ORIGINAL ARTICLE

Severity and multiplicity of microvascular complications are associated with QT interval prolongation in patients with type 2 diabetes

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ABSTRACT

Aims/Introduction: A prolonged QT interval plays a causal role in life-threatening arrhythmia, and becomes a risk factor for sudden cardiac death. Here, we assessed the association between microvascular complications and the QT interval in patients with type 2 diabetes.

Materials and Methods: Patients with type 2 diabetes ($n = 219$) admitted to Nippon Medical School Hospital (Tokyo, Japan) for glycemic control were enrolled. QT interval was measured manually in lead II on the electrocardiogram, and corrected for heart rate using Bazett's formula (QTc). Diabetic neuropathy, retinopathy and nephropathy were assessed by neuropathic symptoms or Achilles tendon reflex, ophthalmoscopy and urinary albumin excretion, respectively.

Results: In univariate analyses, female sex ($P = 0.025$), duration of type 2 diabetes ($P = 0.041$), body mass index ($P = 0.0008$), systolic blood pressure ($P = 0.0011$) and receiving insulin therapy ($P < 0.0001$) were positively associated with QTc. Patients with each of the three microvascular complications had longer QTc than those without: neuropathy ($P = 0.0005$), retinopathy ($P = 0.0019$) and nephropathy ($P = 0.0001$). As retinopathy or nephropathy progressed, QTc became longer ($P < 0.001$ and $P < 0.001$ for trend in retinopathy and nephropathy, respectively). Furthermore, QTc was prolonged with the multiplicity of the microvascular complications ($P < 0.001$ for trend). Multiple regression analyses showed that neuropathy, nephropathy and the multiplicity of the microvascular complications were independently associated with QTc.

Conclusions: Patients with type 2 diabetes with severe microvascular complications might be at high risk for life-threatening arrhythmia associated with QT interval prolongation.

INTRODUCTION

Type 2 diabetes is associated with an increased risk of mortality, not only from cardiovascular diseases, but also from sudden cardiac death[1–3]. Sudden cardiac death is caused by abnormalities in coronary arteries, myocardium and electrical propagation in the heart[4]. In electrical propagation, QT interval, the time elapsed between the ventricular depolarization and repolarization, is a vulnerable period for the occurrence of arrhythmias. A prolonged QT interval plays a causal role in life-threatening arrhythmia, such as torsades de pointes type ventricular tachycardia, and increases a risk of sudden cardiac death[5,6]. Individuals with diabetes have been reported to have a longer QT interval than those without[7–10]. Recent studies have reported that prolonged QT interval is an independent predictor of all-cause and cardiovascular mortalities in type 2 diabetes[11,12]. Thus, it is of great importance to clarify the patient characteristics that influence their QT interval for reducing mortality in type 2 diabetes.

Both macrovascular and microvascular complications are reported to be independent risk factors for sudden cardiac

death in diabetes[3,13]. Indeed, previous studies have shown that diabetes patients with macrovascular[14,15] or microvascular complications (neuropathy[16], retinopathy[16–18] and nephropathy[17,18]) have longer QT intervals than those without these complications. Needless to say, there is a wide variety in the severity and multiplicity of complications among patients with diabetes. However, these previous studies have compared QT intervals only between the presence and absence of each complication; they have not taken the severity and multiplicity into account. Thus, the impact of the compound progression of the complications on QT interval has not been fully elucidated. In the present study, we investigated the relationships between the clinical characteristics, especially the severity and multiplicity of microvascular complications, and the QT interval in patients with type 2 diabetes.

METHODS

Participants

Patients with type 2 diabetes who were admitted to Nippon Medical School Hospital (Tokyo, Japan) for glycemic control were enrolled ($n = 219$, 68 women and 151 men). Exclusion criteria included atrial fibrillation, major ventricular conduction defects (defined as long QRS duration >120 ms), uncontrolled endocrine disease, receiving steroid therapy and ketoacidosis. We also excluded the patients taking medications that can affect the QT interval, such as anti-arrhythmic agents, antipsychotic agents, tricyclic antidepressants, tetracyclic antidepressants, α-blockers, β-blockers, probucol, digoxin, antifungal agents and antibacterial agents. The study protocol was approved by the institutional review board and conformed to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). All participants provided informed consent before enrollment.

Clinical measurements

All participants underwent physical examinations including height, bodyweight and blood pressure on the first morning of hospitalization. Blood samples were taken after an overnight fast on the second day of admission. Fasting plasma glucose was measured by the glucose oxidase method (ADAMS Glucose GA-1170; Arkray, Kyoto, Japan). Glycated hemoglobin was measured by high-performance liquid chromatography (ADAMS A1c HA-8160; Arkray), and is expressed as the percentage value of the National Glycohemoglobin Standardization Program according to the Japan Diabetes Society's guideline[19]. Serum total cholesterol, high-density lipoprotein cholesterol and triacylglycerols were measured enzymatically (Sekisui Medical, Tokyo, Japan). Low-density lipoprotein cholesterol was calculated using the Friedewald formula[20]. Serum calcium level was corrected for the concentration of albumin using the following formula if serum albumin level was <4.0 g/dL: corrected Ca (mg/dL) = Ca (mg/dL) + (4.0 − albumin [g/dL])[21]. Estimated glomerular filtration rate was calculated using the following formula, where Cr is creatinine: estimated glomerular filtration

rate (mL/min/1.73 m^2) = 194 × Cr$^{-1.094}$ × age$^{-0.287}$ (×0.742 if female)[22].

QT interval

The 12-lead electrocardiogram was recorded on the day of admission using an electrocardiograph (ECG-1550; Nihon Kohden Co. Ltd, Tokyo, Japan). QT and RR intervals of three consecutive beats were measured manually on lead II. The QT interval was defined as the length from the beginning of QRS complex to the end of the downslope of the T wave. A corrected QT interval (QTc) was calculated according to Bazett's formula[23]: $QTc = QT / (RR)^{1/2}$. The QTc >440 ms was considered prolonged[14,17,24].

Assessment of microvascular complications

Neuropathy was screened with criteria for typical diabetic peripheral neuropathy proposed by the American Diabetes Association in 2010[25]. The presence of typical diabetic peripheral neuropathic symptoms (decreased sensation, positive neuropathic sensory symptoms [e.g., numbness, prickling or stabbing, burning, or aching pain] in lower legs) or abnormal (decreased or absent) Achilles tendon reflex was diagnosed as neuropathy (including possible neuropathy). Retinopathy was diagnosed using ophthalmoscopy by an ophthalmologist. We categorized the severity of retinopathy as simple, preproliferative and proliferative retinopathy according to the Davis' criteria[26]. Nephropathy was diagnosed by the presence of albuminuria (urinary albumin exertion ≥30 mg/g·Cr [spot]). Normo-, micro- and macroalbuminuria were defined as urinary albumin excretion of <30, 30–300 and ≥300 mg/g·Cr (spot), respectively[27]. The multiplicity of microvascular complications was scored from 0 to 3 by the number of the complications (neuropathy, retinopathy and nephropathy) being diagnosed.

Statistical analysis

Continuous variables were described as the mean ± standard deviation or median and interquartile range. Categorical variables were expressed as the number and percentage. Differences in two independent groups were analyzed by Student's t-test or the Mann–Whitney U-test. Corrections for multiple comparisons were carried out using Dunnett's test. The Jonckheere–Terpstra test was carried out for the trend test. Correlations between QTc and other continuous variables were examined using Pearson's correlation test. Multivariate regression models were used to determine statistically significant predictive factors (neuropathy [model 1], retinopathy [model 2], nephropathy [model 3] and the number of microvascular complications [model 4]) for QTc. Each model was adjusted for age, sex, duration of type 2 diabetes, body mass index, systolic blood pressure and insulin therapy. A P-value of <0.05 was considered significant. All analyses were carried out using JMP 11.2 software (SAS Institute Inc., Cary, North Carolina, USA) or SPSS 21.0 (IBM Co. Ltd., Armonk, New York, USA).

RESULTS

Relationships between clinical characteristics and QTc

Table 1 shows the clinical characteristics of the patients, and the associations between the variables and QTc. The QTc of all participants was 430 ± 22 ms, and 35% of them ($n = 76$) had prolonged QTc. Significant differences were observed in QTc between women and men (436 ± 18 vs 427 ± 23 ms), and between the patients treated with insulin and those without (443 ± 21 vs 427 ± 21 ms). In addition, QTc was positively correlated with duration of type 2 diabetes, body mass index and systolic blood pressure. The patients with each microvascular complication had significantly longer QTc than those without (neuropathy [435 ± 20 vs 424 ± 22 ms], retinopathy [438 ± 21 vs 427 ± 21 ms] and nephropathy [436 ± 24 vs 425 ± 19 ms]).

Severity and multiplicity of microvascular complications and QTc

The QTc of the patients categorized by the severity of retinopathy and nephropathy are shown in Table 2. The patients with proliferative retinopathy had significantly longer QTc as compared with those without. In addition, as the severity of retinopathy progressed, QTc became longer. For nephropathy, the patients with microalbuminuria or macroalbuminuria had significantly longer QTc as compared with those with normoalbuminuria, and QTc was prolonged as the urinary albumin excretion increased. Furthermore, stepwise prolongation of QTc was observed with the multiplicity of the microvascular complications (Figure 1). Table 3 shows the series of multiple regression models of each microvascular complication and the multiplicity for predicting QTc. These analyses showed that neuropathy, nephropathy (the presence of albuminuria) and the multiplicity of microvascular complications were independently associated with QTc (models 1, 3 and 4).

DISCUSSION

Considering that individuals with prolonged QT interval are at high risk of sudden cardiac death[5,6], we should pay more attention to the QT interval in patients with type 2 diabetes. To date, several reports have pointed out the associations between diabetic microvascular complications and QT interval prolongation[16–18]. However, the severity and multiplicity of microvascular complications have not been taken into account in these studies. In the present study, we showed that the

Table 1 | Clinical characteristics and the association with corrected QT interval

Variables	$n = 219$	r	P-value
Age (years)	60 ± 13	0.0068	0.92
Women, n (%)	68 (31)	–	0.025
Duration of type 2 diabetes (years)	6 (1–15)	0.14	0.041
BMI (kg/m^2)	25.0 ± 4.7	0.23	0.0008
Systolic blood pressure (mmHg)	126 ± 15	0.23	0.0011
Diastolic blood pressure (mmHg)	70 ± 11	0.080	0.24
Fasting plasma glucose (mmol/L)	9.79 ± 2.99	0.092	0.17
HbA1c (%)	9.5 ± 2.2	0.012	0.86
Total cholesterol (mmol/L)	5.09 ± 1.21	0.039	0.57
HDL cholesterol (mmol/L)	1.22 ± 0.32	-0.083	0.22
LDL cholesterol (mmol/L)	3.08 ± 0.96	0.021	0.76
Triacylglycerols (mmol/L)	1.76 ± 1.30	0.11	0.10
Serum sodium (mEq/L)	139 ± 2	0.00070	0.99
Serum potassium (mEq/L)	4.1 ± 0.4	-0.095	0.16
Serum chlorine (mEq/L)	104 ± 3	-0.035	0.61
Corrected serum calcium (mg/dL)	9.2 ± 0.4	-0.028	0.68
eGFR (mL/min/1.73 m^2)	86.9 ± 26.5	-0.043	0.52
Microvascular complications			
Neuropathy, n (%)	108 (49)	–	0.0005
Retinopathy, n (%)	50 (23)	–	0.0019
Nephropathy, n (%)	86 (39)	–	0.0001
History of ischemic heart disease	14 (6)	–	0.088
Insulin therapy, n (%)	35 (16)	–	<0.0001
QTc (ms)	430 ± 22	–	–

Continuous variables are expressed as mean ± standard deviation or median (interquartile range). Correlations between continuous variables and corrected QT interval (QTc) were examined by Pearson's correlation test. Differences in two independent groups were analyzed by Student's *t*-test or Mann–Whitney *U*-test. BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low density lipoprotein; QTc, corrected QT interval.

Table 2 | Corrected QT interval according to the severity of retinopathy and nephropathy

Microvascular complications	n	QTc (ms)	P-value
Retinopathy			
None	169	427 ± 21	—
Simple retinopathy	19	432 ± 22	0.78[†]
Preproliferative retinopathy	14	441 ± 17	0.078[†]
Proliferative retinopathy	17	443 ± 23	0.010[†]
Trend			<0.001[‡]
Nephropathy			
Normoalbuminuria	133	425 ± 19	—
Microalbuminuria	60	435 ± 23	0.010[§]
Macroalbuminuria	26	442 ± 24	0.0005[§]
Trend			<0.001[‡]

Corrected QT interval (QTc) values are expressed as mean ± standard deviation. [†]P-values for Dunnett's test vs none. [‡]P-values for the Jonckheere–Terpstra test. [§]P-values for Dunnett's test vs normoalbuminuria.
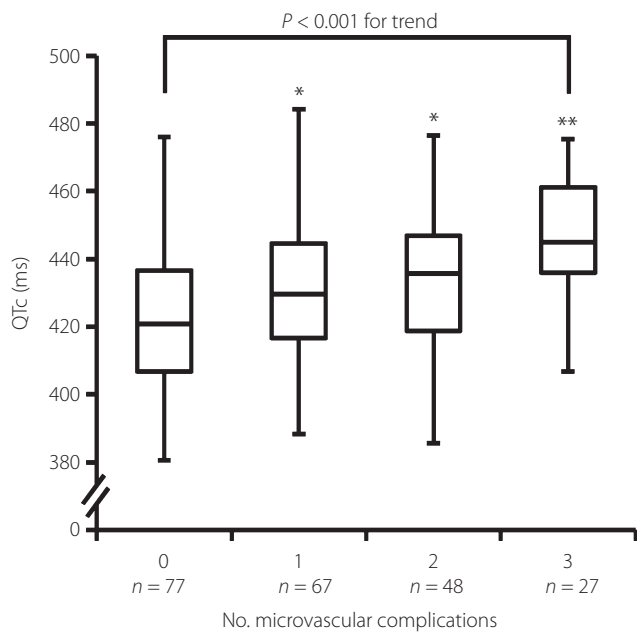

Figure 1 | Multiplicity of microvascular complications and corrected QT interval (QTc). Distribution of the QTc according to the multiplicity of microvascular complications (diabetic neuropathy, retinopathy and nephropathy). The boxes indicate the central rectangular spans from the first quartile to the third quartile (interquartile range). A segment inside the rectangle shows the median. The whiskers display the lowest datum within 1.5 interquartile range of the lower quartile and the highest datum within 1.5 interquartile range of the upper quartile. *P < 0.05 and **P < 0.01 for Dunnett's test vs patients without microvascular complications (0).

Table 3 | Multiple linear regression models for corrected QT interval

Model	Variables	β coefficient	t-value	P-value
1	Neuropathy	3.06	2.14	0.034
2	Retinopathy	1.90	1.03	0.30
3	Nephropathy	4.63	3.16	0.0018
4	Multiplicity of microvascular complications	4.60	3.10	0.0022

Data are expressed as β coefficient (estimated partial regression coefficient), t and P values for the association of corrected QT interval with microvascular complications (neuropathy [model 1], retinopathy [model 2], nephropathy [model 3] and multiplicity of microvascular complications [model 4]) and clinical covariates (age, sex, duration of diabetes, body mass index, systolic blood pressure and insulin therapy).

associated with the QTc prolongation. In multiple regression analyses, the presence of neuropathy, nephropathy and the multiplicity of the microvascular complications were independently associated with the QTc prolongation.

There are several potential mechanisms underlying the relationship between diabetic microvascular complications and QT interval prolongation. Several reports have suggested that microischemia, as a result of a small infarction in the myocardium, can prolong the QT interval[28,29]. Indeed, several markers of early atherosclerosis (e.g., pulse wave velocity and carotid intima-media thickness) have been reported to be positively associated with QT interval in patients with type 2 diabetes[30,31]. Thus, it is highly possible that not only microvascular complications, but also QT interval prolongation, can be induced by the development of atherosclerosis. In the present study, however, no significant association was found between the history of ischemic heart disease and QTc in univariate analysis. This would be partly because of the small number of patients who had a history of ischemic heart disease (14 patients). Another possible reason for QT interval prolongation in patients with diabetes is the functional modulation of ion channels in myocardium. Hyperglycemia-induced nitric oxide reduction can cause the inhibition of Ca^{2+}-adenosine triphosphatase and K^+/Na^+-adenosine triphosphatase activities in cardiomyocytes, leading to an increase of cytosolic free calcium and subsequent prolongation of myocardial repolarization[32]. Such an impaired nitric oxide production, which can lead to endothelial dysfunction, oxidative stress and chronic inflammation in peripheral arteries, is also regarded as a cause of microvascular complications[33]. Overall, these findings strongly suggest that diabetic microvascular complications and QT interval prolongation share common etiologies (i.e., atherosclerosis and impaired nitric oxide production in type 2 diabetes).

In clinical practice, how to manage QT interval in patients with type 2 diabetes should be considered. Some medications, including specific anti-arrhythmics, antipsychotics and antidepressants, are known to prolong QT interval[34]. Thus, we should

severity of retinopathy and nephropathy was associated with QTc prolongation in patients with type 2 diabetes. Furthermore, the multiplicity of microvascular complications was also

monitor QT intervals carefully in patients who receive these medications. In contrast, therapeutic interventions for hypertension and obesity might have favorable effects on QT interval. Previous studies reported that both angiotensin-converting enzyme inhibitor and angiotensin receptor blocker shortened the QT interval in patients with hypertension[35,36]. Another study reported an improved QT interval in obese individuals associated with weight reduction[37]. In addition, amelioration of glycemic control might decrease the QT interval. Although neither fasting plasma glucose nor glycated hemoglobin was associated with QTc in the present study, several previous reports showed that postprandial hyperglycemia[17,32] or acute hyperglycemia (induced by hyperglycemic clamp)[38] prolonged the QT interval. In the present study, patients who received insulin therapy had a longer QTc than those who did not. A previous study also reported that QT interval was prolonged by insulin therapy in patients with type 2 diabetes[39]. Gastaldelli *et al.*[40] suggested that insulin-induced modifications in sympathetic activity and serum potassium concentration cause QT interval prolongation. Some reports also showed prolonged QT interval during insulin-induced hypoglycemia[41,42].

The present study had several limitations. First, as this was a cross-sectional study, we could not determine causal relationships between diabetic microvascular complications and QT interval prolongation. Second, the present study included only hospitalized patients with poor glycemic control. The results might therefore be not representative of all patients with type 2 diabetes. Third, atypical diabetic peripheral neuropathies, for example, painful and autonomic neuropathies, were not screened in the present study, because diagnostic criteria for these neuropathies have not been settled yet[25]. However, several reports have suggested that cardiac autonomic neuropathy affects the QT interval in patients with type 2 diabetes[43,44]. As the heart rate variability test has been suggested to be useful for the assessment of cardiac autonomic neuropathy[25], we also evaluated the coefficient of variation of R-R intervals in 211 of 219 participants. The coefficient of variation of R-R interval was actually associated with QTc negatively and independently in univariate analysis ($r = -0.24$, $P = 0.0004$) and multiple regression analysis ($P = 0.0007$), respectively. These results show that QTc is strongly associated with cardiac autonomic neuropathy, as suggested in the previous studies. Therefore, if atypical diabetic peripheral neuropathies were included in neuropathy, the association between neuropathy and QTc would become stronger.

In conclusion, the present study clearly showed the associations of the severity and multiplicity of diabetic microvascular complications with QT interval prolongation. Furthermore, neuropathy, nephropathy and the multiplicity of microvascular complications were independently associated with the QT interval. These results suggest that patients with type 2 diabetes with severe microvascular complications are at high risk for life-threatening arrhythmia associated with prolonged QT interval.

DISCLOSURE

The authors declare no conflict of interest.

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