DOI: 10.4274/jcrpe.galenos.2021.2021.0165

Original article

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

Oğuz Eğil[1], Fatih Şap[2], Beray Selver Eklioğlu[3], Mehmet Burhan Oflaz[2], Mehmet Emre Atabek[3], Tamer Baysal[2]
[1]Department of Pediatrics, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey
[2]Division of Pediatric Cardiology, Department of Pediatrics, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey
[3]Division of Pediatric Endocrinology, Department of Pediatrics, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey

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 DM. 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 of children with DKA. In this study, cardiac arrhythmia risk markers such as Pd, QTd, QTcd and Tp-e, Tp-e/QT were detected to be increased in children with DKA.

Abstract
Background: Diabetic ketoacidosis (DKA) is an important complication of type-1 diabetes mellitus. We aimed to evaluate effects 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. For statistical analysis, SPSS-22 program was used. P value less than 0.05 was considered significant.
Results: The mean age of 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 the groups. In patient group, statistically significant increase was found in terms of Pd, QTd and QTcd in first ECGs compared to second and third ECGs. Also, when the first and third ECGs were compared, a significant increase in Tp-e and Tp-e/QT was added. It was noteworthy that a significant increase in the values of Pd, QTd, QTcd, Tp-e and Tp-e/QT in the first ECGs, obtained before DKA treatment, was detected compared to control group ECGs.
Conclusions: This is the first article evaluating Pd and Tp-e parameters of children with DKA. In this study, cardiac arrhythmia risk markers were detected to be increased in children with DKA. Therefore, clinicians should be careful about the possibility of development of new arrhythmias during DKA treatment.
Keywords: Cardiac arrhythmia · Children · Diabetic ketoacidosis · Electrocardiography

Corresponding Author: Oğuz Eğil, M.D**,** Department of Pediatrics Meram Medical Faculty, Necmettin Erbakan University
42080, Akyokus-Meram. Konya, Turkey
oguzegil@hotmail.com
0000-0001-5112-5733
14.06.2021
18.08.2021

Published: 18 August 2021

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 by this disease [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 higher than healthy individuals. Incidence of diseases such as myocardial infarction and ischemic stroke has also increased [3].
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 may be associated with cardiac arrhythmias [4, 5]. On ECG, P-wave dispersion (Pd) has been associated with 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) and corrected QTd (QTcd) indicates the heterogeneity of ventricular repolarization. The rise 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 parameter helpful for predicting cardiac arrhythmias and Tp-e/QT and Tp-e/QTc are considered more beneficial than QTd [4].
In the light of recent information, 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.

Materials and methods

Selection of Study Populations

This study was conducted prospectively on DKA diagnosed children between December 2018 and March 2020 in a tertiary child health care center. In patient group, cases with 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 control group were presence of heart disease or dysrhythmia, syndromes and sequences associated with cardiac components, and other chronic diseases.
The diagnosis criteria of DKA were assessed as 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 patient group, history of being previously or newly diagnosed with T1DM, age at diagnosis and follow-up durations, age at the moment 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. Clinical conditions of patients were classified as 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) DKA [6]. No blood tests were performed in the control group.

Electrocardiography

Electrocardiographic examinations were 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; first at the time of DKA, second after the DKA recovered (3-7 days later), and third approximately 1-2 weeks later after discharge from hospital. Only one ECG record was performed in the control group. Standard measurements such as heart rate (HR), PR interval, P-wave duration, QT interval and corrected QT interval (QTc) 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. Corrected QT 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 beginning and end of 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, if not possible, then preferred V4 or V6 derivations. 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 examinations of the patient and control groups were also compared during this study. Evaluations were performedby an experienced pediatric cardiologist using Vivid S5 N (General Electric, Horten, Norway) echocardiography device and 3S (2–4 MHz) probe. Echocardiography studies were performed using standard imaging techniques recommended by the American Society of Echocardiography [8]. Left atrial diameter (LA), aortic root (Ao), left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic dimension (LVEDD), end-diastolic interventricular septal thickness (IVSd), end-diastolic left ventricular posterior wall thickness (LVPWd), left ventricular ejection fraction (EF) and left ventricular fractional shortening (FS) were measured echocardiographically.

Statistical analysis

Analyzes of this study were performed using "IBM SPSS Statistics Version 22" package program. Continuous variables were expressed as "mean±standard deviation (SD)". Descriptive analysis in the analysis of the distribution and frequency of data; Chi-square test was used to evaluate categorical data in independent groups. 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, independent sample T-test (Student's T) was applied in independent groups and 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]. P value of <0.05 was considered statistically significant.

Results

Forty children aged 0-18 years with DKA as patient group and 40 age and gender matched healthy children as control group included to the study, 1 case of patient group was excluded due to incomplete data. Of the cases; 59.0% (n=23) were female and 41.0% (n=16) were male in patient group. The female to male (F/M) ratio was determined to be 1.44 in all patients with DKA (n=39). While the F/M ratio was 3.25 in previously diagnosed T1DM patients; it was found to be 0.83 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 body mass index (p range: 0.301-0.948). General characteristics of the cases were presented in *Table 1*.

Since 43.6% (n=17) of the patient group were previously diagnosed patients, and 56.4% (n=22) were newly diagnosed patients. The mean duration of DM in previously diagnosed patients was 5.18±3.32 years (min:1 and max:12). 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 statistically significant difference in terms of gender, history of being previously or newly diagnosed for T1DM and mean duration of diabetes (p range:0.482-0.922).

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 moment 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: 132.47±4.00 mmol/L, mean potassium level: 4.54±0.96 mmol/L, mean calcium level: 9.37±0.93 mg/dl, mean phosphorus level: 4.21±1.37 mg/dl, and mean magnesium level was 1.95±0.22 mg/dl. In newly diagnosed cases: The mean sodium level: 134.86±4.86 mmol/L, mean potassium level: 4.36±0.72 mmol/L, mean calcium level: 9.30±0.69 mg/dl, mean phosphorus level: 3.79±1.33 mg/dl, and mean magnesium level was 2.01±0.40 mg/dl. Of the patient cases; there were some laboratory abnormalities 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) in15.38% (n=6), hyperkalemia (>5,1 mmol/L) in15.38% (n=6), hypophosphatemia (<2.9 mg/dl) in17.95% (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 range: 0.131-0.806). The mean lipid values of the patient group were in the normal range except mild triglyceride elevation as 216.27±183.43 mg/dl (0-150 mg/dl). The mean HbA1c values were quite above the reference range as %12.65±2.92 (%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 in the control group; therefore, the data could not be analyzed comparatively with patient group. Laboratory findings of the patient group were summarized in *Table 2*.

Among the electrocardiographic findings: there was a statistically significant increase in terms of HR, Pd, QTd and QTcd comparing first ECGs of the patient group, obtained at the time of DKA, to both second and third (after treatment) ECGs (p range:<0.001-0.035). A significant increase in Tp-e and Tp-e/QT was added 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 none of the comparisons (p range:0.134-0.596). Between three ECGs obtained at different times, two-way ANOVA and Friedman tests were also applied and a statistically significant difference was found in regard to HR, Pd, QTd, QTcd and Tp-e/QT (p range:<0.001-0.024). In terms of Tp-e/QT, a significant difference was found in the third ECGs compared to the first and second ECGs in two-way ANOVA (p:0.013). Further examination could not be performed, since other parameters were not normally distributed. Maximum QTc value of nine patients was found to be increased (>450 ms) in the first ECGs. Same situation persisted in two of these patients in the second ECGs and all of them recovered in the third ECGs.

Comparing the control group ECGs with patient group ECGs, there was a statistically significant increase in HR, Pd, PR, QTd, QTcd, Tp-e and Tp-e/QT in the first ECGs (p range:<0.001-0.029). There was a statistically significant increase in PR interval when the second and third ECGs compared to the control ECGs (p:0.005 and p:0.032, respectively). Thus, PR interval was found to be significantly increased in all ECGs of the patient group (p range:0.005-0.032), while Tp-e/QTc was similar between all the groups (p range:0.120-0.979). Electrocardiographic findings of the groups were shown in *Table 3, Figure 1 and Figure 2*.

Evaluating the echocardiographic findings, EF value in the patient group was slightly higher than the control group (p:0.035). Nevertheless, EF values of both groups were in normal range. Other parameters were similar between the groups (p range:0.081-0.986). Comparative results of the echocardiographic examinations of the cases were given in *Table 4*.

Discussion

Diabetes mellitus is a complex metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion and/or insulin receptor level [10]. In T1DM, women and men are affected almost equally. Some populations (Western Europe/USA) have a slight male dominance and some societies (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 the onset of diagnosis of T1DM was found to be higher in boys (female/male: 0.51) [12]. In our study, male gender was more predominant in newly diagnosed patients, consistently with the literature, while the ratio of female to male was determined to be higher in all patients with DKA compared to previous studies. This indicates that the rate of DKA events in our previously diagnosed patients was higher in girls.

Lipid disturbances, including hypertriglyceridemia and low HDL cholesterol, in patients with T1DM have been reported in a previous study [13]. Dyslipidemia has been detected to be associated with poor glycemic control [14]. Studies showing hyperlipidemia in DKA are rarely seen in the literature [15, 16]. In our patient group, only mild mean triglyceride elevation was seen, however lipid profile of our patient group was not taken at the time of DKA. In a multi-center study conducted by Turton et al [17], the average HbA1c level in patients with T1DM was measured between 6.8 and 11.1%. In another study in children with T1DM, mean HbA1c level was found to be 7.59±1.34% between 0-5 years of age, 7.61±1.32% between 6-12 years of age, and 8.46±1.85% between 13-18 years of age[18]. Diabetic ketoacidosis was shown more frequently in children with T1DM and poor glycemic control [2]. Since all our cases consisted of children with DKA and more than 50% of them are newly diagnosed for T1DM, mean HbA1c value 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 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 between 14.7% and 79.8% in various countries [19]. According to this meta-analysis, the rate of T1DM diagnosis with DKA increased in countries closer to the equator or there is a higher sensitivity to diabetic symptoms. In the same article [19], it was reported 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 process [20]. Diabetes is one of the strong and independent risk factors for cardiovascular morbidity and mortality, which are frequently associated with rhythm disturbances such as atrial fibrillation and ventricular arrhythmia [21]. Autoimmune mechanisms which are also found 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 atherosclerosis [23]. It has been reported that cardiovascular risk increased 10 times in individuals with T1DM compared to the healthy population [24].

P-wave dispersion (Pd), QTd, QTcd,Tp-e, Tp-e/QT, and Tp-e/QTc were shown to be accepted as risk markers used to predict the risk of cardiac arrhythmias [4, 5]. Yet, there is limited data on arrhythmia risk markers in children with diabetic ketoacidosis. In studies performed in adult [25] and pediatric patients with T1DM [5, 26], Pd was reported to be significantly increased compared to the control group. In a study conducted in adult type 2 diabetes mellitus patients with DKA, it was observed that Pd 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 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 dealing with the relationship between Pd and DKA in pediatric population. In our study, Pd in the first ECG (before DKA treatment) was found to be significantly higher than both the second and third ECGs (after treatment), and also control group ECGs. Our findings suggest that increased risk of atrial arrhythmia at the time of DKA in children with T1DM may be seen.

QT dispersion and QTcd have been considered to be associated with an increased risk of malignant ventricular arrhythmia [29]. QT dispersion values above 58 ms in healthy individuals increase the cardiovascular mortality risk by 3.2 folds; if QTd is above 80 ms, it has been reported to increase 4 times [30]. QT dispersion and QTcd were found to be related to the risk of cardiac arrhythmia in studies conducted in adults [31, 32] and children [4, 33] with T1DM. In an adult study related to the 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 in some studies that the QTd and QTcd examined during DKA in children with T1DM were shown to be increased compared to the healthy population [35, 36]. Also in our study, QTd and QTcd in the first ECG of patient group 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 the risk of ventricular arrhythmia in children with T1DM particularly increased at the moment 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. [31] were detected these parameters to be increased in adults with T1DM compared to the control group, whereas in another study, these ECG parameters were found to be similar between T1DM patients and control group [37]. In the study of Güney et al [26], conducted in children with T1DM, Tp-e was seen increased compared to the control group, however Tp-e/QT and Tp-e/QTc ratios were found to be similar with the healthy control. To the best of our knowledge, we could not find any data in the literature about Tp-e, Tp-e/QT or Tp-e/QTc in pediatric population with DKA. In our study, a statistically significant increase has been seen in first ECGs (before treatment) in terms of Tp-e and Tp-e/QT compared to the control group. However, these parameters were similar between third ECG (after treatment) and control group. In the study of Guney [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. It may be attributed to the fact that QTc values increases much more than QT as the HR increases; yet still the rise of Tp-e and of its variations in children diagnosed with T1DM related DKA is controversial.

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

In conclusion, the current study is a prospective study conducted in children with DKA. To the best of our knowledge, this is the first article evaluating Pd, Tp-e, Tp-e/QT and Tp-e/QTc parameters of children with DKA. In this study, cardiac arrhythmia risk markers were detected to be increased in children with DKA. While T1DM has already been considered as a risk factor for cardiac arrhythmias, DKA has also been observed to contribute to this process. It was observed that the increase in cardiac arrhythmia risk markers during DKA in children continued for a while immediately after the DKA symptoms and/or signs recovered (second ECGs), but they were similar to the control group after 2-3 weeks (third ECGs). Thus, we suggest that it is important to take into consideration possibility of atrial and/or ventricular arrhythmias that may develop during the treatment and follow-up period of DKA in order to avoid adverse cardiac events. However, further studies, including larger number of patients and longer follow-up periods, are needed on this subject.

Ethics

Ethics Committee Approval: All procedures performed in the current study were in accordance with the 1964 Helsinki Declaration and approved by Necmettin Erbakan University's 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.

Authorship Contributions

Surgical and Medical Practices: OE, FS, BSE, MBO, MEA, TB
Concept: FS, BSE, MBO
Design: FS, BSE, MBO
Data Collection or Processing: OE, FS, BSE
Analysis or Interpretation: MEA, TB
Literature Search: OE, MBO
Writing: OE, FS

Financial Disclosure: This study was funded by Necmettin Erbakan University's Scientific Research Project Coordinator (decision no. 181518017, dated 05.10.2018), which allowed supply of electrocardiography device and its equipments.

Conflict of Interest: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication. All authors declare that they have no conflict of interest.

References

1. Weber DR, Jospe N. Diabetes mellitus. In: Kliegman RM, St Geme JW, Blum NJ, Shah SS, Tasker RC, Wilson KM, Behrman RE, editors. Nelson Textbook of Pediatrics. 21st ed. Philadelphia: Elsevier; 2019. p. 11814-935.

2. Wolfsdorf JI, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes. 2018 Oct;19(27):155-77. https://doi.org/10.1111/pedi.13118.

3. Larsson SC, Wallin A, Håkansson N, Stackelberg O, Bäck M, Wolk A. Type 1 and type 2 diabetes mellitus and incidence of seven cardiovascular diseases. Int J Cardiol. 2018 Jul 1;262:66-70. https://doi.org/10.1016/j.ijcard.2018.03.099.

4. Castro-Torres Y, Carmona-Puerta R, Katholi RE. Ventricular repolarization markers for predicting malignant arrhythmias in clinical practice. World J Clin Cases. 2015;3(8):705-20. https://doi.org/10.12998/wjcc.v3.i8.705.

5. Imamoglu EY, Oztunc F, Eroglu AG, Onal H, Guzeltas A. Dispersion of the P wave as a test for cardiac autonomic function in diabetic children. Cardiol Young. 2008;18(6):581-5. https://doi.org/10.1017/S1047951108003089.

6. von Oettingen JE, Wolfsdorf J, Feldman HA, Rhodes ET. Use of serum bicarbonate to substitute for venous pH in new-onset diabetes. Pediatrics. 2015 Aug;136(2):371-7. https://doi.org/10.1542/peds.2015-0156.

7. Lepeschkin E, Surawicz B. The Measurement of the Q-T Interval of the Electrocardiogram. Circulation. 1952 Sep;6(3):378-88. https://doi.org/10.1161/01.cir.6.3.378.

8. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr. 2010 May;23(5):465-95. https://doi.org/10.1016/j.echo.2010.03.019.

9. Mukaka MM. A guide to appropriate use of Correlation coefficient in medical research. Malawi Med J. 2012 Sep; 24(3): 69–71.

10. Mayer-Davis EJ, Kahkoska AR, Jefferies C, Dabelea D, Balde N, Gong CX, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Definition, epidemiology, diagnosis and classification of diabetes in children and adolescents. Pediatr Diabetes. 2018 Oct;19 (27):7-19. https://doi.org/10.1111/pedi.12773.

11. Wolfsdorf JI, Glaser N, Sperling MA; American Diabetes Association. Diabetic ketoacidosis in infants, children, and adolescents: A consensus statement from the American Diabetes Association. Diabetes Care. 2006 May;29(5):1150-9. https://doi.org/10.2337/diacare.2951150.

12. Dabelea D, Rewers A, Stafford JM, Standiford DA, Lawrence JM, Saydah S, et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. Pediatrics. 2014 Apr;133(4):938-45. https://doi.org/10.1542/peds.2013-2795.

13. O'Brien T, Nguyen TT, Zimmerman BR. Hyperlipidemia and diabetes mellitus. Mayo Clin Proc. 1998 Oct;73(10):969-76. https://doi.org/10.4065/73.10.969.

14. Maahs DM, Dabelea D, D'Agostino RB Jr, Andrews JS, Shah AS, Crimmins N, et al. Glucose control predicts 2-year change in lipid profile in youth with type 1 diabetes. J Pediatr. 2013 Jan;162(1):101-7. https://doi.org/10.1016/j.jpeds.2012.06.006.

15. Blackett PR, Holcombe JH, Alaupovic P, Fesmire JD. Plasma Lipids and Apolipoproteins in a 13-year-old Boy With Diabetic Ketoacidosis and Extreme Hyperlipidemia. Am J Med Sci. 1986 May;291(5):342-6. https://doi.org/10.1097/00000441-198605000-00010.

16. Gianfrate L, Ferraris L. Acute Pancreatitis, Hyperlipidemia, and Diabetic Ketoacidosis: Who Comes First? Am J Gastroenterol. 1998 Aug;93(8):1393-4. https://doi.org/10.1111/j.1572-0241.1998.1393a.x.

17. A Turton JL , Raab R, Rooney KB. Low-carbohydrate Diets for Type 1 Diabetes Mellitus: A Systematic Review. PLoS One. 2018 Mar 29;13(3):e0194987. https://doi.org/10.1371/journal.pone.0194987.

18. Ziegler R, Heidtmann B, Hilgard D, Hofer S, Rosenbauer J, Holl R; for the DPV-Wiss-Initiative. Frequency of SMBG correlates with HbA1c and acute complications in children and adolescents with type 1 diabetes. Pediatric Diabetes 2011 (12): 11–7. https://doi.org/ 10.1111/j.1399-5448.2010.00650.x.

19. Große J, Hornstein H, Manuwald U, Kugler J, Glauche I, Rothe U. Incidence of Diabetic Ketoacidosis of New-Onset Type 1 Diabetes in Children and Adolescents in Different Countries Correlates with Human Development Index (HDI): An Updated Systematic Review, Meta-Analysis, and Meta-Regression. Horm Metab Res. 2018 Mar;50(3):209-22. https://doi.org/10.1055/s-0044-102090.

20. Dhalla NS, Pierce GN, Innes IR, Beamish RE. Pathogenesis of Cardiac Dysfunction in Diabetes Mellitus. Can J Cardiol. Jul-Aug 1985;1(4):263-81.

21. Koektuerk B, Aksoy M, Horlitz M, Bozdag-Turan I, Turan RG. Role of diabetes in heart rhythm disorders. World J Diabetes. 2016;7(3):45-9. https://doi.org/ 10.4239/wjd.v7.i3.45.

22. Frostegård J. Autoimmunity, oxidized LDL and cardiovascular disease. In: Shoenfeld Y, editors. Autoimmunity Reviews.Volume 1, Issue 4.Solna: Elsevier 2002. p233-7.

23. A Feitosa AC, Feitosa-Filho GS, Freitas FR, Wajchenberg BL, Maranhão RC. Lipoprotein metabolism in patients with type 1 diabetes under intensive insulin treatment. Lipids Health Dis. 2013 Feb;11(12)15. https://doi.org/10.1186/1476-511X-12-15.

24. de Ferranti SD, de Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Diabetes Care. 2014;130(13):1110-30. https://doi.org/10.2337/dc14-1720.

25. Yazici M, Ozdemir K, Altunkeser BB, Kayrak M, Duzenli MA, Vatankulu MA, et al. The effect of diabetes mellitus on the P-wave dispersion.Circ J. 2007 Jun;71(6):880-3. https://doi.org/10.1253/circj.71.880.

26. Güney AY, Şap F, Selver Eklioğlu B, Oflaz MB, Atabek ME, Baysal T. Investigation of the Effect of Epicardial Adipose Tissue Thickness on Cardiac Conduction System in Children With Type 1 Diabetes Mellitus. J Pediatr Endocrinol Metab. 2020 May;33(6):713-20. https://doi.org/10.1515/jpem-2020-0001.

27. Fidan C, Bünyamin Yavuz B, Şen Ö, Ertuğrul DT, Yaşar Nazlıgül Y. Increased P Wave Dispersion In Patients With Diabetic Ketoacidosis. TJFM&PC, 2016;10(2):63-8.

28. Aygün D, Aygün F, Nişli K, Baş F, Çıtak A. Electrocardiographic changes in children with diabetic ketoacidosis and ketosis. Turk Pediatri Ars. 2017 Dec;52(4):194-201. https://doi.org/ 10.5152/TurkPediatriArs.2017.4917.

29. Psallas M, Tentolouris N, Cokkinos A, Papadogiannis D, Cokkinos DV, Katsilambros N. QT dispersion: comparison between diabetic and non-diabetic individuals and correlation with cardiac autonomic neuropathy. Hellenic J Cardiol. 2006 Sep-Oct;47(5):255-62.
30. Elming H, Holm E, Jun L, Torp-Pedersen C, Køber L, Kircshoff M, et al. The prognostic value of the QT interval and QT interval dispersion in all-cause and cardiac mortality and morbidity in a population of Danish citizens. Eur Heart J. 1998 Sep;19(9):1391-400. https://doi.org/10.1053/euhj.1998.1094.
31. Veglio M, Giunti S, Stevens LK, Fuller JH, Perin PC; EURODIAB IDDM Complications Study Group. Prevalence of Q-T interval dispersion in type 1 diabetes and its relation with cardiac ischemia : the EURODIAB IDDM Complications Study Group. Diabetes Care. 2002 Apr;25(4):702-7. https://doi.org/10.2337/diacare.25.4.702.
32. Inanır M, Gunes Y, Sincer I, Erdal E. Evaluation of Electrocardiographic Ventricular Depolarization and Repolarization Variables in Type 1 Diabetes Mellitus. Arq Bras Cardiol. 2020 Feb; 114(2): 275–80. https://doi.org/10.36660/abc.20180343.
33. Suys BE, Huybrechts SJ, De Wolf D, Op De Beeck L, Matthys D, Van Overmeire B, et al. QTc interval prolongation and QTc dispersion in children and adolescents with type 1 diabetes. J Pediatr. 2002 Jul;141(1):59-63. https://doi.org/10.1067/mpd.2002.125175.
34. Talebi S, Ghobadi F, Cacacho A, Olatunde O, DeRobertis A, Pekler G, et al. Looking at diabetic ketoacidosis through electrocardiogram window. Am J Emerg Med. 2016 Feb;34(2):263-5. https://doi.org/10.1016/j.ajem.2015.10.032.
35. Kuppermann N, Park J, Glatter K, Marcin JP, Glaser NS. Prolonged QT interval corrected for heart rate during diabetic ketoacidosis in children. Arch Pediatr Adolesc Med. 2008 Jun;162(6):544-9. https://doi.org/10.1001/archpedi.162.6.544.
36. Youssef OI, Farid SM. QTc and QTd in Children with Type 1 Diabetes Mellitus during Diabetic Ketoacidosis. ISRN Pediatrics 2012 (2012): 1–4. https://doi.org/10.5402/2012/619107.
37. Olmez S, Akkoyun M, Sahin M, Namli AR, Akgungor M,Dirnak I, et al. Evaluation of Tp-e Interval and Tp-e/QT Ratio in Patients with Type 1 Diabetes Mellitus. JACC.2013 Oct;62(18-2):147. https://doi.org/10.1016/j.jacc.2013.08.436.

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**

Table 2: Laboratory Findings of the Patient Group

Blood Samples	**Mean±SD**	**Minimum**	**Maximum**	**Laboratory reference range**
Leukocyte count (/mm^3)	**16857±11825**	3900	57300	4000-10000
Hemoglobin (g/dl)	14.18±1.40	10.2	18.0	12.1-17.2
Platelet count (/mm^3)	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, HCO3: bicarbonate, HDL: high density lipoprotein, LDL: low density lipoprotein, pCO2: carbon dioxide partial pressure.

Table 3: Electrocardiographic Findings of the Cases and Comparisons

	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: MaximumQTc duration, QTcd: QTc dispersion, p1: p value between the 1st and 2nd ECG, p2: p value between the 2nd and 3rd ECG, p3: pvalue between the 1st and 3rd ECG, p4: p value between the 1st and control ECG, p5: p value between the 2nd and control ECG, p6: p value between the 3rd and control ECG.

Table 4: Echocardiographic Findings of the Cases and Comparisons

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.

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

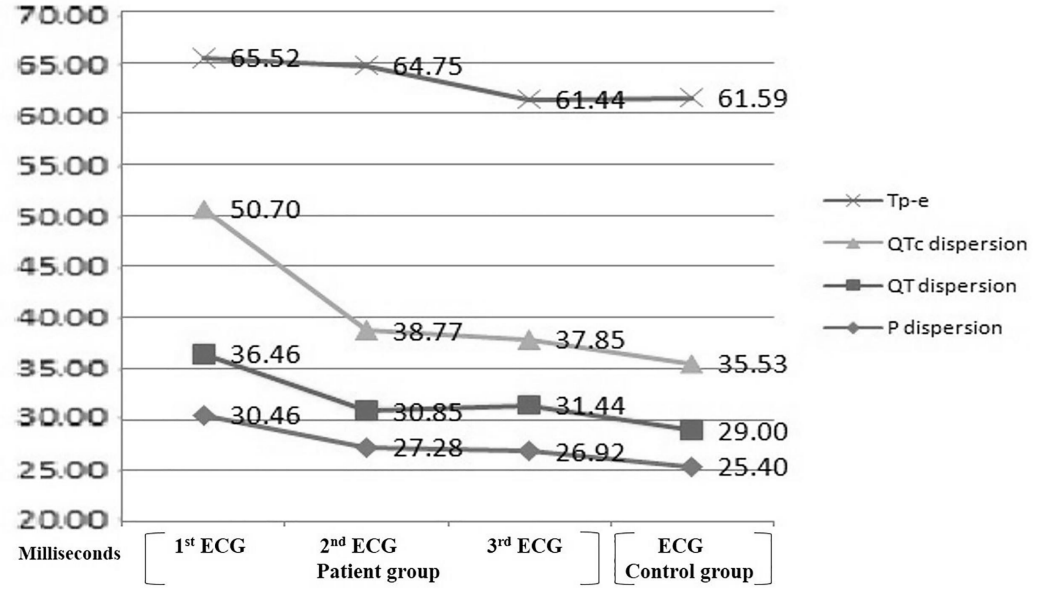

Figure 2 Mean values of Tp-e/QT and Tp-e/QTc ratios in patient and control groups.