Association Between the Corrected QT Intervals and Combined Intimal-Medial Thickness of the Carotid Artery in Patients With Type 2 Diabetes

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The main purpose of this study was to determine whether cardiac autonomic neuropathy or coronary atherosclerosis is the more important factor affecting prolongation of the corrected QT interval (QTc) in patients with type 2 diabetes. We studied the association between QTc and the coefficient of variance of the heart rate variation (CV_{RR}), which reflects cardiac autonomic neuropathy, and the combined intimal-medial thickness (IMT) of the common carotid artery, which reflects coronary atherosclerosis. In addition, we also investigated the relationship between the QTc and blood pressure, serum lipid concentrations, hemoglobin A_{1C} (HbA_{1C}) concentration, and duration of diabetes. We studied 75 patients with type 2 diabetes and 30 age-matched healthy individuals. The QT interval was measured in lead II of the electrocardiogram (ECG) and was corrected using Bazett's formula. Cardiac neuropathy was assessed by measuring CV_{RR}. Atherosclerosis was evaluated by measuring the combined IMT of the common carotid artery using B-mode ultrasonography. The QTc in patients with type 2 diabetes was significantly longer than in healthy individuals ($P < .0001$). The QTc more closely correlated with the IMT of the carotid artery ($r = 0.7206$, $P < .0001$), compared with CV_{RR} ($r = -0.3188$, $P = .0053$), although both were statistically significant. The QTc also correlated positively with the systolic (SBP) and diastolic blood pressure (DBP) ($r = 0.4371$, $P < .0001$, $r = 0.3632$, $P = .0014$, respectively). Based on stepwise regression analysis with the QTc interval as the dependent variable, the IMT of the carotid artery had the most significant association with the QTc ($\beta = 0.6882$, $P = .0004$). In conclusion, QTc prolongation in the setting of diabetes might be caused primarily by coronary atherosclerosis rather than by cardiac autonomic neuropathy.

SEVERAL AUTHORS have reported that there is prolongation of the corrected QT interval (QTc) on electrocardiograms (ECGs) of diabetic patients,[1-5] especially in those with autonomic neuropathy.[2-5] However, QTc prolongation is induced not only by autonomic nerve impairment but also by damage to ventricular muscle cells through other mechanisms, such as congenital disease,[6,7] certain drugs,[8-10] and especially ischemia.[11-14] Diabetes mellitus causes both microangiopathy, resulting in neuropathy, and macroangiopathy, resulting in coronary arteriosclerosis and ischemic heart disease. Therefore, in type 2 diabetic patients, not only autonomic neuropathy but also coronary atherosclerosis can influence the QTc. However, it is not fully understood which of these is the more important factor affecting QTc prolongation in diabetic patients, although recent reports have emphasized the strong association between QTc and coronary atherosclerosis.[14-17]

In our previous study, we investigated the relationship between QTc and autonomic neuropathy assessed by autonomic neurofunctional tests, including the systolic blood pressure (SBP) response on standing (ΔBP) and coefficient of variance of the heart rate variation (CV_{RR}), and found a significant correlation between QTc and these parameters in patients with type 2 diabetes without clinically evident coronary disease.[18] However, these correlations were relatively weak. Furthermore the QTc also had a significant association with SBP and diastolic blood pressure (DBP) and a tendency to be prolonged in patients with obesity, which are both risk factors for coronary atherosclerosis. Based on the results of our previous study and reports emphasizing the effect of atherosclerosis on QTc, we hypothesized that the QTc is predominately influenced by coronary atherosclerosis rather than cardiac autonomic neuropathy in patients with type 2 diabetes, even if they do not have clinically overt coronary disease. The aim of the current study was to confirm this hypothesis by investigating the association between the QTc and the intimal-medial thickness (IMT) of the carotid artery as a marker of atherosclerosis[19-22] and the CV_{RR}, reflecting cardiac autonomic neuropathy. In addition, we reexamined the relationship between the QTc and other factors such as blood pressure, serum lipid concentration, and hemoglobin A_{1C} (HbA_{1C}) concentrations and the duration of diabetes, which may also be associated with QTc prolongation.

MATERIALS AND METHODS

Patients

In the current study, patients with arrhythmias or clinically evident ischemic heart disease (past history of myocardial infarction, presence of abnormal Q waves on the ECG, or angina pectoris) were excluded. Patients taking β-blockers, probucol, astemizole, cisapride, or antiarrhythmic drugs, including mexiletine, which can affect the QTc intervals, were also excluded. In addition, patients with evidence of left ventricular hypertrophy (cardiothoracic ratio >50% on chest roentgenography or ECG: $RV_5 > 2.6$ mV), which may influence the QTc interval, were also excluded.

Initially, 99 type 2 Japanese diabetic patients admitted to our hospital in order to treat poorly controlled hyperglycemia and 30 age-matched healthy individuals were enrolled in the current study. Among these diabetic patients, 4 had arrythmia alone as exclusion criteria. Seven patients showed both arrythmia and left ventricular hypertrophy. On the other hand, 5 patients had past history of myocardial infarction, including 3 patients who showed left ventricular hypertrophy simultaneously. Except for these patients, 8 patients were excluded for the administrated drugs. Therefore, a total of 75 patients were investigated in this study, 24 patients were excluded.

The diabetic patients consisted of 36 men and 39 women with a

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Table 1. Clinical Characteristics of Normal Healthy and Diabetic Individuals

	Normal	Diabetic	*P* Value
No. (male/female)	30 (15/15)	75 (36/39)	—
Age (yr)	60.2 ± 4.9	59.6 ± 8.4	.6493
Duration of diabetes (yr)	—	10.8 ± 8.1	—
FPG (mg/dL)	90.1 ± 6.8	213.3 ± 84.7	<.0001*
HbA_{1c} (%)	4.9 ± 0.3	10.1 ± 2.4	<.0001*
BMI (kg/m^2)	21.7 ± 1.9	23.7 ± 3.9	.0004*
SBP (mm Hg)	119.1 ± 12.3	138.5 ± 23.9	<.0001*
DBP (mm Hg)	69.4 ± 6.9	78.9 ± 14.2	<.0001*

NOTE. Data represent the mean ± SD.

Abbreviations: FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A_{1c}; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*$P < .05$ defined as statistical significance.

mean age of 59.6 ± 8.4 years (range, 39 to 74 years). The healthy control group included 15 men and 15 women with a mean age of 60.2 ± 4.9 years (range, 41 to 66 years). The mean duration of diabetes was 10.8 ± 8.1 years (range, 1 to 40 years). In the diabetic patients, their fasting plasma glucose (FPG), HbA_{1C}, and body mass index (BMI) were 213.3 ± 84.7 mg/dL, 10.1% ± 2.4%, and 23.7 ± 3.9 kg/m^2, respectively. In the healthy group, the mean FPG, HbA_{1C}, and BMI were 90.1 ± 6.8 mg/dL, 4.9% ± 0.3%, and 21.7 ± 1.9 kg/m^2, respectively. These parameters were evaluated in diabetic patients before breakfast on the day after admission. These clinical characteristics of normal healthy and diabetic individuals are presented in Table 1.

Nine patients were treated with diet modification, while 43 patients received oral hypoglycemic agents (OHA), which included glibenclamide or gliclazide. The remaining 23 patients were treated with insulin injections. Thirty-one patients had hypertension, defined as a SBP ≥ 140 mm Hg or a DBP ≥ 90 mm Hg, independent of the use of antihypertensive agents. Twenty-nine patients had been treated with antihypertensive drugs (angiotensin-converting enzyme inhibitor [ACE-I] or calcium channel blocker).

Diabetic nephropathy was assessed based on the measurement of urinary albumin excretion (UAE). The patients were classified into 3 groups: normoalbuminuria (NAU), UAE less than 30 mg/g · creatinine (Cr); microalbuminuria (MIAU), 30 ≤ UAE ≤ 300 mg/g · Cr; and macroalbuminuria (MAAU), UAE greater than 300 mg/g · Cr. There were 33 patients with NAU, 21 with MIAU, and 21 with MAAU. Diabetic retinopathy was assessed by an oculist according to Davis' criteria.[23] There were 29 patients with no diabetic retinopathy (NDR), 23 with simple diabetic retinopathy (SDR), and 23 with proliferative diabetic retinopathy (PDR).

Methods

The QT and RR intervals were simultaneously assessed from 100 consecutive beats on the ECG. The ECGs were recorded at a chart speed of 25 mm/s. During the recording, all of the subjects were at rest in a supine position and were instructed to maintain a respiratory rate greater than 9 breaths/min to decrease any effect of respiratory sinus arrhythmia. As an index of heart variability, the CV_{RR} was calculated according to the formula: CV_{RR} = (standard deviation of RR/mean RR) × 100. No patient had an increased QRS duration. The QT interval was defined as the period from the starting point of the Q wave to the terminal point of the T wave. The terminal point of the T wave was determined as the point at which both the tangential line of the descending T wave (or the ascending one when the T wave was inverted) and the tangent of the baseline intersected. The QT interval was measured manually for 3 suitable consecutive beats in lead II, using calipers. The QTc interval was then calculated for each of these beats based on Bazett's formula ($QTc = QT/RR^{1/2}$).[24] The mean of these 3 consecutive QTc intervals was used as the subject's QTc interval. To prevent the QT intervals from being overvalued or undervalued by application of Bazett's formula, only individuals with a normal pulse rate (60 to 100 beats/min) were enrolled in this study. Antihypertensive drugs were suspended for 3 days before measuring the QTc and CV_{RR}. Although the QTc and RR intervals were recorded generally on the day after admission in the morning, especially in patients with antihypertensive drugs, those were measured several days after admission in relation to the suspicion period of the drugs.

The IMT was assessed using ultrasonography (SSD-1200, Aloka Co, Tokyo, Japan) with a 7.5-MHz linear pulse echo-probe (ASU-35WL-7.5). The axial resolution is less than 0.1 mm with this probe. The extracarotid artery (common carotid artery) in the neck, with a suitable portion selected for the assessment, was scanned in the longitudinal projection on the right side in an anterior-oblique position. These images were photographed simultaneously. By ultrasonography, the intimal-medial complex appears as a complex of 2 layers (inner highly echogenic and outer minimally echogenic portions) and the IMT was defined as the distance from the inside part of the highly echogenic layer to the outside of the minimally echogenic layer. The IMT was measured at the thickest portion in the scanning area, including plaques, and with a 1-cm interval on each side using calipers as demonstrated by Kawamori et al.[25] The mean of three IMT measurements were used as the individual's IMT. In the present study, plaque was defined as an IMT ≥ 1.1 mm according to the criteria of Handa et al.[26]

Blood pressures were measured with the subjects in a sitting position after at least 5 minutes of rest before breakfast on the same day when the QTc intervals or CV_{RR} were measured.

UAE was measured once by enzyme immunoassay in a 24-hour urine specimen. Albumin values were corrected for urinary creatinine concentration.

The fasting plasma glucose concentration was assessed using an automated glucose oxidase method (Glucose Auto STAT GA1160, Arkray Co, Kyoto, Japan). The HbA_{1C} was measured by high-performance liquid chromatography (HPLC; HiAUTO A_{1C}, HA8150, Arkray). By this method, a stable HbA_{1C} alone was evaluated and this normal values were 4.3%~5.8%. Serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) concentrations were measured using enzymatic assays (AU5200, Olympus Co, Tokyo, Japan).

All venous blood samples were collected from patients after a 10-hour overnight fast on the morning following admission. Accordingly, the FPG were not necessarily measured at that time when the IMT and QTc testing were performed.

All subjects gave informed consent to be included in the current study, which was performed according to the guidelines proposed in the Declaration of Helsinki.

Statistical Methods

All data are presented as the mean ± SD. We calculated that a sample of 45 patients was required for 80% power ($\beta = 0.2$) at a significance level of .05 ($\alpha = 0.05$) to detect an achievable r value of 0.4 between the paired values. The sample size was calculated as follows: $n = [2(Z_{\alpha/2} + Z_{\beta}) + \ln(1 + r/1 - r)]^2 + 3$. The significance of correlations between 2 variables was determined by simple regression analysis. Comparisons between 2 groups were examined using an unpaired t test after group normality had been confirmed by chi-square test and the homogeneity of variance of 2 groups was evaluated using the F test (Student's or Welch's t test were used based on results of the calculated homogeneity of variance). For multiple comparisons, homo-

Table 2. QT Intervals in Control Individuals Classified by Gender and in Diabetic Patients Classified by Gender and Various Groups

	n	QT Interval	*P* Value
Normal individuals			
Total	30	398.0 ± 26.4	
Male	15	387.2 ± 20.8	.0246[1]*
Female	15	408.8 ± 28.5	
Diabetic individuals			
Total	75	430.1 ± 33.4	
Male	36	431.7 ± 36.5	.6925[1]
Female	39	428.6 ± 31.3	
Hypertension (+)	31	445.5 ± 30.0	.0006[1]*
Hypertension (−)	44	419.3 ± 32.1	
Plaque (+)	12	474.1 ± 16.7	<.0001[1]*
Plaque (−)	63	421.7 ± 29.3	
Therapy			
Diet	9	397.1 ± 24.4	.0032[1]*
OHA	43	431.2 ± 34.1	.0002[2]*
Insulin	23	440.9 ± 38.4	.1248[3]
Retinopathy			
NDR	29	423.6 ± 32.8	.0500[1]
SDR	23	439.4 ± 34.8	.2746[2]
NDR	23	429.1 ± 32.9	.1538[3]
Nephropathy			
NAU	33	431.9 ± 37.7	.2114[1]
MIAU	21	424.1 ± 28.4	.4474[2]
MAAU	21	433.2 ± 32.5	.1700[3]

NOTE. Data are presented as the mean ± SD

Abbreviations: OHA, oral hypoglycemic agents; NDR, no diabetic retinopathy; SDR, simple diabetic retinopathy; PDR, proliferative diabetic retinopathy; NAU, normoalbuminuria; MIAU, microalbuminuria; MAAU, macroalbuminuria.

In therapy, retinopathy, and nephropathy, *P* values represent those between respective QTc intervals according to the assigned number. *$P < .05$ is defined as statistical signficance.

geneity of variance was evaluated using the Bartlett test. Parametric comparisons used analysis of variance (ANOVA). Significances of individual differences were assessed by using the Bonferroni test if the ANOVA was significant. Multiple regression analysis with the QTc interval as the dependent variable was performed using stepwise regression analysis. The independent variables provided initially were the IMT of the carotid artery, CV_{RR}, SBP, DBP, age, duration of diabetes, BMI, HbA_{1C}, TC, HDL-C, LDL-C, TG, and UAE. Then, each variable with F values less than 2 was excluded. Multiple regression analysis was performed for the remaining dependent variables. In the current study, a *P* value <.05 (2-sided) was defined as statistically significant. The statistical analyses were performed using SPSS programs (SPSS Inc, Chicago, IL).

RESULTS

In the current study, the QTc in the 75 diabetic patients was longer than in 30 healthy subjects ($P < .0001$). There was a significant difference between the QTc in healthy men and women, while no significant gender difference was observed in the diabetic patients. Each QT interval in control individuals classified by gender and in diabetic patients classified by gender and various groups is shown in Table 2.

A significant negative correlation existed between the QTc and the CV_{RR} (Fig 1) and a positive correlation existed between the QTc and the IMT of the carotid artery (Fig 2). Positive correlations were also observed between the QTc and the SBP and DBP (Fig 3). No correlation was noted between the QTc and the HbA_{1C}, TC, LDL-C, HDL-C, or TG concentration. The QTc did not correlate with UAE, and even when UAE was log_{10}-transformed, the correlation did not show statistical significance ($r = 0.0860$, $P = .4633$). In addition, no significant association was detected between the QTc and age, duration of diabetes, or BMI. The coefficients and *P* values for the correlations between the QTc and various parameters based on linear regression analysis are summarized in Table 3.

On the other hand, the IMT significantly correlated with SBP ($r = 0.2970$, $r = 0.0097$), but it did not correlate with HbA_{1C}, duration of diabetes, DBP, TC, LDL-C, HDL-C, TG, and CV_{RR}. When patients were classified by therapies (diet, OHA, and insulin), there were no differences in age, BMI, FPG, and HbA_{1C} among these groups. Mean durations of diabetes in the diet, OHA, and insulin groups were 4.4 ± 4.3, 10.2 ± 7.6, and 14.5 ± 8.9 years, respectively. Significant differences for QTc

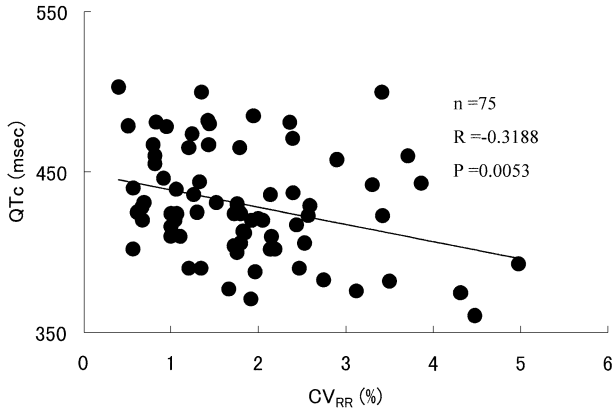

Fig 1. Correlation between corrected QT intervals and coefficient of variance of the heart rate variations (CV_{RR}) in type 2 diabetic patients.

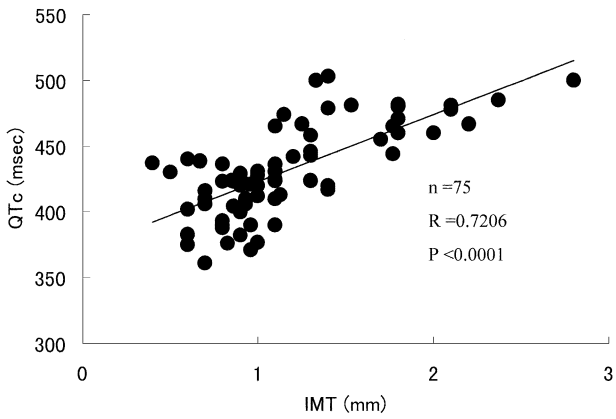

Fig 2. Correlation between corrected QT intervals and intimal-medial complex thickness of the carotid artery (IMT) in type 2 diabetic patients.

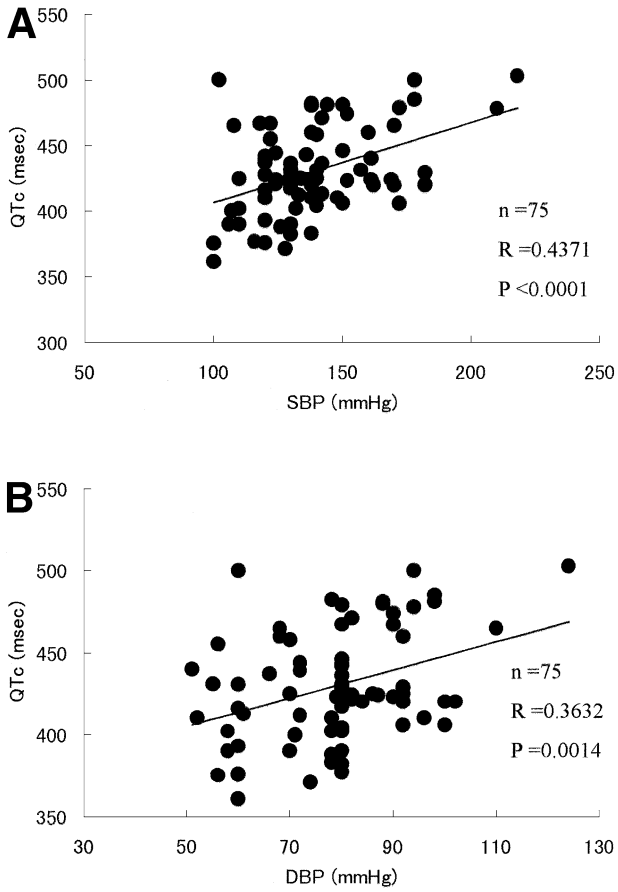

Fig 3. Correlation between corrected QT intervals and (A) systolic blood pressure or (B) diastolic blood pressure in type 2 diabetic patients.

were found between the diet and OHA ($P = .0172$), diet and insulin ($P = .0002$), and the OHA and insulin groups ($P = .0208$). With respect to IMT, the mean IMTs in diet, OHA, and insulin groups were 0.84 ± 0.21, 1.21 ± 0.53, and 1.13 ± 0.41 mm, respectively. There were significant differences for QTc between the diet and OHA ($P = .0014$) or insulin groups ($P = .0244$). In relation to SBP, mean SBPs in the diet, OHA, and insulin groups were 126.2 ± 13.7, 133.3 ± 20.1, and 153.2 ± 26.4 mm Hg, respectively. Significant differences for QTc were noted between the diet and insulin ($P = .0035$) and OHA and insulin groups ($P = .0006$).

Based on stepwise regression analysis, the IMT of the carotid artery, SBP, and serum TG concentration were independent variables that showed significant associations with the QTc.

The results of stepwise regression analysis with the QTc as the dependent variable are shown in Table 4.

DISCUSSION

It is well known that the QTc is prolonged in diabetic patients with autonomic neuropathy.[2-5] However, the role of coronary heart disease in causing QTc prolongation in these patients has also been identified because diabetes causes a systemic atherosclerosis, including the coronary artery.[14-17] Recently, Festa et al[27] demonstrated that the QTc could be prolonged and had a significant association with the IMT as a marker of coronary artery even in nondiabetic individuals without clinically apparent coronary heart disease. Therefore, the QTc might be affected even by latent coronary atherosclerosis.

In our previous study,[18] we could not determine whether autonomic neuropathy or subclinical coronary atherosclerosis had a greater influence on QTc prolongation in diabetic patients. As far as we know, there are no reports investigating this issue before now. We therefore investigated this issue by measuring the IMT of the carotid artery, which reflects coronary atherosclerosis,[20-22] and the CV_{RR}, a marker of cardiac autonomic neuropathy. Based on the results of our previous study[18] and the recent reports that emphasize the strong correlation between the QTc and coronary atherosclerosis,[14-17,27] we hypothesized that the QTc is more strongly correlated with the IMT than the CV_{RR} in patients with type 2 diabetes.

In the current study, we demonstrated the close association between the QTc and the IMT. Furthermore as we expected, in both simple and multiple regression analysis, we found that the QTc is influenced more strongly by the IMT than by the CV_{RR} in patients with type 2 diabetes, even in those who do not have clinically overt coronary heart disease. To our knowledge, this is the first report demonstrating that in patients with type 2 diabetes the QTc prolongation might be determined predominantly by the presence of atherosclerosis rather than by cardiac autonomic neuropathy.

To inhibit the progression of macroangiopathy in diabetic patients, the treatment of other risk factors for atherosclerosis, including hypertension and dyslipidemia in addition to strict glycemic control, might also be important,[28] although such treatments are also effective for inhibition of microangiopathy as nephropathy.[29,30] In the current study, in fact, SBP correlated with not only QTc but also with IMT. However, we could not

Table 3. Relationship Between Various Factors and QTc Intervals in 75 Diabetic Patients

Variable	QTc Interval	
IMT (mm)	$r = 0.7206$	$P < .0001$*
CV_{RR} (%)	$r = -0.3188$	$P = .0053$*
SBP (mm Hg)	$r = 0.4371$	$P < .0001$*
DBP (mm Hg)	$r = 0.3632$	$P = .0014$*
Age (yr)	$r = 0.1949$	$P = .0937$
Duration (yr)	$r = -0.0044$	$P = .9699$
BMI (kg/m^2)	$r = 0.1635$	$P = .1610$
HbA_{1c} (%)	$r = -0.1569$	$P = .1789$
TC (mg/dL)	$r = 0.1339$	$P = .2519$
LDL-C (mg/dL)	$r = 0.0536$	$P = .6481$
HDL-C (mg/dL)	$r = 0.0840$	$P = .4739$
TG (mg/dL)	$r = 0.1357$	$P = .2456$
UAE (mg/g · Cr)	$r = 0.1926$	$P = .0979$

Abbreviations: *r,* Pearson's correlation coefficient, *P, P* value, IMT, intimal-medial complex thickness of the carotid artery, CV_{RR}, coefficient of variation of RR intervals; Duration, duration of diabetes; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; UAE, urinary albumin excretion.

*$P < .05$ is defined as statistical significance.

Table 4. Stepwise Regression Analysis With QTc Intervals as the Dependent Variable

Independent Variable	β	SEM	F	*P*
IMT of the carotid artery (mm)	0.6882	5.1240	90.3969	.0004*
CV_{RR} (%)	−0.1348	2.5321	3.1647	.0797
SBP (mm Hg)	0.1951	0.1120	6.0126	.0167*
HbA_{1c} (%)	−0.1175	1.0713	2.3347	.1311
TG (mg/dL)	0.1714	0.0247	4.9839	.0288*
R^2 for the model: 64.2%				

NOTE. Variables with F values less than 2 were excluded from this multiple regression analysis.

Abbreviations: β, standardized regression coefficient; SEM, standard error of the mean; F, F value; *P, P* value; R^2, coefficient of determination; IMT, intimal-medial complex thickness; CV_{RR}, coefficient of variation of RR intervals; SBP, systolic blood pressure; TG, triglyceride.

*$P < .05$ is defined as statistical significance.

demonstrate a close relationship between IMT or QTc and HbA_{1C}, duration of diabetes, or serum lipid concentration. Therefore, we can only conclude that the treatment of hypertension might especially be beneficial for the prevention of incidents by QTc prolongation in diabetic patients and that, as for the association between QTc and serum lipid concentrations or HbA_{1C}, additional investigations should be performed because of the lack of the close correlation between these parameters in the current study.

We also investigated the association between QTc and UAE. Since it is well known that UAE is generally strongly associated with macroangiopathy,[31] we expected the close association between QTc and UAE. However, although a tendency for a correlation between QTc and UAE was observed, the correlation did not show statistical significance even when UAE was log-transformed. It is difficult to explain the reason for this negative result fully, but since we could measure UAE only once in the current study, the problem of reproducibility of the UAE measured might have influenced the result.

Interestingly, in the current study, QTc in the OHA and insulin groups was significantly prolonged compared to that in the diet group. Although the duration of diabetes among the diet, OHA, and insulin groups increased in turn, since QTc never correlated with the duration of diabetes, it is unlikely that the differences in duration of diabetes among these groups caused the QTc prolongation. On the other hand, IMT significantly increased in the OHA and insulin groups compared to the diet group. Therefore, we concluded that the cause of the differences of QTc among groups classified by therapies could be explained, at least in part, by the similar differences of IMT among these groups although, as for the reason for the increase of IMT in the OHA and insulin groups, more detailed analysis is needed. In addition, since SBP was higher in the insulin group than in the diet group, this also might have influenced the differences of QTc among these groups.

Many limitations for this study design and the interpretation of the results must be pointed out. First, the validity of using the IMT to assess coronary atherosclerosis must be discussed. We could not assess coronary atherosclerosis directly by coronary angiography in the current study. We agree that, for exact assessment of coronary atherosclerosis, angiography is indispensable, although there is evidence showing that the IMT closely reflects the severity of coronary atherosclerosis.[20-22] Therefore, we recommend additional studies using coronary angiography in addition to IMT to evaluate the relationship between QTc and coronary atherosclerosis more clearly.

Second, although in the current study we excluded patients with clinically overt coronary atherosclerosis based on past history or the findings suggesting the presence of coronary artery disease on ECG, the criteria for exclusion may still be somewhat ambiguous.

Third, we must recognize that the methods available for the assessment of cardiac autonomic neuropathy are extremely limited. In the current study, we could measure only the CV_{RR}. This parameter is easily measured noninvasively, which is why we adopted this method. However, it is not necessarily as accurate as other classic autonomic tests. To strengthen the confidence in the results of our study, additional trials using other classic autonomic tests should be performed.

Fourth, in the current study, we investigated QTc for patients with poorly controlled type 2 diabetes. Since QTc and CV_{RR} were measured before euglycemia was fully achieved, all of the patients had relatively high plasma glucose values. This might have masked the true correlation between QTc and CV_{RR} because of a possible influence of plasma glucose values. Therefore, to weaken the influence on the association between QTc and CV_{RR}, ideally we should have measured them after euglycemia had been achieved completely.

In addition, unfortunately we failed to measure IMT in healthy subjects. We believe that it is worth investigating whether the relationships obtained between QTc and IMT or CV_{RR} in the current study were unique to the diabetic subjects. Therefore, we will need to explore these relationships in healthy subjects in the future.

Furthermore, it must be pointed out that the observations identifying the relationship between the QTc and the IMT in our study were cross-sectional. Therefore, we believe a prospective study of the relationship between the QTc and the IMT should also be performed to investigate these correlations more precisely.

In conclusion, the current study confirms that the QTc is prolonged in type 2 diabetic patients without clinically overt coronary heart disease. The QTc was more closely correlated to the IMT of the carotid artery than to the CV_{RR}. Based on

multiple regression analysis, the IMT had the strongest association with the QTc. Therefore, these findings might suggest that the prolongation of the QTc can be attributed primarily to atherosclerosis rather than cardiac autonomic neuropathy in patients with type 2 diabetes, even if they do not have clinically overt coronary heart disease.

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