Patients with Metabolic Syndrome Have Prolonged Corrected QT Interval (QTc)

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ABSTRACT

Background: Prolongation of corrected QT interval (QTc) increases morbidity and mortality and QTc has been found to be longer in patients with diabetes mellitus than in healthy controls. It is still inconclusive whether the metabolic syndrome results in QTc prolongation.

Hypothesis: We hypothesized that metabolic syndrome might contribute to risk of QTc prolongation. The hypothesis was tested in a large population.

Methods: A total of 5,815 individuals (men: 1,950, women: 3,865 aged 20–80 years) were enrolled. Metabolic syndrome was defined according to the revised third National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III). QTc was calculated by using Bazett and Fridericia equations and the corrected JT interval (JTc) was derived by subtracting the QRS duration from the QTc*B*. All individuals had physical examinations, electrocardiograms, echocardiography, and blood tests.

Results: Individuals with metabolic syndrome had longer QTcs and JTc than those without metabolic syndrome (439.84 ms versus 430.90 ms in men, 456.37 ms versus 445.12 ms in women, respectively, $p < 0.001$ using Bazett formula). The more the number of abnormal metabolic parameters they had, the longer the QTcs and JTc they had. Trend analysis indicated that QTc*B*, QTc*F*, and JTc were significantly correlated to the number of abnormal metabolic parameters both in men and in women. After being adjusted for conventional risk factors, QTc*B*, QTc*F*, and JTc remained negatively associated with serum potassium concentration and positively associated with interventricular septal thickness.

Conclusions: Metabolic syndrome is a risk factor for prolonged QTc, which may further increase cardiovascular morbidity and mortality in the subjects with metabolic syndrome.

Key words: QTc, metabolic syndrome, risk factor

Introduction

The QT interval reflects the duration of ventricular myocardial repolarization and depolarization, and is highly dependent on heart rate. QT interval is shorter at a faster heart rate, and longer at a slower heart rate. A prolonged QT interval has been found to be associated with electrical instability of myocardium and leads to adverse cardiovascular outcomes, including ventricular fibrillation and sudden death.[1–3] Prolongation of QTc can also be used to predict cardiac death in patients after myocardial infarction and stoke, in patients with diabetes, or heart failure.[4–7] The prolongation of QT interval has been reported to be associated with cardiovascular morbidity and mortality in apparently healthy adults.[2]

The length of the QTc has been found to be longer in persons with diabetes mellitus than in healthy controls.[8] Recent studies suggest that patients with metabolic syndrome (MetS) have significantly higher value of QTc and early body weight reduction could reverse the prolonged QTc,[9,10] however the number of studied patients and controls were too small to draw a definite conclusion. To clarify the relationship between QTc and MetS, a large population was employed in this study, and a possible pathophysiological mechanism for the relationship was discussed.

Subjects and Methods

Subject Selection

A total of 5,815 participants (those with hypertension: 4,751; those without hypertension: 1,064), aged 20 to 80 years, were consecutively recruited from 6 hypertensive care units from March 2005 to May 2005 from rural areas in China. The criteria of hypertension was systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg. According to the revised third National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III) definition,[11] 2,432 individuals were diagnosed with MetS. Patients treated with antihypertensive, antidiabetes, and antidyslipidemia

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agents or patients taking any medication known to affect QT intervals were excluded from the study. The exclusion was also extended to subjects with histories of coronary heart disease, valvular heart disease, stroke, hepatic, renal, thyroid diseases, and arrhythmia including atrial flutter, atrial fibrillation, and third-degree atrioventricular block or with a cardiac pacemaker. The study was approved by ethics committees in China and informed consent was obtained from each participant before data collection.

Methods

Each participant refrained from smoking, drinking alcohol or coffee, and heavy exercise for 2 h before examination. Two blood pressures were recorded at 5 min intervals using a mercury sphygmomanometer in the sitting position after a 10 min rest in the morning according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7).[12] The average of 2 measurements was used in data analysis. Body weight with light clothing and height were recorded. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the midpoint between the bottom of rib cage and the top of lateral border of iliac crest during minimal respiration.

Blood samples were collected after a 12 h overnight fast. Serum total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), glucose (GLU), and potassium concentrations were determined using an automatic analyzer (Hitachi 7060, Hitachi, Tokyo, Japan).

Metabolic syndrome was diagnosed according to the revised NCEP-ATP III definition, having 3 or more of the following metabolic abnormalities: (1) fasting plasma GLU $\geq$5.6 mmol/L or previously diagnosed type 2 diabetes, (2) arterial blood pressure $\geq$130/85 mm Hg or on antihypertensive medication, (3) TG $\geq$1.7 mmol/L or treatment for this abnormality, (4) HDL-C $<$1.29 mmol/L for women or $<$1.03 mmol/L for men or treatment for this abnormality, (5) waist circumference $\geq$90 cm for men, and $\geq$80 cm for women (criteria for Chinese population).

Each participant underwent a resting standard supine 12-lead ECG at a paper speed of 25 mm/s and amplitude of 10 mm/mv.[13] ECGs (12-leads simultaneously) were recorded for 10 sec by using a MAC PC Personal Cardiograph (GE Medical Systems, Fairfield, Conn., USA). ECGs were interpreted manually at the Core Laboratory in Fuwai Hospital, Chinese Academy of Medical Sciences, and the 2 readers were unaware of the characteristics of the subjects and trained to minimize the intravariability of measurements. QT and R-R intervals was averaged over 3 consecutive cycles on lead V_2 or V_3 using a graduated lens as QT in the anteroseptal leads provides the closest approximation to the maximum QT.[14] In accordance with the latest recommendations for clinical QT interval measurement,[15] QT intervals were measured from the beginning of the QRS complex to the visual return of the T-wave to the isoelectric line. A discrete U-wave after the T-wave has returned to baseline should be excluded from measurement. When T-waves and U-waves are fused the U component should be included.

Corrected QT interval was calculated using the Bazett formula (QTcB = QT/RR1/2) and the Fridericia formula (QTcF = QT/RR1/3). The Bazett formula is commonly applied to adjust QT interval for heart rate, considering the interval is underestimated at low heart rate and overestimated at fast heart rate with the Bazett formula, we also adopted the Fridericia formula.[16] The JTc has been proposed as a more appropriate measure of ventricular repolarization than QTc when QRS duration is $\geq$120 ms.[17] The JTc was derived simply by subtracting the QRS duration from QTcB. The cut off value of QTcB is 430 ms for men and 450 ms for women.[18] Complete left bundle branch block (CLBBB) and complete right bundle branch block (CRBBB) were defined as previously described;[19] CLBBB, as QRS duration $\geq$120 ms in a majority of beats in any of leads I, II, III, aVL, or aVF plus R peak duration $\geq$60 ms in a majority of beats in any of leads I, II, aVL, V_5, or V_6; CRBBB, as QRS duration $\geq$120 ms in a majority of beats in any of leads I, II, III, aVL, or aVF plus R′$>$R in V_1 or QRS mainly upright, plus R peak duration $\geq$60 ms in V_1 or V_2 or S duration $>$R duration in lead I or II.

Echocardiography studies were performed by 2 physicians. Echocardiography images were obtained in the parasternal long-axis and short-axis views, and apical 2-chamber and 4-chamber views with standard transducer positions. Left ventricular internal diastolic (LVID), and interventricular septal thickness (IVS) were measured on up to 3 cardiac cycles at end-diastole according to the recommendations of the American Society of Echocardiography.[20]

Statistical Analysis

The data were analyzed using SPSS version 13.0 for Windows (SPSS Inc. Chicago, Illinois). A Student t test and one-way analysis of variance (ANOVA) Bonferroni test was used for the comparison of continuous variables. The univariate analysis was used to compare the duration of adjusted QTc between different groups. The chi-square test was used for the comparison of categorical variables. A one-way ANOVA polynomial liner test was used for a trend analysis. For assessing independent determinants of the QTcB, QTcF, and JTc, we fitted stepwise multiple regression models including variables (age, sex components of MetS, serum kalium level [K], LVID, IVS, and status of smoking or drinking) probably related to the QTc. A p value of $<$0.05 was considered significant.

Results

The clinical characteristics of the study population are listed in Table 1; 2,432 individuals were diagnosed with

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Table 1. Clinical characteristics

	Men		Women	
	non-MetS	MetS	non-MetS	MetS
n (%)	1,377 (70.6)	573 (29.4)	2,006 (51.9)	1,859(48.1)
age (years)	60.50±9.35	58.10±8.89†	57.25±8.96	58.02±8.31*
QRS (ms)	97.39±12.97	97.61±12.36	92.22±11.50	92.47±11.13
QT (ms)	405.1±35.15	402.83±39.85	407.26±36.36	414.28±42.08†
QTc*B* (ms)	430.90±48.15	439.84±50.89†	445.12±48.09	456.37±56.43†
QTc*F* (ms)	420.23±40.24	427.96±51.93†	432.00±41.36	440.82±48.78†
JT (ms)	302.55±35.85	304.11±40.79	314.68±37.72	319.88±42.62†
JTc (ms)	333.35±50.33	341.38±53.57†	352.83±49.84	364.10±57.64†
prolonged QTc*B* (%)	41.90	49.90†	39.20	45.40†
AA (%)	2.60	1.70	1.60	1.30
VA (%)	2.60	1.60	1.40	1.70
CRBBB (%)	3.10	4.40	2.20	1.50
CLBBB (%)	0.10	0.30	0.30	0.40
K^+ (mmol/L)	4.47±0.52	4.44±0.51	4.41±0.50	4.38±0.50*
IVS (mm)	10.36±1.61	10.72±1.67†	9.67±1.56	9.91±1.46†
LVID (mm)	46.93±5.23	47.74±5.54*	44.45±4.80	45.01±4.75†
SBP (mm Hg)	156.17±27.83	160.94±23.24†	155.41±29.56	163.68±25.30†
DBP (mm Hg)	94.98±13.61	99.90±12.59†	92.83±13.59	96.46±12.47†
GLU (mmol/L)	5.14±1.35	6.28±2.06†	4.98±1.08	6.10±2.25†
HDL-C (mmol/L)	1.57±0.34	1.35±0.31†	1.69±0.31	1.44±0.30†
TG (mmol/L)	1.19±0.67	2.58±2.31†	1.20±0.47	2.24±0.47†
WC (cm)	82.77±9.33	94.83±7.42†	81.28±9.63	89.57±7.87†
BMI (kg/m^2)	24.25±3.13	27.72±2.91†	24.88±3.55	27.52±3.32†
HR (bpm)	70.32±12.62	72.73±12.54†	72.56±11.87	74.15±12.00†
RV_5 (mv)	2.01±0.88	1.88±0.77†	1.72±0.75	1.65±0.67†
SV_1+RV_5 (mv)	3.02±1.21	2.90±1.20	2.71±1.07	2.64±1.03*
Smoking (%)	34.40	29.70*	35.30	43.90†
Drinking (%)	35.30	43.90	3.20	2.40

Results are expressed as mean±SD and percentage (%). * non-MetS versus MetS, $p < 0.05$ †non-MetS versus MetS, $p < 0.001$; *Abbreviations*: AA = atrial arrhythmia; BMI = body mass index; CLBBB = complete left bundle branch block; CRBBB = complete right bundle branch block; DBP = diastolic blood pressure; GLU = glucose; HDL-C = high-density lipoprotein cholesterol; HR = heart rate; IVS = interventricular septal thickness; JT = JT duration; JTc = corrected JT duration; K^+ = serum kalium ion; LVID = diastolic end left ventricular internal diameters; MetS = metabolic syndrome; non-MetS = nonmetabolic syndrome; prolonged QTc = QTc*B*>430 ms in men or QTc*B*>450 ms in women; QRS = QRS duration; QT = QT interval; QTc*B* = corrected QT interval by Bazett formula; QTc*F* = corrected QT interval by Fridericia formula; RV_5 = R-wave amplitude in V_5 lead; SBP = systolic blood pressure; SV_1+RV_5 = S-wave amplitude in V_1 lead plus R-wave amplitude in V_5 lead; TG = triglyceride; VA = ventricular arrhythmia; WC = waist circumference.

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MetS, 3,383 without MetS. QTc*B*, QTc*F*, and JTc were significantly longer in women than in men, after adjusting for age, blood pressure, TC, TG, HDL-C, GLU, and waist circumference, the relation remained ($p<0.001$). Patients with MetS had significantly longer QTcs and JTc than individuals without MetS ($p<0.001$). The MetS group had lower serum potassium levels, thicker IVS, and larger LVID.

The larger the number of abnormal metabolic parameters the subjects had, the longer their QTc and JTc were. In men, with the number of components of MetS from 0 to 5, the JTc was gradually increased from 325.63 ms to 358.63 ms; the QTc*B* was gradually increased from 418.28 ms to 449.11 ms. In women, the JTc, from 345.32 ms to 365.62 ms; the QTc*B*, from 433.86 ms to 457.24 ms. Trend analysis indicated that QTc*B*, QTc*F*, and JTc was significantly prolonged and the percentages of prolonged QTc*B* were significantly increased with the number of abnormal metabolic parameters in both men and women ($p<0.001$;Table 2).

Table 2. Relationship between QTcs/JTc and number of abnormal metabolic syndrome parameters

	Number of Abnormal Metabolic Syndrome Parameters					
	0	1	2	3	4	5
men (n)	103	606	668	383	170	20
Age (years)	55.82±9.88	61.64±9.34	60.18±9.03	58.04±9.07	58.14±8.52	59.01±8.83
SBP ≥130 or DBP ≥85 (mm Hg,%)	0.00	91.42	95.66	98.69	98.82	100.00
GLU ≥5.6 (mmol/L,%)	0.00	3.47	40.57	53.00	85.88	100.00
HDL-C <1.03 (mmol/L,%)	0.00	0.17	2.84	8.62	22.35	100.00
TG ≥1.7 (mmol/L,%)	0.00	2.15	16.92	62.66	95.88	100.00
WC ≥80 (cm,%)	0.00	2.81	44.01	77.02	97.06	100.00
QTc*B*>430 (ms,%)	27.18	41.72	45.43	49.61	50.59	55.00*
QTc*B* (ms)	418.28±33.24	430.67±51.28	433.07±46.95	439.06±49.20	440.50±49.74	449.11±83.93*
QTc*F* (ms)	412.58±27.82	420.65±43.66	421.03±38.56	428.81±54.77	425.74±42.27	430.20±69.40
JTc (ms)	325.63±35.69	333.20±53.68	334.69±49.08	340.05±51.88	342.31±52.87	358.63±83.79*
women (n)	113	639	1254	1125	590	144
Age (years)	52.24±9.18	57.24±9.36	57.69±8.60	57.81±8.45	58.22±8.06	58.87±8.28
SBP ≥130 or DBP ≥85 (mm Hg,%)	0.00	75.27	92.43	95.91	99.15	100.00
GLU ≥5.6 (mmol/L,%)	0.00	4.07	16.57	42.67	62.03	100.00
HDL-C <1.29 (mmol/L,%)	0.00	2.35	5.50	20.53	50.51	100.00
TG ≥1.7 (mmol/L,%)	0.00	4.07	9.88	48.36	91.19	100.00
WC ≥80 (cm,%)	0.00	14.24	75.62	92.53	97.12	100.00
QTc*B*>450 (ms,%)	26.79	37.72	41.22	43.58	48.05	50.00†
QTc*B* (ms)	433.86±38.92	442.03±47.03	447.64±49.13	454.34±56.16	460.02±58.12	457.24±50.80†
QTc*F* (ms)	425.93±32.51	429.27±41.67	433.90±41.88	439.47±49.07	443.07±49.76	442.04±42.02†
JTc (ms)	345.32±44.23	349.97±48.75	354.97±50.91	362.13±57.29	367.46±59.80	365.62±50.46†

Results are expressed as mean±SD and percentage (%) trend analysis $p < 0.05$. *trend analysis $p < 0.01$. †trend analysis $p < 0.001$. *Abbreviations*: DBP = diastolic blood pressure; GLU = glucose; HDL-C = high-density lipoprotein cholesterol; JTc = corrected JT duration; QTc*B* = corrected QT interval by Bazett formula; QTc*F* = corrected QT interval by Fridericia formula; SBP = systolic blood pressure; TG = triglyceride; WC = waist circumference.

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Table 3. The results of multiple regression

	JTc		QTc*B*		QTc*F*	
	Beta	Sig	Beta	Sig	Beta	Sig
Female	0.208	0.000	0.169	0.000	0.168	0.000
K	−0.170	0.000	−0.191	0.000	−0.197	0.000
GLU	0.088	0.000	0.076	0.000	0.054	0.001
Age	0.125	0.000	0.114	0.000	0.088	0.000
DBP	0.145	0.000	0.152	0.000	0.100	0.000
TG	0.089	0.000	0.097	0.000	0.081	0.000
IVS	0.065	0.000	0.039	0.017	0.034	0.040
WC	0.081	0.001	0.091	0.000	0.095	0.000
HDL-C	−0.039	0.021	−0.039	0.021	—	—
SBP	—	—	—	—	0.052	0.013

Linear regression by stepwise method, independent variables including age, sex, WC, SBP, DBP, GLU, TG, HDL-C, IVS, K. *Abbreviations*: DBP = diastolic blood pressure; GLU = glucose; HDL-C = high density lipoprotein cholesterol; IVS = interventricular septal thickness; JTc = corrected JT duration; K = serum kalium level; QTc*B* = corrected QT interval by Bazett formula; QTc*F* = corrected QT interval by Fridericia formula; SBP = systolic blood pressure; TG = triglyceride; WC = waist circumference.

The results of stepwise multiple regressions on QTc*B*, QTc*F*, and JTc were similar. These parameters were independently associated with being female, age, waist circumference, blood pressure, serum GLU, TG, and HDL-C. After adjusting for conventional risk factors, the association remained negatively associated with serum potassium concentration and positively associated with IVS (Table 3).

Discussion

The present study provides evidence that QTc is associated with MetS and its abnormal metabolic parameters. No subjects received antihypertensive, antidiabetes, or antidyslipidemia medication or other medication affecting the duration of QTc before enrollment, which made it possible to reveal the real effect of metabolic parameters on QTc and JTc.

Our study showed that patients with MetS had a significantly longer QTcs (by the Bazett formula and the Fridericia formula) than the controls in both men and women, and confirmed the previous results from a small-sample study.[9] We observed that the length of QTcs and the percentage of prolonged QTc*B* were increased with the number of abnormal metabolic parameters, indicating that abnormalities in cardiac depolarization are aggravated with the development of MetS. The QRS duration was longer in MetS than in the control group, however, the difference was not statistically significant. To eliminate the effect of QRS on QTcs, we adopted JTc as a corrected repolarization interval, and consistent results were found in QTc and JTc. R-wave amplitude in the V_5 lead was lower in subjects with MetS than in controls, which might result from the fact that participants in MetS are more obese.

It is well recognized that insulin resistance plays a central pathophysiological role in the development of MetS. Serum insulin level is significantly higher in patients with MetS than in normal individuals. A study conducted in elderly men without previous myocardial infarction or known diabetes, has shown that QTc prolongation seems to be part of insulin resistance.[21] Insulin hyperpolarizes the plasma membranes of both excitable and nonexcitable tissues, which leads to prolongation of QT interval.[22] Hyperinsulinemia may induce hypokalemia, and one of the influences of hypokalemia on ECG is prolongation of the QTc. In our study, serum potassium concentration was lower in patients with MetS than in controls in both men and women. QTc is negatively associated with serum potassium concentration after adjusting for conventional cardiovascular risk factors.

Patients with hypertrophic cardiomyopathy show an increase in QTc duration.[23] A recent study on 202 patients with good recovery from a cerebrovascular event indicates that long QT is significantly associated with left ventricular mass index (LVMI) even after adjustment for both systolic and diastolic blood pressures.[5] We found that IVS was thicker and LVID was larger in the subjects with MetS than in those without MetS. Both QTcs and JTc were associated with IVS after adjusting for traditional risk

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factors. Our study also showed that the length of QTcs and JTc were independently associated with being female, age, serum GLU, TG and HDL-C concentration, blood pressure, and waist circumference, similar to the results of Grandinetti et al.[24] This may be due to most of these parameters being correlated to insulin resistance and myocardial hypertrophy at a certain degree. It has now been established that visceral obesity is an even more powerful predictor of obesity-related risk and mortality,[25] and waist circumference provides a convenient measure of visceral obesity, which can explain the result of our study that only waist circumference, not BMI, was associated with QTcs.

In conclusion, metabolic syndrome is a risk factor for prolonged QTcs, which may further increase cardiovascular morbidity and mortality in the subjects with metabolic syndrome.

We did not follow-up the outcomes of prolongation of QTc in the patients with MetS in this study. It is well-known that increased QTc has a detrimental effect on cardiovascular outcomes, so prolongation of QTc might be an early marker for predicting the development of cardiovascular disease and a risk factor for adverse outcome in MetS. Treatment of metabolic parameter abnormality might improve morbidity and mortality by preventing the risk of the prolongation of the QTc.

Limitations

Subjects in the present study were recruited from individuals for hypertensive survey, so the proportion of the patients with hypertension is high, and may result in selection bias. Whereas, QTc was prolonged in relation to the number of abnormal metabolic parameters, and hypertension is one of the parameters, we did not think that hypertension contributes to any false association.

The clinical significance of this study needs to be confirmed in longitudinal studies, whether QTc prolongation can increase detrimental outcome of the syndrome and whether reversing the metabolic abnormalities can correct the prolongation of QTc should be investigated.

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