Correlation between metabolic control, serum electrolyte levels, duration of illness and QT interval length parameters in children with type 1 diabetes mellitus

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Background. Cardiac autonomic neuropathy (CAN) is a common complication of type 1 diabetes mellitus (T1DM) that can cause arrhythmia and increase mortality risk. Prolonged corrected-QT (QTc) and dispersion-QT (QTd) intervals can be used for early detection. Few studies have investigated relationships between metabolic control, serum electrolyte levels, duration of illness and CAN in T1DM children.
Objective. To investigate serum haemoglobin A1c (HbA1c) level, serum electrolyte levels, duration of illness and QTc and QTd interval parameters in T1DM children.
Methods. This cross-sectional study included T1DM patients up to 18 yearsof age at the Paediatric Outpatients Clinic, Dr. Soetomo Hospital, Surabaya, Indonesia, between January 2016 and July 2017. Serum HbA1c and sodium and potassium levels were analysed. QTc and QTd intervals were recorded from 12-lead electrocardiograms.
Results. Of the 40 patients, 70% were found to have poor metabolic control. Among patients with poor metabolic control, prolonged QTc and QTd intervals were observed in 21 (75.0%) and 16 (57.1%), respectively. Serum HbA1c levels were significantly correlated with QTc (p=0.001; r=0.541) and QTd interval lengths (p=0.018; r=0.373). Hypokalaemia was observed in 28 patients, with prolonged QTc and QTd intervals seen in 85% (n=17) and 55% (n=11), respectively. We found significant correlations between potassium level and QTc interval length ($p \leq 0.05$; r=0.556), but not between potassium level and QTd interval length.
Conclusion. We suggest that prolonged QTc and QTd intervals could be predictive of a cardiovascular complication in T1DM in children.

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The global prevalence of type 1 diabetes mellitus (T1DM) is increasing.[1,2] In 2017, an estimated 1 106 500 people younger than 20 years were affected and the number of newly diagnosed cases each year was estimated at 132 600.[2]

Cardiac autonomic neuropathy (CAN) is a serious complication in diabetes,[3] which is estimated to account for 5 per 1 000 cardiovascular-related T1DM deaths each year.[2] Arrhythmia, which forms part of CAN, can be detected as prolonged corrected QT (QTc) and dispersion QT (QTd) intervals.[4,5] Prolonged QTc and QTd intervals can trigger ventricular arrhythmia and it may lead to sudden death.[6,7] Poor metabolic control and electrolyte imbalance in diabetic ketoacidosis (DKA) are known to cause prolonged QTc and QTd intervals.[8-10]

Duration of illness also appears to contribute to the process of CAN. In 2018, the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommended screening T1DM patients from the age of 11 for CAN complications within 2 - 5 years of disease onset, followed up annually by physical examination and clinical testing.[11] The American Diabetes Association further recommends screening hyperglycaemic patients for cardiovascular disease by measuring serum haemoglobin A1c (HbA1c) every 3 months as a means of monitoring blood glucose control, with the target set at <7.5%.[12]

Our study aimed to investigate the correlation between serum HbA1c levels, serum electrolyte levels, duration of illness and parameters of QT intervals among Indonesian T1DM patients 18 years old and younger. Few studies have considered the correlations between these parameters and none so far in an Indonesian population.

Methods

We conducted a cross-sectional study at the paediatric endocrinology outpatient clinic and the paediatric ward of the Dr. Soetomo Hospital in Surabaya, Indonesia, from January 2016 to July 2017. All T1DM patients up to 18 years were included. Patients with a history of congenital disorders, including congenital heart disease, were not included in the study. According to the 2014 ISPAD guidelines,[1] diagnosis criteria of T1DM was (*i*) classic symptoms of diabetes or hyperglycaemic crisis, with a plasma glucose concentration ≥11.1 mmol/L (200 mg/dL); (*ii*) a fasting plasma glucose level ≥7.0 mmol/L (≥126 mg/dL); (*iii*) a glucose level ≥11.1 mmol/L (≥200 mg dL) two hours post load as determined by an oral glucose tolerance test; or (*iv*) HbA1c >6.5%. All patients in our study used basal-bolus insulin injection (detemir and short-acting insulin). As per ISPAD criteria, DKA was defined as a condition of hyperglycaemia (blood glucose >11 mmol/L (200 mg/dL)), acidosis (pH <7.3 or bicarbonate levels <15 mmol/L), ketonaemia and ketonuria.[13]

Nutritional status was classified according to the World Health Organization BMI-for-age values defined for children and adolescents (5 - 18 years of age): severe malnutrition ($z<-3$); moderate malnutrition ($-3<z<-2$); normal ($-2<z\leq1$); overweight ($1<z<2$); and obesity ($z>2$).[14] We grouped the subjects into three groups: normal; malnourished; and overweight/obese.

Blood samples were analysed for HbA1c and sodium and potassium levels at the clinical pathology laboratory of the Dr.

Soetomo Hospital, Surabaya. HbA1c results were classified as poor (>9%), suboptimal (7.5 - 9%) or good (<7.5%).[15] Results were subsequently classified as indicative of poor or good metabolic control (HbA1c >9% and HbA1c <9%, respectively). Potassium levels <3.5 mmol/L and >5.5 mmol/L were considered indicative of hypokalaemia and hyperkalaemia, respectively. Potassium levels of 3.5 - 5.5 mmol/L were considered normal.[16] Similarly, sodium levels <136 mmol/L and >145 mmol/L were classified as indicative of hyponatraemia and hypernatraemia, respectively. Sodium levels of 136 - 145 mmol/L were considered normal.[16]

The QTc and QTd values were obtained from 12-lead electrocardiography (Bionet CardioTouch 3000, Bionet, USA). The QTc interval was calculated according to Bazett's formula ($QTc = \frac{QT}{\sqrt{RR}}$), with the RR interval measured relative to the previous QRS complex. A prolonged QTc was taken as >440 ms in boys and >460 ms in girls. QTd was calculated as the difference between QTmax and QTmin; the interval was considered prolonged if the difference was >60 ms.[6]

Statistical analysis

Means and associated standard deviations were calculated for normally distributed data. Data that were not normally distributed were described as medians and the associated range. Correlations between serum levels for HbA1c, sodium and potassium, duration of illness and QT interval parameters were assessed according to a phi association test with the correlation coefficient *r*. All data analyses were performed using SPSS software version 17.0 (SPSS Inc., USA). A significance level of $p \leq 0.05$ and a 95% confidence interval (CI) were used in all analyses.

Ethical approval

Approval was granted by the ethics committee overseeing health research at the Dr. Soetomo Hospital, Surabaya, Indonesia (ref. no. 555/Panke.KKE/IX/2016).

Results

The study included 40 patients with T1DM, of whom 18 were male. Close to two-thirds had a normal nutritional status (60%). DKA was observed in 57.5% of cases. The characteristics of the study population are shown in Table 1. Prolonged QTc and QTd intervals were observed in 23 and 18 patients, respectively. Approximately 90% of these patients showed poor metabolic control. We did not observe any cases of hyperkalaemia, but found that all of the subjects with hypernatraemia (*n*=3) presented with a prolonged QTc interval, as shown in Table 2.

Table 1. Baseline characteristics of the study population (*N*=40)

Characteristics	Total
Gender, *n* (%)	
Male	18 (45.0)
Female	22 (55.0)
Age (months), mean (SD)	144 (38.7)
Weight (kg), mean (SD)	34.5 (13.5)
Height (cm), mean (SD)	135.6 (14.2)
DKA during the study, *n* (%)	
Yes	23 (57.5)
No	17 (42.5)
Nutritional status, *n* (%)	
Normal	24 (60.0)
Malnutrition	14 (34.5)
Overweight/obesity	2 (5.0)
Serum HbA1c (%), mean (SD)	10.27 (2.2)
Potassium level (mmol/L), median (range)	3.8 (1.7 - 5.9)
Sodium level (mmol/L), mean (SD)	136.1 (6.6)
Duration of illness (months), median (range)	16.5 (0 - 132)
QTc interval (ms), mean (SD)	460 (43.0)
QTd interval (ms), median (range)	50 (40 - 120)

SD = standard deviation; HbA1c = haemoglobin A1c.

Discussion

Our results showed significant correlations between serum HbA1c and both QTc (p=0.001; r=0.541) and QTd intervals (p=0.018; r=0.373). Prolonged QTc and QTd intervals were observed in 21 (75.0%) and 16 (57.1%) patients with poor metabolic control. The observation is similar to that of Stern *et al.*,[8] who reported an association between serum HbA1c and QTc interval length (p<0.001). Tesfaye *et al.*[9] suggested that high serum HbA1c levels are caused by neuropathy in T1DM, with a reported odds ratio of 2.48 (p<0.001, 95% CI). Findings from the Diabetes Control and Complications Trial (DCCT)[13] suggested that complications of T1DM may be prevented by optimal metabolic control. The DCCT further reported that intensive treatment reduced the risk of cardiovascular disease by 42% (p=0.02).[17] Circulating endothelial cells, identified by fluorescence microscopy, were suggested as a cause of endothelial vascular damage and have been reported to be elevated in T1DM patients with raised Hb A1c levels.[18] This contradicts the results of a study by Lu *et al.*,[19] which found that serum HbA1c was not significantly correlated with the length of the QTc interval (p=0.77).

CAN is considered a cardiovascular complication of diabetic neuropathy. Earlier studies reported that T1DM patients may suffer cardiovascular events by the age of 30,[20] which often appear after 20 years of the disease.[21] Cardiovascular disease appears not only to occur earlier in T1DM than in type 2 diabetes mellitus, but also to affect men and women at a similar rate by the age of 40.[22] Poor glycaemic control is a risk factor for cardiovascular events in both types of diabetes mellitus.[12] Hypertension, proteinuria, obesity, high serum HbA1c and lipid levels, smoking and a long disease duration may be important risk factors for cardiovascular events.[12] Therefore, screening for prolonged QTc and QTd intervals should be performed to predict a possible cardiovascular event.

Our results showed a significant correlation between serum potassium level and QTc interval length, but not between potassium level and QTd interval length. Serum sodium level was not significantly correlated with a prolonged QTc or QTd interval. No significant correlation was found between the length of the QTc interval and serum levels of potassium (p=0.139) or sodium (p=0.962) in DKA patients in a study by Aygün *et al.*,[23] similar to findings regarding the correlation between potassium level and QTc interval length in DKA patients reported by Kuppermann *et al.*[10] Hypokalaemia, hyperkalaemia, hypocalcaemia, hypophosphataemia and hypomagnesaemia may develop in DKA.[24]

Our results showed prolonged QTc and QTd intervals in 18 (66.7%) and 14 (51.9%) patients, respectively, within 2 years of disease onset. However, the correlation between duration of illness and QT interval lengths was not significant. Uysal *et al.*[25] reported significant differences in QTd interval length in newly diagnosed T1DM patients at follow-up after 1 year, within 5 years and later than 5 years compared

Table 2. Correlation between serum haemoglobin A1c levels, serum electrolytes and QTc and QTd intervals (*N*=40)

	QTc interval				QTd interval			
Variable	Normal, *n* (%)	Elongated, *n* (%)	*p*-value	*r*	Normal, *n* (%)	Elongated, *n* (%)	*p*-value	*r*
Metabolic control*								
Good (*N*=12)	10 (83.3)	2 (16.7)	0.001†	0.541	10 (83.3)	2 (16.7)	0.018†	0.373
Poor (*N*=28)	7 (25.0)	21 (75.0)			12 (42.9)	16 (57.1)		
Potassium								
Normal (*N*=20)	14 (70.0)	6 (30.0)	0.000*†	0.556	13 (65.0)	7 (35.0)	0.204	0.201
Hypokalaemia (*N*=20)	3 (15.0)	17 (85.0)			9 (45.0)	11 (55.0)		
Sodium								
Normal (*N*=23)	11 (47.8)	12 (57.2)	0.769	0.048	14 (60.9)	9 (39.1)	0.175	0.286
Hyponatraemia (*N*=14)	6 (42.9)	8 (57.1)			6 (42.9)	8 (57.1)		
Hypernatraemia‡ (*N*=3)	0	3 (100)	–	–	2 (66.7)	1 (33.3)	0.846	–0.038
Duration of illness, months								
<24 (*N*=27)	9 (33.3)	18 (66.7)	0.091	–0.267	13 (48.1)	14 (51.9)	0.209	–0.198
≥24 (*N*=13)	8 (61.5)	5 (38.5)			9 (69.2)	4 (30.8)		

HbA1c = haemoglobin A1c.
*HbA1c <6.5% considered indicative of good metabolic control; HbA1c ≥6.5% considered indicative of poor metabolic control.
†Statistically significant, $p \leq 0.05$.
‡Not analysed.

with controls (p=0.005, p<0.001, p<0.001, respectively). However, the correlation between QTd interval length and disease duration was not significant.[25]

Study limitations

Owing to demographic and racial differences in our study population, our findings cannot be generalised.

Conclusion

The results of this study showed a significant correlation between serum HbA1c levels and both QTc and QTd interval length in children diagnosed with T1DM. We suggest that screening for prolonged QTc and QTd intervals may be used to predict cardiovascular complications in this patient group.

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