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ORIGINAL ARTICLE

Evaluation of Arrhythmia Risk in Children with Type 1 Diabetes Mellitus

Arrhythmia in Children with Type 1 Diabetes Mellitus

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What is already known on this topic?
Children with type 1 diabetes mellitus are susceptible to arrhythmias and sudden cardiac death.

What this study adds?
This study highlights that early identification of arrhythmia risk in children with type 1 diabetes is achievable through routine electrocardiography—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
BACKGROUND AND AIM: Children with type 1 diabetes mellitus are susceptible to arrhythmias and sudden cardiac death. In this study, we aimed to explore the arrhythmia risk among children with type 1 diabetes mellitus by assessing electrocardiographic parameters.
METHODS: A total of 165 children diagnosed with type 1 diabetes mellitus, aged 10-18 years, and 154 healthy children matched for age and gender without any chronic diseases, were included in the study. The electrocardiographical ventricular depolarization-repolarization parameters of both groups and the correlation of these parameters with length of time since diagnosis of type 1 diabetes mellitus, metabolic control, and the presence of additional complications were evaluated.
RESULTS: The groups were similar in terms of age, gender, weight, height, and BMI ($p>0.05$). 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, Tp-e/ QTc-max values were significantly higher in the diabetic group compared with controls although QTc intervals are within normal ranges. No statistically significant correlation was observed between electrocardiographic findings and length of time since diagnosis of type 1 diabetes mellitus, HbA1c levels, or complications.
CONCLUSION: As children with type 1 diabetes mellitus are at high risk of impaired ventricular depolarization and repolarization, they should undergo cardiac assessment and regular electrocardiographic 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 type 1 diabetes worldwide [1, 2]. As the incidence of diabetes increases, the complications associated with the disease are also becoming more apparent. Young persons with diabetes mellitus have been found to have higher risk for sudden cardiac death compared to those without diabetes [3]. Cardiac autonomic neuropathy (CAN) is one of the most common complications of T1DM in childhood, contributing significantly to both mortality and morbidity. 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 [4–7]. Recognizing and addressing cardiac risk factors early in the disease course is crucial to implementing appropriate management strategies and interventions that aim to reduce mortality and improve overall patient outcomes.
In this study, we aimed to evaluate the arrhythmia risk of diabetic children by electrocardiographic ventricular depolarization and repolarization parameters and correlation of these parameters with length of time since diagnosis of T1DM, HbA1c levels, presence of additional diabetic complications.

METHODS

Study population

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 designed by the principles of the Declaration of Helsinki and approved by the Turkish Ministry of Health and Human Ethics Committee of the hospital with decision number E2-23-3979 dated 24 April 2023. Written informed consent was obtained from all the participants.

Inclusion and exclusion criteria

A total of 165 children with T1DM aged 10-18 years, who were admitted to outpatient clinics, were included in T1DM group in the study. Age and gender-matched 154 healthy children admitted for innocent murmur without any chronic disease were included as the control group. All participants were evaluated using transthoracic echocardiography. Diabetic patients with chronic systemic disease (systemic hypertension[8, 9], chronic renal failure, congestive heart failure, thyroid disease, Cushing syndrome, Celiac disease), congenital/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, atrial-ventricular extrasystoles were excluded (26 patients). All patients' blood electrolyte levels and blood gas values were normal.
Office blood pressure measurements (OBPMs) for all patients and control groups were recorded at each follow-up visit. 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[8–12]. Using OBPMs, children at control group can be diagnosed as hypertensive if systolic blood pressure or diastolic blood pressure is at the 95th percentile or greater for age, sex, and height, measured on at least 3 separate occasions. Diabetic children whose OBPMs exceeded the 90th percentile for age, sex, and height, as measured on at least three separate occasions using automated devices, were excluded from the study and referred to pediatric nephrology for further evaluation.
Age, gender, weight, height, body mass index (BMI), length of time since diagnosis of T1DM, glycated hemoglobin A1c (HbA1c) levels, and average HbA1c levels of the last two years were noted. Microalbuminuria is detected from 24-hour urine collection and is 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 questioned in terms of peripheral neuropathy. Warmth and pinprick sensation in the feet were evaluated as physical examination[13].

Electrocardiography

All electrocardiograms (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 5 minutes of rest. The high-resolution computer software program (Adobe Photoshop CS2) was used for the investigation of ECG results by blinded same 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/√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 Analyses

Before the study, a power analysis was performed using the G*power program 3.1.9.4 version. Power analysis revealed 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 tip1 DM patients and controls in the study of Bezen et al [15]. The data of the study were analyzed by SPSS 25.0 (IBM, USA). The findings of the study 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±standart deviation or median (interquartile range (IQR; with 25-75th percentiles)). 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. Spearman correlation analysis was performed for possible correlations between electrocardiographic intervals and clinical variables. $P<0.05$ was set as the statistical significance value.

RESULTS

The groups are similar in terms of age and gender ($p>0.05$). The weight, height, heart rate, and BMI of the groups did not differ significantly ($p>0.05$). The median length of time since diagnosis of T1DM is 5 years. The demographic characteristics of the participants of the study are shown in Table 1. None of the patients had cardiac complaints. Microalbuminuria has been found in 4,3 % (7/165) 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 2 years was 8.75 ± 1.59%. Ultimately, 35.7% (59/165) of the patient group had an HbA1c level exceeding 9%.

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

A weak positive correlation was observed between Tp-e max and Tp-e min when the patient group was stratified based on HbA1c levels into HbA1c<9 and HbA1c>9 subgroups. (respectively: Rho=.205, p=0.015; Rho=.206, p=0.014). No correlation was found between other variables and the ECG intervals ($p>0.05$). Spearman correlation analysis between clinical variables and ECG intervals is presented in Table 3.

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]. 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.

Ventricular depolarization parameters

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 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 (835 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 that are positively related to arrhythmogenic events and are associated with all-cause mortality in patients who have congestive heart failure [22]. QTd has been recognized as a potential marker for increased risk of ventricular arrhythmias (VAs) and adverse cardiovascular events [22, 23]. People with T1DM exhibit alterations in electrophysiological parameters, including 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. Although within normal limits, we found prolonged values of QTmax, QTc min and max in the T1DM group compared to the controls in this study. Additionally, when compared to the control group, the increased QTc and QTcd values in the patient group indicate a predisposition to arrhythmia in these children. Certain studies involving pediatric patients with T1DM have reported elongation in atrial and ventricular depolarization parameters, irrespective of 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 situation suggests that even in the early stages of T1DM during childhood, there may be a predisposition to arrhythmias 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 more comprehensive insights into the cardiac health of pediatric patients with diabetes.

Ventricular repolarization parameters

The Tp-e and Tp-e/QTc ratios are valuable markers demonstrating transmural repolarization and the 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 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 [21]. Additionally, Eğil et al. found elevated Tp-e values in children with diabetic ketoacidosis. In our study, we demonstrated that even in the absence of

ketoacidosis, Tp-e values in diabetic children were higher compared to non-diabetic children[31]. In a study with adult T1DM patients, repolarization parameters found to be related to length of time since diagnosis of T1DM and HbA1c levels [32]. Also, in another study with adult patients with T2DM, 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 (min and max), Tpe-d and Tp-e/QTc-max values in T1DM group. According to our current knowledge, our study represents the most comprehensive research with the largest number of children with T1DM and control groups. However, in our study, direct comparison was not feasible as our patient cohort comprised pediatric individuals, with only microalbuminuria noted as a complication. It's essential to note that, we only find a weak correlation between Tp-e values and HbA1c levels.

Limitation: The limitation of the study is the lack of long-term follow-up of the patient in terms of arrhythmia. Another limiting aspect of our study is the lack of correlation with 24-hour rhythm and blood pressure Holter monitoring in terms of atrial or ventricular arrhythmias and blood pressure variability. HbA1c is considered the gold standard 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 (CGM) for assessing glycemic control.

CONCLUSION

Considering that pediatric patients with T1DM often have a longer life expectancy and 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 periodic ECG follow-ups during outpatient clinic visits, even in the absence of cardiac symptoms. This proactive approach aims to mitigate the cardiac risks associated with T1DM in children. Additionally, in cases of inadequate metabolic control, we recommend routine 24-hour rhythm Holter monitoring to facilitate the early detection of ventricular arrhythmias, thereby potentially averting adverse outcomes and preserving lives.

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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		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/cm^2)		20.57 ± 3.62	18.99 ± 2.93	0.056*
Length of time since diagnosis of T1DM [a] (Median (IQR))		5.0 (3.2-14.1)	-	

* Student's t-test, BMI: Body mass index, [a] Data are expressed as median with interquartile range in parentheses, [b] Fischer exact test

Table 2: The comparison of electrocardiographic findings of 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 max	361.27 ± 33.60	351.38 ± 30.2	**0.006**
QT min	306.66 ± 28.39	312.16 ± 22.7	0.058
QTd	54.017 ± 16.74	39.22 ± 19.40	**<0.001**
QTc max	410.44 ± 20.45	386.82 ± 22.18	**<0.001**
QTc min	382.96 ± 19.98	375,60 ± 20,87	**0.011**
QTcd	27.50 ± 9.61	11.21 ± 7.75	**<0.001**
Tp-e max	68.11 ± 9.52	61.27 ± 9.02	**<0.001**
Tp-e min	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-max	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*

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*	-.029	.066	-.171	.005	-.001	-.026	-.042	-.087	-.056	.036
	P	.732	.438	.053	.949	.995	.761	.621	.308	.509	.676
HbA1c <9 or >9	*Rho*	.037	.125	-.085	-.045	-.090	.064	**.205**	**.206**	.046	.168
	P	.666	.141	.317	.596	.289	.450	**.015**	**.014**	.593	.058
HbA1c levels*	*Rho*	-.022	.125	-.198	.028	-.003	.003	-.012	.020	-.037	-.019
	P	.797	.141	.19	.741	.972	.975	.888	.813	.660	.823
MAU	*Rho*	-.132	-.126	-.026	-.057	-.080	.063	-.136	-.175	.121	-.084
	P	.121	.138	.762	.502	.345	.461	.108	.039	.154	.326

*** The mean HbA1c of the previous two years,* ***Abbreviations as in Table 2, also LOT:*** *length of time since diagnosis of T1DM****, MAU:*** *Microalbuminuria,*