

METABOLIC SYNDROME IN NONDIABETIC, OBESE, FIRST-DEGREE RELATIVES OF AFRICAN AMERICAN PATIENTS WITH TYPE 2 DIABETES: AFRICAN AMERICAN TRIGLYCERIDES-HDL-C AND INSULIN RESISTANCE PARADOX

Objective: Metabolic syndrome (MetS) defines cardiovascular disease (CVD) risks. Despite higher rates of obesity, type 2 diabetes, and hypertension, African Americans have lower rates of MetS when compared to Caucasians, which is paradoxical, since African Americans are more insulin resistant and have higher rates of cardiovascular morbidity and mortality when compared to White Americans. We hypothesized that genetic inheritance predisposes African Americans to the greater cardiovascular risk and the associated morbidity and mortality. Therefore, we investigated the prevalence of components of MetS in obese, glucose-tolerant, first degree relatives of African American patients with type 2 diabetes.

Methods: We examined the clinical and metabolic characteristics of 201 first-degree relatives (159 females and 42 males, mean age 41 ± 8 years, and mean body mass index (BMI) of 32 ± 8 (kg/m²). The subjects were categorized with MetS according to the Adult Treatment Panel (ATP) III criteria. Insulin sensitivity (Bergman minimal model method) and insulin resistance (homeostasis model assessment [HOMA]) were determined. We compared the clinical and metabolic characteristics in the relatives with and without MetS. Where appropriate, we compared the prevalence of the components of MetS in our African American sample with those of African American data in the National Health and Nutrition Evaluation Survey (NHANES) III.

Results: Comparing the MetS group ($n=65$) vs control subjects ($n=136$), the mean age, BMI, and percent body fat were greater in the MetS group. Mean fasting serum glucose, insulin and C-peptide levels were also greater in the MetS group. Insulin resistance index (HOMA-IR) was higher in the MetS group (HOMA-IR: 3.7 ± 2.7 vs 2.2 ± 1.7 , $P=.0002$). Mean insulin sensitivity tended to be lower in the MetS group (2.16 ± 2.64 vs 2.82 ± 2.31 , $P=.08$). In addition, despite the moderately severe insulin resistance, the MetS group had very low serum triglyceride levels and was the parameter least likely to meet the ATP criteria. The metabolic cutoff points for ATP III criteria were much lower in African American first-degree relatives with MetS. Of the five components of the ATP III criteria, waist circumference was the single most common parameter to likely meet the MetS criteria. We found that the prevalence of MetS was 29% in women and 40% in men

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INTRODUCTION

The metabolic syndrome (MetS) as defined by the National Cholesterol Education Program Adult Treatment Program (NCEP-ATP) III criteria, is a constellation of fasting lipids and lipoproteins, waist circumference, glucose, and blood pressure abnormalities¹ that have been associated with increasing risk for developing cardiovascular disease (CVD) and diabetes.² MetS is becoming an increasing problem in the

when compared with 20.9% in African American women and 13.9% for African American men in the NHANES III.

Conclusion: We found that: 1) the prevalence of MetS is higher in a subgroup of African Americans who were first-degree relatives of patients with type 2 diabetes than that of African Americans in the NHANES III; and 2) waist circumference rather than metabolic parameters was the single most important parameter and was more likely to meet the MetS criteria in African American relatives. (*Ethn Dis.* 2006;16:830-836)

Key Words: Metabolic Syndrome, Insulin Resistance, Normal Glucose Tolerance, Type 2 Diabetic Offspring, African Americans

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United States. When comparing National Health and Nutrition Evaluation Survey (NHANES) (1988-94 vs 1999-2000) data, the prevalence of MetS increased from 23% in 1988-1994 to 26.7% in 1999-2000.³ Using ATP III criteria and the 2000 US Census data, ≈ 47 million US adults had MetS.⁴ According to NHANES III, the prevalence of MetS was 13.9% for African American men and 20.9% for African American women during 1988-1994. The prevalence of MetS was lower in African Americans compared to Caucasians and Mexican Americans during that period.⁵ Ford et al⁴ reported racial and ethnic differences in the various components of MetS in NHANES III. Thus, understanding the predictors of MetS in a specific racial/ethnic population could significantly affect approaches to preventing CVD and type 2 diabetes.

Nondiabetic first-degree relatives manifest greater insulin resistance and hyperinsulinemia than those without family history of type 2 diabetes.⁶⁻¹⁵ These subjects also have been shown to have higher cardiovascular risks.¹⁴⁻¹⁷ In addition, insulin resistance is partly determined by race and ethnicity.¹⁸⁻²⁶ African Americans manifest greater insulin resistance and hyperinsulinemia when compared to White Americans.²¹⁻²⁶ Most importantly, African Americans with known greater insulin resistance also paradoxically have relatively higher high-density lipoprotein cholesterol (HDL-C) and lower triglycerides when compared to their White counterparts.²⁷⁻³² Despite these favorable anti-atherogenic lipid and lipopro-

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tein profiles, African Americans suffer enormously and disproportionately from CVD morbidity and mortality.¹³⁻¹⁷ Thus, the favorable lipid and lipoprotein profile does not appear to protect African Americans against excessive CVD mortality and morbidity. The reasons are unclear.

We sought to characterize the prevalence of MetS and its five components as defined by ATP III criteria in nondiabetic first-degree relatives of African American patients with type 2 diabetes who were genetically predisposed to type 2 diabetes and CVD.

SUBJECTS, MATERIALS, AND METHODS

Populations

During 1994-1996, we undertook a screening for diabetes in first-degree relatives of African American patients with type 2 diabetes who were residing in Franklin County, Ohio. Informed written consent approved by the institutional review board for human biomedical research at the Ohio State University, Columbus, Ohio, was obtained from each subject after the potential risks and benefits entailed in the study had been thoroughly explained. The subjects who qualified for the study then underwent a standard oral glucose tolerance test. World Health Organization criteria were used to define glucose tolerance.³³ The study

identified 159 females and 42 males (mean age 41 ± 8 years) who were glucose-tolerant first-degree relatives (offspring and siblings) of African American patients with type 2 diabetes. The following subjects were excluded: 1) those taking medications known to influence glucose and insulin metabolism; 2) those individuals with liver, heart, lung, and kidney diseases; 3) those with established diabetes on antidiabetic medications; and 4) those who participated in endurance exercise or indulged in regular competitive sport.

Study Protocol

After a 10-12 hour overnight fast, the subjects reported to the General Clinical Research Center of the Ohio State University Medical Center. Body weight and height were measured with the subject wearing a light gown and without shoes. The waist circumference was measured at the level of the umbilicus (with the subject in standing position) and the hip circumference at the level of the greater trochanter (in the standing position). Body fat distribution was measured as the waist-to-hip circumference ratios. Lean body mass and body fat (body composition) was measured with a bioelectrical impedance analyzer. Blood pressure (BP) was measured three times, at 10-minute intervals, with the subject in supine position.³⁴ The average of the three BPs was taken as the mean basal BP. All the subjects answered a simple questionnaire on physical activity. Subjects who participated in endurance exercise or a competitive sport were excluded. In addition, the subjects completed Block's nutritional survey questionnaires.

Metabolic Studies

Oral Glucose Tolerance Test

Each subject was instructed to ingest at least 250 g of carbohydrate in their regular meals for at least three days before the test. After a 10-12 hour

overnight fast, the subjects were admitted to the clinic. With the subject in the supine position, an intravenous needle (heparin lock) was inserted into the forearm vein and kept patent with .9% normal saline infusion. Blood samples were drawn for fasting serum glucose, insulin, and C-peptide levels. The subjects then ingested 75 g of oral glucose load (Glucola) over a two-minute period. Blood samples were drawn at baseline and 120 minutes for serum glucose, insulin, and C-peptide concentrations.

Frequently Sampled Intravenous Glucose Tolerance

With subject in the supine position, two intravenous needles (heparin lock) were inserted into the forearm veins and kept patent with .9% normal saline infusion. One intravenous line was used to draw blood samples, and the other was used to administer the intravenous glucose and exogenous insulin.^{22,35-37} Four blood samples were obtained at -20, -10, -5, and 0 minutes for basal serum glucose, C-peptide and insulin concentrations. The average of the four samples was taken as the basal level. Thereafter, .3 g/kg glucose (50 mL of 50% dextrose water) was infused over a one-minute period. At 19 minutes, intravenous insulin (.05 U/kg, Humulin, Eli Lilly, Indianapolis, Ind) dissolved in 30 mL of .9% normal saline was infused over 60 seconds. Blood samples were obtained at frequent intervals at 2, 3, 4, 5, 6, 8, 10, 12, 16, 19, 22, 24, 25, 27, 30, 40, 60, 70, 90, 120, 140, 150, 160, and 180 minutes for serum glucose, C-peptide, and insulin concentrations. All the samples were centrifuged at 4°C and the sera frozen and stored at -20°C until assayed.

Analytical Methods

Serum glucose concentrations were measured by the glucose oxidase method with a glucose autoanalyzer (Beckman Instruments, Fullerton, Calif). The

serum insulin and C-peptide levels were determined by a standard double antibody radioimmunoassay technique at the Core Laboratories of Ohio State University Hospitals, Columbus, Ohio. The sensitivity of the insulin assay was 2.5:U/mL. The intra- and inter-assay coefficients of variation (CV) were 6% and 10%, respectively. The lower limit of the C-peptide assay was .47 ng/mL, and the intra- and inter-assay CV were 7% and 13%, respectively. During the study period, glycosylated hemoglobin (HbA1) was measured by the cationic, microcolumn chromatographic technique (Isolab, Akron, Ohio). The normal reference range was 4.1%–8.0%. Our previous HbA1 assay measured HbA1A, HbA1B, and HbA1C. HbA1C is the major component of HbA1, accounting for at least 80% of the total HbA1 in our assay. Thus, to be consistent with the HbA1C data that have been used in both Diabetes Control and Complications Trial (DCCT), we have converted the HbA1 to HbA1C equivalent. The HbA1C range in our population was 3.4%–6.6%. The serum cholesterol, HDL-C, and triglycerides were measured with enzymatic methods.

Calculation Analysis

In 1994, glucose intolerance in this population was defined as a fasting and two-hour plasma glucose <110 mg/dL. The Adult Treatment Panel III (ATP III) criteria were used to define MetS in this group.¹ Three or more of the following criteria were diagnostic of MetS: waist circumference >102 cm for men and >88 cm for females; serum triglycerides ≥150 mg/dL; serum HDL-C <40 mg/dL for men and <50 mg/dL for females; systolic BP ≥130 mm Hg or a diastolic BP ≥85 mm Hg or a history of hypertension on antihypertensive medication; and a fasting plasma glucose of ≥110 mg/dL. The body mass index (BMI) was calculated as weight (kg) divided by height squared (m). Obesity

was defined as BMI >30 kg/m² for both females and males. Low-density lipoprotein cholesterol (LDL-C) was calculated by using Friedwald’s equation: LDL-C=total cholesterol – HDL-C – triglyceride/5, for serum triglycerides <400 mg/dL.

Statistical Analyses

Results are expressed as mean ± standard deviation, unless stated otherwise. Insulin sensitivity (Si) and glucose effectiveness (Sg) were calculated by using Bergman’s Minmod software program.^{28,29} Insulin resistance and β-cell function were also calculated by using the homeostasis model assessment (HOMA)³⁸ The HOMA-IR (insulin resistance index) was calculated as fasting insulin (μU/mL) × fasting plasma glucose (mmol/mL)/22.5. HOMA%B (β-cell function) was calculated as 20 × fasting insulin (μU/mL)/fasting glucose (mmol/mL) – 3.5.

The nonparametric data were analyzed by using chi square and Mann-Whitney rank tests. Statistical analyses were performed by using SAS 9.1 for Windows (SAS Institute Inc, Cary, NC). The Student *t* test was used to analyze the data between the groups. Probability (*P*) value <.05 was considered statistically significant.

RESULTS

Clinical Characteristics of MetS and Non-MetS

We found that 65 subjects (32.3%) met the ATP III MetS criteria while 136 did not. The mean age, BMI, WHR, skinfold thickness, and percent body fat were significantly higher in MetS than in non-MetS group. Obesity was common in both groups. However, the MetS group had a higher BMI (35 ± 9 vs 31 ± 8 kg/m², *P*=.005), waist circumference (108 ± 17 vs 94 ± 18 cm, *P*<.0001), waist to hip ratio (WHR) (.93 ± .07 vs .89 ± .14, *P*=.0013) and % body fat (40 ± 9 vs

38 ± 9, *P*=.0934) than the non-MetS group.

Metabolic Characteristics

The mean fasting serum glucose, insulin and C-peptide levels were significantly greater in the MetS than in the non-MetS group. Insulin sensitivity (Si) tended to be lower in the MetS group. In contrast, insulin resistance assessed by HOMA-IR was significantly greater in MetS than in the non-MetS group.

The lipids and lipoprotein levels in the MetS and non-MetS groups are shown in Table 1 and Table 2. Comparing the groups, mean serum triglyceride (156 ± 177 vs 77 ± 38 mg/dl), LDL-C (124 ± 38 vs 107 ± 27 mg/dl) and total cholesterol (195 ± 39 vs 175 ± 29) were significantly higher in the MetS group than the non-MetS group (albeit within normal limits). We found that HDL-C in the females (46 ± 1 vs 53 ± 13 mg/dl) and in the males 36 ± 8 vs 49 ± 11 mg/dl), were significantly lower in the MetS than non-MetS groups, respectively (Table 1).

We examined the prevalence of each of the components of ATP III criteria in our cross-sectional study. MetS was present in 29% of females and 40% of males in our study; these figures are higher than those in NHANES III (20.9% and 13.9%, respectively) in the African American population (Table 3). We found that the waist circumference was the single most common parameter to meet MetS criteria in the African American relatives, followed by HDL-C, BP, and fasting plasma glucose, and least for triglycerides (Table 2). Thus, triglyceride parameters were less likely to meet ATP III criteria in African American relatives with MetS. In summary, we found the following hierarchy of prevalence for the five components of MetS in our NGT African Americans: WC>HDL-C>BP>glucose>triglycerides.

Table 1. Metabolic and clinical characteristics of normal, glucose-tolerant African Americans with first-degree diabetic relatives with and without metabolic syndrome

Parameters	No MS (n=136)	MS (n=65)	P value
<u>Clinical parameters</u>			
Age (years)	40 ± 8	44 ± 8	.003
Weight (kg)	86 ± 22	101 ± 23	<.0001
Height (cm)	167 ± 10	171 ± 11	.002
Waist (cm)	94 ± 18	108 ± 17	<.0001
Hip (cm)	107 ± 16	115 ± 16	.001
WHR	.89 ± .14	.93 ± .07	.001
BMI (kg/m ²)	31 ± 8	35 ± 9	.005
Body fat (%)	38 ± 9	40 ± 9	.093
Lean body fat (kg)	62 ± 10	59 ± 9	.042
Triceps (mm)	27 ± 11	31 ± 10	.013
Biceps (mm)	15 ± 9	19 ± 9	.002
Subscapular (mm)	29 ± 11	35 ± 10	<.0001
Suprascapular (mm)	21 ± 9	26 ± 10	<.0001
<u>Biochemical parameters</u>			
HbA1C (%)	4.7 ± .71	4.8 ± .87	.421
Si [$\times 10^{-4} \times \text{min}^{-1} (\mu\text{U/mL})^{-1}$]	2.8 ± 2.3	2.2 ± 2.6	.082
Sgx [$\times 10^{-2} \times \text{min}^{-1}$]	2.4 ± 1.6	2.1 ± 1.3	.148
Glucose (mg/dL)	78 ± 16	85 ± 18	.005
Insulin ($\mu\text{U/mL}$)	11.6 ± 8.8	16.8 ± 10.2	.0003
C-peptide (ng/mL)	2.5 ± 1.3	3.3 ± 1.3	.0001
HOMA-IR	2.2 ± 1.7	3.7 ± 2.7	.0002
HOMA % B	487 ± 672	378 ± 287	.1183
LDL-C (mg/dL)	107 ± 27	124 ± 38	.003
Total cholesterol (mg/dL)	175 ± 29	195 ± 39	.001
Triglyceride (mg/dL)	77 ± 38	156 ± 177	.001
HDL-C females (mg/dL)	53 ± 13	46 ± 11	.0005
HDL-C males (mg/dL)	49 ± 11	36 ± 8	<.0001

Values are mean ± standard deviation.

MS=metabolic syndrome; WHR=waist/hip ratio; BMI=body mass index; LDL-C=low-density lipoprotein cholesterol; HOMA=homeostasis model assessment; IR=insulin resistance index; %B= β-cell function; HDL-C=high-density lipoprotein cholesterol.

To put our data in proper perspective, we compared our data with those of the African Americans cohort of NHANES III.⁴ As shown in Table 3, family history of type 2 diabetes in

African American relatives was associated with higher percentage of several components that met the ATP III criteria for triglycerides, HDL-C, and WC. However, of the five parameters,

WC was the single most likely parameter associated with MetS, especially in African Americans (Table 3).

DISCUSSION

According to NHANES III, African Americans have a lower prevalence of MetS compared to the general population.⁵ However, NHANES III data did not factor in family history of type 2 diabetes. Our study demonstrated that MetS in obese, first-degree relatives of African American patients with type 2 diabetes was higher when compared to the African American population in NHANES III. However, within our study group of obese relatives, other unknown risk factors, and not just family history of type 2 diabetes, appear to predispose this population to MetS. We found that a significant number of subjects did not have MetS despite strong family history of type 2 diabetes. These non-MetS subjects had unique clinical and biochemical characteristics that were different from those with MetS. In this regard, African American relatives with MetS had greater body weight, BMI, percentage body fat content, and skinfold thickness than in the non-MetS group. Similarly, we found that waist circumference and WHR were also significantly greater in the MetS than non-MetS groups. Metabolically, insulin resistance (as assessed by lower Si and higher HOMA-IR) was greater in the MetS than in non-MetS group, despite normal glucose tolerance. These data suggest that within this group of glucose-tolerant relatives of African Americans, a putative genetic inheritance for MetS deserves further elucidation. To the best of our knowledge, this is the first study that has provided the clinical and metabolic characteristics of glucose-tolerant, but high-risk African Americans with MetS and those without MetS.

Apart from clinical and anthropometric parameters, serum HDL-C and

Table 2. Mean and prevalence of metabolic syndrome in normal, glucose-tolerant African Americans with type 2 diabetic first-degree relatives

ATP III Criteria	No MS (n=136)	MS (n=65)	P value
Triglycerides >150 mg/dL	77 ± 38 (2%)	156 ± 177 (44%)	.001
Glucose >110 mg/dL	78 ± 16 (2%)	85 ± 18 (6%)	.005
Systolic BP >130 mm Hg	116 ± 11 (8%)	132 ± 15 (54%)	.0001
Diastolic BP >85 mm Hg	73 ± 9 (10%)	84 ± 12 (59%)	.0001
HDL-C females <50 mg/dL	53 ± 13 (46%)	46 ± 11 (78%)	.0005
HDL-C males <40 mg/dL	49 ± 11 (20%)	36 ± 8 (76%)	.0001
Waist females >88 cm	93 ± 18 (58%)	108 ± 18 (93%)	.0001
Waist males >102 cm	94 ± 15 (16%)	109 ± 15 (82%)	.004

Values are mean ± standard deviation (%).

Frequency shown as a percentage is in parenthesis.

BP=blood pressure; HDL-C=high-density lipoprotein cholesterol.

Table 3. Prevalence (%) of metabolic syndrome in first-degree relatives of African American patients with type 2 diabetes and in NHANES III participants⁴

ATP III Criteria	Relatives		NHANES III (1988–1994)	
	No MS (n=136)	MS (n=65)	African Americans (n=2412)	Whites (n=3599)
Glucose ≥110 mg/dL	2	6	15.1	11.9
Triglycerides ≥150 mg/dl	2	44	17.1	31.1
BP	9	56	46.3	32.8
Systolic BP ≥130 mm Hg	8	54	—	—
Diastolic BP ≥85 mm Hg	10	59	—	—
HDL females <50 mg/dL	46	78	34	39.3
HDL males <40 mg/dL	20	76	22.6	22.6
Waist females >88 cm	58	93	62.1	43.5
Waist males >102 cm	16	82	23.3	30.5

Values are mean ± standard deviation; frequency shown as a percentage is in parenthesis.

NHANES=National Health and Nutrition Evaluation Survey; MS=metabolic syndrome; BP=blood pressure; HDL=high density lipoprotein.

triglycerides significantly correlate with insulin resistance in some high-risk populations. Weak relationships have been found between serum insulin, insulin resistance, triglycerides, and HDL-C levels and BP in African Americans.²⁶ These findings were confirmed in the present study. These studies suggest that in African Americans, insulin resistance is not consistently associated with the typical lipids and lipoprotein abnormalities found in other ethnic/racial populations.^{30–39} Indeed, in general, serum triglycerides are often greater in nondiabetic Caucasian patients with insulin resistance but paradoxically lower in insulin-resistant African Americans who are genetically predisposed to type 2 diabetes. Furthermore, we found that serum cholesterol and LDL-C levels were two to three times greater in the MetS group than non-MetS group (albeit within normal limits). Only few of the relatives had hypertriglyceridemia as defined by the ATP III. Finally, HDL-C was also significantly lower in our males and females with MetS when compared to those in the non-MetS group. Our present findings in African Americans are different from those in Caucasians and other racial/ethnic populations where hypertriglyceridemia and decreased HDL-C levels are major determinants of MetS (Table 3).^{39–42} When compared with the NHANES III, we

showed that the presence of family history of type 2 diabetes was associated with higher percentage of subjects who met ATP III criteria for triglycerides, HDL-C, and waist circumference but not for BP and glucose. Our study suggests that significant number of nondiabetic, first-degree relatives of African American patients with type 2 diabetes manifest an increased global genetic risk for MetS. Whether the MetS group in our present study portends a greater risk for future CVD remains to be determined in prospective studies.

Our study has several implications. First, our study is unique in that NHANES III did not include measurements of insulin sensitivity as a component of MetS. Second, in view of the increased CVD morbidity and mortality

Our study demonstrated that MetS in obese, first-degree relatives of African American patients with type 2 diabetes was higher when compared to the African American population in NHANES III.

in African Americans, we are tempted to infer that the threshold for these metabolic cutoff points for CVD might be lower in African Americans than in White Americans. Specifically, African Americans at risk for CVD tended to have a much lower serum triglyceride and higher HDL-C levels than their White counterparts. This paradoxical issue has been addressed by Sumner et al³² in a recent publication in nondiabetic African Americans. In their study, they found that serum triglycerides and HDL-C/triglycerides ratio did not reflect insulin resistance in African Americans, unlike White Americans. The HDL-C/triglyceride and insulin resistance paradox cannot fully explain the greater CVD outcomes in African Americans. Thus, whether we need to develop racial and ethnic specific cutoff points for MetS as suggested in the present study and previous studies remains debatable. Nevertheless, we believe, other, unconventional risk factors, such as lower adiponectin and adipocytokines, cardiorespiratory fitness, and socioeconomic and socio-demographic factors^{30,42} may serve as additional major contributors of CVD in African American subjects with MetS and deserves further investigation.

Our findings have some further limitations in the study design. First, we included only normal, glucose-tolerant subjects with parental history

of type 2 diabetes. Indeed, we excluded all patients with impaired glucose tolerance and type 2 diabetes from our study. Thus, we could have underestimated the prevalence of MetS in our study. Hence, our data cannot be generalized to all African Americans. Second, the MetS group tended to be older and more obese (as assessed by BMI and percentage body fat). However, when the data were stratified based on age and obesity indices, the parameters of MetS remained significantly different in the MetS group and non-MetS group.

In summary, obese, glucose-tolerant African Americans who are first-degree relatives of someone with diabetes have greater prevalence of MetS than African Americans in NHANES III. We found that the prevalence of metabolic parameters of ATP III criteria for MetS was remarkably higher in the African American relatives with MetS than those in NHANES III. A simple, readily and clinically available parameter, waist circumference, appears to be the single most important parameter to meet the MetS criteria in African Americans. We found distinct clinical and metabolic differences in relatives with and without MetS. Thus, our study suggests that even among African American first-degree relatives of diabetes patients, a unique and perhaps a putative genetic inheritance appears to predispose this group to MetS.

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