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ORIGINAL ARTICLE

The effect of diabetic ketoacidosis in childhood on heart rate variability: Prospective study

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ABSTRACT

Objective: The study aims to investigate the changes caused by diabetic ketoacidosis (DKA) on heart rate variability (HRV).

Material and Methods: This prospective study was conducted at a tertiary referral center. It is investigated patients with DKA under 18 years old between May 2016 and December 2016. 24-h rhythm Holter electrocardiography recorded during DKA and upward 72nd h after ketoacidosis.

Results: A total of 18 patients with DKA were included in the study in the age range of 1 month–18 year. Repeat Holter electrocardiography recording in the patients took place within an average of 4.6±1.1 days. Heart rate change parameters were found to be shorter at the time of DKA. A statistically significant difference was observed between the values of HRV.

Conclusion: It is an important factor affecting the development of cardiac autonomic neuropathy at acute blood glucose elevation such as DKA.

Keywords: Cardiac autonomic neuropathy, diabetes mellitus, diabetic ketoacidosis, heart rate variability.

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INTRODUCTION

Diabetic ketoacidosis (DKA) is a condition that has high ketone body levels in the blood, dehydration, and acidosis, associated with significant morbidity and mortality. Even in developed countries, DKA rates in the diagnosis of type 1 diabetes mellitus seem to be between 11 and 80%.[1,2] The risk of DKA after type 1 diabetes mellitus in children is 1–10/100 person-years.[1]

Neuropathy is a common complication in (15–35%) diabetes mellitus.[3] Cardiac autonomic neuropathy is the most common clinically seen diabetic autonomic neuropathy.[3] The main reason for starting the study on the pathogenesis of cardiac autonomic neuropathy is hyperglycemia.[3] Clinical manifestations of cardiac autonomic neuropathy may range from latent signs such as nocturnal hypertension with non-dipping to signs of resting tachycardia, exercise intolerance and more severe signs such as orthostatic hypotension, electrocardiography abnormalities, or even silent myocardial infarction.[3]

Heart rate variability (HRV) is the most commonly used method to detect cardiac autonomic neuropathy. HRV is the physiological interval between the interaction of sympathetic and parasympathetic fibers and heartbeat. The beat-to-beat variation is the body's functional response to metabolic needs. High HRV reflects the adaptability of healthy people, it decreases in those with the damaged autonomic nervous system.[4] The earliest finding of cardiac autonomic neuropathy is the decrease in HRV, which can be seen even in the subclinical stage.[4] In type 1 diabetes, risk factors for cardiac autonomic neuropathy are high glycolyzed hemoglobin, hypertension, distal symmetrical polyneuropathy, retinopathy, and poor glycemic regulation.[4]

An important reason for the development of cardiac autonomic neuropathy is impaired long-term blood glucose control. However, HRV has not been previously investigated in acute blood glucose regulation disorders such as DKA. The study aims to investigate the changes caused by DKA on HRV.

MATERIAL AND METHODS

This prospectively study was conducted at a tertiary referral center (Emergency Department of Doctor Behçet Uz pediatrics education and research hospital). It is investigated patients with DKA under 18 years old between date May 2016 and December 2016. Sample size analysis in this study was performed in the light of the study performed by Sasaki et al.[5] The lowest sample size was calculated using the G power analysis program (Faul, Erdfelder, Lang, and Buchner, 2007; version 3.0) with the 80% power and 0.05 type-1 error as 14 patients.[5] The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The ethics committee approval for the study was obtained from Doctor Behçet Uz Pediatrics Education And Research Hospital (2016/0605). Written informed consent was obtained from all patients before the study procedures.

A total of 18 patients with DKA were included in the study between May and December 2016 in the age range of 1 month-18 year. 24-h rhythm Holter electrocardiography recorded during DKA and upward 72nd h after ketoacidosis. HRV examinations of 18 patients presenting at the time of DKA were compared with the values of the same patients 72 h after exiting ketoacidosis. The diagnosis of DKA was made considering the diagnostic criteria of the American Diabetes Association.[6] DKA consists of the biochemical triad of hyperglycemia, ketonemia, and high anion gap metabolic acidosis. It is classified according to various parameters including arterial pH, serum bicarbonate (mEq/L), urine ketone, serum ketone, serum osmolality, and anion gap. We did not make this classification in our patients. We considered patients with hyperglycemia (blood sugar >200), increased anion gap (>10), and ketonemia as DKA. Blood power of hydrogen value, serum bicarbonate (mEq/L) and plasma glucose value (mg/dL), complete urine test, urine ketone, glycolyzed hemoglobin (%), triglyceride (mg/dL), cholesterol (mg/dL), high-density lipoprotein (mg/dL), low-density lipoprotein (mg/dL), urinary protein/creatinine levels besides demographic data, self and pedigree backgrounds, diabetes duration and vital signs, and body mass index values of patients were evaluated. The samples obtained for blood gas measurement were delivered to Doctor Behçet Uz Pediatrics Education and Research Hospital laboratory under cold chain conditions with special injectors containing heparin and studied using the ABL90 FLEX® (Radiometer Medical ApS, Åkadevej 21, DK-2700Brønshøj, Denmark) instrument. The ketone level was determined using the LabStrip U11 Plus GL® strips on the fresh sample for urine ketone measurement. In the test strip, 1, 2, and 3 positive results correspond to 1.5, 5, and 15 mmol/L ketone, respectively.

Insulin dosage in DKA was regulated as such. Children under the age of three started at a dose of 0.05 units/kg/h, however, in children over 3 years, it started at units/kg/h. Sodium chloride 0.45%, additional insulin infusion 20 mEq/L from the 2nd h until DKA improves (total carbon dioxide >15 mEq/L, power of hydrogen >7.30, sodium value is stable between 135 and 145 mEq/L, vomiting) it was continued. A 5% dextrose infusion was also added when the blood glucose level was <250 mg / dL. In the period when DKA improved, oral intake and subcutaneous insulin were started. Intravenous fluids were closed and the first dose of subcutaneous insulin was given with the meal. The first intravenous bolus was evaluated as part of the total daily dose for the first 24 h. Calculation of the amount of fluid to be taken in 24 h for maintenance; 100 mL/kg (for the first 10 kg) +50 mL/kg (for second 10 kg) +25 mL/kg (for the remaining kg). Until DKA was resolved, blood glucose monitoring was taken every 60 min, blood gas was taken every 120 min, and power of hydrogen and bicarbonate were evaluated.

Patients underwent continuous electrocardiography monitoring (SCHILLER MT-200) for 24 h. Time-domain HRV parameters were evaluated using Risingmed- electrocardiography software (version CV-4L), in accordance with the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). In the time domain, we measured the mean R–R interval (NN), the standard deviation of the R–R interval index (SDNN), the standard deviation of the 5-min R–R interval mean (SDANN), the root mean square of successive R–R interval differences (RMSSD) and the percentage of beats with a consecutive R–R interval difference >50 ms (pNN50). SDNNi, the mean of the 5-min standard deviation of the R-R interval calculated over 24 h. All ECGs were evaluated by pediatric cardiologists (T.M. and C.K.).

The distribution of numerical data was evaluated using Shapiro-Wilk analysis and related distribution plots. Descriptive data were expressed in mean and standard deviation, and number and percentage. For variables demonstrating a highly skewed distribution, the

Table 1: Demographic data of the study group

Gender, n (%)	
Female	12 (66.7)
Male	6 (33.3)
Initial diagnosis	10 (55.6)
Patient with follow-up	8 (44.4)
Chronic illness, n (%)	
None	16 (88.9)
Asthma	1 (5.6)
Depression	1 (5.6)
Age, months, Mean±SD	138.5±45.5
Weight, kilogram, Mean±SD	40.1±16.6
Height, centimeter, Mean±SD	147.2±18.6
Glycolyzed hemoglobin (HbA1c), Mean±SD	11.2±1.5
Hemoglobin (million/nanoliter), Mean±SD	14.3±1.3
Free Triiodothyronine (fT3) (picogram/milliliter), Mean±SD	1.9±0.4
Free Thyroxine (fT4) (nanogram/deciliter), Mean±SD	1.0±0.1
Thyrotropin (TSH) (milliliters/liter); Mean±SD	2.1±0.9

SD: Standard deviation.

Wilcoxon rank-sum test was performed. For variables demonstrating a normal distribution, the paired t-test was performed. In the analysis of the nominal data between two groups, Chi-square or fisher-exact analysis was applied as occasions required. Statistical analysis was performed using the Statistical Package for Social Science for Windows version 21.0 software (IBM Corp., Armonk, NY, USA). A $p<0.05$ was considered statistically significant.

RESULTS

The demographic data and clinical features of the patients are given in Table 1. Although 2 patients had DKA, they were not included in the study because they had been followed up for arrhythmia before. Ten patients (55.6%) who applied with the diagnosis of DKA were new patients who were not yet diagnosed with type 1 diabetes mellitus. Eight patients (44.4%) were previously diagnosed with type 1 diabetes mellitus and were followed up with insulin therapy. Patients previously diagnosed with type 1 diabetes mellitus had been followed for an average of 46.5 months. The patients exited from the DKA at an average of 496.6±318.6 min after starting treatment. Repeat Holter electrocardiography recording in the patients took place within an average of 4.6±1.1 days. The values of the criteria required for the diagnosis of DKA in DKA and control time are compared in Table 2.

HRV parameters of the patients, which were examined during the DKA and at the time of control, are compared in Table 3. A statistically significant difference was observed between the values of SDNN, SDANN, the RMSSD, and the percentage of beats with a consecutive R–R interval difference >50 ms and the mean of the 5-min standard deviation of the R-R interval calculated over 24 h. Heart rate change parameters were found to be shorter at the time of DKA.

Table 2: Comparison of parameters between groups

	DKA	Control	p
Blood urea nitrogen (mg/dL)	13.8±6.1	10.2±3.6	0.012[a]
Creatinine (mg/dL)	1.0±0.2	0.7±0.1	0.001[b]
pH	7.1±0.1	7.4±0.1	<0.001[a]
Bicarbonate (mEq/L)	9.3±3.3	21.3±7.2	<0.001[a]
Blood glucose (mg/dL)	511.7±135.6	160.0±49.4	<0.001[b]
Glycosuria*	3.2±0.6	2.0±1.1	0.005[b]
Ketonuria*	2.9±0.3	0.6±0.5	<0.001[b]

a: Paired t-testi; b: Wilcoxon testi; *: Stick urine test; DKA: Diabetic ketoacidosis; mg/dL: Milligrams/deciliter; mEq/L: Milliequivalents/liter.

Table 3: Comparison of heart rate variability data between groups

	DKA	Control	p
SDNN (ms)	70.1±32.3	114.4±26.0	<0.001[a]
SDANN (ms)	66.5±29.9	104.9±28.6	0.001[a]
SDNNi (ms)	30.0±14.2	51.4±11.5	<0.001[a]
rMSSD (ms)	18.2±12.2	32.3±13.0	<0.001[a]
pNN50 (%)	4.0±7.2	10.9±9.3	0.001[b]
VE	193.9±261.0	346.9±495.8	0.184[b]
SVE	80.6±150.5	55.6±69.2	0.257[b]

a: Paired T testi; b: Wilcoxon testi; DKA: Diabetic ketoacidosis; SDNN: The standard deviation of the R–R interval index; SDANN: The standard deviation of the 5-min R–R interval mean; SDNNi: Arithmetic mean of standard deviations of the 5-min R-R intervals; rMSSD: The root mean square of successive R–R interval differences; pNN50: The percentage of beats with a consecutive R–R interval difference >50 ms; ms: Millisecond; VE: Ventricular ectopic beat; SVE: Supraventricular ectopic beat; h: Hour.

DISCUSSION

In this prospective study, the HRV values of the patients with DKA and the repeat HRV values after excluded from the DKA (at least 72 h) were compared. HRV parameters were found to be significantly shorter at the time of DKA. High HRV reflects the ability of healthy people to adapt, and HRV has been shown to decrease in those with the damaged autonomic nervous system. It is known that the decline of HRV leads to fatal arrhythmias in older ages. HRV is one of the early diagnostic methods for cardiac autonomic neuropathy, a type of neuropathy, which is a chronic complication of type 1 diabetes in patients with Type 1 diabetes mellitus.[3–5] Previous work in the literature investigated the effects of poor long-term glycemic control on HRV.[7,8] However, to our knowledge, this is the first study to investigate to effected on HRV of DKA.

HRV is a simple noninvasive clinical test that shows a 24-h electrocardiography record that provides an independent measure of the sympathetic and parasympathetic components of the autonomic nervous system. Another simple and non-invasive marker to predict cardiovascular risk is QT corrected (QTc).[9] In a retrospective study conducted by Perez et al.,[10] 96 DKA patients in the pediatric age group were retrospectively examined and QTc prolongation was found in 31% of them. In this study, QTc prolongation was found to be related to the degree and anion gap of DKA, but its severity and anion gap and the relationship were not explained by abnormalities in serum potassium, calcium, and magnesium In this study, it was emphasized that the mechanism of QTc prolongation is not clear and may be related to intracellular electrolyte irregularities in the acidosis environment. Similarly, the mechanism of HRV degradation in ketoacidosis is unclear. It is thought that mitochondrial free radical production is increased due to hyperglycemia-related oxidative stress. Neuronal activity, mitochondrial function, membrane permeability, and endothelial function are affected by the end product of progressive glycation. Changes in polyol aldose reductase signaling and sodium–potassium adenosine triphosphatase pump function and endoplasmic reticulum stress caused by hyperglycemia impair neuronal perfusion, leading to the initiation of the apoptotic process.[11,12] It has been shown that type 1 and 2 diabetes mellitus, and especially poor glycemic control, are a risk factor for the reduction of HRV values and consequently for cardiac autonomic neuropathy.[7,8,13–16] However, some authors argue that glycemic status is not associated with HRV.[17] In the literature, diabetic and non-diabetic similar patient groups considering age and gender for each were compared and the heart rate parameters were found to be significantly shorter in the diabetes group.[13,18–20]

Rigorous glycaemic control—reflected by low glycolic hemoglobin goals—is of the utmost importance in the prevention and management of complications in patients with type 1 diabetes mellitus. However, previous studies suggested that short-term glycaemic variability is also important to consider as excessive glucose fluctuations may have an additional impact on the development of diabetic complications.[3] The potential relationship between glycaemic variability and the risk of cardiovascular autonomic neuropathy, clinical expression of cardiovascular autonomic dysfunction, is of increasing interest.[3] In a study investigating changes in HRV measurements against acute changes, HRV values were significantly shorter in the group with severe hypoglycemic episodes.[21] In this study, no significant difference was found between the glycolyzed hemoglobin levels of these two groups. Therefore, it can be considered that ketoacidosis experienced at the time of DKA is more effective than long-term hyperglycemia exposure on HRV variability in the severe DKA group. In our cohort, HRV values were compared at the time of DKA occurring with acute blood glucose elevation and after DKA. Repeat electrocardiography recording was done at least 72 h after DKA recovered. SDNN, SDANN, the RMSSD, and the percentage of beats with a consecutive R–R interval difference >50 ms and the mean of the 5-min standard deviation of the R-R interval calculated over 24 h values were shorter at DKA than the moment of control. According to this result, acute blood glucose changes were found to be an important factor in the development of cardiac autonomic neuropathy.

Nonetheless, there were some limitations to this study. First, the urine ketone is replaced with the blood ketone to diagnose DKA. This analysis is unfortunately not possible in our hospital. In the second limation, it was not possible to determine the factors, that could cause a decrease in HRV parameters, by performing logistic regression analysis, because of the inadequate number of cases. However, determining the risk factors that may cause a decrease in HRV parameters is not the purpose of this study. The absence of an independent variable group in our study also creates a limitation. Comparing autonomic neuropathy, which may already be present in patients with type 1 diabetes mellitus, with a healthy control group would be statistically more valuable. A large number of cases are needed to be included in the study to meet these needs. Despite these limitations, the similarities of the demographic characteristics in the study population and the reports of expert pediatric cardiologists increased the validity of our results and diminished weaknesses. The availability of good follow-up data also increased the validity of the results and mitigated the weaknesses.

CONCLUSION

It is an important factor affecting the development of cardiac autonomic neuropathy at acute blood glucose elevation such as DKA. The short-term glucose values are as important as the long-term regulation of blood glucose.

Statement

Ethics Committee Approval: The Dr. Behçet Uz Children's Hospital Clinical Research Ethics Committee granted approval for this study (date: 28.04.2016, number: 2016/06-05).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – AG; Design – HA; Supervision – GC; Resource – AG; Materials – HA; Data Collection and/or Processing – CK; Analysis and/or Interpretation – Rİ; Literature Search – ÖN; Writing – AG; Critical Reviews – TM.

Conflict of Interest: The authors have no conflict of interest to declare.

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