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ORIGINAL ARTICLE

ARE QT INTERVALS ASSOCIATED WITH METABOLIC SYNDROME AMONG CENTRAL AFRICANS?

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ABSTRACT

Background and Objectives: We investigated the relationship between QT corrected (QTc) or non-corrected for heart rate (QT) with different components and definitions of metabolic syndrome (MetSyn) among Central African patients (all from sub-Saharan African (SSA) countries). **Methods:** This observational case–control study was conducted at Lomo Medical Center, a specialized cardiology center in Kinshasa, DRC. Data were collected from 400 patients with MetSyn and 1400 patients without MetSyn. **Results:** The rates of NCEP ATPIII MetSyn, International Diabetes Federation MetSyn, and MetSyn SSA were 0%, 0.3%, and 13.6%, respectively. There was a positive and significant association between age, body mass index (BMI), triglycerides, uric acid, QT, and MetSyn in SSA. However, only QT (OR = 2.7 95%, CI: 1.8 - 3.4; *P* = 0.039) and uric acid (OR = 1.248 95%, CI: 1.04 - 1.5; *P* = 0.021) were identified as independent determinants of MetSyn in SSA. **Conclusions:** QT and uric acid were identified as independent determinants of MetSyn in SSA after adjusting for sex, age, BMI, and lipids. QT intervals may, therefore, serve as valuable markers for MetSyn definition and management of patients in SSA.

Key words: QT, Electrocardiography, Metabolic Syndrome, Sub-saharan Africa, Risk Factors

1. INTRODUCTION

The QT interval reflects the time between the initial fast depolarization of the ventricle and its repolarization. Because of the variability of the left sympathetic nerve activity, the QT interval has to be corrected for heart rate to compare individuals with different heart rates. A prolonged QTc interval (heart rate corrected using Bazett's formula) has been associated with an increased risk for coronary heart disease, subclinical atherosclerosis, higher levels of certain indicators of metabolic syndrome (MetSyn), and uncomplicated MetSyn in developed countries (1-4). In the USA, the QT-associated risk was reported higher among the black populations as compared to Caucasian (5). Thus, significant associations between prolonged QTc and ethnicity, but not cholesterol or triglycerides (TG) levels, suggest that genetic factors may play a more important role in determining

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QTc interval length than conventional biochemical and metabolic cardiovascular disease risk factors (6).

In sub-Saharan Africa (SSA), higher levels of high-density lipoprotein-cholesterol (HDL-C) are contrasting with low levels of total cholesterol (TC) and TG (7). Furthermore, in SSA, HDL-C, TC and TG have not been useful to predict the MetSyn, stroke and coronary heart disease (8-11). Applying to people from SSA without atherogenic dyslipidemia, the different definitions of MetSyn predominantly used in USA (NCEP ATPIII criteria) (12) and Europe International Diabetes Federation (IDF) (13); it is not surprising that its definition and its indicators have been subject to considerable debate and individual variability between the combination of the risk factors associated with MetSyn (14-17). For this reason, it appears to be very difficult to understand the pathophysiology of MetSyn through traditional components among black Africans. Data on conventional components (12,13) and other indicators of MetSyn such as QT interval (3) and uric acid (18) are lacking in SSA. Therefore, we investigated the relations between QT intervals and different components as well as definitions of MetSyn among black and Central African patients.

2. METHODS

2.1. Study populations

This observational and clinical research was retrospectively carried out among consecutive series of black patients, and a case–control study was conducted within the age group 30-60 years patients admitted at LOMO Medical Center, Kinshasa Limete - DRC between January 2004 and December 2006. Anyone with carotid artery intima-media thickness, sickle cell disease, stroke, drugs (antimalarial, cephalosporin, amiodarone, digitalis, beta-blockers, ACE inhibitors, antiarrhythmics Type I-A and Type III) known to lead to QT prolongation, bundle branch block, insulin treatment, sarcoidosis, hypokalemia, and tachyarrhythmia was excluded from the study. The ethics committee of the University of Kinshasa in DRC approved the study.

Relative frequencies of MetSyn defined by different criteria and the relations of QT intervals with the components of the MetSyn were investigated among 2950 consecutive patients from 3150 eligible patients (response rate: 93.7%) without personal history of coronary heart disease, heart failure, other chronic non-communicable diseases (cancers and chronic renal disease), neither infections. These eligible participants were referred for chest pain and examined with normal echocardiogram-Doppler, chest X-ray, rest-exercise/treadmill-, 24 h Holter electrocardiograms, blood electrolytes, and cardiac enzymes (CK, CK-MB, and Troponin).

Out of 2950 consecutive patients included in the study, 0 patients (0%), 10 patients (0.3%), and 400 patients (13.6%) presented with MetSyn defined according to the Adult Treatment Panel III criteria NCEP 12, the IDF criteria 13, and locally specific diagnosis 16, respectively. MetSyn for SSA patients was defined by waist circumference (WC) of 94 cm or greater for both men and women, plus systolic blood pressure (SBP)/diastolic blood pressure (DBP) 130/85 mmHg or greater, and fasting plasma glucose (FPG) 100 mg/dL or greater (or in drug treatment for specific risk factors). TG 1.7 mmol/L or greater or HDL-cholesterol <1.03 mmol/L were absent among these black African patients suffering from coronary heart disease around 40% arterial hypertension around 80%, and diabetes mellitus around 20%.

These 400 patients with uncomplicated MetSyn in SSA were matched with 1400 healthy participants as controls without MetSyn for sex, age, the level of BP, the level of FPG and the period of admission to the LOMO Medical Center.

2.2. Data collection

Demographic data (sex and age), cigarette smoking, alcohol intake, anthropometric parameters (body mass index or body mass index [BMI] and WC), components of BP (SBP, DBP, pulse pressure as SBP-DBP), and other traditional components of MetSyn measured in blood (glucose, uric acid, TC, TG, HDL-cholesterol, low-density lipoprotein (LDL)-cholesterol) were obtained from each medical chart. Blood samples are measured in our laboratory using the commercial kits of Biomérieux (France) and standard techniques, as described previously (9,10).

QT interval (non-adjusted for heart rate) and QTc interval (adjusted for heart rate) according to Bazett's formula: QTc=QT/QT/a: QTc=QT/ed for heart rate according to lead resting electrocardiography (ECG) records using an automated EASTOTE-ACTA cardiograph (Italy) at a sampling frequency of 500 Hz during 10s with a resolution of 5 mV and stored digitally. A senior medical Registrar, blinded for other study parameters, was in charge of gathering all QT and QTc intervals' results.

2.3. Statistical analysis

Data were expressed as means ± standard deviation (SD) or percentages. Analyses of variance were used to assess differences among groups for the continuous variables. Chi-squared tests were used to compare percentages of categorical variables among all groups. Relations of QT intervals (QT and QTc as dependent variables) with other components of the MetSyn were assessed through simple correlation r coefficient and linear multiple regression. Logistic regression analyses were conducted using MetSyn as the dependent variable (presence 1, absence 0) and the following as the independent variables: Sex (male 1, female 0), age (continuous), QT (continuous) or QTc (continuous), BMI (continuous), uric acid (continuous), TC (continuous),

HDL-cholesterol (continuous), TG (continuous), and LDL-cholesterol (continuous). Smoking status (confounding effect on BMI) and alcohol intake (colinearity with QT and QTc) were not entered in the logistic regression analyses. All statistical analyses were performed using SPSS 21.0 for windows (SPSS Inc., Chicago, Illinois, USA), and statistical significance was set at $P < 0.05$.

3. RESULTS

The consecutive series included 49.8% of men, 50.2% of women, 22.7% of cigarette smokers, and 38.6% with alcohol intake. Table 1 shows the mean values of the study characteristics and their univariate associations with mean QT (SD) of 0.377 (0.021) ms and mean QTc (SD) of 0.432 (0.032) ms. Only the respective univariate associations between age, SBP, pulse pressure, and QT were significantly positive (Table 1). The levels of age and DBP were positively and significantly correlated with QTc, whereas BMI, HDL-cholesterol, and TG were negatively and significantly correlated with QTc, respectively (Table 1).

The mean QT (SD) for men: (0.373 [0.01] ms vs. 0.380 [0.01] ms) and mean QTc (SD) for men: (0.428 [0.01] ms vs. 0.435 [0.01] ms).

QT interval was significantly increased by alcohol intake but not by cigarette smoking status, whereas QTC interval was significantly increased by both cigarette smoking status and alcohol intake (Table 2). The only determinant of QT interval was age as follows: Y: QT = 0.337 + 0.289 age (years); standard error of 0.008 and $P < 0.0001$. However, in considering the heart rate and after adjusting for TG, the independent determinants of QTc interval were DBP increasing ($P < 0.01$), BMI decreasing ($P < 0.01$), and HDL-C decreasing ($P < 0.01$) as follows: R^2 of 7.1%; Y: QTc = 0.461 ± 0.194 DBP-0.179 BMI-0.185 HDL-C.

Comparisons of parameters were not possible with the underestimated proportions of NCEP ATPIII MetSyn (0%) and IDF MetSyn (0.3%). Table 3 shows respective and significant associations between age, BMI, QT non-corrected for heart rate, uric acid, TG (although low average), and MetSyn in SSA (13.6% in the study population), whereas QTc, TC, HDL-C, and LDL-C were similar ($P > 0.05$) between presence and absence of MetSyn among SSA patients.

The logistic regression analysis identified QT interval non-corrected for heart rate and uric acid as the independent predictors of the MetSyn in these black patients after adjusting for sex, age, BMI, TC, HDL-C, LDL-C, and TG (Table 4). Thus, the increase of 0.001 ms of QT interval multiplied 3 times the risk of the MetSyn SSA, and the increase of 1 mg/dL of uric acid multiplied 1.3 times the risk of the MetSyn in SSA.

Table 1: Mean values of general characteristic ans their simple correlation coefficients with QT interval types in the study population

Variables	Mean (SD)	QT interval types			
		QT		QTc	
		r	Pvalue	r	Pvalue
Age (years)	54.4 (14.2)	0.360	<0.0001	0.172	0.023
BMI (Kg/m)	26.8 (5.6)	-0.025	0.769	-0.179	0.034
WC (cm)	96 (14.1)	0.104	0.184	-0.093	0.243
SBP (mmHg)	159 (30.8)	0.225	<0.01	0.081	0.297
DBP (mmHg)	97.4 (19.5)	0.060	0.429	0.222	0.004
Pulse pressure (mmHg)	61.4 (21.3)	0.269	<0.0001	-0.076	0.329
Blood					
• Glucose (mg/dL)	103.3 (47.1)	-0.017	0.836	0.032	0.706
• Uric acid (mg/dL)	6.7 (2.4)	0.038	0.670	0.167	0.062
• Total cholesterol (mg/dL)	210.4 (56.7)	-0.47	0.665	0.044	0.690
• HDL-cholesterol (mg/dL)	60.6 (22.8)	-0.006	0.968	-0.456	0.002
• Triglycerides (mg/dL)	85.9 (44.7)	-0.373	0.072	-0.563	<0.010
• LDL-cholesterol (mg/dL)	107.5 (37.9)	-0.020	0.951	-0.207	0.518
Values are mean(standard deviations)					

Table 2: Relationship between tobacco use, alcohol intake and QT interval types

Behaviour habit	QT interval	QTc interval
Cigarette smoking		
▪ Yes	0.382 (0.029)	0.452 (0.019)
▪ No	0.375 (0.013)	0.426 (0.011)
▪ P	0.386	<0.0001
Alcohol intake		
▪ Yes	0.386 (0.027)	0.449 (0.017)
▪ No	0.371 (0.038)	0.428 (0.012)
▪ P	0.030	<0.01
Values are mean(standard deviations)		

4. DISCUSSION

This observational study examined the relations between components of MetSyn, definitions of MetSyn and the QT intervals (initial fast depolarization and repolarization of the ventricle) among Central African patients. These associations were independent of sex and the majority of indicators of dyslipidemia. Paradoxical associations were also shown.

4.1. Determinants of QT intervals

This study demonstrates the importance of both QT non-corrected for heart rate and QTc adjusted for heart rate in managing the risk of the MetSyn and coronary heart diseases in Africans with low lipid profile (7) and in course of epidemiologic, demographic and nutritional

Table 3: Patients characteristics according to the presence and absence of the locally and specific-African defined metabolic syndrome(Mets)

Variables	Presence of MetSyn SSA	Absence of MetSyn SSA	Pvalue
Age (years)	58.5 (9.3)	53.7 (14.8)	0.051
BMi (kg/m)	31.4 (5.1)	26.1 (5.4)	<0.0001
QT (ms)	0.397 (0.026)	0.374 (0.037)	0.021
QTc (ms)	0.431 (0.016)	0.432 (0.013)	0.906
Uric acid (mg/dL)	7.6 (2.9)	6.6 (2.3)	0.022
TC (mg/dL)	215.1 (46.7)	209.2 (59.2)	0.618
HDL-C (mg/dL)	61.2 (19.8)	60.4 (23.9)	0.894
LDL-C (mg/dL)	104.7 (11.5)	108.5 (44.5)	0.830
Triglycerides (mg/dL)	106.1 (59.7)	68.4 (35.9)	<0.01
Values are mean(standard deviations)			

Table 4: QT interval and uric acid identified as independent predictors of the metabolic syndrome

Independent variables	Beta	SE	OR(95%CI)	Pvalue
QT interval	12.5	6.1	2.7 (1.8 – 3.4)	0.039
Uric acid	0.221	0.095	1.248 (1.04 – 1.5)	0.021
Constant	-8.014	2.587		0.002
Adjusted for sex, age, BMI, TC, HDL-C, LDL-C and triglycerides.				

transitions (19,20). ECG is usually available in developing countries, but not echocardiography, coronarography, CT scan and MRI. Accurate ECG-derived QT and QTc intervals were significantly correlated with age, SBP, DBP, pulse pressure, HDL-cholesterol, cigarette smoking, and alcohol intake. Age was the significant and independent determinant of QT interval, whereas DBP, BMI, and HDL-C were identified as significant and independent determinants of QTc interval. These findings confirm many data reported from developed and rich societies (1-5).

The negative association between TG and QT as well as the negative association between BMI, TG, LDL-C, and QTc are not ease to understand in these black patients with low lipid profile (7) and nutrition transition (concomitant presence of traditional and westernized diet, presence of both malnutrition and obesity). Sarcopenic obesity reported in elderly from developed countries (21) may be present in both young and adult Africans in course of demographic transition.

In this study, there was no significant association between sex, WC, blood glucose, uric acid, TC, HDL-cholesterol, LDL-cholesterol, and QT intervals. The gender difference for QT interval, longer QT interval in women than men reported elsewhere (4), is till now unknown. For other researchers, sex hormones may play a role in regulating cardiac repolarization and thus QT interval (22). The significant and independent association between the decrease of HDL-C and the increase of QTc interval may exist beyond the effects of DBP and pulse pressure toward atherosclerosis in these Africans (23). Indeed, these data are in opposition to those reported in developed societies: BMI and TG positively related to QTc interval, but LDL-C and HDL-C not related to QTc interval in a multiethnic population from USA (4). Alternatively, though entirely speculative at this time, a common gene might exist which modifies both the cardiometabolic risk, atherosclerosis process, and repolarization anomalies reflected by QT intervals (4).

4.2. MetSyn definitions

This study shows the underestimation of rates of MetSyn using the NCEP ATPIII criteria (12) and IDF criteria (13) in defining the MetSyn in SSA. For this reason, WC cutoff point of 94 cm in men and women used as marker of abdominal obesity in SSA (16) and significant risk factor of arterial hypertension among Africans (24) and insulin resistance (16), clustered with blood glucose and BP, but not with HDL-C and TG, defined MetSyn in SSA for 13.6% patients. Although the diagnostic criteria of MetSyn are problematic (14-17), this study showed a significant univariate association between increased age, higher BMI (total obesity), increased QT, higher uric acid, low TG and MetSyn among SSA patients in accord with the literature data (1-5,10,14,15,18). Lower cutoff point of TG should be used in diagnosing the MetSyn among Africans. Our multivariate analysis found an increased and independent association between QT interval, uric acid, and MetSyn SSA.

Traditional low fat diet or genetics may explain the transient neutral effect of dyslipidemia on MetSyn development in SSA. The predictive value of QT interval continuously for MetSyn SSA may be attributed to high sympathetic activity and stress. Therefore, the new worldwide definition of MetSyn (25) should propose specific new criteria for Africa, in which the Europoid WC cutoff points and the controversial lipids (HDL-C, LDL-C, TG) (8,14,15) are replaced by WC ≥94 cm, QT non corrected and corrected for heart rate, uric acid, fibrinogen (or CRP) and *Helicobacter pylori* infection. Uric acid, fibrinogen and *H. pylori* (significantly correlated with TC increase, TG increase and HDL-C decrease) have been established as independent risk factors for MetSyn (10) and atherosclerotic diseases (stroke and coronary heart disease) in these Africans (9,10).

4.3. Limitations of the study

The study, being an observational study, is subject to a number of potential errors. However, there is no reason to

suspect important limitations as bias because on differential error in QT measurements, interobserver difference, drugs and certain diseases effects were excluded from the study.

5. CONCLUSION

There is a strong and significant relationship between age, smoking, alcohol intake, HDL-C, MetSyn without dyslipidemia, uric acid, and QT intervals duration. Because WC, QT intervals and uric acid are easily measured and significantly associated with MetSyn in these African patients; they may provide additional information for cardiovascular risk stratification and management MetSyn SSA despite the transient low and less atherogenic lipid profile in Central Africans.

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