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Evaluation of Arrhythmia Risk in Children with Type 1 Diabetes Mellitus

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What is already known on this topic?

Children with type 1 diabetes mellitus (T1DM) are susceptible to cardiac arrhythmias and even sudden cardiac death.

What this study adds?

This study demonstrated that early identification of risk of arrhythmia in children with T1DM is achievable through routine electrocardiography. This technique is a cost-effective, non-invasive method compatible with daily activities. Implementing this approach may reduce mortality and morbidity in this high-risk, vulnerable population.

Abstract

Objective: Children with type 1 diabetes mellitus (T1DM) are susceptible to cardiac arrhythmias and even sudden cardiac death. The aim of this study was to explore the risk of arrhythmia among children with T1DM by assessing electrocardiographic (ECG) parameters.
Methods: Children diagnosed with T1DM, aged 10-18 years, and healthy children matched for age and gender were included. The ECG ventricular depolarization-repolarization parameters of both groups and the correlation of these parameters with length of time since diagnosis of T1DM, markers of metabolic control, and the presence of additional complications were evaluated.
Results: There were 165 children with type 1 diabetes and 154 controls in the groups, which were similar in for age, gender, weight, height, and body mass index. The median length of time since diagnosis of diabetes was 5 years. QT (maximum), QTc (minimum and maximum), QT and QTc dispersion, Tp-e (minimum and maximum), Tp-e dispersion, and Tp-e/QTc-maximum values were significantly higher in the diabetic group compared with controls, although QTc intervals were within normal ranges. No significant correlation was observed between ECG findings and length of time since diagnosis of T1DM, HbA1c levels, or complications.
Conclusion: As children with T1DM are at high risk of impaired ventricular depolarization and repolarization, they should undergo cardiac assessment and regular annual ECG monitoring.
Keywords: Children, diabetes, dispersion, arrhythmia, sudden death

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Introduction

Type 1 diabetes mellitus (T1DM) is a common metabolic disorder of childhood and as of 2021, there are more than 1.5 million children with T1DM worldwide (1,2). As the incidence of diabetes increases, the complications associated with the disease are also becoming more apparent. Young people with diabetes mellitus have been found to have higher risk for sudden cardiac death compared to those without diabetes (3). Cardiac autonomic neuropathy is one of the common complications of T1DM ranging from 12% to 76% in childhood and youth, contributing significantly to both mortality and morbidity (1,2,3,4). This dysfunction can adversely affect the regulation of heart rate, blood pressure, and other cardiovascular functions, leading to increased risks of life-threatening events, such as arrhythmias and sudden cardiac death but underlying mechanisms are still underdiagnosed (4,5,6,7). Recognizing and addressing cardiac risk factors early in the disease course would be important so that appropriate management strategies and interventions can be started that will reduce mortality and improve overall patient outcomes.

In the present study, the aim was to evaluate the arrhythmia risk in diabetic children by assessing electrocardiographic (ECG) ventricular depolarization and repolarization parameters compared to healthy matched peers. In addition, it was planned to investigate any correlation of these parameters with length of time since diagnosis of T1DM, hemoglobin A1c (HbA1c) levels (a recognized marker of metabolic control in T1DM), and the presence of additional diabetic complications.

Methods

This prospective, cross-sectional, controlled study was conducted between May 2023 and October 2023 in the Department of Pediatric Cardiology and Pediatric Endocrinology of Ankara Bilkent City Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Human Ethics Committee of Ankara City Hospital, University of Health Sciences of Türkiye, with the decision numbered E2-23-3979, dated 25.04.2023. Written informed consent was obtained from all the participants.

Study Population and Inclusion and Exclusion Criteria

Children diagnosed with T1DM and aged 10-18 years, who were admitted to the outpatient clinics during the study period, were eligible to be included in T1DM group. Healthy age- and gender-matched children admitted for innocent murmur and without any known chronic disease were included as the control group. Diabetic patients with chronic systemic disease including systemic hypertension defined as previously described (8,9), chronic renal failure, congestive heart failure, thyroid disease, Cushing syndrome, and/or celiac disease, congenital or acquired heart disease (cardiomyopathy, operated or unoperated atrial septal defects, ventricular septal defects, patent ductus arteriosus, bicuspid aortic valve, pulmonary hypertension) which may lead ventricular hypertrophy or/and dilatation, atrioventricular conduction disorders and bundle branch blocks, and atrial-ventricular extrasystoles were excluded (n = 26, Figure 1). All patients' blood electrolyte levels and blood gas values were normal.

Office blood pressure measurements (OBPMs) were recorded for all children included during the study period. Measurements were conducted with patients seated, feet flat on the floor, arm supported at heart level, following a 5-minute rest period, using appropriately sized cuffs, in alignment with guideline recommendations (8,9,10,11,12). Using OBPMs, children eligible for the control group could be diagnosed as hypertensive if systolic blood pressure or diastolic blood pressure was at the 95th percentile or greater for age, sex, and height, measured on at least three separate measurements. Children diagnosed in this fashion were excluded (n = 4). Diabetic children whose OBPMs exceeded the 90th percentile for age, sex, and height, as measured on at least three separate measurements using automated devices, were excluded from the study and referred to pediatric nephrology for further evaluation (n = 3).

All participants were evaluated using transthoracic echocardiography. Age, gender, weight, height, body mass index (BMI), and for those with T1DM length of time since diagnosis, glycated HbA1c levels, and average HbA1c levels over the last two years were noted. Microalbuminuria was screened for using 24-hour urine collection and was defined as 30-300 mg/day (6). All children diagnosed with diabetes were evaluated for, diabetic retinopathy and other ocular complications through fundus examination. In the patient group, burning, tingling sensation and/or paresthesia, numbness, fatigue, cramping or pain in their lower extremities were investigated in order to assess evidence of peripheral neuropathy. Warmth and pinprick sensation in the feet were evaluated as physical examination (13).

Electrocardiography

All ECG were analyzed from the medical records of the patients with 12-lead at a speed of 25 mm/s and amplitude of 10 mm/mV with the patient lying down after at least five minutes of rest. The high-resolution computer software program (Adobe Photoshop CS2, Adobe System Incorporated,

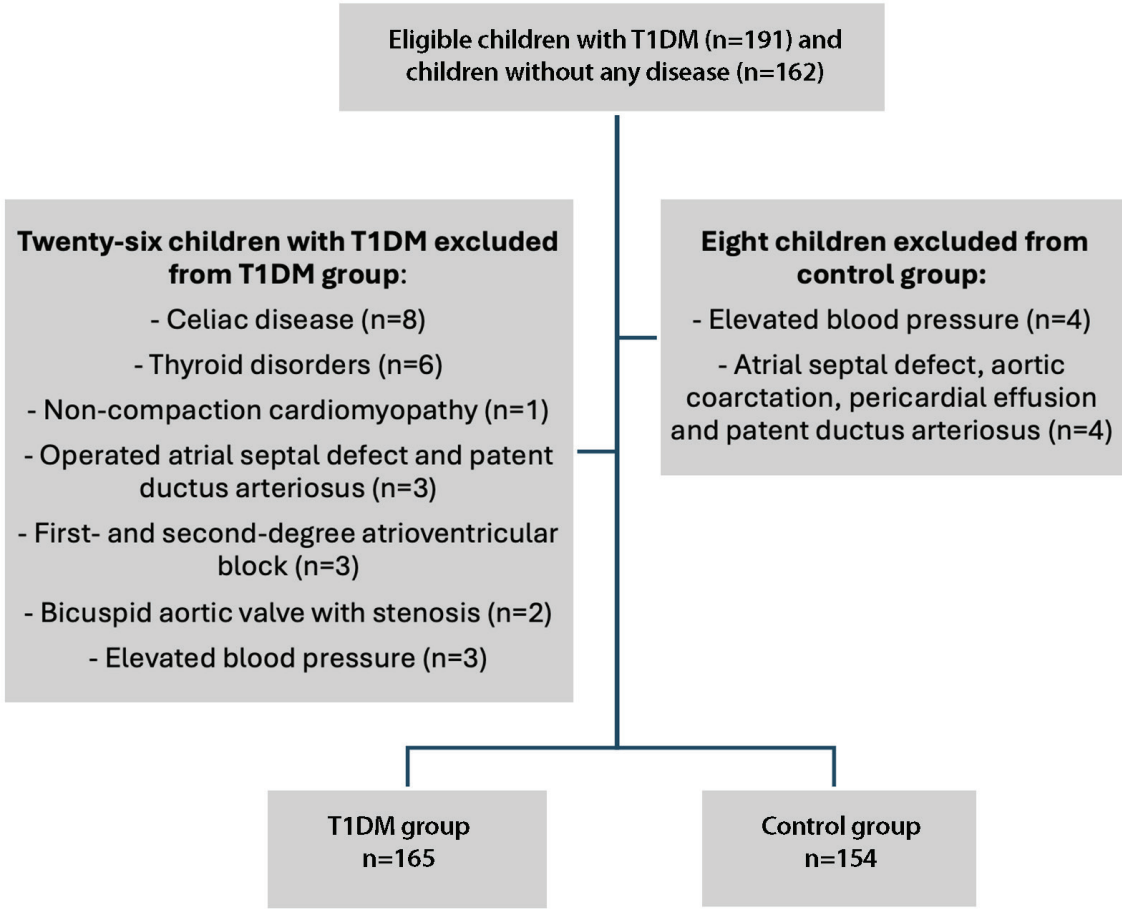

Figure 1. Flow chart of study population

T1DM: type 1 diabetes mellitus

San Jose, CA, USA) was used for the investigation of ECG results by a single blinded pediatric cardiologist. The measurement of the QT interval started from the onset of the QRS complex until the end of the T-wave. A discrete U-wave after the T-wave was excluded from measurement. The QT corrected for heart rate (QTc) duration was calculated using Bazett's formula ($QTc = QT/\sqrt{RR}$). QT and QTc dispersion (QTd, QTcd) was calculated as the difference between the maximum and minimum QT and QTc duration. Measuring from the peak of the T-wave to the end of the T-wave provided the Tp-e interval, which was defined as the intersection of the isoelectric line with the tangent to the downslope of the T-wave in precordial leads (14). The Tp-e duration was calculated by measuring the distance between the two points in the isoelectric line. The difference between the maximum and the minimum Tp-e in the precordial leads was the Tp-e dispersion (Tpe-d). Based on these measurements, Tp-e, Tp-e dispersion, and Tp-e/QTc ratio were calculated.

Statistical Analysis

Before the study, a power analysis was performed using the G*power program 3.1.9.4 version. Power analysis showed that 139 patients should be included in both groups at the 0.300 effect size with α: 0.05 and 80% power based on the comparison of QT (ms) between T1DM patients and controls in the study of Bezen et al. (15).

The data of from the present study were analyzed using Statistical Package for the Social Sciences, version 25.0 (IBM Inc., Armonk, NY, USA). Data are expressed as frequency and percentages. Normality analysis was carried out using the Kolmogorov-Smirnov test. The variables with or without normal distribution are presented as mean ± standard deviation or median (interquartile range; with 25-75th percentiles), respectively. Categorical variables were compared with the chi-square test. Numerical variables with and without normal distribution were compared using the independent samples t-test or Mann-Whitney U, respectively. Pearson and Spearman correlation analysis

was used to investigate possible correlations between ECG intervals and clinical variables. The statistical significance was set at $p < 0.05$.

Results

There were 165 children in the T1DM group and 154 matched individuals in the control group. The demographic characteristics of the participants of the study are shown in Table 1. The groups were similar in terms of age and gender.

Table 1. The demographic features of the patient and control groups

		T1DM group (n = 165) (mean ± SD)	Control group (n = 154) (mean ± SD)	p
Age (years)		13.72 ± 2.64	13.18 ± 2.41	0.522*
Gender, n (%)	Female	85 (50.1)	80 (51.9)	0.654[b]
	Male	80 (48.5)	74 (48.1)	
Weight (kg)		48.15 ± 14.59	46.5 ± 14.24	0.296*
Height (cm)		155.15 ± 15.86	153.37 ± 17.69	0.348*
BMI (kg/cm²)		20.57 ± 3.62	18.99 ± 2.93	0.056*
BMI SDS		1.01 ± 0.09	1.03 ± 0.13	0.17*
Length of time since diagnosis of T1DM [a]Median (IQR)		5.0 (3.2-14.1)	-	

*Student's t-test, [a]Data are expressed as median with interquartile range in parentheses, [b]Fisher's exact test.
BMI: body mass index, IQR: interquartile range, T1DM: type 1 diabetes mellitus, SDS: standard deviation (SD) score

Table 2. The comparison of electrocardiographic findings in the T1DM and control group

Electrocardiographic measurements (ms) (mean ± SD)	T1DM (n = 165)	Control group (n = 154)	p*
Heart rate (/min)	92 ± 16	89 ± 17	0.675
QT maximum	361.27 ± 33.60	351.38 ± 30.2	**0.006**
QT minimum	306.66 ± 28.39	312.16 ± 22.7	0.058
QTd	54.017 ± 16.74	39.22 ± 19.40	**< 0.001**
QTc maximum	410.44 ± 20.45	386.82 ± 22.18	**< 0.001**
QTc minimum	382.96 ± 19.98	375.60 ± 20.87	**0.011**
QTc-d	27.50 ± 9.61	11.21 ± 7.75	**< 0.001**
Tp-e maximum	68.11 ± 9.52	61.27 ± 9.02	**< 0.001**
Tp-e minimum	46.39 ± 8.33	42.63 ± 9.27	**0.017**
Tpe-d	23.91 ± 7.32	14.89 ± 5.32	**< 0.001**
Tp-e/QTc-maximum	0.19 ± 0.03	0.16 ± 0.03	**< 0.001**

*Student's t-test.
Tp-e: T-peak-to-end, Tpe-d: Tp-e dispersion, QTc: corrected QT interval, QT-d: QT interval-dispersion, T1DM: type 1 diabetes mellitus

The weight, height, heart rate, and BMI of the groups also did not differ significantly. The median length of time since diagnosis of T1DM was five years. None of the patients had cardiac complaints. Microalbuminuria was present in 7/165 (4.3%) of the T1DM patients. No one had retinopathy as target organ damage. There were no peripheral neuropathic symptoms and findings on physical examination in the patient group. The mean HbA1c level over the past two years was 8.75 ± 1.59%. Moreover, 59 (35.7%) of the patient group had an HbA1c level exceeding 9%.

The ECG findings of the groups are summarized in Table 2. All ECG intervals associated with depolarization and repolarization were notably higher in the T1DM group compared to the control group ($p < 0.05$).

Spearman correlation analysis between clinical variables and ECG intervals is presented in Table 3. A weak positive correlation was observed between Tp-e maximum and Tp-e minimum when the patient group was stratified based on HbA1c levels into HbA1c < 9 and HbA1c > 9 subgroups. (respectively; Rho = 0.205, p = 0.015; Rho = 0.206, p = 0.014). No correlation was found between other variables and the ECG intervals ($p > 0.05$).

Discussion

Young individuals with diabetes have a two to tenfold increased risk of sudden cardiac death compared with people without diabetes. Underlying mechanisms are multifactorial (3,7,16). Although numerous studies have focused on cardiovascular risk in adolescents and young adults with T1DM, the etiology of sudden cardiac death remains underdiagnosed in childhood, despite the heightened risks of mortality and morbidity.

The prolongation of QT and QTc intervals serves as independent predictors of high cardiovascular mortality in the general population (17,18). Children with T1DM have a sixfold increased risk for QT and QTc prolongation (19). Prolonged QTc interval and ventricular arrhytmias (VAs) have been identified as predictors of increased mortality in individuals with T1DM (3,20). 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, particularly among the youth. The increase was negatively correlated with the age (21). QTd and QTcd are the markers positively related to arrhythmogenic events and are associated withall-cause mortality in patients who have congestive heart failure (22). QTd has been recognized as a potential marker for increased risk of VAs and adverse cardiovascular events (22,23). People with T1DM exhibit alterations in electrophysiological parameters, including

Table 3. Correlation analysis of electrocardiographic intervals with clinical variables in the patient group (n = 165)

		QT-max	QT-min	QTd	QTc-max	QTc-min	QTcd	Tp-e max	Tp-e min	Tpe-d	Tp-e/QTc-max
LOT	Rho	-0.029	0.066	-0.171	0.005	-0.001	-0.026	-0.042	-0.087	-0.056	0.036
	p	0.732	0.438	0.053	0.949	0.995	0.761	0.621	0.308	0.509	0.676
HbA1c < 9 or > 9	Rho	0.037	0.125	-0.085	-0.045	-0.090	0.064	**0.205**	**0.206**	0.046	0.168
	p	0.666	0.141	0.317	0.596	0.289	0.450	**0.015**	**0.014**	0.593	0.058
HbA1c levels*	Rho	-0.022	0.125	-0.198	0.028	-0.003	0.003	-0.012	0.020	-0.037	-0.019
	p	0.797	0.141	0.19	0.741	0.972	0.975	0.888	0.813	0.660	0.823
MAU	Rho	-0.132	-0.126	-0.026	-0.057	-0.080	0.063	-0.136	-0.175	0.121	-0.084
	p	0.121	0.138	0.762	0.502	0.345	0.461	0.108	0.039	0.154	0.326

*The mean HbA1c of the previous two years.
HbA1c: hemoglobin A1c, Tp-e: T-peak-to-end, Tpe-d: Tp-e dispersion, QTc: corrected QT interval, QT-d: QT interval-dispersion, LOT: length of time since diagnosis of type 1 diabetes mellitus, MAU: microalbuminuria, max: maximum, min: minimum

QTd, which is indicative of ventricular depolarization and repolarization variability (24). Studies conducted with adult diabetic patients have shown an association between prolonged QTc interval and increased QTd with mortality (25,26). In pediatric patients with T1DM, certain studies have shown an elevation in QTcd and QTd, consistent with our findings (15,19,27). Although within normal limits, prolonged values of QT maximum, and QTc minimum and maximum were found in the T1DM group compared to the controls in the present study. In addition, when compared to the control group, the increased QTc and QTcd values in the patient group may indicate a predisposition to arrhythmia in these children. Certain studies involving pediatric patients with T1DM have reported elongation of atrial and ventricular depolarization parameters, irrespective of history of diabetic ketoacidosis (DKA) occurrence, length of time since diagnosis of T1DM, and metabolic status (15,27). Similarly, our findings revealed that these parameters associated with ventricular depolarization remained independent of length of time since diagnosis of T1DM, HbA1c levels, and diabetic complications, such as microalbuminuria, aligning with existing literature (24,27). This suggests that even in the early stages of T1DM during childhood, there may be a predisposition to arrhythmias, and this appears to be independent of metabolic status. Closer cardiac monitoring should be provided to this vulnerable group with a high risk of arrhythmia. Diabetic complications are less commonly observed in the pediatric age group. Therefore, it is imperative to conduct further research in order to elucidate this relationship and provide a more comprehensive understanding of the cardiac health of pediatric patients with diabetes.

The Tp-e and Tp-e/QTc ratios are valuable markers demonstrating transmural repolarization and prolongation of the Tp-e indicates risk for VAs, even in people with normal QTc (28,29). Elevated Tp-e/QT ratios are regarded as arrhythmogenic indices (14,30). In a recent study, depolarization parameters were found to be increased in T1DM patients of any age but repolarization parameters were only increased in young people with T1DM and this may be related to sudden cardiac death and the "dead in bed" syndrome (21). Furthermore, Eğil et al. (31) reported elevated Tp-e values in children with DKA. In the present study, even in the absence of ketoacidosis, Tp-e values in diabetic children were higher compared to non-diabetic peers. In a study with adult T1DM patients, repolarization parameters were found to be related to length of time since diagnosis of T1DM and HbA1c levels (32). In another study with adult patients with type 2 diabetes mellitus, Tp-e interval, and Tp-e/QTc ratio were found to be associated with severity of microvascular complications. Similar to the literature, we found higher Tp-e (minimum and maximum), Tpe-d and Tp-e/QTc-maximum values in the T1DM group. To the best of our knowledge, our study represents the most comprehensive research to date with the largest number of children with T1DM and largest control group size. However, direct comparison was not feasible as our patient cohort comprised pediatric individuals, with only microalbuminuria noted as a complication. Furthermore, the correlation between Tp-e values and HbA1c levels was notably weak, even given the relatively poor mean HbA1c in our cohort.

Study Limitations

One limitation of the study was the lack of long-term follow-up of patients in terms of arrhythmia. Another limiting aspect was the lack of correlation with 24-hour rhythm and blood pressure Holter monitoring in terms of atrial or VAs and blood pressure variability. HbA1c is the most pragmatic marker for assessing overall glycemic control in patients with type 1 diabetes; however, it does not reflect acute glucose excursions or indicate the severity of hypo/hyperglycemia (33). Another limitation of our study is the lack of continuous glucose monitoring for assessing glycemic control.

Conclusion

Considering that pediatric patients with T1DM often have a longer life expectancy and will therefore be expected to live with a greater length of time since diagnosis of T1DM compared to adults, and given their heightened susceptibility to impaired ventricular depolarization and repolarization along with associated cardiac arrhythmias, we assert that meticulous cardiological surveillance is essential. We advocate for routine ECG for all children diagnosed with T1DM, and annual ECG follow-ups during outpatient clinic visits, even in the absence of cardiac symptoms. This proactive approach would aim to mitigate the cardiac risks associated with T1DM in children. In addition, in cases of inadequate metabolic control, which is often a large proportion of the pediatric and especially adolescent population with T1DM, we recommend routine 24-hour rhythm Holter monitoring to facilitate the early detection of VAs, thereby potentially averting adverse outcomes and preserving lives.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Human Ethics Committee of Ankara City Hospital, University of Health Sciences of Türkiye, with the decision numbered E2-23-3979, dated 25.04.2023.

Informed Consent: Written informed consent was obtained from all the participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Mehmet Boyraz, İbrahim İlker Çetin, İbrahim Ece, Concept: Yasemin Özdemir Şahan, Gönül Büyükyılmaz, Mehmet Boyraz, İbrahim İlker Çetin, İbrahim Ece, Design: Yasemin Özdemir Şahan, Gönül Büyükyılmaz, Mehmet Boyraz, İbrahim İlker Çetin, İbrahim Ece, Data Collection or Processing: Oğuzhan Doğan, Analysis or Interpretation: Oğuzhan Doğan, Literature Search: Yasemin Özdemir Şahan, Gönül Büyükyılmaz, Writing: Yasemin Özdemir Şahan.

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