



Electrocardiographic changes in children with diabetic ketoacidosis and ketosis

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Abstract

Aim: We aimed to study electrocardiographic changes in children with diabetic ketoacidosis and ketosis and to evaluate the relation of the changes with serum electrolyte levels and ketosis.

Material and Methods: This study was performed in Istanbul Medical Faculty, Pediatric Emergency and Intensive Care Department between May 2008 and May 2009. The electrocardiographic parameters and QT length of children with diabetic ketoacidosis and ketosis were evaluated at diagnosis and after the treatment.

Results: Forty patients were included in the study; 16 (40%) were diagnosed as having diabetic ketosis and 24 (60%) had diabetic ketoacidosis. Twenty-four (60%) patients were male and 16 (40%) were female and the mean age was 9.21±4.71 years (range, 1-16 years). Twelve (30%) cases of diabetic ketoacidosis were mild, three (7.5%) were moderate, and nine (22.5%) were severe. One patient had pre-

mature ventricular beats, and four had ST depression. The electrocardiographic parameters were all normal beyond the QTc length prolongation. The mean QTc length was 447±45 ms (380-560 ms) at diagnosis and 418±32 ms (350-500 ms) after treatment. The change in the QTc length was statistically significant. None of the patients had significant electrolyte disturbance and the prolongation of QTc length was not correlated with serum electrolyte levels. The prolongation of QTc length was statistically correlated with anion gap ($r=0.33$, $p=0.03$).

Conclusions: In our study, we showed QTc length prolongation and the importance of performing electrocardiography during the diagnosis of diabetic ketoacidosis and ketosis. We also demonstrated that ketosis was responsible for the prolongation of QTc length.

Keywords: Diabetic ketoacidosis, electrocardiography, ketosis, QTc length

Introduction

Diabetic ketoacidosis (DKA), which is an acute complication of type 1 diabetes, is characterized by hyperglycemia, metabolic acidosis, and ketonemia. Diabetic ketoacidosis develops as a result of insulin deficiency and increased epinephrine, glucagon, cortisol, and growth hormone. The cardiovascular complications of diabetic ketoacidosis have been known for a long time. Cardiovascular complications including cardiac arrhythmia, acute myocardial infarction, and cardiac arrest may be observed during diabetic ketoacidosis, and this leads to mortality with a rate of 2-10% (1, 2).

Arrhythmia and cardiac arrest have also been described during DKA in children. Prolongation of the QTc interval is an important electrocardiographic (ECG) finding, which is observed frequently in DKA and leads to a risk of sudden death. It is thought that it generally develops secondary to electrolyte imbalance as with the other cardiac complications of diabetic ketoacidosis (3, 4).

QTc prolongation is also observed in ketogenic conditions other than diabetic ketoacidosis. For example, QTc prolongation has been reported in children with epilepsy treated with a ketogenic diet without electrolyte imbalance (4). In these children, a signif-

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icant correlation was shown between QTc prolongation and beta hydroxybutyrate and systemic acidosis. Sudden death and QTc prolongation have also been reported during low carbohydrate diets in adults (4). It is thought that direct effect on cardiac repolarization is responsible for QTc prolongation in the ketogenic process (5, 6).

In this study, we aimed to determine QTc prolongation and other changes that might develop on ECG during DKA or diabetic ketosis (DK) and the correlation of these changes with serum electrolytes and ketoacidosis in patients with diabetes mellitus.

Material and Methods

Patients: Forty patients aged between 1 and 16 years (mean age: 9.21 ± 4.71 years) who presented to Istanbul University Faculty of Medicine Department of Pediatrics, Pediatric Emergency and Intensive Care Unit, with a diagnosis of diabetic ketosis and ketoacidosis were included in the study.

Sixteen of the patients had a diagnosis of DKA and 24 had a diagnosis of DK. Patients who presented because of ketosis and metabolic acidosis other than diabetes were not included in the study. Patients who were using drugs that could lead to electrocardiographic changes were excluded from the study.

Physical examinations were performed on the patients who presented to Istanbul University Faculty of Medicine, Department of Pediatrics, Pediatric Emergency Unit at presentation. The patients' identity data, sex, birth date, weight, height, body mass index, symptoms, consciousness state, dehydration findings, and DKA degrees were recorded. The study was approved by Istanbul Medical Faculty Local Ethics Committee (Project number: 2009-159). Written informed consent was obtained from children who were aged above 12 years and from all parents.

The diagnosis of diabetic ketoacidosis was made with hyperglycemia (200 mg/dL), acidosis (pH <7.3), decreased sodium bicarbonate level (<15 mEq/L), glycosuria, and ketonuria. Acidosis grading was made with pH and bicarbonate levels in blood gas tests. Patients with a venous pH value of 7.30-7.2 and a bicarbonate value of 10-15 mmol/L were considered to have mild acidosis, patients with a pH value of 7.20-7.10 and a

bicarbonate level of 5-10 mmol/L were considered to have moderate acidosis and patients with a pH value of <7.1 and a bicarbonate value of <5 mmol/L were considered to have severe acidosis (7).

Plasma glucose, sodium, potassium, chloride, calcium, phosphorous, magnesium levels and pH, and sodium bicarbonate and anion gap in venous blood gas tests were measured in all patients at the time of diagnosis. The anion gap was calculated using the formula: Anion Gap = $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$, and the normal value was considered <10. Serum osmolality values and corrected sodium levels were calculated. Urine density and presence of ketonuria and glucosuria were evaluated in complete urinalysis. The amount of ketone in urine was not measured.

Electrocardiographic examination: Twelve-derivation electrocardiography with a speed of 25 mm/h was performed initially in the patients who were included in the study (Philips 2008 Seattle, WA, USA). The second electrocardiographic assessment was performed when acidosis and metabolic values recovered. The PR interval, QT and RR time, QRS time, and cardiac rate were calculated on an ECG paper on which the interval between two thin lines was 0.04 seconds and the interval between two horizontal lines was 1 mm. The QTc time was calculated using the Bazett formula by measuring the time from the beginning of the QRS complex to the end of the T wave and dividing this to the square root of the RR interval. The heart rate was calculated by dividing 1500 to the RR interval. The widths, heights, and characteristics of the P and T waves were evaluated and the cardiac axes were specified. All ECGs were evaluated by a pediatric cardiologist in terms of presence of arrhythmia. All procedures were repeated on ECG samples after acidosis and ketosis.

Statistical Analysis

Statistical analyses were performed using the SPSS 15.0 for Windows program. The Shapiro-Wilk test was used for analysis if the data were compatible with the normal distribution in the statistical analyses. The Wilcoxon test was used to analyze matched sequences. The correlations between the variables were examined using Spearman's correlation analysis. Descriptive values are expressed as mean \pm standard deviation (SD), and minimum+maximum value. A p value of <0.05 was considered statistically significant.

Results

Forty patients were included in the study. The ages of the patients ranged between 1 and 16 years and the mean age was found as 9.21 ± 4.72 years. Twenty-four (60%) of the patients were male and 16 (40%) were female. Sixteen (40%) of the patients had a diagnosis of diabetic ketosis and 24 (60%) had a diagnosis of diabetic ketoacidosis. Thirty-six (90%) patients had been diagnosed newly diagnosed and four (10%) had been diagnosed before and were being followed up in our hospital. Twelve (30%) of the patients with diabetic ketoacidosis were affected mildly, three (7.5%) were affected moderately, and nine (22.5%) were affected severely. Intravenous fluid treatment was given to 27 (67.50%) of the patients and oral fluid treatment was given to 13 (32.5%) patients. Intravenous fluid treatment was continued until the picture of ketoacidosis recovered (sodium bicarbonate >18 mEq/L). The mean treatment period was 9.96 ± 4.30 hours. Intravenous bicarbonate treatment was administered in seven (17.50%) patients who had severe ketoacidosis ($\text{pH} < 6.90$ and sodium bicarbonate < 5 mEq/L).

Laboratory Findings

The mean blood glucose value was found as 422 ± 103.66 mg/dL, 133.72 ± 4.51 mmol/L for sodium, 138.88 ± 4.40 mmol/L for corrected sodium, 4.27 ± 0.58 mmol/L for potassium, 98.90 ± 4.53 mmol/L for chloride, 9.7 ± 0.69 mg/dL for calcium, 3.60 ± 1.11 mg/dL for phosphorus, and 2.12 ± 0.20 mg/dL for the level of magnesium in the patients who participated in the study.

In the blood gas test, the mean venous pH level was found as 7.23 ± 0.16 , the mean sodium bicarbonate level was 14.64 ± 6.49 mmol/L, and the mean anion gap was 20.56 ± 6.14 mmol/L.

Electrocardiographic Findings

The mean heart rate was found as 112.00 ± 29.22 beats/min at the time of diagnosis (min-max: 68-187 beats/min) and 97.10 ± 25.86 beats/min after treatment (min-max: 58-167 beats/min). The change in the heart rate was found to be statistically significant ($p < 0.0001$).

The mean PR interval period was found as 148 ± 23 ms (min-max: 120-200 ms) at the time of diagnosis and 135 ± 19 ms after treatment (min-max: 120-200 ms). Although the PR interval period was within

the normal limits in both periods, the change in the PR interval was found to be statistically significant ($p < 0.0001$).

The mean QRS complex time was measured as 70 ± 15 ms before treatment (min-max: 40-120 ms) and 63 ± 16 ms after treatment (min-max: 40-120 ms). Although the QRS complex time was within the normal limits in both periods, the change in the QRS complex time was found to be statistically significant ($p < 0.0001$).

The cardiac axis was measured as $64.22 \pm 17.15^\circ$ (min-max: $10-89^\circ$) before treatment and $67.75 \pm 19.35^\circ$ after treatment (min-max: $10-120^\circ$). Although both results were within the normal limits, the change was found to be statistically significant ($p < 0.0001$).

The mean P wave height was found as 0.91 ± 0.32 mm (min-max: 0.5-1.5 mm) on the initial ECG at the time of diagnosis and 0.80 ± 0.25 mm (min-max: 0.5-1.5 mm) after treatment. The mean P wave heights were found as normal on both ECGs. However, this change was found to be statistically significant ($p = 0.01$).

The mean P wave width was found as 86 ± 133 ms (min-max: 40-900 ms) on the initial ECG and 77 ± 118 ms (min-max: 30-800 ms) on the follow-up ECG. This change was found to be statistically significant ($p = 0.003$).

The mean Q wave voltage was found as 0.40 ± 0.28 mm (min-max: 0.1-1 mm) before treatment and 0.44 ± 0.27 mm (min-max: 0.1-1 mm) after treatment. The change in the mean Q wave voltage was not statistically significant ($p = 0.18$).

The mean R/S ratio was found as 0.63 ± 0.48 (min-max: 0.2-2) before treatment and 0.53 ± 0.41 (min-max: 0.2-2) after treatment. This change in the mean R/S ratio was found to be statistically significant ($p = 0.008$).

The mean QTc time was found as 447 ± 45 ms (min-max: 380-560 ms) at the time of diagnosis and 418 ± 32 ms (min-max: 350-500 ms) after treatment. The initial QTc time was found to be at the upper limit of normal and the follow-up values were found to be within the normal limits. The change in the QTc time (30 ms) was found to be statistically significant ($p < 0.0001$).

Table 1. Evaluation and comparison of the electrocardiographic data belonging to the patients

	Pretreatment	Posttreatment	p
Heart rate (m±SD) beats/min minimum-maximum	112.0±29.22 68-187	97.10 ± 25.86 58-167	<0.0001
PR interval (ms) (m±SD) minimum-maximum	148±23 120-200	135±19 120-200	<0.0001
QRS time (ms)(m±SD) minimum-maximum	70±15 40-120	63±16 40-120	<0.0001
QTc time (ms) (m±SD) minimum-maximum	447±45 380-560	418±32 350-500	<0.0001
QRS axis (ms) (m±SD) minimum-maximum	64.22±17.15 10-89	67.75±19.35 10-120	0.005
P wave length (mm)(m±SD) minimum-maximum	0.91±0.32 0.5-1.5	0.80±0.25 0.5-1	0.013
P wave width (ms)(m±SD) minimum-maximum	86±133 40-900	77±118 30-800	0.003
Q voltage (mm) (m±SD) minimum-maximum	0.40±0.28 0.1-1	0.44±0.27 0.1-1	0.180
R/S ratio (m±SD) minimum-maximum	0.63±0.48 0.2-2	0.53±0.41 0.2-2	0.008

m±SD: mean±standard deviation

Table 2. Relationship of the serum variables with the QTc interval

	Correlation coefficient	p
Serum glucose	-0.139	0.391
Serum sodium	0.238	0.139
Serum corrected sodium	0.207	0.199
Serum potassium	-0.008	0.962
Serum chloride	0.097	0.552
Serum calcium	-0.275	0.085
Serum phosphorous	-0.220	0.172
Serum magnesium	0.068	0.675
pH	-0.227	0.159
Bicarbonate	-0.220	0.173
Base excess	-0.231	0.152
Anion gap	0.395	0.012

ECG assessments before and after treatment and the comparison of the data are shown in Table 1.

The QTc time was found as 450 ms and above in 15 of 40 patients (min-max: 450-560 ms). All patients who were found to have prolonged QTc interval had been diagnosed newly. Twelve of these patients had a diagnosis of DKA and three had a diagnosis of DK. Among the patients who had a diagnosis of diabetic ketoacidosis, five (41.6%) were classified as having mild DK, two (16.6%) had moderate DK, and five (41.6%) were classified as having severe DK. Intravenous sodium

bicarbonate treatment had to be administered in five patients.

Hypokalemia (a serum potassium level below 3.5 mmol/L) was present in only four children at the time of diagnosis (min-max: 2.8-3.2 mmol/L). The QTc interval was above 450 ms in two of the four children who had hypokalemia. ECG findings were found to be normal in the other two patients.

The serum calcium level was found to be below 8.8 mg/dL in three children (min-max: 8.5-8.6 mg/dL). The QTc interval was prolonged in two of these patients (QTc: 460 and 560 ms).

Arrhythmia was not observed on ECG except for a slight depression in the ST segment in four patients who were found to have a prolonged QTc intervals. After treatment, the QTc interval continued to be above 450 ms in only four patients (10%); the QTc interval was slightly prolonged (min-max: 460-489 ms). Repeated ECGs revealed normal sinus rhythm and a QTc interval below 450 ms in three patients.

The correlation of prolonged QTc interval with the variables of serum electrolytes, blood gases, and anion gap was evaluated. Prolongation of the QTc interval showed no correlation with serum potassium levels ($p=0.751$). The QTc interval showed no correlation with

Table 3. Prolongation of QTc in patients with diabetic ketoacidosis and diabetic ketosis

	Diabetic ketosis		Diabetic ketoacidosis		p
	n	%	n	%	
QTc prolongation					
Yes	13	81.3	12	50.0	0.046
No	3	18.8	12	50.0	

Table 4. Prolongation of QTc according to the degree of diabetic ketoacidosis

	Mild		Moderate		Severe		p
	n	%	n	%	n	%	
QTc prolongation							
Yes	7	58.3	1	33.3	4	44.4	0.742
No	5	41.7	2	66.7	5	55.6	

serum glucose levels ($p=0.39$), serum sodium ($p=0.203$), serum corrected sodium ($p=0.305$), serum calcium ($p=0.063$), serum phosphorous ($p=0.165$), serum magnesium ($p=0.483$), serum chloride ($p=0.817$), bicarbonate ($p=0.304$), and serum pH ($p=0.404$) levels. A positive significant correlation was found between prolonged QTc interval and high anion gap ($r=0.336$, $p=0.034$). The relationship of the serum variables with QTc interval is shown in Table 2.

Heart rate was found to be increased at the time of DKA and DK in all patients. Heart rate was found to be within the normal limits after treatment. No significant correlation was found between increased heart rate and prolongation of the QTc interval. The heart rate correlation coefficient before treatment (p) was found as 0.104 ($p=0.524$) and 0.077 ($p=0.638$). These values were not statistically significant.

Prolongation in the QTc interval during diabetic ketoacidosis (450 ms and above) was found to be greater compared with DK and this result was statistically significant ($p=0.046$) (Prolongation in the QTc interval during DKA and DK is shown in Table 3).

No statistically significant correlation was found between prolongation in the QTc interval and the degree of ketoacidosis during diabetic ketoacidosis ($p=0.742$) (Prolongation in the QTc interval by the degree of diabetic ketoacidosis is shown in Table 4).

Discussion

Arrhythmia, acute myocardial infarction, and sudden death may be observed during diabetic ketoacidosis. Acute cardiac complications observed in diabetic ke-

toacidosis have generally been attributed to electrolyte imbalance. Hypokalemia, hyperkalemia, hypocalcemia, hypophosphatemia, and hypomagnesemia may develop in diabetic ketoacidosis (8). Hypokalemia is the most commonly observed electrolyte imbalance and most frequently leads to fatal arrhythmia. Hypokalemia at the time of diagnosis was observed in only four of our patients and the severity of hypokalemia was low. Ventricular premature beat on ECG was found in only one patient who had hypokalemia. ECG assessments were found to be normal in four children who were found to have hypokalemia and in four children whose corrected sodium level was found to be low.

ST segment change is an important finding during diabetic ketoacidosis. ST segment change has even been reported on fetal ECGs in pregnant women with diabetic ketoacidosis (9). Slight ST segment depression developed during DKA in only four of our patients and there was no significant correlation between ST segment depression and heart rate.

Another ECG change that develops during diabetic ketoacidosis and carries a risk for sudden death is prolongation of the QTc interval, which is related with increased risk for ventricular arrhythmia including especially Torsades de Pointes (10). In 2008, Kuppermann et al. (4) evaluated QTc prolongation during DKA and normalization after ketoacidosis.

In our study, QTc prolongation was described during DKA and DK in 15 of 40 patients. After treatment, QTc prolongation continued in three patients. The mean QTc interval in these patients was found to be 460 ms

and they had no symptoms. Follow-up was terminated in these patients in accordance with the Schwartz criteria (11) (they were asymptomatic, had no family history of sudden death and hearing loss, and follow-up ECGs revealed no bradycardia or T wave changes).

In our study, the relationship between QTc prolongation and electrolytes was evaluated. The QTc interval was prolonged in two of four children who developed hypokalemia and in only one of three children who were hypocalcemic. There was no significant correlation between QTc prolongation and electrolyte changes. However, the QTc interval was found to be positively correlated with anion gap and low pH ($p=0.03$).

Many studies have been conducted in relation with the presence and importance of QTc prolongation in diabetes (1, 4, 9). QTc prolongation may be observed in children with long-term diabetes in the absence of ketoacidosis. Diabetic autonomic neuropathy may affect many organs including the cardiovascular system. Cardiac autonomic neuropathy (CAN) consists of sympathetic and parasympathetic dysfunction and it is known to lead to sudden death in adults. QTc interval has been used to demonstrate CAN in adults rather than prolonged ventricular depolarization and repolarization (12). Marthur et al. (13) conducted a study with 50 asymptomatic adult patients with diabetes in 2006 and found findings of CAN in 19 patients; QTc prolongation was found in 15 of these patients.

Whether cardiac autonomic neuropathy might lead to sudden death by prolonging the QT interval has also been examined in children. In the study conducted by Bert et al. (14) in 2002 with 60 children with diabetes, the QTc interval was found above 440 ms in 14 patients. Prolongation in QT interval was attributed to cardiac autonomic neuropathy. Alteration in diastolic ventricular function and diabetic cardiomyopathy have been reported in patients with diabetes. Increased afterload is thought to lead to prolonged QTc. Cardiac autonomic neuropathy has also been shown in patients with newly diagnosed diabetes. Verotti et al. (15) showed CAN in 10 of 55 children aged 10.3-20.7 years with newly diagnosed diabetes who had no ketoacidosis.

Experimental studies directed at explaining QTc interval in diabetes have been reported. Chen et al. (16) observed an increase in α_1 adrenoreceptor in the

hearts of experimental mice that developed diabetes and predicted that this could be responsible for QTc prolongation. Lengyel et al. (17) found a decrease in slow potassium channels in mice that were observed to have QTc prolongation.

QTc prolongation is also observed in the other clinical conditions leading to ketoacidosis in addition to diabetic ketoacidosis and DK. QTc prolongation may be observed in ketoacidosis that develops during long-term fasting, rapid weight loss following a strict diet, obesity, alcoholism, and ketogenic diets. Metabolic complications have been reported during ketogenic diet therapy including high fat, low carbohydrate, and low protein, which is used for treatment of resistant convulsions (4-6). Best et al. (5) observed QTc prolongation in three of 20 patients with epilepsy who were given ketogenic diet therapy. In these patients, QTc prolongation was found to be positively correlated with low carbohydrate levels and increased beta-hydroxybutyrate levels. Reduction in any other electrolyte or in selenium was not found. Normalization of the QTc interval with termination of ketogenic diet suggests the importance of ketosis and acidosis in the pathophysiology. In our study, a positive correlation was found between anion gap and QTc interval, though ketone levels could not be determined.

The QTc interval also prolongs during acute hyperglycemia. Gordin et al. (18) performed ECG assessments following 120-minute hyperglycemia in 22 adult patients with type 1 diabetes and 13 healthy individuals. They found that acute hyperglycemia prolonged QTc both in diabetics and in healthy individuals. Acute hyperglycemia predisposes ventricular fibrillation by leading to an increase in cytosolic calcium concentrations in myocytes and a decrease in extracellular calcium concentrations. Acute hyperglycemia causes cytotoxic action by increasing sympathetic activity, which leads to oxidative stress. In our patients, a significant correlation between hyperglycemia and QTc prolongation was not found.

Our study showed that QTc prolongation occurred during DKA and DK. When the picture of ketoacidosis improves, QTc normalizes to a great extent. Cardiac functions are affected during diabetic ketoacidosis. Therefore, ECG should be obtained during DKA, the heart rhythm should be evaluated, and the QTc interval should be calculated.

Our study has some deficiencies and limitations. A positive correlation between ketosis and QTc prolongation could not be demonstrated because serum ketone levels could not be measured. On the other hand, the pathogenesis of QTc prolongation was not studied, though a correlation between ketosis and QTc prolongation was demonstrated. In addition, the heart rates of the patients were not the same on both ECGs. Most patients had tachycardia during DKA. QT dispersion was not examined in our patients; however, the QTC interval was calculated by applying correction according to the heart rate. QT dispersion is calculated by subtracting the minimum QT interval from the maximum QT interval. It has been proposed to differentiate between myocardium showing non-homogeneous conduction from myocardium showing homogeneous conduction. This parameter was developed as an indicator of spatial dispersion of ventricular recovery times. However, it is also thought that QT dispersion does not directly reflect dispersion of recovery times and arises from changes in T wave morphologies and errors in calculations of QT interval (19). Besides, QTc changes during ketoacidosis in our study are remarkable because the formula in the calculation of QTc interval is standard and there is no significant correlation between heart rate and QTc interval.

In conclusion, QTc prolongation, which may lead to sudden death, may be observed during DKA and DK. Therefore, ECG evaluation is important during treatment. In addition, ECG should also be evaluated during other ketotic events in addition to diabetes because ketosis and ketoacidosis are responsible for QTc prolongation.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethics committee of İstanbul University İstanbul Medical Faculty (2009-159).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

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