, P=0.012), Tp-e/QTc (OR=1.215, 95% CI=0.874-1.612, P=0.029), and DM duration (OR=1.422, 95% CI= 1.146–1.712, P<0.001) were independent predictors of DR.
Conclusion: We showed that DM patients with retinopathy may also have an increased risk for sudden cardiac death due to ventricular arrhythmogenesis.

Keywords: Ventricular repolarization, Diabetic retinopathy, Sudden cardiac death, Tp-e interval, Tp-e/QTc interval

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Introduction

Type 2 diabetes mellitus (DM) is a risk factor for both coronary artery disease (CAD) and atherosclerosis [1]. DM leads to the development of both micro- and macrovascular diseases [2]. On the other hand, it is well known that both micro- and macrovascular complications are independent risk factors for sudden cardiac death (SCD) among DM patients [3].

Retinopathy, one of the vascular complications of DM, is among the earliest findings of microvascular involvement and can lead to blindness [4]. The perivascular structural changes or new aberrant vessels are classified as non-proliferative or proliferative [5].

Ventricular repolarization (VR) anomalies in electrocardiography (ECG) are well-known markers for increased mortality risk [6-8]. Various ECG markers were proposed to predict people at elevated risk for ventricular arrhythmias [9, 10]. Even in patients with normal QTc values, the Tp-e interval, a new ECG marker, shows VR [11]. The transmural dispersion of repolarization in the left ventricle is indicated by the interval from the T wave peak to the end of the T wave (Tp-e) in the ECG. The ratio of Tp-e/QT has recently been used for VR distribution as a relatively new ECG marker [12]. Malignant ventricular arrhythmias are correlated with both the Tp-e value and the ratio of Tp-e/QT [13].

This study aimed to investigate whether type 2 DM patients with retinopathy have increased ventricular repolarization abnormalities, as calculated with Tp-e value and the ratio of Tp-e/QT.

Materials and methods

The study began after Bolu Abant Izzet Baysal University Clinical Research Ethics Committee (decision number: 2020/172) granted approval and was conducted according to the principles of the Helsinki Declaration. Participation was voluntary. All patients were informed about the study and their verbal and written consents were obtained.

This retrospective cohort study was performed at the Department of Cardiology in a university hospital in Turkey between January 2019 and May 2020. One hundred and twenty-four diabetic patients who visited the cardiology department between these dates and did not meet the exclusion criteria were included and divided into two groups: The diabetic group without retinopathy (NDR) (n=45) and patients with diabetic retinopathy (DR) (n=79).

All medical data of the subjects were obtained from the electronic database of the hospital. Patient's demographics and clinical characteristics including gender, age, smoking history, hypertension (HT), ischemic heart disease, and familial history, and laboratory parameters including serum fasting glucose, hemoglobin A1c, creatinine, hemoglobin, and total cholesterol and high- and low-density lipoprotein cholesterol were recorded. Additionally, diastolic, and systolic blood pressure (DBP and SBP), electrocardiographic and echocardiographic findings, the current smoking status of the patients were noted. Hypertension was diagnosed in at least two different measurements when SBP ≥140mmHg or DBP ≥90mmHg, or the patient was using any antihypertensive drugs. The body mass index (BMI) was calculated by weight in kilograms divided by the square of the height in meters.

Patients with a history of ischemic and valvular heart disease, cardiomyopathy, atrial fibrillation, implantation of the previous pacemaker, those using an antiarrhythmic drug affecting the ventricular repolarization duration (i.e., antiarrhythmic drugs, beta- and alpha-blocker, non-dihydropyridine calcium antagonist, digoxin, antifungal agents and antibacterial agents, antipsychotic agents, or antihistamines), patients with cancer, or other major illnesses, abnormal electrolyte values, abnormal thyroid function tests, low-amplitude T waves, U waves, and bundle branch block on their ECGs were excluded.

DM and retinopathy definition

Patients with a history of DM diagnosis and/or a prescription (insulin or anti-diabetic drugs) and/or fasting blood glucose ≥126 mg/dl and/or glycated hemoglobin (HbA1c) ≥6.5% were considered to have DM. International Clinical Diabetic Retinopathy Disease Severity Scale was used to diagnose the DR [14].

Electrocardiographic evaluation

After a 10-minute rest, twelve-lead ECGs were obtained in supine position with 10 mm/mV amplitude and 25 mm/s rate using a commercially available system (Nihon Kohen Cardiofax ECG-1950 VET). The ECG duration was 10 seconds, thus, there were 4 to 6 beats per lead, depending on the heart rate. Two cardiologists, blinded to the information of the patients, manually assessed ECGs using a magnifying glass (TorQ 150 mm Digital Caliper LCD). QT intervals were measured from the onset of the QRS complex until the end of the T wave, defined as its return to the baseline TP. The QT interval was calculated at the curve's nadir between the T and U waves if U waves were present.

The R-R and QT intervals were noted. QT dispersion (QTd) was calculated as the difference in precordial leads between the maximum and minimum QT intervals. The Bazett formula was used to measure the corrected QT (QTc) [15]. The Tp-e interval was measured from the T wave peak to the end of the T wave. JT intervals were calculated from the end of the QRS complex (J point) to the end of the T wave (JTend interval). Corrected JT (JTc) interval was calculated using the Bazett formula. Also calculated were the Tp-e/QT, Tp-e/QTc, Tp-e/JT, and Tp-e/JTc ratios. No patient had a measurable lead of less than nine. The intra- and interobserver differences for the measurements were less than 5%.

Statistical analysis

SPSS 18.0 Windows Statistical Package Program (SPSS Inc, Chicago, Illinois, USA) was used to analyze the data. Quantitative variables were expressed as mean (standard deviation (SD)) and qualitative variables, as numbers and percentages. Normally distributed parameters were analyzed with a one-way ANOVA test, and post-hoc tests with Tukey's HSD were conducted. The Kruskal-Wallis test was used to compare variables in various research subgroups for parameters with a heterogeneous distribution or in the case of variance inequality. In-group variations were analyzed with the Bonferroni-corrected Mann-Whitney U-test. Numeric and nominal data were assessed with Pearson's correlation and Spearman's correlation tests, respectively. Logistic regression

tests were used to evaluate the independent predictors of DR. A *P*-value <0.05 was considered significant.

Results

The demographic, clinical features, and laboratory results of the groups were similar (Table 1).

The mean Tp-e and median Tp-e/QT_{mean} values were significantly higher in the DR group compared to the NDR group (*P*=0.04 and *P*=0.002, respectively). In other electrocardiographic parameters, there were no major variations between the groups (Table 2).

Table 1: Baseline characteristics, clinic, and laboratory findings of the study groups

	Non-DR (n=45)	DR (n=79)	*P*-value
Age, years	64 (10)	62 (0.9)	0.39
Body mass index, kg/m^2	30 (5)	31 (5)	0.85
Male/female, n	23/22	41/38	0.16
Hypertension, %	28(62%)	57(62%)	0.09
Smoking, %	1(2%)	10(12%)	0.14
Family history, %	12(27%)	35(45%)	0.15
CAD history, %	19(42%)	31(30%)	0.22
DM duration, months	46 (12)	44 (13)	0.75
Fasting glucose, mg/dl	121.1 (32.4)	126.4 (33.5)	0.29
Hemoglobin A1c, %	7.1 (1.1)	7.3 (1.2)	0.52
LDL-cholesterol, mg/dl	107 (35)	115 (28)	0.21
HDL-cholesterol, mg/dl	49 (12)	41(10)	0.06
Triglyceride, mg/dl	135 (54)	155 (58)	0.019
Hemoglobin, mg/dl	13.1 (1.4)	13.5 (1.3)	0.39
Systolic BP, mmHg	136 (23)	132 (25)	0.56
Diastolic BP, mmHg	80 (13)	78 (11)	0.25
Creatinine, mg/dl	0.82(0.61-3.35)	0.87(0.65-5.49)	0.18
LA diameter, mm	36(22-48)	40(26-49)	0.03
LVEF, %	60(40-65)	57(45-65)	0.09

DR: Diabetic retinopathy, CAD: Coronary artery disease, DM: Diabetes Mellitus, SD: Standard deviation, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, BP: Blood Pressure, LA: Left atrium, LVEF: Left ventricular ejection fraction

Table 2: Electrocardiographic findings of the study groups

	Non-DR (n=45)	DR (n=79)	*P*-value
Tp-e, msn	71.62 (7.01)	82.15 (8.93)	<0.001
QT, msn	346.2 (33.0)	348.4 (27.6)	0.53
QTc, msn	393.7 (21.3)	388.7 (22.5)	0.29
JT, msn	253.9 (35.6)	255.9 (24.5)	0.49
JTc, msn	287.8 (25.9)	289.7 (27.7)	0.65
Tp-e/QT ratio	0.208 (0.024)	0.236 (0.025)	<0.001
TPe/QTc ratio	0.18(0.15-0.23)	0.22(0.15-0.26)	<0.001
TPe/JT ratio	0.29(0.20-43)	0.31(0.21-0.44)	0.19
Tp-e/JTc ratio	0.253 (0.034)	0.268 (0.042)	0.012
QRS, msn	90(64-126)	92(72-140)	0.70
QT dispersion	12(4-31)	13(5-36)	0.31

Correlation analysis showed that both Tp-e and Tp-e/QTc were significantly associated with DM duration and age (r=0.325/*P*<0.01, r=0.285/*P*<0.01 for DM duration and r=0.251/*P*=0.02, r=0.274/*P*=0.012 for age) (Table 3).

Variables, found to relate to DR in multivariate logistic regression analysis, were also assessed in univariate analysis. Tp-e (OR=6.01, 95% CI=4.17-7.52, *P*=0.012) and Tp-e/QTc (OR=1.215, 95% CI=0.874-1.612, *P*=0.029), together with DM duration (OR=1.422, 95% CI=1.146–1.712, *P*<0.001), were independent predictors of DR (Table 4).

Table 3: The correlation analysis results of Tp-e value and Tp-e/QTc ratio with the other study parameters in all patients

Parameters	Tp-e	Tp-e/QTc ratio
Age	(r=0.251/ *P*=0.02)	(r=0.274/ *P*=0.012)
Body mass index	(r=0.144/ *P*=0.31)	(r=0.187/ *P*=0.34)
DM duration	(r=0.325/ *P*<0.01)	(r=0.285/ *P*<0.01)
Glucose	(r=0.05/ *P*=0.74)	(r=0.08/ *P*=0.54)
LDL-C	(r=0.101/ *P*=0.42)	(r=0.133/ *P*=0.21)
LVEF	(r=-0.133/ *P*=0.11)	(r=-0.151/ *P*=0.20)
LA diameter	(r=0.114/ *P*=0.21)	(r=0.07/ *P*=0.82)

DM: Diabetes mellitus, LDL-C: Low-density lipoprotein cholesterol, LVEF: Left ventricular ejection fraction, LA: Left atrium

Table 4: Univariate and Multivariate logistic regression analysis showing parameters associated with DR

	Unadjusted OR/ 95%CI	*P*-value	Adjusted OR/ 95%CI	*P*-value
Age	0.92(0.26-1.84)	0.36		
Glucose	4.21(2.14-5.45)	0.23	2.021 /1.486–2.043	0.72
DM duration	3.12(2.97-3.29)	<0.001	1.422/1.146–1.712	<0.001
Tp-e/QTc	0.95(0.901-1.08)	0.012	1.215/0.874-1.612	0.029
Tp-e	8.31(6.77-10.32)	<0.001	6.01(4.17-7.52)	0.012
LA	2.32(0.97-3.57)	0.09	0.422/0.346–1.132	0.10
LVEF	1.44(0.38-2.81)	0.53		
Body mass index	0.78(0.62-1.35)	0.81		

DM: Diabetes mellitus, LA: Left atrium, LVEF: Left ventricular ejection fraction

Discussion

To the best of our knowledge, this is the first study to assess the relationship between DR and myocardial repolarization dispersion indexes. We observed that left ventricular repolarization indices, including Tp-e interval and Tp-e/QTc ratio, were substantially increased in the DR population compared to DM patients without retinopathy. Additionally, we found that DR can be predicted by Tp-e/QTc in DM patients.

As DR reflects microangiopathy, increases in Tp-e/QTc and Tp-e, observed in patients with DR led us to think that microangiopathy may influence ventricular myocardium electrical activity. Thus, microvascular circulation in diabetic patients' hearts was disturbed due to the prothrombotic and proinflammatory status, and autonomic neuropathy. This causes an increased risk of quiet myocardial infarction (MI), life-threatening ventricular arrhythmia, and even SCD [16]. In addition, there is an elevated risk of ventricular and atrial arrhythmias, perhaps due to structural defects in DM patients due to chronic hyperglycemia and increased fibrosis in the cardiac tissue [17, 18].

In the previous studies, traditional VR parameters such as QT, QTc, and QTc dispersion were significantly increased in the DR group compared to the group without DR [19-22]. In both DM patients and healthy individuals, QT interval prolongation predicts increased risk of all-cause and cardiovascular mortality [8, 23]. In this study, we wanted to investigate Tp-e and Tp-e/QT_{mean} intervals, and the ratio of Tp-e/QTc, which are relatively novel parameters in the electrocardiographic assessment of repolarization. In predicting arrhythmia, they were shown to be superior to the QT interval and QTd, and their prolongations are related to increased risk of arrhythmogenesis. Thus, even in patients with a normal QTc, the Tp-e value was proven to show VR dispersion [13, 24, 25].

Microvascular complications of DM are independent risk factors for SCD [3,26]. The most common microvascular complication of DM is DR [27]. Epidemiologic studies have shown the effects of hyperglycemia, hypertension, and dyslipidemia on the incidence and progression of DR. These risk factors are also predisposing factors for SCD [28-31]. Clemente et al. studied the effects of DM on VR parameters in 110 diabetic patients comparatively with 110 control subjects. The authors detected the significantly higher QTc_{max} and QTc_{mean} values, and QT, QTc, Tpeak-Tend, and jTpeak-jTend dispersions in diabetic patients compared to the control subjects. They concluded that diabetes led to VR prolongation and spatial dispersion, which may lead to electrical ventricular instability and potential malignant ventricular arrhythmias afterward [32]. However, Takebayashi et al. showed that QTc intervals were not related to

retinopathy in diabetic patients [33]. Besides, Veglio et al. revealed that no significant relationship existed between QT interval duration and DR [34]. Similarly, in our sample population, we did not find any significant differences in QT dispersion between the groups.

Patients with known CAD were excluded. There was also no statistically significant difference in terms of HT and hyperlipidemia between the groups. On the other hand, occult CAD may exist in diabetic patients, and silent coronary ischemia in this patient population might be responsible for prolonging the Tp-e interval. We found significant associations between DR and VR parameters. According to our results, we consider that it is crucial to assess these electrocardiographic parameters to determine the arrhythmia risk in DM patients with DR. We also showed that Tp-e value and ratio of Tp-e/QTc were predictors for DR development in regression analysis. In patients with DM, we suggest that increased VR might be correlated with the degree of DR. Our regression analysis revealed that the duration of DM was also significantly associated with DR. Since diabetic microvascular complications such as DR are associated with decreased life expectancy, prolonged VR parameters in patients with DM can be considered mortality markers in these patients. Nevertheless, more prospective, well-designed large-scale studies are needed to confirm the current findings, support our observations, obtain more substantial scientific evidence, and establish the prognostic value of increased VR parameters in DR patients.

Limitations

There were some limitations to our research. First, the ECG parameters of our sample were manually measured. Manual measurements have been acknowledged scientifically and several experiments have been conducted according to this approach, but the measurements carried out by a high-resolution monitor with digital ECG recordings are substantially more precise and standardized. Second, we had a relatively small sample size. Third, because it was not possible to conduct coronary angiography in clinical practice in all patients, subclinical ischemic heart disease may have been missed in the study group. Finally, we did not prospectively follow the patients for adverse cardiovascular outcomes.

This survey showed a strong correlation between diabetes and changes in the electrophysiological parameters that suggested prolonged and more heterogeneous repolarization of diabetic patients, in contrast to healthy subjects despite some methodological limitations. The greater susceptibility of these diabetic patients to cardiac arrhythmias could be associated with this fact. Therefore, for improved risk stratification of diabetic patients, it may be important to test these new markers for arrhythmogenic risk. Since these parameters are easy to assess, it may help to identify high-risk patients in daily clinical practice.

Conclusions

According to our study results, we think that myocardial VR parameters such as Tp-e value and ratio of Tp-e/QTc may be useful to assess and stratify DM patients who have retinopathy according to high-risk ventricular arrhythmia. Patients with DR may be at an increased risk of SCD, not only because of DM complications but also because of ventricular arrhythmias. Further studies are needed in patients with DR to assess the function of these parameters for predicting ventricular arrhythmias.

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