First Evaluation of P Dispersion and Tp-e Parameters in Electrocardiograms of Children with Diabetic Ketoacidosis

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What is already known on this topic?

Diabetic ketoacidosis (DKA) is one of the leading causes of morbidity and mortality in children with type 1 diabetes mellitus. Atrial and ventricular arrhythmias are commonly seen during DKA. On electrocardiography (ECG), P-wave dispersion (Pd) has been associated with risk of atrial arrhythmias. QT dispersion (QTd), corrected QTd (QTcd), Tp-e duration, Tp-e/QT and Tp-e/QTc indicate the risk of ventricular arrhythmias.

What this study adds?

To the best of our knowledge, this is the first article evaluating Pd, Tp-e, Tp-e/QT and Tp-e/QTc parameters in children with DKA. In this study, cardiac arrhythmia risk markers, including Pd, QTd, QTcd and Tp-e, Tp-e/QT, were found to be increased in children with DKA.

Abstract

Objective: Diabetic ketoacidosis (DKA) is an important complication of type 1 diabetes mellitus. We aimed to evaluate the effect of metabolic disorders of DKA on electrocardiography (ECG) parameters in children.

Methods: This study was performed between December 2018 and March 2020 and included 39 children with DKA and 40 healthy children. Three ECGs (one before and two after treatment) were obtained from the patient group. P-wave dispersion (Pd), QT dispersion (QTd), QTc dispersion (QTcd), Tp-e intervals, and the ratios of Tp-e/QT and Tp-e/QTc were measured electrocardiographically. ECG parameters from children with DKA and healthy controls were compared statistically.

Results: The mean age of the patient group was 10.50 ± 4.12 years. There was no significant difference in terms of age, gender, weight, height and body mass index between patients and controls. In the patient group, a statistically significant increase was found in Pd, QTd and QTcd in the initial ECG compared to the second and third ECGs. Also, when the first and third ECGs were compared, a significant increase in Tp-e and Tp-e/QT was evident in the first ECG. There was a significant difference in the values of Pd, QTd, QTcd, Tp-e and Tp-e/QT in the first ECGs, obtained before DKA treatment, and those values obtained from the control group.

Conclusion: This is the first article evaluating Pd and Tp-e parameters in children with DKA. Cardiac arrhythmia risk markers were increased in children with DKA compared to controls. Therefore, clinicians should be aware of the possibility of developing new arrhythmias during DKA treatment.

Keywords: Cardiac arrhythmia, children, diabetic ketoacidosis, electrocardiography

Introduction

Type 1 diabetes mellitus (T1DM) accounts for about 10% of all diabetic cases, and more than 3 million people in the United States and 15 million people worldwide are affected (1). Diabetic ketoacidosis (DKA) is one of the leading causes of morbidity and mortality in children with T1DM (2). In diabetic individuals, morbidity and mortality of cardiovascular diseases were found to be increased when compared to healthy individuals. The incidence of diseases such as myocardial infarction and ischemic stroke has also increased (3).

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Malignant cardiac arrhythmias resulting in sudden cardiac death may be present in individuals who are presumably healthy or with medical problems (4). There are some electrocardiographical (ECG) markers that may be associated with cardiac arrhythmias (4,5). On ECG, P-wave dispersion (Pd) has been associated with a risk of atrial arrhythmias. Increased Pd represents non-homogeneous propagation of sinus impulses and atrial depolarization abnormalities associated with atrial arrhythmia (5). QT dispersion (QTd), corrected QT (QTc), and corrected QTd (QTcd) indicate heterogeneity of ventricular repolarization. An increase in ventricular heterogeneity increases myocardial electrical sensitivity and predisposes to ventricular arrhythmias. Tp-e duration, the interval between the peak and the end of the T wave, is also a useful parameter for predicting cardiac arrhythmias and Tp-e/QT and Tp-e/QTc are considered more beneficial than QTd (4).

In the light of recent evidence, we aimed to evaluate atrial (Pd) and ventricular arrhythmia risk markers (QTd, QTcd, Tp-e, Tp-e/QT and Tp-e/QTc) on ECG during and after DKA in children with T1DM.

Methods

Selection of Study Populations

This study was conducted prospectively in children diagnosed with DKA between December 2018 and March 2020 in a tertiary child health care center. In the patient group, cases with pre-existing heart disease or dysrhythmia, or syndromes and sequences associated with cardiac components, or chronic disease other than diabetes mellitus (DM) were excluded from the study. Exclusion criteria for the control group were the presence of known heart disease or dysrhythmia, syndromes and sequences associated with cardiac components, and other chronic diseases.

The diagnostic criteria for DKA were hyperglycemia (blood glucose > 200 mg/dL), ketosis (ketone positivity in blood or urine) and metabolic acidosis (pH < 7.3 in venous blood sample or plasma bicarbonate < 15 mEq/L), in accordance with literature (2).

In the patient group, a history of being previously or newly diagnosed with T1DM, age at diagnosis and follow-up duration, age at the occurrence of DKA, gender, weight, height and body mass index (BMI), blood pressure and biochemical values, including blood glucose levels at the time of DKA, hemoglobin A1c (HbA1c) and lipid panel taken in the last three months were examined. The clinical severity of DKA in patients was classified into: mild (pH: 7.2-7.3, bicarbonate: 10-15 mEq/L); moderate (pH: 7.1-7.2, bicarbonate: 5-9 mEq/L); and severe (pH: < 7.1, bicarbonate: < 5 mEq/L) (6). No blood tests were performed in the control group.

Electrocardiography

ECG examination was performed in all cases. Recordings were obtained with a speed of 25 mm/s and amplitude of 10 mm/mV using SeaMed ECG 1200G (Qinhuangdao, China) 12-channel/12-lead ECG device. All ECGs were scanned at a resolution of 300 DPI and transferred to electronic medium. Images were analyzed with "Adobe Photoshop CS2 version 9.0" program at a resolution of 1500 DPI and accuracy of four milliseconds. A total of three ECG recordings were obtained from the patient group; the first at the time of DKA, the second shortly after recovery from the DKA (3-7 days later), and the third approximately 1-2 weeks later after discharge from hospital. Only one ECG record was performed in each subject in the control group. Standard measurements, such as heart rate (HR), PR interval, P-wave duration, QT interval and QTc interval were performed on all ECGs, and then Pd, QTd, QTcd, Tp-e, and the ratios of Tp-e/QT and Tp-e/QTc were measured electrocardiographically. P-wave duration was evaluated as the duration between initial deflection and its return junction to the isoelectric baseline. QT interval was calculated as the duration between the beginning of the QRS complex and the end of T-wave in isoelectric baseline. QTc was measured using Bazett's formula ($QTc = QT/\sqrt{RR}$). Tp-e interval was evaluated as the duration between the peak and the end of the T wave on isoelectric baseline. If the beginning and end of the T waves were not clearly seen, it was determined according to the tangent method defined by Lepeschkin and Surawicz (7). In this study, Pd, QTd and QTcd were measured from at least nine leads, and the Tp-e interval was evaluated primarily using V5, and if not possible, then preferentially by V4 or V6 derivation. Measurements were made in three consecutive heartbeats and the average was calculated. The U wave, if present, was not included in the Tp-e range. While calculating Tp-e/QT and Tp-e/QTc ratios, QT and QTc were measured from the same derivation where Tp-e interval was measured.

Echocardiography

Echocardiographic (ECHO) examination of the patient and control groups were also compared during this study. Evaluations were performed by an experienced pediatric cardiologist using a Vivid S5 N (General Electric, Horten, Norway) ECHO device and 3S (2-4 MHz) probe. ECHO studies were performed using standard imaging techniques recommended by the American Society of Echocardiography (8). Left atrial diameter, aortic root, left ventricular end-systolic dimension, left ventricular end-diastolic dimension,

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end-diastolic interventricular septal thickness, end-diastolic left ventricular posterior wall thickness, left ventricular ejection fraction (EF) and left ventricular fractional shortening were measured echocardiographically.

All procedures performed in the current study were in accordance with the 1964 Helsinki Declaration and ethical approval for the study was obtained from Necmettin Erbakan University Ethical Committee with a decision no. 2018/1321, dated 03.05.2018.

Informed consent was obtained from all individual participants and/or their legal guardians included in the study.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences statistics, version 22 (IBM Inc., Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation when normal distribution is observed. Descriptive analysis was used in the analysis of the distribution and frequency of data. Chi-square test was used to evaluate categorical data in independent groups. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether the continuous variables fit the normal distribution or not. When homogeneous distribution was observed, an independent sample t-test (Student's t-test) was applied in independent groups and a dependent samples t-test (paired t) and two-way ANOVA tests were applied in dependent groups. In cases where normal distribution was not observed, Mann-Whitney U tests in independent groups, and Wilcoxon and Friedman tests in dependent groups were used. For correlation analysis, Pearson's correlation analysis was performed when the continuous variables were parametrically distributed and, if not, Spearman correlation analysis was used. During correlation examinations, the r-value was rated as: negligible between 0.00-0.29; weak between 0.30-0.49; moderate between 0.50-0.69; strong between 0.70-0.89; and very strong between 0.90-1.0 (9). A $p < 0.05$ was considered statistically significant.

Results

Patient Demographic and Clinical Characteristics

Forty children, aged 0-18 years with DKA as patient group and 40 age- and gender-matched healthy children as control group were included. However, one case from the patient group was excluded due to incomplete data. In the patient group 59.0% (n = 23) were female (F) and 41.0% (n = 16) were male (M) in patient group with a female to male (F/M) ratio of 1.44:1 in all patients with DKA (n = 39). While the F/M ratio was 3.25:1 in previously diagnosed T1DM patients, it was 0.83:1 in newly diagnosed patients. Mean ages of the patient and control groups were 10.50 ± 4.12 and 10.47 ± 4.11 years, respectively. There was no statistically significant difference between the patient and control groups in terms of gender, age, weight, height and BMI. General characteristics of the patients and controls are presented in Table 1.

The patient groups consisted of 43.6% (n = 17) previously diagnosed patients and 56.4% (n = 22) newly diagnosed patients. The mean duration of DM in previously diagnosed patients was 5.18 ± 3.32 years (range: 1-12 years). Of the patients, 33.3% (n = 13) presented with mild, 20.5% (n = 8) moderate and 46.2% (n = 18) severe DKA. Between these severity groups, there was no significant difference in terms of gender, history of being previously or newly diagnosed for T1DM and mean duration of diabetes (p > 0.05 for all).

There was a statistically significant decrease in both systolic and diastolic blood pressure in the patient group compared to the control group (p = 0.006 and p = 0.04, respectively) (Table 1). As expected, leukocyte count and blood glucose values obtained at the time of DKA were above and sodium, pH and bicarbonate were below the laboratory reference ranges. Other data were within normal range according to laboratory references. In previously diagnosed cases the mean sodium level was 132.47 ± 4.00 mmol/L, mean potassium level was 4.54 ± 0.96 mmol/L, mean calcium level was 9.37 ± 0.93 mg/dL, mean phosphorus level was 4.21 ± 1.37 mg/dL, and mean magnesium level was 1.95 ± 0.22 mg/dL. Similarly, in newly diagnosed cases

Table 1. General characteristics of the cases

	Patient group (n = 39)	Control group (n = 40)	p
Gender (female/male)	23/16	24/16	0.926
Age (year)	10.50 ± 4.12	10.47 ± 4.11	0.948
Weight (kg)	34.86 ± 14.92	38.51 ± 18.49	0.341
Height (cm)	138.54 ± 23.53	143.19 ± 24.16	0.398
Body mass index (kg/m²)	17.34 ± 4.60	17.88 ± 3.74	0.301
Systolic blood pressure (mm/Hg)	101.89 ± 13.69	108.79 ± 10.83	**0.006**
Diastolic blood pressure (mm/Hg)	63.46 ± 6.60	68.18 ± 9.51	**0.040**

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the mean sodium level was 134.86 ± 4.86 mmol/L, mean potassium level was 4.36 ± 0.72 mmol/L, mean calcium level was 9.30 ± 0.69 mg/dL, mean phosphorus level was 3.79 ± 1.33 mg/dL and mean magnesium level was 2.01 ± 0.40 mg/dL. In the patient group some laboratory abnormalities were seen, such as hyponatremia (< 136 mmol/L) in 61.54% (n=24), hypernatremia (> 145 mmol/L) in 2.56% (n=1), hypokalemia (< 3.5 mmol/L) in 15.38% (n=6), hyperkalemia (> 5.1 mmol/L) in 15.38% (n=6), hypophosphatemia (< 2.9 mg/dL) in 17.95% (n=7), hyperphosphatemia (> 5.1 mg/dL) in 17.95% (n=7), hypocalcemia (< 8.4 mg/dL) in 10.26% (n=4), and hypercalcemia (> 10.2 mg/dL) in 15.38% (n=6). There was no statistically significant difference between the previously and newly diagnosed T1DM patients in terms of mean electrolyte levels of the patient group (p > 0.05 for all). The mean lipid values of the patient group were in the normal range, except for mild mean triglyceride elevation of 216.27 ± 183.43 mg/dL (0-150 mg/dL). The mean HbA1c values were markedly above the reference range at 12.65 ± 2.92% (normal range 4-6%). There was no significant difference between the previously and newly diagnosed T1DM cases in terms of mean HbA1c values of the patient group (p = 0.975). No blood test was performed inthe control group and therefore no comparison was made with patient group. Laboratory findings of the patient group are summarized in Table 2.

Electrocardiographic Findings

In the patient group there was a statistically significant increase in terms of HR, Pd, QTd and QTcd in the first ECGs, obtained at the time of DKA, when compared to both the second and third (after treatment) ECGs (Table 3). A significant increase in Tp-e and Tp-e/QT was found when the first ECGs were compared to third ECGs (p = 0.045 and p < 0.001, respectively) and there was a significant increase in Tp-e/QT in the first and second ECGs compared to the third ECGs (p < 0.001 and p = 0.013, respectively). There was no significant difference in Tp-e/QTc in any of the inter-group comparisons (p > 0.05). Significant differences were found in the parameters HR, Pd, QTd, QTcd and Tp-e/QT between the three ECGs obtained at different times. In terms of Tp-e/QT, a significant difference was found when comparing the third ECGs with the first and second ECGs (p = 0.013). The maximum QTc value of nine patients was found to be increased (> 450 ms) in the first ECG. This persisted in two of these patients in the second ECGs but all of them had recovered by the third ECG.

Table 2. Laboratory findings of the patient group				
Blood samples	Mean ± SD	Minimum	Maximum	Laboratory reference range
Leukocyte count (/mm³)	**16857 ± 11825**	3900	57300	4000-10000
Hemoglobin (g/dL)	14.18 ± 1.40	10.2	18.0	12.1-17.2
Platelet count (/mm³)	331143 ± 123929	33.000	700.000	150000-400000
Blood glucose (mg/dL)	**446.17 ± 133.83**	225	947	Fasting: 70-105/ Postprandial: 80-140
Urea (mg/dL)	33.94 ± 21.28	12.5	125.6	16.6-48.8
Creatinine (mg/dL)	0.84 ± 0.30	0.40	1.91	0.39-0.87
Sodium (mmol/L)	**133.82 ± 4.61**	125	147	136-145
Potassium (mmol/L)	4.44 ± 0.82	2.6	6.4	3.5-5.1
Chlorine (mmol/L)	99.03 ± 6.79	82	115	98-107
Calcium (mg/dL)	9.33 ± 0.80	6.88	10.71	8.4-10.2
Phosphorus (mg/dL)	3.97 ± 1.35	1.71	7.82	2.9-5.1
Magnesium (mg/dL)	1.98 ± 0.33	1.56	3.37	1.7-2.2
Albumin (g/dL)	4.56 ± 0.56	3.10	5.56	3.2-4.5
pH	**7.12 ± 0.12**	6.88	7.29	7.35-7.45
pCO_2 (mmHg)	22.53 ± 6.80	10.2	41.2	35-45
HCO_3 (mEq/L)	**7.70 ± 3.88**	3	15	21-27
Ketone (serum)	**2.08 ± 0.77**	1	3	0
Total cholesterol (mg/dL)	167.30 ± 47.09	70	277	0-200
Triglyceride (mg/dL)	**216.27 ± 183.43**	42	979	0-150
HDL (mg/dL)	40.21 ± 13.55	10	66	35-70
LDL (mg/dL)	90.33 ± 35.19	32	163	0-100
HbA1c (%)	**12.65 ± 2.92**	5.5	18.0	4-6

HbA1c: hemoglobin A1c, HCO_3: bicarbonate, HDL: high density lipoprotein, LDL: low density lipoprotein, pCO_2: carbon dioxide partial pressure, SD: standard deviation

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The parameters HR, Pd, PR, QTd, QTcd, Tp-e and Tp-e/QT all differed significantly between the first ECG performed in the patient group and the values obtained from the control group. There was a statistically significant increase in PR interval when the second and third ECGs were compared to the control ECGs ($p = 0.005$ and $p = 0.032$, respectively). Thus, PR interval was found to be significantly increased compared to controls in all patient group ECGs, while Tp-e/QTc was similar between all the groups. ECG findings of the groups were summarized in Table 3 and illustrated in Figure 1 and Figure 2.

The EF value in the patient group was slightly but significantly greater than in the control group ($p = 0.035$). Nevertheless, the EF values of both groups were within the normal range. Other parameters were similar between the groups. Comparative results of the ECHO examinations of the cases are given in Table 4.

Discussion

DM is a complex metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion and/or insulin sensitivity (10). In T1DM, women and men are affected almost equally. Some populations, including Western Europe and the USA, have a slight male dominance and some societies, such as Japan, have a female dominance (1). It has been reported that the incidence of
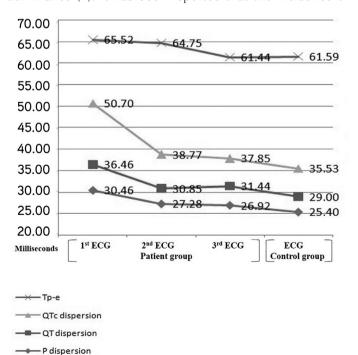
DKA in children does not change with gender (11). However, the incidence of having DKA at first presentation leading to diagnosis of T1DM was found to be higher in boys (female/male ratio 0.51:1) (12). In our study, male gender was more predominant in newly diagnosed patients, consistent with the literature, while the female to male ratio was determined to be higher in all patients with DKA compared to previous studies. Thus the rate of DKA events in our previously diagnosed patients was greater in girls.

Lipid disturbances, including hypertriglyceridemia and low high density lipoprotein cholesterol, in patients with T1DM have been recognized for some time (13). Dyslipidemia has been associated with poor glycemic control (14). However, studies showing hyperlipidemia in DKA are rarely seen in the literature (15,16). In our patient group, only mild mean triglyceride elevation was seen, although it should be noted that the lipid profiles in our patient group was not taken at the time of DKA. In a multi-center study conducted by Turton et al (17), the HbA1c level in patients with T1DM ranged between 6.8 and 11.1%. In another study in children with T1DM, mean HbA1c level was found to be $7.59 \pm 1.34\%$ between 0-5 years of age, $7.61 \pm 1.32\%$ between 6-12 years of age, and $8.46 \pm 1.85\%$ between 13-18 years of age (18). DKA was more frequent in children with T1DM and poor glycemic control (2). Since all our cases, by definition, were children with DKA and more than 50% of them were newly diagnosed for T1DM, the mean HbA1c value in our cohort was much higher than previous studies.

In a previous study, the rate of DKA in children with T1DM was found to be inversely proportional to age. The

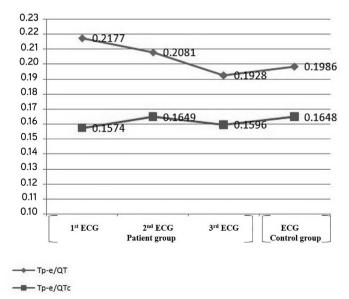**Figure 1.** Mean values of P-wave dispersion, QT dispersion, corrected QT dispersion and Tp-e in patient and control groups

ECG: electrocardiography

Figure 2. Mean values of Tp-e/QT and Tp-e/QTc ratios in patient and control groups

ECG: electrocardiography

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Table 3. Electrocardiographic findings incases and controls

	Mean ± SD				p values		
	Patient group 1st ECG	Patient group 2nd ECG	Patient group 3rd ECG	Control group ECG	p1	p2	p3
					p4	p5	p6
HR (/min)	118.12 ± 23.91	97.52 ± 25.15	89.48 ± 18.48	92.20 ± 27.78	< 0.001	0.067	< 0.001
					< 0.001	0.133	0.992
P-min (ms)	126.20 ± 22.09	128.74 ± 20.38	125.13 ± 17.84	116.09 ± 18.15	0.455	0.498	**0.006**
					0.218	**0.041**	**0.007**
P-max (ms)	55.08 ± 8.81	56.46 ± 8.82	57.53 ± 7.88	52.70 ± 7.24	0.286	0.535	0.893
					0.001	**0.008**	**0.002**
Pd (ms)	85.64 ± 10.53	83.74 ± 10.38	84.44 ± 9.69	78.10 ± 7.58	**0.035**	0.927	**0.017**
					0.003	0.398	0.272
PR (ms)	30.46 ± 7.56	27.28 ± 7.16	26.92 ± 5.89	25.40 ± 4.40	0.363	0.179	0.854
					0.029	**0.005**	**0.032**
QT-min (ms)	280.31 ± 28.41	308.72 ± 38.23	314.39 ± 29.26	303.10 ± 36.05	< 0.001	0.127	< 0.001
					< 0.001	1.000	0.370
QT-max (ms)	316.77 ± 27.26	339.56 ± 39.17	345.83 ± 30.92	332.10 ± 36.83	< 0.001	0.145	< 0.001
					0.015	0.821	0.193
QTd (ms)	36.46 ± 7.87	30.85 ± 9.61	31.44 ± 9.89	29.00 ± 5.26	**0.002**	0.969	**0.005**
					< 0.001	1.000	0.613
QTc-min (ms)	387.89 ± 22.00	384.92 ± 20.67	379.09 ± 23.33	367.01 ± 23.58	0.533	0.352	0.127
					< 0.001	**0.001**	**0.028**
QTc-max (ms)	438.60 ± 17.77	423.69 ± 21.28	416.94 ± 22.45	402.54 ± 25.09	**0.001**	0.176	< 0.001
					< 0.001	< 0.001	**0.015**
QTcd (ms)	50.70 ± 12.01	38.77 ± 12.38	37.85 ± 11.38	35.53 ± 8.15	< 0.001	0.585	< 0.001
					< 0.001	0.462	0.603
Tp-e (ms)	65.52 ± 8.48	64.75 ± 10.05	61.44 ± 8.04	61.59 ± 8.29	0.691	0.054	**0.045**
					0.041	0.132	0.934
Tp-e/QT	0.21 ± 0.03	0.21 ± 0.04	0.19 ± 0.03	0.20 ± 0.02	0.143	**0.013**	< 0.001
					0.001	0.195	0.292
Tp-e/QTc	0.16 ± 0.02	0.16 ± 0.03	0.16 ± 0.02	0.16 ± 0.02	0.134	0.090	0.596
					0.120	0.979	0.319

HR: heart rate, P-min: minimum P wave duration, P-max: maximum P wave duration, Pd: P-wave dispersion, QT-min: minimum QT duration, QT-max: maximum QT duration, QTd: QT dispersion, QTc-min: minimum QTc duration, QTc-max: maximum QTc duration, QTcd: QTc dispersion, p1: p value comparing 1st and 2nd ECG, p2: p value comparing 2nd and 3rd ECG, p3: p value comparing 1st and 3rd ECG, p4: p value comparing 1st case and control ECGs, p5: p value comparing 2nd case and control ECGs, p6: p value comparing 3rd case and control ECGs, SD: standard deviation, ECG: electrocardiography

Table 4. Echocardiographic findings inpatient and control groups

Mean ± SD	Patient group (n = 39)	Control group (n = 40)	p values
LA (mm)	24.38 ± 4.10	24.47 ± 4.15	0.949
Ao (mm)	20.38 ± 3.59	20.43 ± 2.98	0.960
LA/Ao	1.20 ± 0.10	1.20 ± 0.13	0.986
LVESD (mm)	21.95 ± 3.88	23.63 ± 4.51	0.081
LVEDD (mm)	37.42 ± 6.22	39.46 ± 6.69	0.159
IVSd (mm)	6.66 ± 1.10	7.03 ± 1.18	0.127
LVPWd (mm)	6.74 ± 1.09	6.94 ± 1.30	0.473
EF (%)	72.79 ± 3.82	71.00 ± 3.60	**0.035**
FS (%)	40.72 ± 4.62	40.03 ± 3.44	0.113

Ao: aortic root, EF: left ventricular ejection fraction, FS: left ventricular fractional shortening, IVSd: end-diastolic interventricular septal thickness, LA: left atrial diameter, LVEDD: left ventricular end-diastolic dimension, LVESD: left ventricular end-systolic dimension, LVPWd: end-diastolic left ventricular posterior wall thickness, SD: standard deviation

prevalence of DKA was 36% under 5 years of age, whereas it was 16% in those older than 14 years old (11). The incidence of having DKA at the onset of diagnosis of T1DM varies widely between 14.7% and 79.8% in various countries (19). Große et al (19) reported that the rate of DKA at the time of T1DM diagnosis increased in countries closer to the equator or there was a higher sensitivity to diabetic symptoms. The same article reported the rate of

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concurrent DKA and T1DM diagnosis as 65.9% for Turkey, in accordance with our data.

The use of insulin in diabetic patients has greatly reduced the risk of mortality due to DKA, but cardiovascular dysfunction continues to be an important cause of mortality in the chronic disease process (20). Diabetes is recognized as a strong and independent risk factor for cardiovascular morbidity and mortality, which in turn are frequently associated with rhythm disturbances, such as atrial fibrillation and ventricular arrhythmia (21). Autoimmune mechanisms, which are also important in the etiology of T1DM, may be involved in the pathogenesis of cardiac autoimmunity (22). Lipid disorders have also been shown to contribute to this process by increasing atherosclerotic risk (23). It has been reported that cardiovascular risk was increased tenfold in individuals with T1DM compared to the healthy population (24).

The ECG parameters Pd, QTd, QTcd,Tp-e, Tp-e/QT, and Tp-e/QTc have been shown to berisk markers and are used to predict the risk of cardiac arrhythmias (4,5). Yet, there is limited data on arrhythmia risk markers in children with DKA. In studies performed in adult (25) and pediatric patients with T1DM (5,26), Pd was reported to be significantly increased compared to controls. In a study conducted in adult T2DM patients with DKA, it was observed that Pd was increased significantly before DKA treatment compared to after treatment (27). In another study evaluating children with DKA, it was reported that the mean P wave duration before DKA treatment was significantly increased compared to after treatment, however Pd assessment was not performed in that study (28). To the best of our knowledge, there has been no study reporting the relationship between Pd and DKA in a pediatric population. In our study, Pd in the first, pre-DKA treatment, ECG was found to be significantly higher than both the second and third ECGs, which were obtained after treatment, and the Pd value concurrent with DKA was also greater than in the control group ECGs. Our findings suggest that there may be an increased risk of atrial arrhythmia at the time of DKA in children with T1DM.

QTd and QTcd have been associated with an increased risk of malignant ventricular arrhythmia (29). QTd values above 58 ms in healthy individuals increase the cardiovascular mortality risk by 3.2 times and if QTd is above 80 ms, it has been reported to increase four times (30). QTd and QTcd were associated with a risk of cardiac arrhythmia in studies conducted in adults (31,32) and children (4,33) with T1DM. In an adult study of T1DM patients with DKA, QTc was found to be prolonged (>450 ms) in 38 (62.3%) of 61 patients, regardless of potassium level (34). It was also reported that the QTd and QTcd values obtained during

DKA in children with T1DM were increased compared to the healthy population (35,36). In our study, QTd and QTcd in the first patient group ECG were found to be significantly prolonged compared to both second and third ECGs, as well as the ECGs of the control group. This also suggests that there is an increased risk of ventricular arrhythmia in children with T1DM especially during episodes of DKA.

The results of studies on Tp-e, Tp-e/QT and Tp-e/QTc values in adult T1DM patients are controversial. Inanır et al (32) reported these parameters to be increased in adults with T1DM compared to their control group, whereas in another study, these ECG parameters were found to be similar between T1DM patients and controls (37). In the study of Güney et al (26), conducted in children with T1DM, Tp-e was increased compared to the control group, but Tp-e/QT and Tp-e/QTc ratios were similar with healthy controls. We could not find any data in the literature about Tp-e, Tp-e/QT or Tp-e/QTc in a pediatric population with DKA. In our study, a statistically significant increase was found in pre-treatment ECGs in Tp-e and Tp-e/QT values compared to the control group. However, these parameters were similar between the values obtained at the third ECG and controls. In the study of Güney et al (26), all patients with T1DM were previously diagnosed, whereas our patient group was composed of more than half newly diagnosed T1DM. Additionally, there was no significant difference in regard to Tp-e/QTc in our study. This may be attributed to the fact that QTc values increases much more than QT as the HR increases. So the rise in Tp-e and of its variations in children diagnosed with T1DM related DKA remains controversial.

Study Limitations

Due to the limited number of cases, the previously and newly diagnosed T1DM patients could not be differentiated during the evaluation. ECG examinations were not standardized during the episode of DKA, since the focus of this study was mostly ECG markers related to cardiac arrhythmia risk.In addition, 24-hour holter monitoring couldn't get recorded due to technical incompetence.

Conclusion

In conclusion, the current study was a prospective study conducted in children with T1DM and experiencing an episode of DKA. To the best of our knowledge, this is the first article evaluating Pd, Tp-e, Tp-e/QT and Tp-e/QTc parameters in children with DKA. In this study, cardiac arrhythmia risk markers were increased in children with DKA. While T1DM is already considered a risk factor for cardiac arrhythmias, DKA has been observed to contribute

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to this process. We found that the increase in cardiac arrhythmia risk markers during DKA persisted for a while immediately after the DKA symptoms and/or signs recovered, at the time of the second ECG, but they were similar to the control group 2-3 weeks after the episode of DKA. Thus, we suggest that it is important to consider the possibility of atrial and/or ventricular arrhythmias that may develop during treatment and immediate follow-up period in children with T1DM who have an episode of DKA in order to avoid adverse cardiac events. However, further prospective studies, including larger numbers of patients and longer follow-up periods, are needed to better understand the risks.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from Necmettin Erbakan University Ethical Committee with a decision no. 2018/1321, dated 03.05.2018.

Informed Consent: Informed consent was obtained from all individual participants and/or their legal guardians included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Oğuz Eğil, Fatih Şap, Beray Selver Eklioğlu, Mehmet Burhan Oflaz, Mehmet Emre Atabek, Tamer Baysal, Concept: Fatih Şap, Beray Selver Eklioğlu, Mehmet Burhan Oflaz, Design: Fatih Şap, Beray Selver Eklioğlu, Mehmet Burhan Oflaz, Data Collection or Processing: Oğuz Eğil, Fatih Şap, Beray Selver Eklioğlu, Analysis or Interpretation: Mehmet Emre Atabek, Tamer Baysal, Literature Search: Oğuz Eğil, Mehmet Burhan Oflaz, Writing: Oğuz Eğil, Fatih Şap.

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