Uncomplicated Metabolic Syndrome Is Associated with Prolonged Electrocardiographic QTc Interval and QTc Dispersion

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Aim: Metabolic syndrome is associated with increased risk of mortality and morbidity. The present study evaluates the repolarization abnormalities in patients with uncomplicated metabolic syndrome measuring corrected QT interval (QTc) and corrected QT dispersion (QTd) on electrocardiogram.

Methods: The study involved 83 subjects. A total of 50 individuals met criteria of metabolic syndrome (Group A: 11 men, 39 women, mean body mass index (BMI) 36.7 kg/m^2, mean waist circumference 117.3 cm). And 33 participants were healthy normal volunteers (Group B: 9 men, 24 women, mean BMI 21.3 kg/m^2, mean waist circumference 76.2 cm). The two groups were matched for age and sex. Metabolic syndrome was diagnosed according to the Adult Treatment Panel III criteria. The QTc intervals and QTd were measured.

Results: Patients with uncomplicated metabolic syndrome had significantly higher values of QTc-min, QTc-max, and QTd than control group ($P < 0.001$).

Conclusion: Patients with uncomplicated metabolic syndrome have a greater dispersion of ventricular repolarization time and increased QTc-min and QTc-max.

A.N.E. 2006;11(4):313–317

metabolic syndrome; corrected QT interval; corrected QT dispersion

Being overweight has a detrimental impact on physical health. Visceral obesity is the driving force for the development of the metabolic syndrome.[1] Individuals with metabolic syndrome are at increased risk for cardiovascular heart disease.[2] A prolonged QT interval reflects the myocardial refractoriness and electrical instability of myocardium and has been associated with adverse cardiovascular outcomes including ventricular fibrillation and sudden death.[3–5] The length of the QT interval adjusted for heart rate has been found to be longer in persons with diabetes mellitus than in healthy controls.[6] The corrected QT dispersion (QTd), defined as the difference between the maximum and minimum corrected QT interval (QTc) occurring in any of the 12 electrocardiogram leads, has been suggested to be an electrocardiographic index reflecting the physiological variability of regional ventricular repolarization. A number of studies have found that an increased QTd was a marker for arrhythmic events and sudden death.[7–10] QTc and QTd are two related electrocardiographic variables that, apart from assessing the autonomic dysfunction, can also predict cardiac death in diabetic patients.

Although the prolongation of the QT interval has been reported to be associated with sudden cardiac death or a bad prognosis, by inducing arrhythmia, in healthy adults and in diabetic patients, the relationship between insulin resistance and the QT interval has not been clearly identified.[11] Given the evidence that a metabolic syndrome is associated with insulin resistance and with adverse cardiovascular outcomes, we hypothesized that persons with uncomplicated metabolic syndrome may be at a markedly increased risk for increased QTd and increased QTc.

This study was designed to measure the corrected minimum and maximum interval between Q and T waves of the electrocardiogram (QTc), and also QTd in subjects with uncomplicated metabolic

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syndrome. In order to investigate this aspect, a cross-sectional cohort study of subjects with uncomplicated metabolic syndrome was undertaken. To the best of our knowledge, no data are currently available concerning uncomplicated metabolic syndrome in relation to QTc and QTd.

METHODS

Patient Selection

The study comprised 83 subjects. A total of consecutive referred 50 individuals met criteria of metabolic syndrome (Group A: 11 men, 39 women, mean body mass index (BMI) 36.7 kg/m^2, mean waist circumference 117.3 cm). And 33 participants were healthy, normal-weight volunteers belonging to the medical and student staff of our department (Group B: 9 men, 24 women, mean BMI 21.3 kg/m^2, mean waist circumference 76.2 cm). The two groups were matched for age and sex. The subjects with metabolic syndrome were consecutively recruited from the outpatients attending to our Cardiology Unit. Metabolic syndrome was diagnosed according to the Adult Treatment Panel III criteria, including three or more of the following metabolic abnormalities: abdominal obesity (waist circumference >102 cm in men and >88 cm in women), high blood pressure (>129 mmHg systolic or >84 mmHg diastolic), hypertriglyceridemia (serum triglycerides >149 mg/dL), low high-density lipoprotein (HDL) cholesterol (serum HDL-cholesterol <40 mg/dL in men and <50 mg/dL in women), and high fasting glucose (fasting serum glucose >109 mg/dL).[12]

Excluding Criteria

All of the subjects underwent a 75-g oral glucose tolerance test according to World Health Organization criteria. Patients with diabetes were excluded. Patients with normal or impaired glucose tolerance test were included in the study. All of the subjects underwent to exercise stress test to rule out the coronary ischemia. All of the subjects underwent echocardiographic evaluation for excluding patients with left ventricular hypertrophy. Patients on glucose-lowering agents or antihypertensive medication were excluded from the study. Subjects with a history of ischemic heart disease, previous arrhythmic episodes, hepatic, renal, thyroid diseases, mitral valve prolapse, acquired cerebral lesions, and neurosurgery were also excluded. None of the subjects were taking medication known to affect electrocardiographic intervals. The obese and overweight patients had been weight stable during the 3 months preceding the study. Blood pressure was measured using a mercury sphygmomanometer with the subjects in a sitting position after a 10-minute rest period, with the mean of three determinations being recorded. Using standard laboratory methods, blood samples were drawn after an overnight 12-hour fast to determine levels of fasting serum glucose, total cholesterol, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Information on smoking was collected by interviews. The hospital's Institutional Review Board approved the study, and all patients gave written, informed consent. Fifty patients were eligible for inclusion criteria.

The ECGs were analyzed by one reader (M.A.) who was unaware of the characteristics of the subjects. Simultaneous 12-lead ECGs were at a paper speed of 50 mm/s and an amplitude of 10 mm/mV. The QT intervals were measured manually from the onset of the interval between Q and S waves of the electrocardiogram to the end of the T wave at the level of the interval between the end of the T wave and the subsequent P wave isoelectric baseline and corrected according to Bazett's formula ($QTc = QT/\sqrt{RR}$). QTd was defined as the difference between the maximum and the minimum QTc across the 12-lead ECG. In the presence of a U wave, the QT interval was measured using the tangent method, by which the end of the T wave is defined at the intersection with the baseline of the tangent on the descending limb of the T wave. If the T wave could not be reliably determined, the lead was excluded from the analysis. QT interval was measured in all 12 leads in each subject. The reader was trained to obtain the minimum of intravariability of measurements. Intraobserver variability for QTd was 4.5 ms (95% confidence interval 4.6–7.4), and the correlation of the measurements on separate days was significant ($P < 0.0001$).

Statistical Analysis

Differences between patients with and without metabolic syndrome were tested with chi-square (categorical variables), unpaired *t*-test (continuous normal distributed variables). For assessing independent determinants of the QTd, we fitted stepwise multiple regression models including variables significantly related to the QTd. P values of

Table 1. Clinical Characteristics of the Study Population

	Group A (Metabolic Syndrome Present)	Group B (Metabolic Syndrome Absent)	P Values
N (men/women)	50 (11/39)	33 (9/24)	
Age years mean (SD)	40.5 (8.9)	38 (7.6)	NS
TA > 130/85 (%)	78	(–)	<0.001
Fasting glucose >109 (%)	54	(–)	<0.001
Smoking (%)	22	30	NS
Family history (%)	24	9	NS
BMI (kg/m^2), mean (SD)	36.7 (5.2)	21.3 (2.4)	<0.001
Waist circumference (cm) mean (SD)	117.3 (10)	76.2 (7.8)	<0.001
Total cholesterol (mg/dL) mean (SD)	207.3 (43.9)	150.6 (35.4)	<0.001
Triglyceride (mg/dL) mean (SD)	212.3 (61)	110.5 (48.2)	<0.001
HDL-C (mg/dL) mean (SD)	34.1 (5.5)	45 (8.9)	<0.001
LDL-C (mg/dL) mean (SD)	135.1 (42.5)	82.7 (33.6)	<0.001
QTc-min (ms) mean (SD)	372.6 (26.2)	354.2 (31.6)	0.005
QTc-max (ms) mean (SD)	427.3 (25.2)	388.5 (31.4)	<0.001
QTd (ms) mean (SD)	55.3 (17.7)	34.4 (12.7)	<0.001
RR interval (ms) mean (SD)	805 ± 181	796 ± 210	NS

QTc-min = minimum corrected QT interval; QTc-max = maximum corrected QT interval; QTd = corrected QT dispersion; NS = nonsignificant.

<0.05 were considered significant. The data are expressed as mean values ± SEM and were analyzed using the Statistical Package for the Social Sciences for Windows 10.0 (SPSS, Chicago, IL).

RESULTS

The baseline characteristics of the study population are listed in Table 1, according to the presence of the metabolic syndrome: 50 patients (60%) with the metabolic syndrome, and 33 patients without the metabolic syndrome (40%). Age, gender, and smoking habits were equally distributed. All lipid parameters were significantly different between two groups; however, lipid parameters are not interrelated statistically with measured repolarization abnormalities. Patients with uncomplicated metabolic syndrome had significantly higher values of QTc-min, QTc-max, and QTd than control group (372.6 ms vs 354.2 ms; 427.3 ms vs 388.5 ms; 55.3 ms vs 34.4 ms, respectively). As expected, all five diagnostic parameters of the metabolic syndrome were more prevalent in patients with the metabolic syndrome than in patients without the metabolic syndrome ($P < 0.001$). From 50 patients diagnosed with the metabolic syndrome, 27 (54%) had abnormal fasting glucose level and did not use glucose lowering agents. Group A and group B have different values in relation to BMI (36.7 kg/m^2 vs 21.3 kg/m^2) and waist circumference (117.3 cm vs 76.2 cm). Pearson's correlation analysis of the study population as a whole showed that QTc-min, QTc-max, and QTd did correlate significantly with BMI and waist circumference (Table 2). In multiple regression analysis, QTd was independently correlated with the waist circumference ($P = 0.006$) and to the BMI ($P < 0.001$) but not to the other variables tested.

DISCUSSION

In the present study, we found that patients with uncomplicated metabolic syndrome had a significantly higher values of QTc-min, QTc-max, and QTd than control group. The QTd on the 12-lead surface ECG is considered to be an indirect measure of spatial heterogeneity of repolarization.[13] Most cases of sudden death are due to ventricular express nonuniform ventricular repolarization.[13,14]

Table 2. Pearson's Correlations (r and P values) between QTc-Min, QTc-Max, QTd, and BMI, Waist Circumference

	BMI	Waist Circumference
QTc-min	r = 0.68, P = 0.018	r = 0.85, P = 0.03
QTc-max	r = 0.75, P < 0.001	r = 0.86, P < 0.001
QTd	r = 0.57, P < 0.001	r = 0.66, P < 0.001

Abbreviations as in Table 1.

It has been well recognized that prolonged QTd and QTc (congenital or acquired) on the surface ECG are measurable indices of ventricular arrhythmias risk.[7,8] Our result showed that the association between QTd and metabolic syndrome indicates that abnormalities in cardiac repolarization exist in metabolic syndrome even in the setting of absence of overt diabetes mellitus or severe left ventricular hypertrophy. Insulin resistance is believed to play a central pathophysiological role in the metabolic syndrome. In our view, one of the reasons of the increased QTc and QTd is possibly due to insulin resistance. Hyperinsulinemia has been reported to increase QTc and QTd in healthy subjects;[15] however, the clinical significance of this result is unclear. Moreover, association of the QTd with an increased plasma insulin level during an oral glucose tolerance test in healthy volunteers has been reported.[16]

High insulin levels are associated with increases in sympathetic nerve activity, which in turn enhances myocardial cell membrane refractoriness.[17,18] Insulin hyperpolarizes the plasma membranes of both excitable and nonexcitable tissues, with consequences ranging from baroreceptor desensitization to cardiac refractoriness (prolongation of QT interval). It is well known that insulin may induce hypokalemia. One of the influences of hypokalemia on ECG is prolongation of the QTc.[19]

All of the mentioned effects and influence of insulin may explain our results. Further study is required to clarify its clinical significance.

Although relation between obesity and increased QT has been suggested in few reports,[20] controversial results also existed.[21] However, obesity and the metabolic syndrome/insulin resistance do not uniformly coexist; a significant proportion of persons defined as obese do not develop insulin resistance.[22] It has now been established that body fat distribution is an even more powerful predictor of obesity-related risk factors and mortality.[23] Waist circumference provides a convenient measure of visceral obesity, and its reduction should be the target of clinical intervention in obese individuals. The visceral fat area, which is associated with insulin resistance, appears to be an important link among many components of the metabolic syndrome, such as dyslipidemia and hypertension. Thus, the present study should be differentiated from previous studies that showed correlation between obesity without metabolic syndrome component and QTd.

The impact of insulin (actions and resistances) on cardiovascular risk and health remains an open issue. The clinical significance of our observed changes in ventricular repolarization is unknown. We recommend weight reduction and lifestyle modification in uncomplicated metabolic syndrome patients not merely for prevention of coronary heart disease but also for prevention of the risk of the prolongation of the QTc and QTd, therefore for possible improvement of morbidity and mortality.

LIMITATIONS

The results of the present study are subject to several limitations:

- The number of studied patients and controls is small to draw conclusions on possible arrhythmic risk. Much higher number of patients and long-term follow-up are mandatory to assess the risk of arrhythmic events in these patients and to correlate it with QTc or QTd values.
- Although patients with uncomplicated metabolic syndrome had a significantly higher values of QTc-min, QTc-max, and QTd than control group ($P < 0.001$), the absolute mean values are not grossly abnormal in our study; however, the QT interval prolongation, even within the normal range, has been reported to be associated with cardiovascular morbidity[3] and mortality[11,24,25] in longitudinal studies.
- The use of QT interval abnormalities to predict cardiac death has attracted controversy because of their sometimes poor interobserver reproducibility. Methodological concerns are especially problematic in patients with abnormal ECGs caused by established severe cardiac disease, where defining the end of the T wave is difficult. These methodological concerns are much less important in patients, such as in this study, where the ECGs are generally morphologically normal or only mildly abnormal.
- Data on the actual arrhythmic risk of these patients are not presented in this study. There is no Holter ECG monitoring which would have documented increased frequency of ventricular arrhythmias in patients with metabolic syndrome, no electrophysiological data on inducibility of dangerous ventricular arrhythmias, neither long-term follow-up which would have been the best end point to verify the hypothesis that increased

QTc or QTd identify patients at risk. Thus, the finding of increased QTc or QTd is not verified by any end point, which would have confirmed the importance of this finding. On these topics further study needs to be performed. In addition, the way is now open to perform trial to see whether risk stratification with QT interval followed by intensive cardiac investigations would be beneficial to reduce ventricular arrhythmias.

CONCLUSION

In conclusion, uncomplicated metabolic syndrome appears to increase the likelihood of a prolonged dispersion of ventricular repolarization time and increased QTc-min and QTc-max. This implication deserve further study for clarifying the possible linkage between metabolic syndrome and ventricular arrhythmia. Long-term follow-up is mandatory to assess the risk of arrhythmic events in these patients.

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