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Original Article

Comparison of Tp-e interval, QTc interval and Tp-e/QTc ratios between non-diabetic and prediabetic population

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Abstract

Aim: Increased blood glucose concentration and cardiac autonomic nerve dysfunction are associated with an increased risk of malignant ventricular arrhythmia. Tp-e interval, Tp-e/QT, and Tp-e/QTc are novel parameters used to assess ventricular arrhythmogenicity. This study aimed to compare these parameters with the healthy control group in prediabetics.

Materials and Methods: The ECGs of 58 prediabetic patients (29 male, 59.74 ±13.25 years) were examined and matched with the ECGs of 59 healthy controls (28 male, 61.75 ± 12.66 years) that were matched with gender, age and body mass index. From the 12-lead ECG Tp-e and QT intervals were measured and by Bazett's formula QTc was calculated. Tp-e/QT and Tp-e/QTc proportions were also determined.

Results: In prediabetic patients, the mean Tp-e interval was significantly longer than the control group (79.07 ± 8.17 vs 72.03 ± 9.77 ms, respectively; p <0.001). Also in prediabetic, Tp-e/QT and Tp-e/QTc were significantly higher than the controls (respectively 0.21 ± 0.25 vs 0.19 ± 0.03 and 0.19 ± 0.02 vs 0.17 ± 0.02; p <0.001). Other ECG parameters were similar in both groups. HbA1c levels and glucose levels were positively correlated with Tp-e / QT and Tp-e / QTc.

Conclusion: Prediabetes increases the risk of ventricular arrhythmogenesis by increasing the transmural dispersion of repolarization. The addition of Tp-e interval and TP-e / QT measurements to the routine ECG evaluation of prediabetic patients can be used to predict arrhythmia risk.

Keywords: Prediabetes; Tp-e interval; Tp-e/QT ratio; Tp-e/QTc ratio; ventricular arrhythmia

INTRODUCTION

The definition of prediabetes is used for cases where the blood glucose concentration is higher than normal values but does not exceed the diabetes threshold, and it is an increased risk of developing diabetes. Its prevalence is gradually increasing in the general population, depending on the diet and sedentary lifestyle. Prediabetes is explicitly characterized as impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG). IGT is the plasma glucose value measured between 140mg / dL to 199 mg / dL in the 2nd hour in the oral glucose tolerance test. Another diagnostic criterion is that HbA1c is between 5.7 - 6.4 % (1). Approximately 5-10% of people with prediabetes progress to diabetes each year.

In diabetic patients, the risk of arrhythmia increases as a result of impaired microvascular circulation due to autonomic neuropathy, prothrombotic and proinflammatory status (2). Also, autonomic regulation is disrupted due to the increase in sympathetic autonomic nervous system activity in a patient with diabetes mellitus (DM). This condition is related to malignant ventricular arrhythmias, independent of coronary artery disease (CAD) and heart failure (HF) (3,4). Autonomic neuropathy can be seen in the prediabetes stage before evident DM develops (5). Prediabetes is associated with decreased heart rate variability, postural changes in heart rate, and a worse profile in sympathetic and parasympathetic function tests (6-8). Therefore, we think that arrhythmias occurring in DM other than CAD and HF can also occur in prediabetes. QT interval (QT), corrected QT (QTc), QT dispersion are electrocardiographic (ECG) parameters that indicate the repolarization phase of the myocardium and can be used to predict ventricular arrhythmogenesis (9,10). Prolongation of these parameters has been shown in studies to be prognostic measures for cardiac mortality in diabetics (11,12).

Tp-e interval, Tp-e/QT, and Tp-e/QTc measured on the ECG are nowel parameters utilized in recent studies to assess ventricular arrhythmogenicity in many diseases (13-17). These parameters, which are not used frequently in routine ECG assessment, are more dependable for evaluating ventricular repolarization, as they are not affected by heart

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rate, such as QT and QTd (18,19). Studies are showing that these parameters are prolonged in DM patients compared to the healthy control group (20-21).

In this study, we aimed to compare Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc with a healthy group in a condition that is a risk factor for cardiovascular disease (CVD), such as prediabetes. To our knowledge, these electrocardiographic parameters have not been investigated as markers of ventricular arrhythmogenesis in prediabetics in any previous study.

MATERIALS and METHODS

Study population

The study was conducted in Bilecik Training and Research Hospital. 58 prediabetic patients admitted to the endocrinology and cardiology clinics between January 2020 and May 2020 were included in the study. Prediabetes diagnosis was made according to the American Diabetes Association criteria (1). 59 healthy volunteers, whose gender, age, and body mass index were harmonized, formed the control group.

A history of known CAD and myocardial infarction, severe valvular disorder, heart failure with mid-range ejection fraction (left ventricular ejection fraction (LVEF) between 40%-49%), heart failure with reduced ejection fraction (LVEF<40%), atrial fibrillation, cerebrovascular disease, apparent diabetes mellitus (Type 1 / Type 2), obesity (body mass index (BMI) > 30), ECG changes that make electrolyte disturbances (hypokalemia, hypercalcemia, hypomagnesemia, etc.), renal failure (GFR <% 60 mL/min), those who were suspected of measuring TP-e and QT intervals, those with history of cardioverter defibrillator or pacemaker implantation and antiarrhythmic drug use were excluded. A complete physical examination was made and weight, height, waist circumference measured to all individuals participating in the study, and the medical history was questioned. BMI was calculated using the formula (weight (kg) / length (m^2). After resting for at least 15 minutes in the sitting position, blood pressure was measured while the feet touched the ground. All participants were normotensive and at least two consecutive measurements, the blood pressure was <140/90 mmHg. Venous blood was collected from all participants after 12 hours of fasting. Complete blood count and biochemical analysis were performed from these samples. In the biochemical analysis, fasting blood sugar, lipid profile, liver enzymes, kidney function tests, thyroid hormones were measured. HbA1c levels were measured with the Abbott CI-8000 device. Echocardiographic evaluation was performed using the Philips Epiq 7c ultrasound system (Amsterdam, Netherlands) in the left lateral decubitus position. From the parasternal long axis; aortic, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVEDD), and left ventricular wall thicknesses were measured. LVEF was determined utilizing the modified Simpson's method and Teicholz formula.

All participants in the study were informed about the research subject and their written assent was acquired. Ethics committee approval was received at local ethics committee (2020/17).

Electrocardiographic evaluation

12 lead superficial ECG recordings were taken at 50 mm/s paper speed and 10 mm/mV voltage using Nihon Kohden (Tokyo, Japan) ECG recorder. All ECGs were taken at least 10 minutes after rest and in the supine position in a normal breathing pattern. ECG recordings were scanned and carried to the digital platform and examined by enlarging x300%. P wave time, PR interval, QRS time, RR distance, QT interval and TP-e interval were measured manually. The distance between the peak of the T wave and the end part interacting with the isoelectric line was determined as the Tp-e interval (Figure 1). V2 and V5 derivatives were used for TP-e measurements. Tp-e/QT and Tp-e/QTc ratios were calculated utilizing these obtained parameters. QTc was calculated according to the heart rate using Bazett's formula (QT / √ RR interval). All ECGs were evaluated by two different cardiologists who did not have patient information.

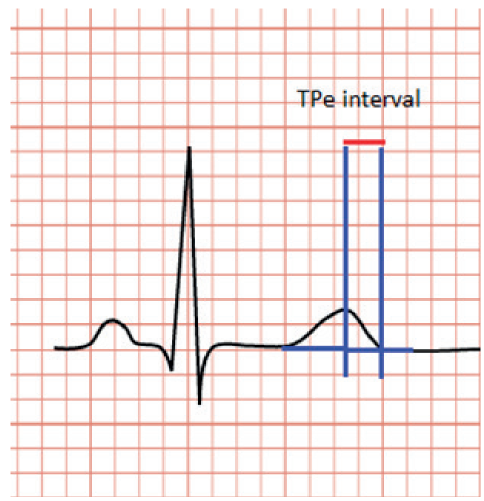

Figure 1. Measurement of peak and the end of the T wave (Tp-e) interval

Statistical analysis

Statistical analysis of the data was performed with SPSS software (Version 22.0, SPSS Inc., Chicago, IL, USA). The normality distribution was calculated with the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation. Student's t-test was used for data with normal distribution and Mann-Whitney U test was used for abnormally distributed data. Categorical variables were expressed as numbers and percentages, and the chi-square test was used for comparison. The correlation among variables was examined using the Pearson correlation test. P values of <0.05 were accepted as statistically significant.

RESULTS

A total of 117 participants, 60 women and 57 men were included for the study. The mean age of the study group was 60.75 ± 12.95 years. Age and gender distribution were similar in both groups. The number of hypertensive

Table 1. Clinical and laboratory findings for groups

Parameters	Prediabetic group (58) (Mean ± SD)	Controls (59) (Mean ± SD)	p-value
Age (years)	59.74 ±13.25	61.75 ± 12.66	0.405
Sex (female /male)	29/29	31/28	0.783
Hypertension (n,%)	13 (22.4 %)	9 (15.2)	0.322
BMI (kg/ m^2)	26. 87 ± 2.71	26.45 ±2,89	0.213
Waist circumference (cm)	97.60 ± 9.84	95.41 ± 7.53	0.178
SBP (mm-Hg)	129.01 ± 13.1	127.36 ± 10.82	0.462
DBP (mm-Hg)	79.51 ± 7.77	78.69± 5.98	0.522
LVEF (%)	61.54 ± 4.43	62.14 ± 3.86	0.440
IVS (mm)	9.74±2.09	9.71±1.99	0.938
PW (mm)	9.75±1.90	9.72±1.69	0.889
Fasting glucose (mg/dL)	111.24 ± 10.05	87.51 ± 8.25	**<0.001**
Hemoglobin A1c (%)	6.11± 0.32	5.28 ± 0.25	**<0.001**
Hemoglobin (g/dL)	14.17 ± 1.20	14.26 ± 1.18	0.706
Creatinine (mg/dL)	0.84 ± 0.18	0.83 ± 0.14	0.745
Sodium (Na) (mEq/L)	138.12 ± 3.18	138.18 ± 3.15	0.911
Potassium (K) (mEq/L)	4.21 ± 0.42	4.23 ± 0.45	0.808
Calcium (Ca) (mg/dL)	9.07 ± 0.44	9.19 ± 0.47	0.166
Total cholesterol (mg/dL)	200.63 ± 17.54	195.84 ± 24.21	0.224
Triglycerides (mg/dL)	170.65 ± 57.47	145.74 ± 27.52	**0.003**
HDL-C (mg/dL)	43.25 ± 6.48	44.77 ± 5.31	0.167
LDL-C (mg/dL)	131.35 ± 20.43	125.61 ± 18.92	0.117
TSH (uIU/mL)	2.33 ± 0.92	2.12 ± 0.89	0.815

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; LVEF: Left Ventricular Ejection Fraction; IVS: Interventricular Septum; PW: Posterior Wall; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; TSH: Thyroid-Stimulating Hormone

patients was similar in both groups (p = 0.322) Blood pressure, BMI, waist circumference, LVEF, interventricular septum (IVS) and posterior wall (PW) thicknesses were similar among the groups (p >0.05 for each). Glucose and HgA1c levels were significantly higher in the prediabetic group (111.24 ± 10.05 vs 87.51 ± 8.25), (6.11± 0.32 vs 5.28 ± 0.25), as expected (p <0.001 for each). Triglyceride levels were significantly higher in prediabetics (p = 0.003). Other biochemical parameters were similar between groups. Demographic and laboratory measurements between prediabetes and the control group are shown in Table 1.

Table 2 shows the electrocardiographic comparison of the study groups. HR (76.78 ± 13.33 vs. 75.95 ± 12.65 beats/min; p = 0.731), QT interval (377.67 ± 25.19 vs 373.49 ±

Table 2. Electrocardiographic findings between groups

Parameters	Prediabetic group (58) (Mean ± SD)	Controls (59) (Mean ± SD)	p-value
HR (beats/min)	76.78 ±13.33	75.95 ± 12.65	0.731
QT (ms)	377.67 ± 25.19	373.49 ± 26.38	0.383
QTc (ms)	406.22 ± 19.01	404.64 ±19.71	0.660
QRS (ms)	90.48 ± 6.96	91.07 ± 10.83	0.728
Tp-e (ms)	79.07 ± 8.17	72.03 ± 9.77	**<0.001**
TP-e / QT	0.21± 0.25	0.19 ± 0.03	**<0.001**
Tp-e / QTc	0.19 ± 0.02	0.17 ± 0.02	**<0.001**
QT / QRS	4.21 ± 0.44	4.15 ± 0.56	0.633
QTc / QRS	4.52 ± 0.46	4.51 ± 0.62	0.908

HR: Heart Rate; QTc: Corrected QT; TP-e: Peak and the end of the T wave

26.38 ms; p = 0.383), QTc (406.22 ± 19.01 vs 404.64 ± 19.71 ms; p = 0.660), QRS duration (90.48 ± 6.96 vs 91.07 ± 10.83 ms; p = 0.728), QT/QRS (4.21 ± 0.44 vs 4.15 ± 0.56; p = 0.633) and QTc/QRS (4.52 ± 0.46 vs 4.51 ± 0.62; p = 0.908) were similar in both groups. Tp-e intervals (79.07 ± 8.17 vs 72.03 ± 9.77 ms; p <0.018) were significantly longer in the prediabetics. Tp-e / QT, Tp-e/QTc ratios were statistically significantly higher in prediabetes group (0.21 ± 0.25 vs 0.19 ± 0.03 ms and 0.19 ± 0.02 vs 0.17 ± 0.02 respectively; p <0.01 for each). A positive correlation was detected between HgA1c and Tp-e (r = 0.370, p <0.001), Tp-e/QT (r = 0.311, p <0.01) and Tp-e/QTc (r = 0.332, p <0.01) (Figure 2). A positive correlation was observed between fasting blood glucose and Tp-e (r = 0.342, p <0.01), Tp-e/QT (r = 0.868, p <0.01) and Tp-e/QTc (r = 0.928, p <0.01) (Figure 3).

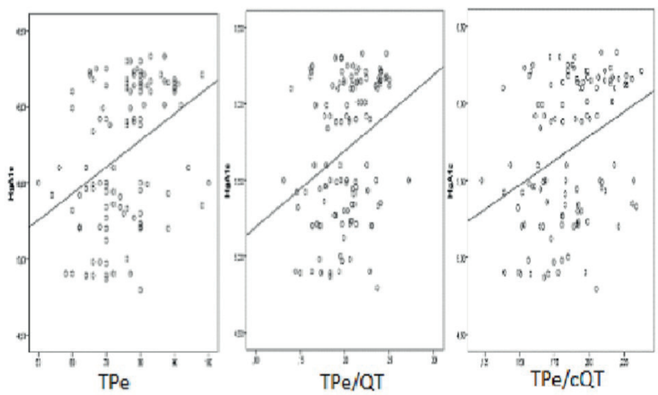

Figure 2. Correlation between hemoglobin A1c (HbA1c) and peak and the end of the T wave (Tp-e) interval, Tp-e/QT ratio, and Tp-e/corrected QT interval (QTc) ratio

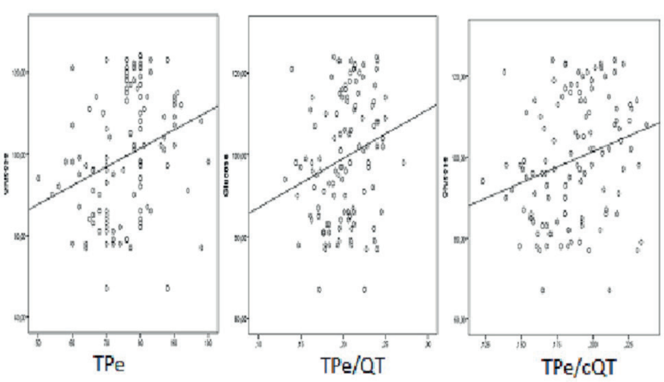

Figure 3. Correlation between glucose level and peak and the end of the T wave (Tp-e) interval, Tp-e/QT ratio, and Tp-e/cor¬rected QT interval (QTc) ratio

DISCUSSION

In this study, we found that the rate of TP-e interval, Tp-e/QT and Tp-e/QTc, which are the ECG parameters showing ventricular repolarization, increased in prediabetic patients. We also observed that HbA1c and serum glucose levels were shown positively correlated with Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio. This was the first study on prediabetic patients on this topic.

In prediabetic patients, cardiovascular diseases are more likely than normal healthy individuals, and frequent CVDs are ischemic coronary artery diseases and diastolic dysfunctions (22,23). It has also been shown in previous studies that arrhythmic events such as p wave dispersion, heart rate variability, heart rate turbulence and AF have been seen in prediabetes (24-28). The possible reason for this may be conditions that develop secondary to ischemia. At the same time without ischemia, arrhythmic conditions can also develop as a result of autonomous neuropathy, which develops due to increased sympathetic system activity.

TP-e interval, TP-e/QT and TP-e/QTc are well-defined markers of increased distribution of ventricular repolarization (19,29). Also, TP-e/QT and TP-e/QTc ratios are relatively novel parameters that predict transmural dispersion of repolarization (TDR) better than TP-e interval (19,30). However, it has also been shown in previous studies to be superior to QT and QTc in demonstrating arrhythmias because it is not influenced by heart rate and BMI (31). It is known that Tp-e and Tp-e/QT increases in heart diseases with increased risk of malignant ventricular arrhythmia, such as Brugada syndrome, long QT syndrome, short QT syndrome, acute myocardial infarction and myocarditis (16,32). In electrophysiological studies, it has been shown that homogeneity in the duration of the cardiac action potential leading to arrhythmias by causing electrical imbalance (33). QT interval is the most generally utilized noninvasive mark for eliciting electrical heterogeneity, but recent studies have also used TDR in addition to QT to measure myocardial homogeneity (34,35). The completion of repolarization is the earliest in epicardial M cells, while the longest action potential duration is in mid myocardial M cells. The peak and the end of the T waves represent the end of the action potential time of the epicardium and mid myocardium, respectively. Based on this physiological information, we can say that the Tp-e range is the reflection of TDR on the ECG. It has been proven in animal experiments that Tp-e prolongation is related to ventricular arrhythmogenesis (36). Besides, prolongation of TP-e and increase of Tp-e/QT have been shown to increase the risk of ventricular arrhythmia in many cardiac diseases and to be related to incremented mortality (31,37). It has been shown in studies that the TP-e interval is increased and the rate of TP-e/QT, Tp-e/QTc increases since silent CAD can occur in diabetic patients (20,21). Since there may be silent ischemic heart disease in prediabetic patients, we think that the parameters that indicate this arrhythmogenesis may change. Hyperglycemia is a condition that prolongs the action potential by changing the ionic currents in the sarcolemma. In light of this physiological information, we can conclude that hyperglycemia directly affects the ventricular repolarization phase. Indeed, we found that TP-e, Tp-e/QT and TP-e/QTc expanded in the aftereffects of our investigation. It is important to detect the increase of these parameters earlier in the prediabetic period to take early measures. These measures can be lifestyle changes and medical treatment.

Another pathophysiological condition that causes arrhythmia in hyperglycemic patients is the development of autonomic neuropathy. Cardiac autonomic neuropathy (CAN) is one of the common chronic complications of hyperglycemic conditions such as diabetes and prediabetes, with effects such as orthostatic hypotension, cardiovascular instability, arrhythmia, silent infarction, sudden cardiac death, and cardiomyopathy (38). CAN is brought about by the disruption of autonomic nerve filaments that regulate pulse, myocardial contractility, cardiovascular electrophysiology, and vessel contraction and dilation and as a result, the sympathetic system tone increases while the parasympathetic tone decreases. The most prominent among these is the dysfunction of the nervus vagus, which has a parasympathetic function and provides autoregulation of many systems. Increased sympathetic activity and a decrease in parasympathetic activity have been reported to be firmly associated with an increase in the risk of ventricular arrhythmia (5). In the KORA S4 study, the prevalence of CAN was shown to increase in individuals with IGT and IFG as well as in DM patients (39).

In previous studies, parameters such as QT dispersion, QTc interval, TP-e, Tp-e/QT and Tp-e/QTc, which are the markers of ventricular arrhythmogenesis, were examined in DM patients. However, there was no study related to this in prediabetes, which could make complications even without apparent DM.

In our study, we found that there was no noteworthy distinction in QT and QTc distances with the control group, while other ventricular repolarization parameters increased significantly in prediabetes. A possible reason for this may be the disruption of neurohumoral balance due to hyperglycemia. We believe that the deteriorating neurohumoral system may predispose to ventricular arrhythmia and may have increased the ECG parameters mentioned.

LIMITATION

Our study had some limitations. The first was that there was a relatively small number of patients and the study was designed as a single center. The other was that it was a cross-sectional study and no long-term patient follow-up. Also, since ECG parameters may have diurnal variations, evaluation with 24-hour rhythm holter recordings can provide more reliable information about the TDR. As an additional limitation, we evaluated repolarization indices on 12-lead ECG recordings, global arrhythmia incidence and future risk for arrhythmia development could be predicted more precisely with 24-hour rhythm holter monitoring.

CONCLUSION

The fundamental discoveries of the study were prolonged TP-e distance and increased Tp-e / QT, Tp-e / QTc ratio in prediabetics. In prediabetes, which is accepted as the previous stage of diabetes, the risk of ventricular arrhythmia can be reduced by early detection of this condition. In prediabetic patients, proarrhythmic screening can be done by performing the routine evaluation of these parameters together with basal ECG.

Conflict of interest : The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Ethics committee approval was received from the local ethics committee (Bilecik Provincial Health Directorate). Protocol number: (2020/17).

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