# Evaluation of cardiac repolarization inhomogeneity in children with type 1 diabetes mellitus

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### ABSTRACT

**Objective:** Type 1 diabetes mellitus is the most common endocrine-metabolic disease in childhood, which progresses with insulin deficiency and can cause serious cardiovascular complications. Atrial and ventricular arrhythmias are important cardiovascular complications of diabetes. In this study, cardiac repolarization inhomogeneity in children with Type 1 diabetes mellitus was evaluated electrocardiographically.

**Method:** Between February 2021 and April 2021, 48 patients with Type 1 diabetes mellitus and an equal number of healthy control groups were included in the study. Demographic characteristics of all cases were analyzed. P wave dispersion (PWd), QT interval (QT), QT dispersion (QTd), QTc interval (QTc), QTc dispersion (QTcd), Tpeak-Tend interval (Tp-e), Tp-e dispersion (Tp-ed) were evaluated with 12-lead electrocardiography, Tp-e/QT, Tp-Te/QTc ratios were calculated, and parameters were compared between both groups.

**Results:** The mean age of the patient group was 11.44 ± 4 years, and the mean age of the control group was 9.97 ± 4.5 years. The study group consisted of 18 girls (37.5%) and 30 boys (62.5%). In the control group, there were 21 girls (43.7%) and 27 boys (56.3%). There was no significant difference between the patient and control groups in terms of age and gender. The disease duration of the cases was 35.10±30.7 months, and the HbA1c value was 8.4±1.75%. When heart rates, P wave duration, and PWd, QT, QTd, QTc, QTcd, Tp-e, Tp-ed values were compared between the patient and control groups, there was no statistically significant difference between the PWd, QT and QTc intervals, QTd, QTcd, Tp-e interval, Tp-e dispersion, Tp-e/QT, Tp-e/QTd measurements and ratios of the two groups (p>0.05).

**Conclusion:** In our study, ventricular repolarization parameters of children with Type 1 diabetes and healthy children were found to be similar. Although we think the data we have obtained will contribute to the literature due to the limited number of studies on this subject in children, we believe that long-term and prospective studies involving more patients are needed.

Keywords: type 1 diabetes mellitus, p wave dispersion, QT dispersion, QTc dispersion, Tp-e interval

# **INTRODUCTION**

Type 1 diabetes mellitus (DM) is the most common endocrinological and metabolic disease of childhood and adolescence, which progresses with abnormalities in carbohydrate, fat, and protein metabolism and causes serious cardiovascular complications. Cardiovascular complications are the main cause of mortality and morbidity in diabetic patients.<sup>1</sup> It is under consideration that conditions such as cardiac conduction abnormalities, myocardial damage, autonomic system dysfunction, and ventricular repolarization changes, which are caused by



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diabetes, may predispose individuals to arrhythmias. The most common heart rhythm disorders that can cause mortality in these patients are atrial fibrillation and ventricular dysrhythmias.<sup>2</sup>

P wave dispersion (PWd), QT interval (QT), QT dispersion (QTd), QTc interval (QTc), QTc dispersion (QTcd), Tpeak-end dispersion (Tp-ed), Tp-e/QT, Tp-e /QTc ratios are parameters that can be calculated non-invasively from superficial electrocardiography and can be used to predict the risk of developing arrhythmia.<sup>3-6</sup> Increased PWD duration indicates impaired interatrial and intraatrial conduction.<sup>7</sup> QT and QTc values corrected for heart rate indicate the duration of ventricular myocardial depolarization and repolarization. QT dispersion indicates ventricular repolarization heterogeneity. This heterogeneity may be the cause of fatal ventricular arrhythmia.<sup>1</sup>

Prolongation of QT and QTc durations and increased QTd were found in patients with diabetes, and it was found to be associated with sudden cardiac death and arrhythmias in these patients.<sup>8</sup> The Tp-e interval indicates transmural dispersion of ventricular repolarization and has been associated with an increased risk of sudden cardiac death by causing ventricular arrhythmias. Tp-e is affected by changes in heart rate and body weight.<sup>9</sup> Tp-e/QT and Tp-e/QTc ratios are newly defined parameters that are recommended as more accurate measurements for the dispersion of ventricular repolarization since they are not affected by heart rate changes compared to other parameters.<sup>10,11</sup>

Studies on cardiac repolarization changes in pediatric patients with Type 1 diabetes are rare in the literature. Our aim in this study was to evaluate cardiac repolarization inhomogeneity in children with type 1 diabetes.

# **MATERIALS AND METHODS**

The study was conducted prospectively in the Pediatric Cardiology and Pediatric Endocrinology outpatient clinic of Kütahya Health Sciences University Evliya Çelebi Training and Research Hospital between February 2021 and April 2021. Forty-eight patients followed up with the diagnosis of Type 1 DM in the Pediatric Endocrinology outpatient clinic were included in the study group. Those with congenital and/or acquired heart disease were excluded from the study. The control group was selected from healthy children under the age of 18 who applied to the Pediatric Cardiology outpatient clinic for reasons such as innocent heart murmur

or non-specific chest pain, had normal heart examination and tests, and had no other diseases. A detailed history of all cases in the patient and control groups was taken, and via routine physical examinations, anthropometric measurements were recorded. The fasting blood glucose, HbA1c level, blood lipid panel, liver and kidney function tests, thyroid function tests, and hemogram values of the patient group in the last 3 months, age at diagnosis, and duration of being diabetic were obtained from the pediatric endocrine outpatient clinic files.

Heart rate was measured by calculating three consecutive R-R intervals from the derivation of DII. P wave duration was calculated as the time between the separation and junction of the P wave from the isoelectric line. P wave durations were measured in milliseconds, and the difference between the longest and the shortest duration was evaluated as PWd. QT duration was measured as the time between the onset of the QRS complex and the junction of the T wave with the isoelectric line. QT durations were measured in milliseconds, and the difference between the longest and the shortest duration was evaluated as QTd. QT measurements in each lead were corrected for heart rate with Bazett's formula (QTc = QT/VRR), and QTc calculation was made. The difference between the longest QTc and the shortest QTc duration was evaluated as QTcd. Tp-e time was calculated by measuring the time in milliseconds between the peak of the T wave in the chest leads V5 and V6 corresponding to the left ventricle and the junction of the tangential line from the peak to the junction of the isoelectric line. Tp-e time was not calculated in cases where the end of the T wave could not be clearly distinguished and/or the T wave height was less than 1.5 mm. Tp-e/QT and Tp-e/QTc ratios were calculated by measuring QT and QTc from the same lead in which the Tp-e interval was measured.

#### Statistical analysis

All analyses of the study were performed using the "IBM SPSS Statistics Version 25" package program. Continuous variables were expressed as "mean ± standard deviation". The distributions of all data were analyzed using Kolmogorov-Smirnov tests. In comparing the means of two independent groups, the independent Student T-test was used for normally distributed variables, and the Mann-Whitney U test for non-normally distributed variables. The significance level of all statistical analyses was accepted as p value below 0.05.

# RESULTS

The study group consisted of 18 girls (37.5%) and 30 boys (62.5%), and the mean age was 11.44±4 years. In the control group, there were 21 girls (43.7%) and 27 boys (56.3%), and the mean age was 9.97±4.5 years. There was no significant difference between the patient and control groups in terms of age and gender. The disease duration of the cases was 35.10±30.7 months, and the HbA1c value was 8.4±1.75%. Fasting blood glucose was 257.46±116.35 mg/ dL, total cholesterol level 165.9±24.7 mg/dL, triglyceride level 96.02±46.3 mg/dL, LDL level 91.4±19,8 mg/dL, and HDL level was determined as 52.8±13.9 mg/dL. When the results of the patients were compared with the laboratory reference values, fasting blood glucose, HbA1c, and lipid panel values were found to be high. When the biochemical parameters were examined, AST was 25.5±15.6 IU/I, ALT was 17±9.4 IU/I, BUN was 13.1±3 mg/dL, and creatinine values were 0.6±0.13 mg/dL. AST and ALT values of 2 patients were higher than laboratory reference values (Table 1).

When heart rates, P wave duration, and PWd, QT, QTd, QTc, QTcd, Tp-e, and Tp-ed values were compared between the patient and control groups, there was no statistically significant difference between the two groups. Tp-e/QT and Tp-e/QTc ratios were also similar between the groups (Table 2).

## DISCUSSION

It is under consideration that conditions such as cardiac conduction abnormalities, Myocardial damage, autonomic system dysfunction, and ventricular repolarization changes that, due to diabetes, predispose to arrhythmias.<sup>2</sup> In this study, cardiac repolarization inhomogeneity was examined in children with Type 1 diabetes and evaluated in terms of possible ventricular and atrial arrhythmias, and no difference was found between children with DM diagnosis and healthy children in terms of cardiac repolarization abnormality.

In diabetic patients, HbA1c is a reliable parameter that shows the mean blood glucose value in the last 2-3 months and is used to monitor the success of treatment.<sup>12</sup> According to the 2020 recommendations of the American Diabetes Association (ADA), the target HbA1c level should be <7.5%.<sup>13</sup> According to the 2018 guideline of ISPAD (International Society for Pediatric and Adolescent Diabetes), the target HbA1c level should be <7% in the treatment of diabetes.<sup>14</sup>

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Table 2. Comparison of electrocardiographic measurements of						
the patient and control groups						
	Patient (n: 48)	Control (n: 48)				
	Mean ± SD	Mean ± SD	Р			
Herat rate (/min)	95.15±17.6	96.6 ±21.9	0.71			
P wave duration (ms)	91.46±13.5	95.2 ±15.1	0.20			
P dispersion (ms)	41.67±11.5	45.6 ±12.8	0.11			
QT interval (ms)	331.88±39.7	346.8± 41.4	0.07			
QT dispersion (ms)	50.42±24	58.5 ± 23.6	0.09			
QTc interval (ms)	418.31± 32.2	427.4 ± 24	0.12			
QTc dispersion (ms)	64.0 ± 31.9	76.2 ±35.4	0.08			
Tp-e interval (ms)	83.75± 20.8	91.25±18.05	0.07			
Tp-e dispersion (ms)	40.4 ±17.2	36.8±14.6	0.28			
Tp-e/QT rate	0.24 ±0.06	0.26 ± 0.04 0.1				
Tp-e/QTc rate	0.20±0.08	0.20±0.04	0.61			

Table 1. Laboratory findings and reference ranges of the patient group						
	Minimum	Maximum	Mean±SD	The reference range		
Blood glucose (mg/dL)	89	427	257.46± 116.3	70-100		
HbA1c (%)	5.9	10.2	8.40±1.7	<6.5		
T. cholesterol (mg/dL)	127	240	165.94±24.7	0-200		
LDL cholesterol (mg/dL)	50	155	91.48±19.8	0-100		
HDL cholesterol (mg/dL)	8	75	52.89±13.9	>35		
Triglyceride (mg/dL)	38	264	96.02±46.3	0-150		
AST (IU/I)	11	94	25.56±15.6	0-50		
ALT (IU/I)	8	68	17.02±9.4	0-50		
BUN (mg/dL)	7	19	13.10±3	7.9-20		
Creatinine (mg/dL)	0.4	1.0	0.6±0.1	0.8-1.4		

HbA1c: Hemoglobin A1c, HDL: High-density lipoprotein, LDL: Low-density lipoprotein,

T. cholesterol: Total cholesterol, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen

In Wood et al.'s study, which included 13.316 pediatric patients followed up with a diagnosis of type 1 diabetes, only about one-third of the participants met the age-specific ADA and ISPAD targets for HbA1c.<sup>15</sup> In a multicenter study conducted by Hatun et al. in Turkey, it was found that 29.1% of the patients had an HbA1c value of <7.5%.<sup>16</sup> The mean HbA1c value of the cases in our study was 8.4%, and the target HbA1c value was reached only in one-third of the patients, similar to other studies.

In patients with type 1 diabetes mellitus, hypertriglyceridemia, low HDL cholesterol, and high LDL cholesterol levels can be observed due to hepatic lipase activities related to abnormal lipoprotein lipase and exogenously administered insulin.<sup>17,18</sup> According to the study of Zabeen et al., including 422 Type 1 DM patients with an average age of 15 and a mean diabetes duration of 3 years, the overall dyslipidemia frequency was found to be 65%, and the mean HbA1c level was 9.8.19 In our study it was determined that the mean age of the patient group was 11.4, the mean duration of being diabetic was 35 months, and the frequency of dyslipidemia was 37.5%. It was found that 6.2% of the patients have high total cholesterol, 10.4% low HDL, 25% high LDL, and 8.3% high triglyceride. Although our study is similar to the study of Zabeen et al. in terms of diabetes duration, the incidence of dyslipidemia is lower. This may be because the patients in our study had better glycemic control and had a lower mean age.

Diabetes can affect the conduction system of the heart due to autonomic dysfunction, atrial and ventricular remodeling, mitochondrial changes, inflammation, and blood glucose irregularities.<sup>20,21</sup> Given the limited number of studies focusing on adolescents and young adults with T1DM, the etiology of sudden cardiac death remains underdiagnosed in childhood despite the heightened risks of mortality and morbidity. Patients with Type 1 Diabetes Mellitus (T1DM) face a significantly elevated risk of ventricular arrhythmias and sudden cardiac death. Potential mechanisms underlying these arrhythmias include reentry circuits, triggered activity, and heightened autonomic tone. However, the exact pathophysiological pathways responsible for arrhythmogenesis in diabetic individuals remain incompletely understood. Chronic hyperglycemia may induce structural cardiac alterations, including myocardial fibrosis and cellular loss within viable myocardial tissue and conduction pathways. These changes are thought to facilitate the development of micro-reentry circuits. Furthermore, disruptions in the heart's electrical homeostasis, combined with increased sympathetic nervous system activity, may further contribute to the initiation of ventricular arrhythmias.<sup>5</sup> It has been shown that cardiac autonomic dysfunction can be diagnosed by ECG even if type 1 DM patients are asymptomatic.<sup>22</sup>

QT, QTc, and QT dispersion (QTd) have been identified as useful predictors of ventricular arrhythmic events and sudden cardiac death across various clinical conditions. The QT interval reflects the duration from the onset of ventricular depolarization to the end of repolarization. Given that the QT interval is influenced by heart rate, the corrected QT interval (QTc) has been introduced to provide a more reliable assessment independent of heart rate variations. QTc prolongation has been documented in numerous cardiovascular and systemic diseases, and it has also been proposed as an independent risk marker for ventricular arrhythmias, sudden cardiac death, and increased mortality in individuals with Type 1 Diabetes Mellitus (T1DM). In T1DM patients, QTc prolongation has been positively associated with advancing age, longer disease duration, and suboptimal glycemic control. A study by Inanir et al. further supports this association, reporting a significant correlation between QTc interval, duration of diabetes, and elevated HbA1c levels.5

In a study conducted by Uysal et al. in 150 children with Type 1 DM with a mean age of 11.61 ± 3.72 years, QT and QTc intervals and QTcd duration were found to be significantly higher in diabetic children compared to the healthy control group.<sup>22</sup> In a study conducted by Köken et al. on 33 children with type 1 diabetes with a mean age of 12.3 years, P wave duration and PWd were found to be significantly higher than the healthy control group.<sup>23</sup> In a study conducted by Şahan et al. on 165 children with type 1 diabetes, when compared to the control group, the increased QTc and QTcd values in the patient group indicate a predisposition to arrhythmia in these children.<sup>24</sup> In our study, unlike these studies, no significant difference was found between the PWd, QT, and QTc interval and QTcd durations between the patients and the control group. This may be due to the limited sample size of our study, which is a cross-sectional study.

Studies on Tp-e interval, Tp-e/QT, and Tp-e/QTc values in patients with type 1 DM are limited. The Tp-e interval is a relatively new ECG parameter that indicates ventricular repolarization. Tp-e measurement is an important parameter associated with sudden cardiac death, especially in cases where the QTc duration is normal or cannot be measured due to prolonged QRS duration. The Tp-e/QT ratio has also

recently been used as a novel electrocardiographic marker for ventricular repolarization and has been reported to be associated with malignant ventricular arrhythmias.<sup>25,26</sup> In a study with a large number of people with T1DM (855 patients, 1710 controls), depolarization parameters were observed to be higher in people with T1DM. In this study, depolarization parameters were found to be higher in T1DM patients of any age, but repolarization parameters are only increased in young people with T1DM, and this situation is thought to be related to sudden cardiac death and the dead-in-bed syndrome.<sup>27</sup>

The Tp-e/QT ratio includes the transmural dispersion (Tp-e) and dimensional dispersion (QT) values of ventricular repolarization. In the study of Güney et al., it was observed that Tp-e increased in children with Type 1 DM compared to the control group, but Tp-e/QT and Tp-e/QTc ratios were similar to the healthy control group.<sup>1</sup> In the study conducted by Olmez et al. in 35 patients with Type 1 DM, they found that the Tp-e interval and Tp-e/QT ratio were similar in both groups, while QT and QTc durations were increased in the patient group compared to the control group.<sup>28</sup> In our study, no significant difference was found between the QT durations, QTc durations, and QTcd, Tp-e, Tp-ed, Tp-e/QT, Tp-e/QTc measurements of children with type 1 diabetes and healthy children. We think that the reason for this is the low sample size and short follow-up period.

The most important limitation of this study is that it is a cross-sectional, not a long-term study. Pediatric patients with T1DM have a long life expectancy after diagnosis, and given the impaired ventricular depolarization and increased sensitivity to repolarization, meticulous cardiological surveillance for arrhythmias may be necessary. Even in the absence of T1DM and cardiac symptoms, periodic ECG monitoring can be performed during outpatient clinic visits. We think it would be more useful to compare the ECG obtained at the time of diagnosis with the ECG obtained after long-term follow-up. In addition, since our study was a single-center study with a low sample size, multicenter studies with large participation should confirm the data obtained.

In conclusion, this study examined the effect of new repolarization parameters on cardiac arrhythmia in patients with type 1 diabetes and QT durations, QTc durations, and QTcd, Tp-e, Tp-ed, Tp-e/QT, Tp-e/QTc measurements were found to be similar between children with type 1 diabetes and healthy children. We think the data we obtained will contribute to the literature since there are very limited articles examining the possible effects on the cardiac

conduction system in children with Type 1 DM. However, long-term prospective studies involving larger numbers of patients are needed.

## **Ethical approval**

This study has been approved by the Kütahya Health Sciences University Non-Interventional Clinical Research Ethics Committee (approval date 16.12.2020, number 2020/17-18). Written informed consent was obtained from the participants.

# **Author contribution**

The authors declare contribution to the paper as follows: Study conception and design: iE, RÖ; data collection: iE, DG; analysis and interpretation of results: iE, RÖ, VNB; draft manuscript preparation: iE, RÖ, VNB. All authors reviewed the results and approved the final version of the article.

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The authors declare the study received no funding.

# **Conflict of interest**

The authors declare that there is no conflict of interest.

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