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ScienceDirect
Metabolism Clinical and Experimental 59 (2010) 1115 – 1123
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Differential impact of serum glucose, triglycerides, and high-density lipoprotein cholesterol on cardiovascular risk factor burden in nondiabetic, obese African American women: implications for the prevalence of metabolic syndrome

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Received 4 September 2008; accepted 11 September 2009

Abstract

Metabolic syndrome (MetS) as defined by the Adult Treatment Panel (ATP) III criteria includes 3 metabolic parameters: serum glucose, triglycerides, and high-density lipoprotein cholesterol (HDL-C) measurements. However, the impact of each of the 3 metabolic parameters on cardiovascular disease (CVD) risk in African American women (AAW) is unknown. Therefore, we investigated CVD risk clusters associated with each of the 3 metabolic components of MetS in adult nondiabetic, overweight/obese AAW. We studied the clinical and metabolic CVD risk factors of 258 AAW (mean age, 42.4 ± 8.4 years; mean body mass index, 33.4 ± 8.0 (kg/m^2). Fasting serum insulin, glucose, and C-peptide levels were obtained in each subject. Waist circumference and systolic and diastolic blood pressure were measured. Insulin sensitivity (Bergman minimal model method) and insulin resistance (homeostasis model assessment) were calculated. We examined the prevalence of MetS and its components associated with each of the 3 metabolic components (ie, serum glucose, HDL-C, and triglycerides) of the MetS as defined by ATP III. Worsening of any of the 3 metabolic parameters was associated with increasing waist circumference but not with age and body mass index nor with insulin, C-peptide, homeostasis model assessment of insulin resistance, and insulin sensitivity. As a group, the prevalence of MetS was 35.5% in our AAW. The prevalence of MetS increased 3-fold from first to third tertiles of serum glucose (14.1% and 42.3%, respectively). Worsening of serum HDL-C from tertiles 3 to 1 was associated with significant increases in the prevalence of MetS (1.2% vs 42.3%, respectively). Comparing first with third tertile of triglycerides, there was no significant increase in MetS in our AAW (7% vs 17%). Contrasting the 3 metabolic components, the prevalence of MetS was higher in the third tertile of glucose (43.2%) and first tertile of HDL-C (42.3%) and least with the third tertile of triglycerides (17%). In summary, each of the metabolic components of MetS was associated with different degrees of the clustering of CVD risk factors in AAW. We found that alterations in serum glucose and HDL-C were more predictive of MetS, each yielding approximately 40% of the prevalence of MetS in our nondiabetic, obese AAW. We found that triglycerides had the least impact on MetS in our AAW. We propose (1) that the 3 metabolic parameters for MetS defined by ATP III should be *weighted* differently with respect to their potential for CVD risks and perhaps outcomes and (2) that nondiabetic AAW in our third tertile of serum glucose (>100 mg/dL) and/or first tertile of HDL-C (<40 mg/dL) should be targeted for screening for MetS.

1. Introduction

Obesity and type 2 diabetes mellitus have become epidemic [1]. Both contribute significantly to cardiovascular diseases (CVDs) [1-5]. African American women (AAW) have greater rates of type 2 diabetes mellitus, hypertension, obesity, and CVD morbidity and mortality when compared with white women [2,4,5]. The reasons are uncertain. However, despite the favorable antiatherogenic lipoproteins, AAW suffer 2- to 4-fold higher rates of CVD mortality and morbidity than white women [2-5].

The *metabolic syndrome* (MetS) as defined by the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP) III criteria is a constellation of fasting lipids and lipoproteins, waist circumference (WC), glucose, and blood pressure (BP) abnormalities [6]. Metabolic syndrome has been associated with increasing risk for developing CVD and type 2 diabetes mellitus and is

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doi:10.1016/j.metabol.2009.09.035

becoming an increasing problem in the United States [7,8]. Using ATP III criteria and the 2000 US census data, there were approximately 47 million US adults who met the metabolic criteria for MetS. When comparing the National Health and Nutrition Examination Survey (NHANES) I and II, the prevalence of MetS increased from 23% to 26.7%, respectively [7]. The NHANES III also revealed that there are racial/ethnic differences in the prevalence and incidence of MetS in the United States. According to NHANES III, the prevalence of MetS was 13.9% for African American men and 20.9% for AAW during 1988 to 1994 [4,7,8]. The rates of MetS were 25% in white men and 23% in white women for the same period. A recent report by Taylor et al [9] of the Jackson Heart Study, a large prospective population-based study of African Americans residing in Jackson, MS, found that 39.4% of the study cohort met the metabolic criteria for MetS (43.3% in women and 32.7% in men). Note that the prevalence of MetS in the Jackson Heart Study was double that found in the NHANES III for African Americans. The reasons for the racial/ethnic and geographical differences in CVD risk factors in African Americans remain unknown. We should note that the International Diabetes Federation (IDF) has specific racial/ethnic guidelines for MetS [10]. First, WC is a prerequisite for MetS using the IDF criteria. Second, the IDF recommends different cutoff points for Asians and non-Asian minority populations. Therefore, understanding the cardiovascular risk burden associated with the 5 components of MetS is necessary in each ethnic/racial population. Based on the higher CVD outcomes in AAW, it is important to ask the question as to whether there are also differences on the impact of the 5 components of MetS for future CVD and type 2 diabetes mellitus or whether the 5 components carry different CVD risk burdens in African Americans.

Insulin resistance (IR) is generally regarded as the pivotal lesion for MetS. We have previously shown that African Americans manifest greater IR and hyperinsulinemia when compared with white Americans [11,12]. Most importantly, African Americans with known greater IR also paradoxically have relatively higher high-density lipoprotein cholesterol (HDL-C) and lower triglycerides levels when compared with their white counterparts [13,14]. Recently, Haffner et al [15] have shown that, in addition to relatively lower triglycerides and higher HDL-C levels, African Americans also have also larger low-density lipoprotein cholesterol (LDL) particles size when compared with whites in the Insulin Resistance Atherosclerosis Study. Despite these favorable antiatherogenic lipid and lipoprotein profiles, African Americans continue to suffer enormously and disproportionately from CVD morbidity and mortality than white Americans, with a 2- to 4-fold greater morbidity and mortality in AAW. Thus, clearly, the favorable lipid and lipoprotein profile does not appear to protect African Americans against excessive CVD mortality and morbidity, especially in AAW. The reasons are unclear. We believe that the thresholds for CVD metabolic risk factors in African Americans could be substantially different than the conventional cutoff limits defined by the ATP III criteria for MetS.

The MetS is defined by having any 3 or more of the following 5 components: serum glucose of at least 100 mg/dL, HDL-C less than 50 mg/dL for women and less than 40 mg/dL for men, triglycerides of at least 150 mg/dL, WC greater than 40 in for men and greater than 35 in for women, and BP of at least 130/85 mm Hg [6]. None of these components have been singularly examined to determine whether there are differences in CVD risk attributed to the components in AAW. Most importantly, the relationship among the various metabolic components of MetS is complex. Indeed, despite the greater IR in black women, we found no significant relationships between IR and conventional CVD risk factors such as HDL-C–triglycerides ratio and BP in AAW, in contrast with those of white women [11,12,15].

The MetS according to ATP III criteria assumes that each of the metabolic components carries an identical risk for CVD across ethnic/racial populations and even among sexes. This may not be true especially in AAW who suffer disproportionately from higher CVD mortality and morbidity than black men [2-5]. In this regard, the major paradox in defining MetS often centers on the 3 metabolic components. Thus, it is important to define the CVD risk burden of each of the 3 metabolic components of MetS in overweight/obese AAW that could predict CVD events. Given the above background, we tested the hypothesis that the serum glucose, triglycerides, and HDL-C levels of MetS independently determine CVD risk burden in AAW. To this end, in the present study, we characterized the CVD risk burden using the tertiles of serum glucose, triglycerides, and HDL-C levels to assess the prevalence of MetS in nondiabetic, overweight/obese AAW who were genetically predisposed to type 2 diabetes mellitus and CVD.

2. Subjects, materials, and methods

2.1. Populations

We recruited 258 first-degree relatives of AAW (mean age, 42.4 ± 8.4 years) whose parents and offspring had type 2 diabetes mellitus to participate in studies on CVD risk and type 2 diabetes mellitus program at The Ohio State University, Columbus, OH. The subjects responded to local mailing and advertisement in local newspaper and by word-of-mouth solicitation. Fifteen subjects did not qualify because of failing the inclusion screening criteria often because of preexisting undiagnosed type 2 diabetes mellitus, uncontrolled hypertension, and lack of adequate venous access. Informed written consent approved by the Institutional Review Board for human biomedical research at The Ohio State University, Columbus, OH, was obtained from each subject after the potential risks and benefits entailed in the study had been thoroughly explained. The subjects who initially qualified for the study then underwent a standard

oral glucose tolerance test. The World Health Organization criteria were used to define glucose tolerance [16]. The following subjects were excluded: (*a*) those taking medications known to influence glucose and insulin metabolism; (*b*) those individuals with liver, heart, lung, and kidney diseases; (*c*) those with established diabetes on antidiabetic medications; and (*d*) those who participated in endurance exercise or indulged in regular competitive sport.

2.2. Study protocol

After a 10- to 12-hour overnight fast, the subjects reported to the General Clinical Research Center (GCRC) of The OSU Medical Center, Columbus, OH. Body weight and height were measured with the subject wearing a very light gown and without shoes. The WC 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). The body fat distribution was measured as the waist to hip circumference ratios (WHRs). Lean body mass and body fat (body composition) were measured with a bioelectrical impedance analyzer [17]. Blood pressure was measured 3 times at 10-minute intervals with the subject in supine position. The average of the 3 BPs was taken as the mean basal BP. All the subjects answered a simple questionnaire on physical activity. In addition, the subjects completed the Block Nutritional Survey questionnaires.

2.3. Metabolic studies

2.3.1. Oral glucose tolerance test

Each subject was instructed to ingest at least 250 g of carbohydrate in their regular meals for at least 3 days before the test. After a 10- to 12-hour overnight fast, the subjects were admitted to the GCRC. With the subject in the supine position, an intravenous needle was inserted into the forearm vein and kept patent with 0.9% isotonic sodium chloride solution infusion. Blood samples were drawn for fasting serum glucose, insulin, and C-peptide levels. The subjects then ingested 75 g of oral glucose load (Rolodex, Baltimore, MD) over a 2-minute period. Blood samples were drawn at t = 0 and 120 minutes for serum glucose, insulin, and C-peptide concentrations. *Diabetes* was defined as fasting glucose greater that or equal to 126 mg/dL. *Impaired fasting glucose* (IFG) was defined as fasting glucose greater than or equal to 100 mg/dL but less than 126 mg/dL. *Impaired glucose tolerance* (IGT) was defined as 2-hour glucose between 140 and 199 mg/dL.

2.3.2. Frequently sampled intravenous glucose tolerance

With subject in the supine position, 2 intravenous needles were inserted into the forearm veins and kept patent with 0.9% isotonic sodium chloride solution infusion. One intravenous line was used to draw blood samples and the other to administer the intravenous glucose and exogenous insulin. Four blood samples were obtained at t = −20, −10, −5, and 0 minute(s) for basal serum glucose, C-peptide, and insulin concentrations. The average of the 4 samples was taken as the basal level. Thereafter, 0.3 g/kg glucose (50 mL of 50% dextrose water) was infused over a 1-minute period. At t = 19 minutes, intravenous insulin (0.05 U/kg; Humulin; Eli Lilly, Indianapolis, IN) dissolved in 30 mL of 0.9% isotonic sodium chloride solution was infused over 60 seconds. Blood samples were obtained at frequent intervals at t = 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 were frozen and stored at −20°C until assayed.

2.3.3. Analytical methods

Serum glucose concentrations were measured by the glucose oxidase method using glucose autoanalyzer (Beckman Instruments, Fullerton, CA). The serum insulin and C-peptide levels were determined by a standard double-antibody radioimmunoassay technique at The Core Laboratories of The OSU Hospitals, Columbus, OH. The sensitivity of the insulin assay was 2.5 μU/mL. The intra- and interassay coefficients of variation were 6% and 10%, respectively. The lower limit of the C-peptide assay was 0.47 ng/mL; and the intra-and interassay coefficients of variation were 7% and 13%, respectively. During the study period, the hemoglobin A_{1c} (HbA_{1c}) was measured by the cationic, microcolumn chromatographic technique (Isolab, Akron, OH). The reference range was 4.1% to 8.0%. The serum cholesterol, HDL-C, and triglycerides were measured using enzymatic methods.

2.3.4. Calculations and definitions

The ATP III criteria were used to define MetS cutoff limits in this group. Three or more of the following criteria were diagnostic of MetS: WC greater than 35 in for women; serum triglycerides of at least 150 mg/dL; serum HDL less than 50 mg/dL for women; systolic BP (SBP) of at least 130 mm Hg, diastolic BP (DBP) of at least 85 mm Hg, or a history of hypertension on antihypertensive medication; and a fasting plasma glucose of at least 100 mg/dL. In our study, we defined cutoff points as clusters in the third tertiles of serum glucose and triglycerides and first tertile for HDL-C levels. The body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. *Overweight* was defined as BMI of at least 25.1 but less than 29 kg/m^2. *Obesity* was defined as BMI greater than 30 kg/m^2. Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald equation: LDL-C = total cholesterol − HDL-C − triglyceride/5, for serum triglycerides less than 400 mg/dL. Insulin sensitivity (Si) was calculated using the Minmod software program of Bergman et al [18]. Insulin resistance and β-cell function were also calculated using the homeostasis model assessment (HOMA) [19]. The HOMA-IR (IR index) was calculated as fasting insulin (in microunits per milliliter) × fasting plasma glucose (in millimoles per milliliter)/22.5. The HOMA of β-cell function (HOMA-%B) was calculated as 20 × fasting insulin (in microunits per

milliliter)/fasting glucose (in millimoles per milliliter) − 3.5. The metabolic components of MetS, namely, serum glucose, HDL-C, and triglycerides, were divided according to tertiles.

2.3.5. Statistical analyses

Statistical analyses were performed using SAS 9.1 or JUMP for Windows 2002-2003 by SAS Institute, Cary, NC. Results are expressed as mean ± SD, unless stated otherwise. The nonparametric data were analyzed using χ^2 and Mann-Whitney ranked test. Student *t* test and multiple *t* test were used to analyze the data between the groups. Multiple linear regression analysis was performed to examine the relationships among Si, HDL-C, glucose, triglycerides, MetS parameters, and CVD risk factors. Probability (*P*) value less than .05 was considered statistically significant.

3. Results

3.1. Clinical and metabolic characteristics of subjects

The mean age of the study population was 42.4 ± 8.4 years, and mean BMI was 33.3 ± 8.0 kg/m^2. The mean SBP was 122 ± 17 mm Hg, and DBP was 76 ± 11 mm Hg (Table 1). Only subjects with normal glucose tolerance, IFG, and IGT were allowed in the study. In addition, we excluded those subjects with new-onset of type 2 diabetes mellitus and those individuals with triglycerides greater than 400 mg/dL.

Table 1
Clinical and biochemical characteristics of AAW with normal glucose tolerance

Parameters	Value
n	255
Clinical characteristics	
Age (y)	42.4 ± 8.4
Height	164.5 ± 7.7
Body weight (kg)	90 ± 22
BMI (kg/m^2)	33.34 ± 804
BFM (%)	42.2 ± 12.4
WC (cm)	99.3 ± 18.3
WHR	0.90 ± 0.10
SBP(mm Hg)	122 ±17
DBP(mm Hg)	76 ± 11
Biochemistry (fasting)	
Glucose (mg/dL)	83.5 ± 20.3
Insulin (μU/mL)	13 ± 11
C-peptide (ng/mL)	2.80 ± 1.30
HOMA-IR (%)	2.97 ± 2.94
HOMA-%B	394 ± 545
HbA_{1c} (%)	5.0 ± 0.8
Si × 10^{-4} min^{-1} (μU/mL)$^{-1}$	2.3 ± 2.3
Lipids and lipoproteins (mg/dL)	
Total cholesterol	181 ± 34
Triglycerides	88 ± 54
HDL-C	50.6 ± 13.2
LDL-C	113 ± 31
MetS	
MetS (%)	35.5

Values are mean ± SD. BFM indicates body fat mass.

Table 2
Clinical and biochemical characteristics of African American subjects with normal glucose tolerance divided in tertiles of serum glucose levels

Parameter	Tertile 1	Tertile 2	Tertile 3
n	85	85	85
Age (y)	42.6 ± 8.65	43.0 ± 8.72	41.6 ± 8.4
BMI (kg/m^2)	33.30 ± 8.33	33.91 ± 9.00	32.93 ± 6.63
WC (cm)	92.4 ± 20.5[a]	99.7 ± 5.6[c]	105.4 ± 14.8[f]
SBP (mm Hg)	118 ± 16	122 ± 16[d]	127 ± 17[f]
DBP (mm Hg)	74 ± 11	76 ± 10	78 ± 11[g]
Biochemistry (fasting)			
Glucose (mg/dL)	68 ± 5[a]	79 ± 3[c]	103 ± 24[f]
Insulin (μU/mL)	13.9 ± 11.5	14.9± 9.8	11.6 ± 11.8
C-peptide (ng/mL)	2.97 ± 1.47	2.79 ± 1.29	2.75 ± 1.22
HOMA-IR	3.07 ± 3.07	3.29 ± 2.59	2.73 ± 3.31
HOMA-%B	334 ± 404	439 ± 516	405 ± 690
HbA_{1c} (%)	5.02 ± 0.87	4.84 ± 0.82	5.25 ± 0.78
Si × 10^{-4} min^{-1} (μU/mL)$^{-1}$	2.08 ± 1.99	2.39 ± 1.99	2.63 ± 3.26
Lipids and lipoproteins (mg/dL)			
Total cholesterol	186 ± 37	179 ± 35	181± 33
Triglycerides	75 ± 41	85 ± 46[e]	106 ± 68[f]
HDL-C	54.15 ± 8.15[a]	48.6 ± 11.7[c]	48.1 ± 11.9[f]
LDL-C	118 ± 35[b]	108 ± 31[d]	115 ±32
MetS			
MetS (%)	14.1	20	42.3

Values are mean ± SD. To convert to SI, multiply insulin by 6 (picomoles per liter); C-peptide by 0.331 (nanomoles per liter); glucose by 0.0555 (millimoles per liter); cholesterol, HDL-C, and LDL-C by 0.0258 (millimoles per liter); and triglycerides by 0.0111 (millimoles per liter).

[a] *P* = .001 tertiles 1 vs 2.
[b] *P* = .05 tertiles 1 vs 2.
[c] *P* = .001 tertile 2 vs 3.
[d] *P* = .05 tertile 2 vs 3.
[e] *P* = .02 tertiles 2 vs 3.
[f] *P* = .0001 tertile 1 vs 3.
[g] *P* = .01 tertile 1 vs 3.

3.2. Clinical and metabolic CVD risk factors based on glucose tertile

To detect the impact of glucose on clustering of CVD risk factors in AAW, we compared the clinical and metabolic characteristics based on tertile of fasting serum glucose levels in our AAW. We found the plasma serum glucose levels to be within normal limits in all 3 tertiles for our nondiabetic AAW. The mean age and BMI did not differ with the worsening of glucose tertiles. However, WC significantly (*P* = .001) increased with increasing glucose tertiles. With worsening of serum glucose from tertiles 1 to 3, mean serum insulin, C-peptide, HOMA-IR, and Si were surprisingly not significantly different. Whereas serum triglycerides increased, HDL-C decreased with increasing glucose tertiles. In contrast, serum cholesterol and LDL-C levels were not different among the 3 tertiles. However, SBP and DBP significantly increased (*P* = .001) with the worsening of glucose tertiles (1 vs 3) (Table 2).

3.3. Clinical and metabolic CVD risk factors based on serum triglyceride tertiles

To detect the impact of serum triglycerides on clustering of CVD risk factors in AAW, we compared the clinical and

metabolic characteristics based on tertiles of fasting serum triglyceride levels in our population. We found that the mean age and BMI were not different among the 3 triglyceride tertiles. Mean WC and SBP increased with increasing triglyceride tertiles but not DBP. Despite progressive increase in serum triglycerides from tertiles 1 to 3, serum glucose, insulin, C-peptide, HOMA-IR, and Si were not different. Similarly, serum cholesterol and LDL-C levels were not different among the 3 tertiles. Whereas serum triglycerides increased from tertiles 1 to 3, HDL-C significantly decreased from tertile 1 to tertile 3 (Table 3).

3.4. Clinical and metabolic CVD risk factors based of HDL-C tertile

To examine the impact of HDL-C on clustering of CVD risk factors in AAW, we compared the clinical and metabolic characteristics based on tertile of fasting serum HDL-C levels in our population. There was a progressive increase in HDL-C from tertiles 1 to 3. When we examined the HDL-C tertiles, the mean age and BMI were not different among the 3 tertiles. Mean WC was highest at the first HDL-C tertile and lowest at the third tertile of HDL-C. Despite progressive increases in HDL-C tertile from tertiles 1 to 3, serum glucose, insulin, C-peptide, Si, and HOMA-IR did not significantly differ among the 3 HDL-C tertile groups. Mean serum cholesterol and LDL-C levels were not changed with worsening of HDL-C tertiles (third vs first). In contrast, serum triglycerides significantly ($P = .001$) decreased as the HDL-C levels increased from tertile 1 to tertile 3. Worsening of HDL tertiles (third vs first) was not associated with significant changes in SBP and DBP (Table 4).

Table 3
Clinical and biochemical characteristics of African American subjects with normal glucose tolerance divided in tertiles of triglycerides levels

Parameter	Tertile 1	Tertile 2	Tertile 3
n	85	85	85
Age (y)	42.7 ± 8.65	42.7 ± 8.7	41.6 ± 8.3
BMI (kg/m^2)	33.0 ± 3.3	33.3 ± 8.3	32.9 ± 6.59
WC (cm)	91.1 ± 24.0[a]	99.4 ± 15.6[b]	105.9 ± 15.9[c]
SBP	119 ± 17[a]	122 ± 16	126 ± 16[c]
DBP	75 ± 11	76 ± 10	77 ± 12
Biochemistry (fasting)			
Glucose (mg/dL)	79 ± 20	84 ± 19	87 ± 21[d]
Insulin (μU/mL)	13.9 ± 11.6	13.9 ± 11.6	11.6 ± 11.7
C-peptide (ng/mL)	2.97 ±1.47	2.97 ± 1.47	2.75 ± 1.22
HOMA-IR	3.07 ± 3.07	3.07 ± 3.07	2.73 ± 3.29
HOMA-%B	334 ± 404	334 ± 404	405 ± 606
HbA_{1c} (%)	5.01 ± 0.87	5.02 ± 0.87	5.24 ± 0.77
Si × 10^{-4} min^{-1} (μU/mL)$^{-1}$	2.03 ± 1.57	2.03 ± 1.58	2.14 ±1.66
Lipids and lipoproteins (mg/dL)			
Total cholesterol	186 ± 37	186 ± 37	181 ± 32
Triglycerides	44 ± 9[a]	77 ± 11[b]	146 ± 57[c]
HDL-C	55.7 ± 13.7[a]	49.5 ± 13[b]	46.2 ± 11.0[c]
LDL-C	117 ± 35	117 ± 35	115 ± 31
MetS			
MetS (%)	7	20	17

Values are mean ± SD. To convert to SI, multiply insulin by 6 (picomoles per liter); C-peptide by 0.331 (nanomoles per liter); glucose by 0.0555 (millimoles per liter); cholesterol, HDL-C, and LDL-C by 0.0258 (millimoles per liter); and triglycerides by 0.0111 (millimoles per liter).

[a] $P = .001$ tertiles 1 vs 2.
[b] $P = .001$ tertile 2 vs 3.
[c] $P = .0001$ tertile 1 vs 3.
[d] $P = .01$ tertile 1 vs 3.

Table 4
Clinical and biochemical characteristics of African American subjects with normal glucose tolerance divided into tertiles of HDL-C levels

Parameter	Tertile 1	Tertile 2	Tertile 3
n	85	85	85
Age (y)	42.7 ± 8.65	43 ± 8.2	41.6 ± 8.3
BMI (kg/m^2)	33.0 ± 8.3	33.9 ± 9.0	32.9 ± 6.6
WC (cm)	103 ± 17	101 ± 19	92 ± 21[†]
SBP	121 ± 14	125 ± 18	121 ± 17
DBP	76 ± 9.6	77 ± 12	76 ± 11
Biochemistry (fasting)			
Glucose (mg/dL)	85 ± 20	84 ± 18	81 ± 21
Insulin (μU/mL)	13.9 ± 11.6	14.9 ± 9.8	11.6 ± 11.7
C-peptide (ng/mL)	2.97 ± 1.47	2.79 ± 1.29	2.75 ± 1.22
HOMA-IR	3.07 ± 3.07	3.29 ± 2.56	2.73 ± 3.29
HOMA-%B	334 ± 404	439 ± 516	405 ± 686
HbA_{1c} (%)	5.0 ± 0.87	4.84 ± 0.82	5.24 ± 0.77
Si × 10^{-4} min^{-1} (μU/mL)$^{-1}$	2.08 ± 1.99	2.39 ± 1.99	2.63 ± 3.22
Lipids and lipoproteins (mg/dL)			
Total cholesterol	186 ± 37	179 ± 35	181± 33
Triglycerides	107 ± 68	86 ± 42*	71 ± 42[†]
HDL-C	38.1 ± 4.2	48.3 ± 2.5[‡]	65.5 ± 11.2[†]
LDL-C	117 ± 35	108 ± 31	115 ± 32
MetS			
MetS (%)	42.3	32.9	1.2

Values are mean ± SD. To convert to SI, multiply insulin by 6 (picomoles per liter); C-peptide by 0.331 (nanomoles per liter); glucose by 0.0555 (millimoles per liter); cholesterol, HDL-C, and LDL-C by 0.0258 (millimoles per liter); and triglycerides by 0.0111 (millimoles per liter).

* $P = .01$ tertile 1 vs 2.
[†] $P = .001$ tertile 1 vs 3.
[‡] $P = .001$ tertile 2 vs 3.

3.5. Prevalence of components of MetS associated with tertiles of serum glucose, triglycerides, and HDL-C

To assess the importance of each metabolic component on the prevalence of MetS, we divided our subjects into tertiles of serum glucose, triglycerides, and HDL-C levels. Metabolic syndrome increased from first to third tertiles for serum glucose and triglycerides. Conversely, increasing tertile of HDL-C was associated with reduced MetS in a linear fashion. The prevalence of MetS was least with triglyceride levels from tertiles 1 to 3 (7%, 20%m and 17%, respectively). Comparing the 3 metabolic parameters, we found that MetS was highest in tertile 1 for HDL-C (42.3%) and tertile 3 for glucose (42.3%) and least in tertile 3 for triglycerides (17%).

3.6. Correlation coefficients

We examined the relationships among the components of MetS and CVD risk factors using linear regression. Serum HDL-C ($r^2 = 0.7888$) was associated negatively with LDL-C

($P < .0001$), BMI ($P = .001$), and HOMA-IR ($P = .001$) and positively with total cholesterol ($P = .0001$). Likewise, serum triglyceride ($r^2 = 0.5496$) was associated negatively with LDL-C ($P = .0001$) and positively with total cholesterol ($P < .0001$), BMI ($P = .001$), and HOMA-IR ($P = .001$). We found that serum fasting glucose ($r^2 = 0.7929$) was associated negatively with fasting serum insulin ($P < .0001$), HOMA-B ($P = .0005$), and BMI ($P = .03$) and positively with HOMA-IR ($P < .0001$) and percentage body fat ($P < .001$). Finally, in a logistic regression model, we examined the relationship between Si ($r^2 = 0.1077$) and MetS risk factors. We found that Si was associated positively with HOMA-IR ($P = .0002$), lean body mass (.01), and triglycerides (.02) and negatively with HOMA-%B (−.002).

4. Discussion

African American women suffer 2- to 4-fold greater rates of CVD mortality and morbidity than their white women counterparts. The reasons for the higher CVD mortality in African Americans have been partly attributed to higher rates of obesity, type 2 diabetes mellitus, hypertension, sedentary lifestyle (physical inactivity), socioeconomic factors, and lack of access to appropriate health care, especially when compared with whites. In this regard, we [11,12,20] and others [13-15] have shown that there are several metabolic differences in African Americans and white Americans. These include greater IR, hyperinsulinemia, and BP; lower serum triglycerides; higher HDL-C; lower adiponectin; and higher carotid intimal-medial thickness as well as decreased visceral adiposity in AAW than their white counterparts. Unlike other ethnic and racial populations, IR is only weakly associated with triglycerides and HDL-C in African Americans [12-15,20]. Indeed, the lack of significant association between IR and serum HDL-C–triglycerides ratios is paradoxical and does not totally explain the higher CVD deaths in blacks than whites [2,3]. These raise concerns as to (1) whether the current clinical and metabolic components defined by ATP III for the MetS carry the same CVD risks and (2) whether the notion of IR as the pivotal lesion underlying MetS is a universal prerequisite for MetS in blacks, particularly in AAW.

According to NHANES III, African Americans have a lower prevalence of MetS compared with the white population [4,7,8]. This lower prevalence does not translate into lower CVD morbidity and mortality. This lower rate of MetS can be partly ascribed to the lower prevalence rates of 2 major components of MetS, namely, triglycerides and HDL-C levels, in African Americans [4,7,8,12-15,21]. Thus, the increased mortality and morbidity in AAW cannot be explained by traditional lipid and lipoprotein parameters.

Recently, the Jackson Heart Study [9], a large population sample of African Americans residing in Jackson, MS, found a higher prevalence of individuals who met the criteria for MetS, which was approximately 2-fold higher in their population, irrespective of sex, than that in the NHANES III. The major determinants of the MetS in the African Americans in this study were low HDL-C, high BP, and increasing WC. In another study by our group [22], we found that 35.5% of our overweight/obese AAW with family history of type 2 diabetes mellitus met the metabolic criteria for MetS. However, none of these studies examined critically the association of CVD risk clusters for each of the 3 metabolic components of MetS. To this end, we have postulated that each of the 3 metabolic components carries different CVD risk burden in nondiabetic, obese AAW who are genetically prone to type 2 diabetes mellitus.

Patients with prediabetes (IGT and IFG) and type 2 diabetes mellitus have greater cardiovascular risk events and stroke as well as the associated morbidity and mortality than nondiabetic women. Thus, we first examined the clinical and metabolic clusters of CVD risk factors based on serum glucose tertiles in our nondiabetic AAW. As expected, the fasting glucose levels were highest in the third tertile when compared with the first and second tertiles. Note that the third tertile revealed individuals with IFG and IGT, but not diabetes. Surprisingly, we found that the serum insulin and C-peptide levels did not significantly differ with worsening of the tertiles of glucose probably because of the fact that these changes were minimal in the nondiabetic subjects. Moreover, we found that the Si as assessed by frequently sampled intravenous glucose tolerance (FSIGT) and HOMA-IR did not change with increasing tertiles of serum glucose levels in our study. In addition, worsening of serum glucose tertiles was not associated with changes in total serum cholesterol and LDL-C levels in our obese AAW. However, we found that the increasing serum glucose tertiles were associated with increasing SBP, DBP, and serum triglycerides and conversely with decreasing HDL-C levels. Thus, clearly, worsening serum glucose levels (even within normal limits) were pivotal perturbations associated with significant changes in major CVD risk factors , namely, SBP, DBP, serum triglycerides, and HDL-C levels, in AAW. These changes occurred starting at fasting serum glucose levels that are within normal limits and less than those recommended by NCEP (ATP III) criteria for MetS.

High serum triglycerides are common in insulin-resistant, obese humans residing in the Western world. It is well known that intervention studies of CVD outcomes targeting reduction of serum triglycerides (with concomitant rise in HDL-C) in patients with modest elevations result in significant reduction in CVD morbidity and mortality [23,24]. Thus, the extraordinarily lower levels of serum triglycerides (in the face of elevated HDL-C) in obese, insulin-resistant African Americans when compared with whites should theoretically result in decreased coronary artery disease (CAD) and CVD. However, this is not the case in nondiabetic AAW. Of interest, we [10-12] and others [13-15,25-27] have reported a weaker association between IR and triglycerides in African Americans. In the Jackson Heart

Study [9], the overall prevalence of elevated triglycerides was 16.6% and was similar to other studies including that of the NHANES III.

In the present study, we found that increasing tertiles of triglycerides (albeit within normal limits) were associated with significant changes in serum glucose, SBP, and WC. The increasing tertiles of triglycerides were not associated with changes in Si as assessed by FSIGT and HOMA-IR nor in insulin and C-peptide levels in our obese AAW. This is in contrast with several previous studies in other populations where IR is a major predictor of serum triglycerides levels [25]. Thus, clearly, we found a dissociation between insulin and Si and triglycerides in our study, consistent with the metabolic *paradox in African Americans*. Furthermore, the increasing tertiles of triglycerides were not associated with changes in serum total cholesterol and LDL-C levels in AAW. In contrast, we observed that mean HDL-C tended to decrease as triglyceride increases from first to third tertile consistent with several reports [11-15,20]. Most importantly, we were again surprised by the extremely low levels of serum triglycerides in the third tertile, despite the obesity as assessed by BMI and WC, in our AAW (Table 3). We should note that lower serum triglyceride levels have been reported in insulin-resistant, nondiabetic, obese African Americans [12-14] and Black South African women [28] when compared with white women. There have been several potential explanations for this phenomenon of low triglycerides in black women. These have been attributed to differences in hepatic lipoprotein lipase activity in the liver and lipid metabolism in African Americans when compared with whites. Further studies are needed to elucidate the mechanisms in large population-based studies.

Serum HDL-C levels are very important and independent predictor of CAD. African Americans and other people of African ancestry have higher levels of HDL-C than their white counterparts [5,7,8,12-15,20,21]. Thus, theoretically, African Americans should have lower rates of CVD and CAD based on traditional risk factor estimation than whites. However, this is not the case in African Americans. Indeed, AAW have 2- to 4-fold greater CVD mortality and morbidity than white women probably because of high rates of stroke and congestive heart failure [2-4]. Paradoxically, it is well established that the severity of CAD in African Americans is either equal or less severe than that in whites, despite the higher CVD mortality and morbidity. Thus, the relatively higher HDL-C does not appear to be cardioprotective of CAD in AAW.

In the present study, we found that increasing HDL-C tertiles were not associated with significant changes in serum glucose, insulin, and C-peptide as assessed by the HOMA-%B (Table 4). We found that Si as assessed by FSIGT and HOMA-IR slightly improved, but insignificantly, with increasing HDL-C tertiles. As serum HDL-C increased from first to third tertile, the serum triglycerides significantly decreased in our nondiabetic, obese AAW, similar to other populations [13-15]. However, serum cholesterol and LDL-C levels were not affected by the increasing tertiles of HDL-C. Thus, worsening of HDL-C inversely correlated with triglycerides and WC but not LDL-C or cholesterol nor additional CVD risks in AAW. We should note that, in our present study, we did not measure the particle sizes and subspecies nor functionality of the HDL-C. Of interest, Haffner et al [15] have reported that LDL-C particles are larger and more buoyant in African Americans than whites. Furthermore, it is well known that apolipoprotein A-I levels are higher in African Americans than whites. However, we found that HDL-C less than or equal to 50 mg/dL meeting ATP III criteria in the first tertile was associated with higher prevalence of persons meeting the metabolic criteria for MetS (42.3%), similar to that of the Jackson Heart Study for AAW (39.5%) [9]. Our study is the first to show that the level of HDL-C recommended by ATP III is associated with very modest CVD risk burden in AAW who are genetically predisposed to CVD. However, the clinical and metabolic CVD risk factor burden in obese AAW with different levels of HDL-C that could predispose or protect against CVD remains uncertain and needs to be further investigated in a large prospective study.

We found that 35.5% in our genetically enriched, overweight/obese AAW met the metabolic criteria for MetS. However, the prevalence of MetS and its components differed among the 3 metabolic parameters. The MetS for the third tertile of glucose and the first tertile of HDL-C was 42.3% compared with 17% for the third tertile of triglycerides in our AAW. These were surprisingly similar to the prevalence of the MetS found in the Jackson Heart Study [9]. We found that the metabolic components associated with MetS were most important in AAW with HDL-C less than or equal to 50 mg/dL and fasting serum glucose greater than or equal to 100 mg/dL and least with triglycerides (≥150 mg/dL). In this regard, the mean glucose for tertile 3 was 103 ± 24 mg/dL. In the Jackson Heart Study [9], the percentage of women who had elevated serum glucose levels greater than 100 mg/dL was 29.7%. This was slightly higher than the 10.2% in our study and the 15.5% in the NHANES III [8].

4.1. Implications of the present findings with respect to MetS and CVD in AAW

Our study has several implications with respect to defining MetS and attributing CVD risk burden and thresholds of metabolic components for MetS in nondiabetic, overweight/obese AAW. First, we found that the 3 metabolic components of MetS are associated with different clustering of CVD risk factors in our subjects. This issue is very important because the current NCEP-ATP III criteria assume that these metabolic parameters are equally *"weighted" in terms of risk for CVD in all racial and ethnic populations who meet MetS criteria.* Second, our study suggests that the thresholds of metabolic factors that may be associated with

CVD appear to be lower (glucose and triglycerides) in AAW when compared with NCEP ATP III criteria. Because our study is cross-sectional, this hypothesis needs to be reinvestigated in a prospective head-to-head CVD outcome study of African American and White women. Third, if we accept the current cutoff thresholds for MetS defined by ATP III, our study clearly shows that other nontraditional risk factors could also play a more significant role for CVD events than traditional risk factors in AAW. For example, adiponectin levels [29-31] and cytokines [28], which are known risk factors for CVD, are different in African Americans and South African blacks when compared with white women [28]. Fourth, we studied only women; therefore, we cannot extrapolate our findings to men. In this regard, NHANES III [5,7,8] and the Jackson Heart Study [9] found higher prevalence of MetS in women than men. These findings are consistent with our previous report of higher CVD risk factors in AAW compared with age-, BMI-, and WHR-matched African American men [20]. Fifth, our study was cross-sectional. Hence, causal effect relationships for CVD (and its outcomes) and the metabolic risk factors cannot be ascertained from our present study. Finally, we studied only first-degree relatives of patients with type 2 diabetes mellitus who were genetically enriched with CVD risks. Hence, we cannot extrapolate our findings to the general AAW population.

In summary, we found that each of the metabolic components for MetS was associated with different clustering of CVD risk factors in the nondiabetic AAW. Worsening of serum glucose and HDL-C carried the most CVD risk factors cluster and greater prevalence of MetS than worsening of serum triglyceride. However, worsening of the 3 metabolic components of MetS, without exception, was consistently associated with significant increases in WC, but not BMI or IR in AAW. We concluded that, of the 3 metabolic components of MetS, serum HDL-C and glucose are the most powerful and perhaps the most cost-predictive surrogates for MetS in AA, each yielding approximately 40% of the prevalence of MetS in our nondiabetic, overweight/obese AAW. Conversely, we found that serum triglycerides had the least impact on the prevalence of MetS in our AAW. We propose (1) that the 3 metabolic parameters for MetS defined by ATP III should be *weighted* differently with respect to their potential as CVD risks and (2) that nondiabetic AAW in our third tertile of serum glucose (>100 mg/dL) and/or first tertile of HDL-C (<40 mg/dL) should be targeted for screening for MetS. We recommend a prospective CVD outcome study to confirm our hypotheses in AAW. If confirmed or substantiated, these results could have serious public health implications as well as definition of the MetS in African Americans.

Acknowledgment

We wish to thank the staff of the Endocrinology and Diabetes Clinical Research Unit of The Ohio State University College of Medicine and the Nursing Staff of the GCRC RR-0034, Bethesda, MD.

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