

The QT Interval Could be a Marker of Subclinical Atherosclerosis in Patients with Type 2 Diabetes

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Abstract

Several studies have shown that prolongation of QT interval predicts the risks of all-cause and cardiovascular mortality. Moreover, a close association was reported between prolongations of QT interval and pulse wave velocity (PWV) in general population without preexisting cardiovascular disease. The aim of this study was to evaluate the relationship between QT interval and PWV in patients with type 2 diabetes without preexisting cardiovascular disease. In a cross-sectional study of 251 Japanese patients with type 2 diabetes, we examined the correlation of the heart rate-corrected QT interval duration (QTc) with PWV or other various parameters, including age, duration of diabetes, body mass index, systolic blood pressure, hemoglobin A1c, serum cholesterol, creatinine, uric acid, potassium, severity of diabetic nephropathy or retinopathy and current treatment of diabetes. The QTc correlated positively with PWV ($r=0.268$, $p<0.0001$). Multiple regression analysis demonstrated that the QTc was independently correlated with PWV ($\beta=0.155$, $p=0.0119$), after adjustment for known risk factors. According to the receiver operator characteristic analyses (ROC), the area under the ROC curve (AUC) of QTc and the Framingham 10-year coronary heart disease risk score (FRS) for arterial stiffness were 0.69 and 0.64, respectively. The AUC of QTc for arterial stiffness was similar to that of FRS for arterial stiffness ($p=0.6532$). In conclusion, the QT interval could be a marker of subclinical atherosclerosis in patients with type 2 diabetes.

Keywords: Pulse wave velocity; Arterial stiffness; Framingham score

Abbreviations: PWV: Pulse Wave Velocity, QTc: Heart Rate-corrected QT Interval Duration; NT-proBNP: n-Terminal Pro-Brain Natriuretic Peptide; CVD: Cardiovascular Disease; UAE: Urinary Albumin Excretion; FRS: Framingham 10-year Coronary Heart Disease Risk Score; CHD: Coronary Heart Disease; ROC: Receiver Operator Characteristic Analyses; AUC: Area Under the ROC Curve

Introduction

The number of patients with type 2 diabetes is progressively increasing all over the world, and diabetic vascular complications have become a public health problem of considerable magnitude. Cardiovascular disease (CVD) is the primary cause of mortality and morbidity in patients with type 2 diabetes, and several related metabolic disorders including hypertension, dyslipidemia, and hyperuricemia combined with diabetes have been shown to accelerate the progression of CVD [1,2]. Thus, one of the main targets of practice in patients with type 2 diabetes is to detect early atherosclerotic changes. Arterial stiffness can be assessed simply, noninvasively, and reproducibly by measuring pulse wave velocity (PWV) along the thoracoabdominal aorta. PWV is a marker for both severity of vascular damage and prognosis in atherosclerotic vascular disease [3].

However, given the current medical circumstances where the number of diabetic patient increases rapidly, more easily applied and cost effective clinical tools are required to screen the early atherosclerosis with limited medical resources. Several studies have been revealed that prolongation of QT interval predicts the risks of all-cause and cardiovascular mortality in healthy population [4]. Recently, a close relationship was reported between prolongation of QT interval and PWV in general population without preexisting CVD [5]. However, it remains to be elucidated the association between QT interval and PWV in patients with type 2 diabetes without preexisting CVD. In this study, therefore, we evaluated the relationship between heart rate-corrected QT interval duration (QTc) and PWV in patients with type 2 diabetes without preexisting CVD.

Materials and Methods

Patients

We performed a cross-sectional study in 251 consecutive patients with type 2 diabetes who were recruited from the outpatient clinic at Kyoto Prefectural University of Medicine. We then evaluated the relationship of the QTc with PWV as well as various parameters, including serum cholesterol, creatinine, uric acid, fasting plasma glucose, hemoglobin A1c, severity of diabetic nephropathy or retinopathy and current treatment for diabetes. All patients provided details of their demographics, medical history and medication usage. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Type 2 diabetes was diagnosed according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes mellitus [6]. Retinopathy was graded as follows: no diabetic retinopathy (NDR), simple diabetic retinopathy (SDR), or proliferative diabetic retinopathy (PDR). Patients were classified as smoker or non-smoker, according to a self-administered. The Framingham 10-year coronary heart disease (CHD) risk score (FRS), which allows physicians to predict multivariate CHD risk in patients without overt CHD, was recorded based on total and high density lipoprotein cholesterol, systolic blood pressure and diastolic

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blood pressure, age, sex, the presence of diabetes mellitus and current smoking habits [7].

Patients with a history of cardiovascular disease (myocardial infarction, coronary revascularization or stroke), malignant disease, liver cirrhosis or hematologic disease were excluded from this study. Patients taking medication affecting the QT interval duration (i.e., antiarrhythmic drugs, β -blocker, α -blocker, diltiazem, antibiotics, antipsychotic agents or antihistamines) [8] were excluded. Patients with abnormal Electrocardiogram (ECG) (atrial fibrillation or intraventricular conduction disturbance (QRS interval over 120 ms)) were also excluded. Furthermore, patients, whose serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels >47 pmol/L, were excluded because of the high possibility of chronic heart failure [9]. Approval for the study was obtained from the local research ethics committee, and informed consent was obtained from all participants.

Biochemical analysis

Fasting blood samples were obtained in the morning. Serum triglyceride, total cholesterol, creatinine, uric acid and fasting plasma glucose concentrations were assessed using standard enzymatic methods. Hemoglobin A1c was assayed using high-performance liquid chromatography and was expressed as National Glycohemoglobin Standardization Program (NGSP) unit. Urinary albumin and creatinine concentrations were determined using early morning spot urine. A mean value for urinary albumin excretion (UAE) was determined from three urine collections. Serum NT-proBNP levels were measured with a fully automated "sandwich" electrochemiluminescence method using an Elecsys proBNP II (Roche Diagnostics, Mannheim, Germany).

Measurements of QTc and PWV and ankle-brachial index

Standard, resting 12-lead ECG was performed using an ECG device (FCP-4266; Fukuda Denshi, Tokyo, Japan) in the supine position in the morning. Heart rate (bpm) and QT interval duration (ms) were determined automatically using the PI-10 ECG Analysis Program (Fukuda Denshi). The program calculated the QT interval duration from the beginning of QRS to the end of the T wave. The QT interval duration was corrected for heart rate to calculate QTc according to Bazett's equation [10]. $QTc = QT \text{ interval duration [ms]} / (60/\text{heart rate})^{1/2}$. The brachial-ankle (ba) PWV were measured using a Colin Waveform analyser (form PWV/ABI; Colin Medical Technology, Komaki, Japan), which simultaneously measures pulse volumes in the brachial and posterior tibial arteries using an oscillometric method and bilateral arm and ankle blood pressure, respectively. Both were measured after allowing the patient to rest in the supine position for at least 5 min. For measuring baPWV, pulse volume waveforms of the brachial and tibial arteries were recorded. The full description of the method has been given elsewhere [3]. After determining baPWV bilaterally, the higher value was taken as a representative for each patient. Ankle-brachial index (ABI) was calculated bilaterally as the ratio of systolic pressure in the ankle to systolic pressure in the arm, with the lower value considered a representative for each patient.

Statistical analysis

The statistical analyses were performed using the JMP version 8.0 software (SAS Institute Inc., Cary, North Carolina) and p value <0.05 was considered statistically significant. Mean, median or frequencies of potential confounding variables were calculated. Skewed variables such as triglycerides and UAE were presented as median (interquartile range), and continuous variables were presented as the mean \pm standard deviation (SD). Mann-Whitney U tests, Kruskal-Wallis rank

tests were conducted as appropriate to assess statistical significance of differences between groups. Because triglycerides and UAE showed skewed distributions, logarithmic transformation was carried out before performance of correlation and regression analyses. The relationships between QTc and PWV or other variables were examined by liner regression analysis. For examination of the effects of various factors on PWV, the following factors were considered simultaneously as independent variables for multivariate linear regression analysis: age, sex, duration of diabetes, BMI, systolic blood pressure, hemoglobin A1c, total cholesterol, log triglycerides, creatinine, uric acid, potassium, smoking status, use of antihypertensive drugs or statin, insulin treatment and QTc. Receiver operator characteristic (ROC) analyses were performed to calculate area under the ROC curve (AUC) of QTc or FRS for arterial stiffness defined as $PWV >1800 \text{ cm s}^{-1}$ [11], using the ROCKIT (http://xray.bsd.uchicago.edu/krl/roc_soft.htm).

Results

Clinical characteristics of 251 patients with type 2 diabetes enrolled in this study are shown in Table 1. Of 251 patients, hemoglobin A1c was below 7.0% in 103 (41.0%) patients and hemoglobin A1c was equal to or above 7.0% in 148 (59.0%) patients. Mean PWV was 1819.1 cm/sec, and mean QTc was 0.42 sec. Relationships between the QTc and other variables are shown in Table 2. The QTc was positively correlated with age, systolic blood pressure, log UAE or PWV. The QTc was negatively correlated with creatinine, potassium or ABI. The QTc was significantly different between sex ($p=0.0002$) and slightly longer in patients with non-smoker than that in patients with smoker ($p=0.0369$) (Table 3). Multiple regression analysis on PWV is shown in Table 4. Age ($\beta=0.236$, $p=0.0002$), BMI ($\beta=-0.13$, $p=0.0433$), systolic blood pressure ($\beta=0.213$, $p=0.0004$), total cholesterol ($\beta=-0.12$, $p=0.0455$), uric acid ($\beta=0.147$,

N	251
Age (years)	66.4 \pm 8.6
Sex (male/female)	147/104
Duration of diabetes (years)	14.4 \pm 10.2
Body mass index (kg/m ²)	23.2 \pm 3.8
Systolic blood pressure (mmHg)	128.9 \pm 14.2
Heart rate (bpm)	71.7 \pm 12.2
Fasting glucose (mmol/L)	7.4 \pm 1.8
Hemoglobin A1c (%)	7.4 \pm 1.1
Total cholesterol (mmol/L)	4.9 \pm 0.8
Triglycerides (mmol/L)	1.5 (0.9-1.9)
Creatinine (μ mol/L)	68.5 \pm 31.1
Uric acid (μ mol/L)	313.5 \pm 87.2
Potassium (mmol/L)	4.5 \pm 0.4
Smoking (-/+)	233/18
Antihypertensive drugs (-/+)	108/143
Statins (-/+)	131/120
Insulin treatment (-/+)	175/76
Retinopathy (NDR/SDR/PDR)	173/41/37
Urinary albumin excretion (mg/g creatinine)	22.0 (11.0-77.3)
Framingham risk score (%)	15.6 \pm 8.4
Ankle-brachial index	1.1 \pm 0.1
Pulse wave velocity (cm/sec)	1819.1 \pm 449.6
QTc (sec)	0.42 \pm 0.02

Data are number of patients, mean \pm SD or median (interquartile range). NDR: No Diabetic Retinopathy; SDR: Simple Diabetic Retinopathy; PDR: Proliferative Diabetic Retinopathy; QTc: Heart Rate-Corrected QT Interval Duration

Table 1: Clinical characteristics of patients.

	<i>r</i>	<i>p</i>
Age	0.213	0.0007
Duration of diabetes	0.005	0.9328
Body mass index	0.008	0.8984
Systolic blood pressure	0.196	0.0018
Fasting glucose	0.023	0.7158
Hemoglobin A1c	0.112	0.0673
Total cholesterol	0.056	0.3794
Log triglycerides	0.123	0.0525
Creatinine	-0.148	0.0192
Uric acid	0.001	0.9922
Potassium	-0.138	0.0294
Log UAE	0.253	<0.0001
Framingham risk score	0.068	0.3388
Ankle-brachial index	-0.127	0.0450
Pulse wave velocity	0.268	<0.0001

QTc: Heart Rate-Corrected; QT Interval Duration; Log: Logarithm; UAE: Urinary Albumin Excretion

Table 2: Correlation between QTc and other variables.

	QTc	<i>p</i>
Sex (male/female)	0.42 ± 0.02/0.43 ± 0.02	0.0002
Smoking (-/+)	0.42 ± 0.02/0.41 ± 0.02	0.0369
Antihypertensive drugs (-/+)	0.42 ± 0.02/0.42 ± 0.02	0.1055
Statins (-/+)	0.42 ± 0.02/0.42 ± 0.02	0.8409
Insulin treatment (-/+)	0.42 ± 0.02/0.42 ± 0.02	0.7002
Retinopathy (NDR/SDR/PDR)	0.42 ± 0.02/0.42 ± 0.02/0.43 ± 0.02	0.2156

QTc: Heart Rate-Corrected QT Interval Duration; NDR: No Diabetic Retinopathy; SDR: Simple Diabetic Retinopathy; PDR: Proliferative Diabetic Retinopathy

Table 3: Comparisons of QTc in various groups.

	β	<i>p</i>
Age	0.236	0.0002
Male	-0.033	0.6127
Duration of diabetes	0.067	0.2793
Body mass index	-0.13	0.0433
Systolic blood pressure	0.213	0.0004
Hemoglobin A1c	-0.093	0.1304
Total cholesterol	-0.12	0.0455
Log triglycerides	0.07	0.2631
Creatinine	-0.109	0.1222
Uric acid	0.147	0.0407
Potassium	0.002	0.9705
Smoking	-0.111	0.0596
Antihypertensive drugs	0.097	0.1160
Statins	-0.053	0.3703
Insulin treatment	0.04	0.5172
QTc	0.155	0.0119

PWV: Pulse Wave Velocity; Log: Logarithm; QTc: Heart Rate-Corrected QT Interval Duration

Table 4: Multiple regression analysis on PWV.

$p=0.0407$) and QTc ($\beta=0.155$, $p=0.0119$) were independently correlated with PWV, after adjustment for sex, duration of diabetes, hemoglobin A1c, log triglycerides, creatinine, potassium, smoking status, use of antihypertensive drugs or statin and insulin treatment. According to the ROC analyses (Figure 1), the optimal cut-off point of QTc was 0.428 sec ($p<0.0001$), and that of FRS was 11.0 ($p=0.0004$). The AUC of QTc and FRS for arterial stiffness, defined as PWV >1800 cm s⁻¹ [11] were

0.69 and 0.64, respectively. There was no difference between the AUC of QTc and that of FRS for arterial stiffness ($p=0.6532$).

Discussion

In the present study, the QTc correlated with PWV, which has been shown to be a functional marker for subclinical atherosclerotic disease in central and peripheral arteries [3,12]. In addition, the association was independent of systolic blood pressure, glycaemic control, duration of diabetes or other conventional CVD risk factors, suggesting an independent relationship between the QTc and subclinical atherosclerosis. To our knowledge, our study firstly showed the association between the QTc and PWV in patients with type 2 diabetes without preexisting CVD.

The QT interval duration on an ECG represents the duration of ventricular depolarization and repolarization [8]. It has been suggested that disturbance of cardiac ion channels [8] and myocardial ischemia/infarction [13] extend the QT interval duration. Although mechanisms that could explain the association between the QTc and subclinical atherosclerosis have not been clear, there are some studies which support the association. Subclinical atherosclerosis may increase ventricular load, by blood return from periphery toward the heart rapidly [14]. And this ventricular load may promote myocardial and electrophysiological remodeling and then lead to prolongation of QT interval [14,15]. Another possible mechanism is that microvascular atherosclerosis in the coronary artery, which is strongly related to subclinical atherosclerosis, may lead to subendocardial ischemia [16]. And peak systolic pressure is displaced toward the latter third of the ejection period by subendocardial ischemia and this lead to prolongation of QT interval [17]. Therefore, the QTc is likely to associate with microvascular atherosclerosis, subendocardial ischemia and subclinical atherosclerosis.

Prevalence of prolonged QT interval is higher in patients with

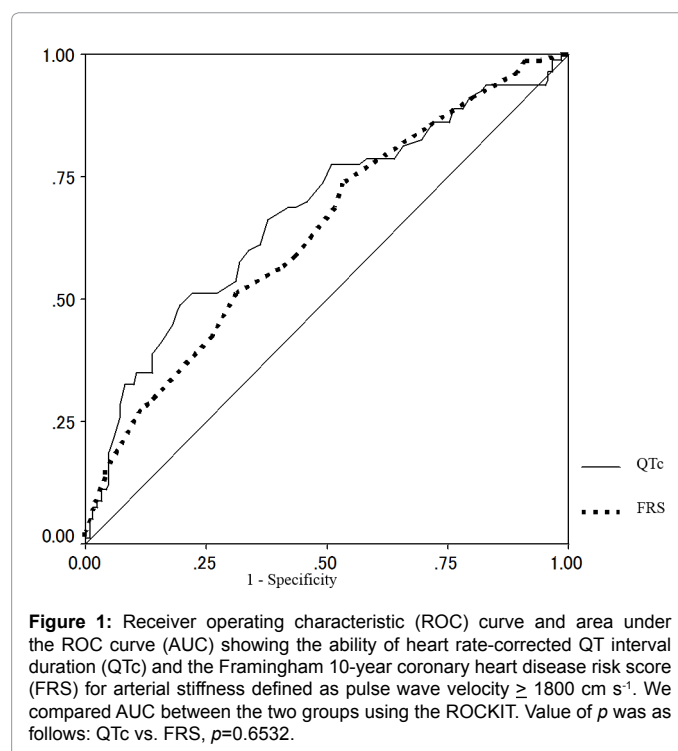


Figure 1: Receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) showing the ability of heart rate-corrected QT interval duration (QTc) and the Framingham 10-year coronary heart disease risk score (FRS) for arterial stiffness defined as pulse wave velocity ≥ 1800 cm s⁻¹. We compared AUC between the two groups using the ROCKIT. Value of p was as follows: QTc vs. FRS, $p=0.6532$.

type 2 diabetes as compared to patients without diabetes mellitus [18,19]. Moreover, prolongation of QT interval predicts the risks of all-cause and cardiovascular mortality not only in healthy population [4], but also in patients with diabetes mellitus [20]. In patients with diabetes, several risk factors of prolongation of QT interval have been cited in the literature, including age [19], gender [21], components of insulin resistance syndrome such as BMI [21], hypertension [21,22], insulin concentration [23] and hyperglycemia [24], diabetic microvascular complications such as diabetic retinopathy [21], neuropathy [21] and microalbuminuria [19,22] and preexisting coronary heart disease [19,22]. Our data shown that age, systolic blood pressure and log UAE were also correlated with the QTc in patients with type 2 diabetes, as previous studies shown. And, there is a small size study which investigated the association between prolongation of QT interval and carotid intima thickness, which is another structural marker of subclinical atherosclerosis in patients with type 2 diabetes mellitus [25]. Taking these findings together, it seems plausible that the QTc is associated with subclinical atherosclerosis in patients with type 2 diabetes without preexisting CVD. We showed that the AUC of QTc for arterial stiffness was similar to that of FRS, a marker of CHD. Thus, this result also showed that the QTc could be a marker for arterial stiffness. The diagnostic relevance concerns the diagnostic utility of QTc evaluated by ECG as a provisional new risk marker of subclinical atherosclerosis that can be measured easily in the clinical laboratory and applied in medical practice.

This study has some limitations that require consideration. First, this study was a cross-sectional design, which did not permit the determination of causality. Second, this is a single-site study and the sample size was relatively small. Thus the study population might not accurately represent the underlying population. Third, this study included only Japanese patients and thus cultural and sociodemographic differences might have affected our results. Fourth, we had no data of the QTc in non-diabetic subjects in this study. Therefore, we could not compare the QTc in patients with type 2 diabetes with that in non-diabetic subjects. Lastly, we did not check serum calcium and magnesium which is known to the cause of QTc prolongation. However, to the best of our knowledge, the present study is the first report on the relationship between the QTc and PWV in patients with type 2 diabetes. Large prospective trials are needed to better assess the relationship between the QTc and subclinical atherosclerosis in patients with type 2 diabetes.

Conclusion

The QTc could be a marker of subclinical atherosclerosis as well as CVD events in patients with type 2 diabetes, and the examination of the QT interval could be a practical screening tool to predict subclinical atherosclerotic disease and it is beneficial to recognize the segment of the patients with type 2 diabetes whose QTc is longer to protect them from the development of subclinical atherosclerotic disease.

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