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Evaluation of Electrocardiographic Parameters in Diabetes Mellitus Type I in Children and Adolescent

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Abstract

Background
Cardiovascular complications are continuing to be a major cause of morbidity and mortality in diabetes mellitus type I (DMTI). The study aimed to evaluate the rate of changes in ECG parameters in children with DMTI compared with healthy children.

Materials and Methods
This case-control study was performed on 140 participants which consisted of 70 patients with DMTI (case group) matched in sex and age with 70 healthy ones (control group) in two centers in collaboration with Ali Asghar Hospital, Zahedan, Iran, between March 2017 and April 2018. Electrocardiography was performed in all participants (patients and healthy), and heart rate, QT (start of the Q wave and the end of the T wave) QTc interval (QT/ $\sqrt{}$ RR), QTd (dispersion between maximum and minimum of QT), and QTcd (dispersion between maximum and minimum of QTc) were measured. Duration of diabetic and level of HbA1c were obtained for patients and the effects of these parameters on ECGs were investigated.

Results
Height, weight and heart rate were higher in the patients ($P<0.001$) when S in V_1 was higher in case (6.16±3.23) compared to the control group (4.33± 2.22) ($P<0.001$). QT (356.71±27.28 compared to 347.00±23.55), QTd (49.00±14.66 compared to 41.21±8.32), and QTcd (60.47±17.32 compared to 49.93±10.44) were higher in case group ($p<0.05$). Hemoglobin A1C ($p=0.043$) was higher in boys and heart rate was higher in girls ($p<0.001$). Diabetic time duration and HbA_{1c} normality states did not change the length of these parameters in diabetic patients.

Conclusion
Based on the results, QT, QTd, QTc and QTcd were higher in patients with DMTI. Diabetic time duration and HbA1c states did not change the ECG parameters in diabetic patients.

Key Words: Adolescents, Children, Diabetes mellitus, QT changes.

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1- INTRODUCTION

Diabetes mellitus type I (DMTI) is an autoimmune disease with a strong genetic component and is one of the chronic diseases that involves all ages and races of people (1, 2). It occurs at any age, but tends to be developed in childhood, so it has long been called 'juvenile diabetes' (3). DMTI is characterized by destruction of pancreatic β-cells, culminating in absolute insulin deficiency (4). The frequency of diabetes mellitus is estimated as 387 million people worldwide (5), of which DMTI accounts between 5 and 10% in different areas (6). In Iran, the prevalence of DMT1 is 40 in 100,000 (7), and is expected to increase in future (7, 8). Diabetic complications are continuing to be a major cause of morbidity and mortality in DMTI (9). Great efforts have been made to assess the incidence and prevalence of DMTI but unfortunately, the exact etiology and pathogenesis of DMTI is still unknown. Generally, longitudinal or cross-sectional studies are often conducted locally or regionally (10), and consequently, it is difficult to access generalizable results because the epidemiology of DMTI is known to be heterogeneous regarding geography and ethnicity (11).

Diabetes is associated with higher risk of some macro and microvascular complications so that the growing rates of diabetes mellitus (DM) makes a considerable economic burden for both the patient and the healthcare system. Diabetic autonomic dysfunction is a common complication of DMTI and is associated with cardiac autonomic function disorder (CAFD), which is a frequent but less well-known form of this autonomic dysfunction (10). A close link exists between diabetes mellitus and cardiovascular disease (CVD). CVD is the most prevalent cause of mortality and morbidity in diabetic populations even in the general population (12). This increased risk of CVD mortality in diabetic patients is found in both men and women (13). As a result, the mortality rate of diabetic patients with CVD tends to be about twice as much as that of non-diabetic CVD of a similar age (14, 15). In addition, factors including obesity, hypertension and dyslipidemia, increased oxidative stress, coagulation disorders, endothelial dysfunction and autonomic neuropathy are common in patients with DM and may directly contribute to the development of CVD (12). There is increasing evidence that a prolonged corrected QT (QTc) interval is a significant predictor of mortality in DMTI (16), celiac (17), and thalassemia patients (18). Prolonged QTc, and QT dispersion (QTd) are also predictors in reflecting abnormalities of ventricular myocardial repolarization in DMTI subjects and the mentioned diseases (16-18).

Patients who are suffering from many diseases such as heart failure, diabetes types I and II, celiac, thalassemia and QT syndrome are at risk of prolonged QT and its parameters. It has also been shown that QTc length can be used as a predictor like QT of increased mortality rate in DMTI adults (19). In children and adolescents with DMTI, however, there are few studies in terms of QT, QTd, QTc, and QTcd measurement and their effect on autonomic dysfunction. QT dispersion may reflect electrical myocardial inhomogeneity predisposing to ventricular arrhythmia. Moreover, increased dispersion of QT and QTc was detected in some of the recently diagnosed DMTI patients (19, 20). Considering the above mentioned reports and that diabetic autonomic dysfunction is one of the general complications of DMTI that can cause mortality and morbidity (1). Cardiac autonomic function disorder (CAFD), which is one of the most severe complications of diabetes, is a common but less well-known form of this autonomic dysfunction (19), the present

study aimed to evaluate the rate of changes in QT, QTd, QTc and QTcd in children with diabetes mellitus type I compared with healthy children.

2- MATERIALS AND METHODS

2-1. Study Design

This case-control study was performed on 140 participants which consisted of 70 controls (children who referred to hospital for checkup), and 70 patients with diabetes type I. The study was run in two centers in collaboration with the endocrinology and cardiology departments in Ali Asghar Hospital, Zahedan city, Sistan and Baluchestan province (Southeast Iran), between March 2017 and April 2018. Eligible participants were aged 5-18 years old and were referred to the heart clinic after required examinations by endocrinology center. In sampling we attempted to match participants with regards to patients and healthy ones in age and sex.

2-2. Inclusion and Exclusion Criteria

Inclusion criteria were DMT1 patients either symptomatic or asymptomatic. The diabetes was confirmed by clinical manifestations such as polyuria, polydipsia, weight loss, laboratory measures such as fasting blood glucose > 125 mg/dl, and random blood glucose >200 mg/dl (7). However, exclusion criteria were age higher than 18 years, documented evidence of other cardiac disease like ischemic, hypertension, cardiomyopathy, valvular heart disease, and congenital heart disease, and myocarditis, features of hypothyroidism, uremia and random blood sugar > 140 mg/dL for the control group. In addition, participants whose body mass index (BMI) were out of normal range were checked for exclusion. The patients with BMI higher than 95th percentiles were excluded from the study (7).

2-3. Electrocardiography measures

Electrocardiogram (ECG) was detected with an electrocardiogram by Saadat device made in Iran. Electrocardiogram in standard scheme was obtained after patients or controls had rested for 10 min in a supine position in a quiet room. All 12-ECG leads were simultaneously recorded at a paper speed of 25 mm/s and a voltage of 10 mm/mV. The following measurements were made by a single experienced investigator. To evaluate intra observer variation, the same ECG leads were measured twice by the same observer on two separate occasions. QT interval was accepted as the distance from the beginning of the Q wave to the end of the T wave. In the derivations in which T waves were not recognizable, estimation was omitted. When the T wave was notched, if the second notch was smaller than 50% of the first wave, the spot where the first wave had reached the isoelectric line was accepted as the end of the T wave.

In each derivation, the duration from the beginning of the Q wave to the end of the T wave was calculated in milliseconds and their average was taken (QT average) for the consecutive three beats. The maximum and minimum duration of the QT wave was selected from the 12 leads of the surface ECG. The difference between maximum and minimum duration was defined as QTd. Average QTc was calculated using the same QT interval measured using the Bazett formula (QTc= QT/ $\sqrt{}$ RR), and among all derivations, the difference between the longest and the shortest QTc was calculated (QTcd) (17). Three consecutive ventricular heart rates were calculated in lead II and their average was taken and each participants' average heart rate was specified.

2-4. Diabetic measures

Duration time of diabetic and hemoglobin A1c (HbA1c) during follow-up were obtained from patient and recorded. We

grouped the patients according to HbA1c states into two groups and diabetic duration in three groups. HbA1c was measured for all the study participants at three month intervals and according to the mean of the last three HbA1c levels, patients were divided into two groups of normal and abnormal. The grouping was based on the age of patients so that children aged less than 5 years were abnormal with HbA1c levels higher than 9% and for the children aged 5-12 years were abnormal with the level of higher than 8% and for the patients higher than 12 years, the cut point for normality was 7%.

The diabetic duration considered the time between onsets of the diseases and diagnosed by pediatric endocrinology till the time that they referred to the pediatric cardiologist for performing ECG and the patients were grouped into three.

2-5. Anthropometric measurements

The patients' height and weight were measured by an experienced expert using standard equipment. Then, BMI was calculated according to the 2000 sex specific BMI-for-age growth charts of the Centers for Disease Control and Prevention. Participants' height was measured in the standing position with a balance using a scaled ruler and weight was calculated using a RASA scale factor with an error of 100 g (made in Iran).

2-6. Ethical Approval

Informed consent was obtained from all individual participants included in the study after the study approval. The study was approved as a project proposed (ID-code: 7230) to the Children and Adolescent Health Research Center by the Ethics Committee of Zahedan University of Medical Sciences, Zahedan, Iran.

2-7. Data analysis

Data was analyzed by SPSS version 18.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were presented in mean ±SD. Comparisons between DMTI subjects and the controls were done using Mann-Whitney U test. When comparing more than two groups, the Kruskal–Wallis test was used and correlations between the variables were calculated using Pearson's correlation. $P < 0.05$ was considered as significant level.

3- RESULTS

To analyze changes in ECG parameters in the diabetes patients and healthy children, first we used the Kolmogorov-Smirnov test for data distribution in participants and only patients. In participants, all the variables in the study were in free distribution because of the p-value lower than 0.05. In terms of patients, height, weight and heart rate came from normal distribution ($p<0.05$).

Of 70 diabetes patients, 45.7% were boys when this value for the healthy ones was 44.29%. The sex distribution of participants in the diabetes patients and healthy children was not significant and showed a similar consistency of gender in groups of participants.

Table.1 shows the results of the ECG parameters and anthropology indices in the case and control. Participants age ranged from 4 to 18 years and the means of age were 10.67±3.55 and 10.51±3.45 in diabetes patients and healthy children, respectively ($p>0.05$). Height, weight and heart rate were higher in the healthy ones significantly [$p<0.001$ when S in V_1 was higher in patients (6.16 ±3.23 compared to 4.33± 2.22) significantly ($P<0.001$)].

Among the principal values of electrocardiography, QT (356.71±27.28 compared to 347.00±23.55), QTd (49.00±14.66 compared to 41.21±8.32), and QTcd (60.47±17.32 compared to 49.93±10.44) were higher in the case significantly ($p<0.001$). The QTc parameter had the higher value of

436.35±42.67 in the case group and419.79±27.54 in the control and this pattern showed a significant difference (p=0.048).

Table-1: ECG parameters in diabetic and healthy children.

Parameters	Groups	Mean	SD	Mean Rank	Sum of Ranks	MWU	P-value
Age (year)	Patients	10.67	3.55	72.75	5092.50	2292.50	0.509
	Healthy	10.51	3.45	68.25	4777.50		
Height (cm)	Patients	135.81	19.91	51.74	3621.50	1253.50	<0.001
	Healthy	153.17	13.64	89.26	6248.50		
Weight (kg)	Patients	32.00	11.95	53.41	3738.50	2212.50	<0.001
	Healthy	44.13	13.15	87.59	6131.50		
R in V_5 (mm)	Patients	9.27	3.10	73.89	5172.50	2212.50	0.318
	Healthy	8.61	2.62	67.11	4697.50		
S in V_1 (mm)	Patients	6.16	3.23	84.44	5911.00	1474.00	<0.001
	Healthy	4.33	2.22	56.56	3959.00		
Heart Rate (beat/min)	Patients	91.89	16.23	58.56	4099.50	1614.50	<0.001
	Healthy	100.41	20.68	82.44	5770.50		
QT (ms)	Patients	356.71	27.28	80.24	5616.50	1768.50	0.004
	Healthy	347.00	23.55	60.76	4253.50		
QTd (ms)	Patients	49.00	14.66	81.94	5735.50	1649.50	<0.001
	Healthy	41.21	8.32	59.06	4134.50		
QTc (ms)	Patients	436.35	42.67	64.16	4491.00	1976	0.048
	Healthy	419.79	27.54	76.84	5379.00		
QTcd (ms)	Patients	60.47	17.32	63.54	4448.00	1533.5	<0.001
	Healthy	49.93	10.44	77.46	5422.00		

SD: Standard deviation, MWU: Mann-Whitney U test, QT: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, QTc: QT / √ RR, QTd: the difference between the maximum and minimum QT values. QTcd: the difference between the maximum and minimum QTc values. R in v5: (R wave in V5) the amplitude of R wave in left Precordial. S in v1: (S wave in V1) the amplitude of S wave in right, HR: Heart Rate.

Table.2 shows the sex comparison of the mentioned parameters in diabetic patients. From the table, it is reported that Qt max (p=0.035), Qt min (p=0.014), RR (p=0.036), and HbA1C (p=0.043) were higher in boys and heart rate (p<0.001) was higher in girls significantly. **Table.3** shows the results of ECG measures in diabetic patients based on the diabetic time duration of < 12 months, 12-60 months and > 60 months with the frequency of 13, 53, and 4 patients, and the results showed non-significant difference between ECG parameters based on length of diabetic duration. In terms of HbA1C states of normal and abnormal with 41 and 29 patients, respectively, from the analysis, it was reported that QT, QTd, QTc and QTcd changes were not significant in patients based on this variable categorization.

Table-2: ECG parameters based on gender of the patients.

Parameters	Gender	Number	Mean	SD	Mean Rank	Sum of Ranks	MWU	P- value
QT_{max} (ms)	Boy	32	364.69	28.17	40.78	1305.00	439.00	0.035
	Girl	38	350.00	24.93	31.05	1180.00		
QTd (ms)	Boy	32	49.69	13.32	36.30	1161.50	582.50	0.747
	Girl	38	48.42	15.86	34.83	1323.50		
QTc_{max} (ms)	Boy	32	436.54	45.39	35.69	1142.00	602.00	0.944
	Girl	38	436.19	40.86	35.34	1343.00		
QTcd (ms)	Boy	32	59.76	15.19	33.58	1074.50	546.50	0.468
	Girl	38	61.07	19.11	37.12	1410.50		
R in V_5 (mm)	Boy	32	9.88	3.06	39.53	1265.00	479.00	0.126
	Girl	38	8.76	3.08	32.11	1220.00		
S in V_1 (mm)	Boy	32	6.06	3.02	34.70	1110.50	582.50	0.761
	Girl	38	6.24	3.44	36.17	1374.50		
Heart Rate	Boy	32	84.34	13.18	25.73	823.50	295.50	0.000
	Girl	38	98.24	15.97	43.72	1661.50		
R in V_5 / S in V_1	Boy	32	1.92	0.96	38.34	1227.00	517.00	0.283
	Girl	38	1.65	0.71	33.11	1258.00		
QT_{min} (ms)	Boy	32	314.38	27.93	41.78	1337.00	407.00	0.014
	Girl	38	300.53	24.38	30.21	1148.00		
RR interval (s)	Boy	32	0.72	0.10	41.06	1314.00	430.00	0.036
	Girl	38	0.66	0.11	30.82	1171.00		
QTc min (ms)	Boy	32	376.78	48.09	35.84	1147.00	597.00	0.897
	Girl	38	375.12	43.29	35.21	1338.00		
Diabetic duration (month)	Boy	32	31.88	19.36	36.48	1167.50	576.50	0.708
	Girl	38	31.42	20.22	34.67	1317.50		
Hb A1c (%)	Boy	32	8.40	1.33	40.84	1307.00	437.00	0.043
	Girl	38	7.81	1.75	31.00	1178.00		

SD: Standard deviation, QT: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, QTc: QT / $\sqrt{}$ RR, QTd: the difference between the maximum and minimum QT values. QTcd: the difference between the maximum and minimum QTc values. R in v5: (R wave in V5) the amplitude of R wave in left Precordial. S in v1: (S wave in V1) the amplitude of S wave in right, HR: Heart Rate.

Table-3: ECG parameters based on diabetic duration, and HbA1c level in patients.

Parameters	Diabetic Duration (months)	Mean Rank	Chi-square	P- value	HbA1c	Mean Rank	MWU	P-value
QT (ms)	0-12	30.35	1.156	0.561	Normal	35.63	589	0.945
	12-60	36.59			Abnormal	35.31		
	> 60	37.75						
QTd (ms)	0-12	35	2.115	0.347	Normal	32.87	486.5	0.167
	12-60	34.61			Abnormal	39.22		
	> 60	48.88						
QTc (ms)	0-12	30	2.06	0.357	Normal	36.35	559.5	0.676
	12-60	37.45			Abnormal	34.29		
	> 60	27.5						
QTcd (ms)	0-12	33.54	1.362	0.506	Normal	33.48	511.5	0.322
	12-60	35.13			Abnormal	38.36		
	> 60	46.75						
R in V_5	0-12	36.77	0.28	0.868	Normal	34.29	545	0.552
	12-60	35.56			Abnormal	37.21		
	> 60	30.63						
S in V_1	0-12	44.92	3.65	0.1622	Normal	33.98	532	0.451
	12-60	33.08			Abnormal	37.66		
	> 60	37						
Heart rate (beats per min)	0-12	36.58	1.3	0.521	Normal	36.43	556.5	0.65
	12-60	36.08			Abnormal	34.19		
	> 60	24.25						
R-R interval	0-12	35.08	0.79	0.675	Normal	35.34	588	0.938
	12-60	34.94			Abnormal	35.72		
	> 60	44.25						
QT min (ms)	0-12	31.04	1.31	0.521	Normal	36.55	551.5	0.578
	12-60	37.02			Abnormal	34.02		
	> 60	29.88						
QTc min (ms)	0-12	31	2.19	0.334	Normal	37.83	499	0.255
	12-60	37.41			Abnormal	32.21		
	> 60	24.88						
BMI (kg/m^2)	0-12	30.5	1.1	0.578	Normal	34.12	538	0.5
	12-60	36.37			Abnormal	37.45		
	> 60	40.25						

HbA1c: Hemoglobin A1C, QT: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, QTc: QT / √ RR, QTd: the difference between the maximum and minimum QT values. QTcd: the difference between the maximum and minimum QTc values. R in v5: (R wave in V5) the amplitude of R wave in left Precordial. S in v1: (S wave in V1) the amplitude of S wave in right, HR: Heart Rate, BMI: Body Mass Index

4- DISCUSSION

The present study aimed to evaluate the rate of changes in QT, QTd, QTc and QTcd in children with diabetes mellitus type I compared with healthy children. Unmistakably, the fundamental finding in our investigation was that the ECG parameters of QT, QTd, and QTcd were higher in patients but QTc was not noteworthy. In diabetes patients, QT, QTd, QTc and QTcd changed marginally in light of diabetic time terms and HbA1c results expresses that were non-noteworthy. Boys had more elevated amounts of QT min, RR, QT max and HbA1c than girls but they had lower heart rate.

Ninkovic et al. (15) detailed that exclusively 2% of the patients exhibited delayed QTc whereas the present examination indicated 27%. This high distinction is probably due to poor control of diabetes in our patients. QTc length and scattering were influenced by the sexual orientation with females exhibiting essentially higher commonness of delayed QTc than male and QTc scattering. This part of the outcome is comparable with the present examination that showed that young men had lower levels of QTc, however, it was not significant. Patients with delayed QTc interim had essentially higher body mass index.

Youssef et al. (20), like the present investigation revealed that QTc was observed to be prolonged in the patients. They also announced that the mean QTc estimations of patients during diabetic ketoacidosis were reduced after treatment. Aygun et al. (21) directed an investigation on electrocardiographic changes in kids with diabetic ketoacidosis and ketosis. From the study, it was demonstrated that mean heart rate of patients was higher significantly after treatment but mean R/S proportion was observed to be higher significantly before treatment with respect to the time after treatment. The mean QTc time was discovered to be higher at the season of analysis in contrast to after treatment. The underlying QTc time was observed to be at the maximum furthest reaches of ordinary and the subsequent qualities were observed to be inside as far as possible. The adjustment in the QTc time was observed to be measurably significant. In the present examination, no distinctions were observed in the ECG finding of patients with respect to diabetic duration. Uysal et al. (18) carried out an investigation on patients with DMTI that matched with age and sex of healthy children, and assessed the electrocardiographic parameters for early conclusion of autonomic dysfunction. First, they grouped patients in newly diagnosed and followed-up for one year as group one and follow up, 1–5 years in the second group and the third were followed up for more than 5 years. They found that QT, QTd, QTc and QTcd were significantly higher in DMTI children compared to the controls, but were not associated with the duration of diabetes.

Our study was somehow similar to Uysal et al.'s study in the methodology and would be confirmed strongly because of similar findings in terms of all findings except QTc. The present study resulted in non-significant differences between diabetic and healthy children considering QTc. Rossing et al. (19) conducted a study on adult DMTI with duration of diabetes > 5 years and reported that prolonged QTc was presented in 49% of all patients. Whereas this prolonged QTc was lower in our study and very low in Ninkovic et al.'s study (15). This higher percentage of patients with prolonged QTc max interval in Rossing et al.'s study (19) was probably due to the patients' age and the duration of diabetes. From their study, it was also reported that an increase in QTc was correlated with gender, age and heart rate. Surprisingly, from the present study, it was reported that QTc max interval was correlated with only heart rate in patients

with DMTI. Similar to our findings, Rossing et al., found non-significant correlation of QTc with duration of diabetes and HbA1c. Kittnar et al. (22) reported that diabetes mellitus (DM) has been known to be an associated factor with poor cardiovascular complications such as complications of tachycardia, shortening of the QRS and QT intervals, increase of the dispersion of QT interval, decreased amplitudes of depolarisation waves, shortened activation time of ventricular myocardium and a flattening of T waves confirmed by the lower value of maximum and minimum in repolarisation body surface isopotential maps. Heller (23) performed a study and detected in DMTI patients QT and QTc intervals prolongation. In the study, it was observed that increasing autonomic neuropathy confirms that autonomic dysfunction does not contribute to hypoglycemia-induced QTc prolongation. Zdarska et al. (24) have found only non-significant lengthening of the QTc in the healthy controls.

4-1. Study Limitations

The study limitations were low sample size and lack of proper co-operation by participants especially the controls in ECG measuring.

5- CONCLUSION

Based on the results, it is concluded that QT, QTd, QTc and QTcd were higher in patients with diabetes mellitus type I. Diabetic time duration and HbA1c states did not change the ECG parameters in diabetic patients. Electrocardiogram assessment is an excellent method to detect cardiac involvements in DMTI children. If these disorders in childhood continue into adulthood, this might cause overt cardiac autonomic dysfunction that could increase the risk of cardiac mortality and morbidity. If these changes are detected at an earlier asymptomatic period on ECG and reversed with good glycemic state, these patients also might be protected from these cardiac side effects.

6- AUTHOR CONTRIBUTIONS

Noori and Nakhaee Moghadam contributed to the study concept and design, Kasravi contributed to the data collection and Teimouri is involved with analysis, interpreted the data, and drafted the manuscript. Noori, Nakhaee Moghadam and Teimouri contributed to the discussion, and reviewed the manuscript.

7- CONFLICT OF INTEREST: None.

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