

Cardiometabolic Risk Among African American Women

A Pilot Study

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Objective: This study aimed to determine the associations of the Homeostatic Model of Assessment-insulin resistance (HOMA-ir), acanthosis nigricans, high-sensitivity C-reactive protein (hs-CRP), and plasminogen activator inhibitor-1 (PAI-1) with 2 of the commonly used definitions of metabolic syndrome (Adult Treatment Panel III [ATP III] and International Diabetes Federation [IDF]) among reproductive-age, healthy, free-living African American women. **Methods:** A pilot study with a cross-sectional design examined 33 African American women aged 20 to 46 years (mean [SD], 31.24 [7.25] years) for the presence of metabolic syndrome determined by ATP III and IDF criteria, insulin resistance (HOMA-ir and/or acanthosis nigricans), degree of inflammation (hs-CRP), and presence of dysfibrinolysis (PAI-1). **Results:** HOMA-ir identified insulin resistance in 27 (81.8%) women, whereas the presence of acanthosis nigricans indicated that 16 (48%) of these women manifested insulin resistance. Metabolic syndrome was found in 7 women (21.2%) by ATP III or in 9 (27.3%) women by IDF criteria. Bivariate correlations showed associations between HOMA-ir and waist circumference, body mass index (BMI), acanthosis nigricans, and the ATP III and IDF definitions for metabolic syndrome. Plasminogen activator inhibitor-1 was significantly correlated with waist circumference, BMI, fasting glucose, HOMA-ir, and ATP III. Both HOMA-ir and PAI-1 were significantly and negatively correlated with high-density lipoprotein cholesterol. High-sensitivity CRP was significantly correlated with BMI and 2-hour postglucose. **Conclusion:** Both dysfibrinolysis (PAI-1 levels) and insulin resistance (HOMA-ir), when individually regressed on the ATP III definition of metabolic syndrome, explained 32% and 29% of the respective variance. The addition of HOMA-ir measurement may significantly improve early recognition of cardiometabolic risk among reproductive-age African American women who have not yet met the criteria for the ATP III or IDF definitions of metabolic syndrome. Likewise, acanthosis nigricans is potentially a clinically significant screening tool when used to determine early recognition of insulin resistance and/or cardiometabolic risk among this population. African American women's risk for cardiovascular disease is likely underestimated based on the sole use of ATP III criteria for diagnosis of metabolic syndrome. Clinicians should consider a broader definition of risk than that contained within ATP III. Inclusion of biomarkers of inflammation and dysfibrinolysis, along with measures of insulin resistance, may add to early detection of cardiometabolic risk and ultimate reduction in cardiovascular health disparities among African American women.

KEY WORDS: dysfibrinolysis, health disparity, high-sensitivity C-reactive protein (hs-CRP), Homeostatic Model of Assessment-insulin resistance (HOMA-ir), inflammation, insulin resistance, metabolic syndrome, plasminogen activator inhibitor-1 (PAI-1)

Recommendations from Healthy People 2010 emphasize the need to eradicate racial disparities in cardiovascular health.¹ African American women ex-

perience higher age-adjusted prevalence rates for obesity, hypertension, coronary heart disease, stroke, and type 2 diabetes than compared with any other group

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of US women.²⁻⁶ However, these disparities are not fully explained by conventional risk factors. Obesity and hyperinsulinemia have been strongly associated with an inflammatory state leading to release of substances associated with inflammation and impaired fibrinolysis or dysfibrinolysis (the propensity to form thrombus).²⁻⁵ African American women typically have a higher body mass index (BMI), increased levels of circulating insulin, lower levels of insulin sensitivity (otherwise known as “insulin resistance”), and a higher acute response of insulin to glucose when compared with white US women.^{7,8} These findings suggest an earlier risk for beta cell failure and a higher likelihood for early development of type 2 diabetes than among white women.^{7,9-11}

The American Diabetes Association defines cardiometabolic risk as a set of risk factors that, when viewed together, serve as an indicator of an individual's risk for developing type 2 diabetes and/or cardiovascular disease (CVD).¹² African American women may be more predisposed than whites to cardiometabolic risk factors for type 2 diabetes and atherosclerosis. These cardiometabolic risk factors are believed to act synergistically through inflammation, which stimulates the onset of impaired fibrinolysis, leading to atherothrombosis and arteriosclerosis.

Background

Generally, before the development of type 2 diabetes or CVD, the precursor condition, metabolic syndrome, often develops. In certain individuals, metabolic syndrome is associated with vascular inflammation, which can lead to increased clotting, rupture of vulnerable plaque, and vascular injury and, subsequently, to the development of CVD and acute events such as myocardial infarction (MI) or stroke.¹³⁻¹⁷ Metabolic syndrome is strongly associated with low levels of insulin sensitivity and higher degrees of insulin resistance, which act in concert to foster inflammation and, in turn, impaired fibrinolysis or dysfibrinolysis. Inflammation transforms normal hemostasis or fibrinolysis toward dysfibrinolysis, which is the propensity to form thrombi, and this pathway also may lead to rupture of vulnerable plaque.¹⁸⁻²⁰ Individuals with increased plasma inflammatory biomarkers and biomarkers of dysfibrinolysis exhibit vascular inflammation and are at greater risk of developing thrombi or plaque rupture. Biomarkers such as high-sensitivity C-reactive protein (hs-CRP) or plasminogen activator inhibitor-1 (PAI-1), when increased, have been strongly associated with the onset of either MI or stroke.²¹⁻²⁵ Elevated circulating levels of hs-CRP, insulin, triglycerides, and various cytokines have been known to stimulate abdominal adipocytes and foster excess release of PAI-1, which is

indicative of impaired fibrinolysis. Insulin, hs-CRP, triglycerides, and PAI-1 are all cardiometabolic risk factors and correlates of metabolic syndrome.²⁶

The most common definition of metabolic syndrome used within the United States is from the National Cholesterol Education Program Adult Treatment Panel III (ATP III) and consists of the presence of 3 of the following 5 components: central (abdominal) obesity, hypertension, impaired fasting glucose, hypertriglyceridemia, or low high-density lipoprotein cholesterol (HDL-C) level (see Box 1 for description of ATP III diagnostic criteria and Box 2 for categories of abnormal glucose homeostasis).¹⁷ Recently, the International Diabetes Federation (IDF) released a new definition of metabolic syndrome which has been used primarily in Europe and the Asian Pacific Rim region and contains more stringent waist circumference measures, but only for Asians (see Box 1 for a comparison of 2 common definitions of metabolic syndrome). However, the general IDF criteria for metabolic syndrome offer a different combination of the same components plus use of BMI greater than 30 kg/m² used for the diagnosis of metabolic syndrome.²⁹ Comparison of these 2 definitions potentially may assist in determining which one is more sensitive for early identification of cardiometabolic risk among high-risk minority populations.

Paradoxically, African American women do not have the highest prevalence rates for metabolic syndrome among US women even though they possess the highest prevalence rates for type 2 diabetes, obesity,

Box 1 2 Common Definitions of Metabolic Syndrome

National Cholesterol Education Program Adult Treatment Panel III ¹⁷	International Diabetes Federation ²⁷
Any 3 or more of the following	Abdominal obesity: waist circumference for Asians (only): >94 cm for men and >80 cm for women
Abdominal obesity: waist circumference >40 in (102 cm) in men and >35 in (88 cm) in women	Must have either central obesity ^a or an increased BMI plus 2 of the following:
Triglycerides ≥150 mg/dL	Triglycerides ≥150 mg/dL
HDL-C <40 mg/dL in men and <50 mg/dL in women	HDL-C < 40 mg/dL in men and <50 mg/dL in women
Blood pressure ≥130/85 mm Hg	Blood pressure ≥130/85 mm Hg
Fasting glucose ≥100 mg/dL	Fasting glucose ≥100 mg/dL or previously diagnosed diabetes

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol.

^aCentral obesity based on waist circumference for Asian women is greater or equal to 33 in., but for all other women, it is greater than or equal to 35 in.

An increased BMI is equal to or greater than 30 m²/kg.

Box 2 Categories of Abnormal Glucose Homeostasis^{36–39}

Glucose Level	Terminology
Fasting glucose	
<100 mg/dL	Euglycemia
100–125 mg/dL	Impaired fasting glucose (IFG)
≥126 mg/dL	Diabetes mellitus
Glucose level after a 2-h post-oral glucose tolerance test (OGTT)	
140–199 mg/dL	Impaired glucose tolerance (IGT)
≥ 200 mg/dL	Diabetes mellitus
Prediabetes	
100–125 mg/dL	Impaired fasting glucose (IFG)
140–199 mg/dL	Impaired glucose tolerance (IGT)

Source: American Diabetes Association.²⁸

hypertension, and stroke among US women.^{30,31} The cardiovascular health disparity experienced by African American women may relate to the findings that these women typically have a higher BMI, increased levels of circulating insulin, and lower levels of insulin sensitivity indicating a higher level of insulin resistance than their whites counterparts do.⁹ However, African American women without diabetes also have a propensity for manifesting normal triglyceride and HDL-C levels until they develop type 2 diabetes. This benign lipid profile among African American women without diabetes lowers the sensitivity of the ATP III to identify them as manifesting metabolic syndrome. Among other populations (ie, white and Hispanics), there is a close correlation to hypertriglyceridemia and insulin resistance, and this lack of an early abnormal lipid profile may reduce the sensitivity of the current ATP III definition for diagnosis of metabolic syndrome among African American women.^{6,10,11}

Insulin resistance can be closely correlated with use of a simple mathematical calculation of the Homeostatic Model of Assessment-insulin resistance (HOMA-ir), which, among euglycemic individuals, closely approximates the sophisticated gold standard for determining the level of insulin sensitivity and its reverse insulin resistance with use of the intravenous glucose clamp measurement^{32–34} (see Box 2 and Box 3). Likewise, acanthosis nigricans presents as a noticeable darkening of skin and is a sign of insulin resistance that is easily and commonly seen among individuals with dark skin pigmentation. Hyperinsulinemia stimulates the melanocytes to produce increased melanin, which leads to thickening and darkening of the skin, especially on the back of the neck. Acanthosis nigricans presents as a smooth, and often raised velvety plaque, first noticed at the back of the neck in a single line. In extreme cases, the acanthosis nigricans may extend to the frontal plane of the neck and becomes obviously visible when standing in front of the individual.³⁵ Acanthosis

nigricans can also be found in all body folds (ie, back of neck, axillae, groin, elbows, or knees). Burke et al³⁵ showed that acanthosis nigricans found on the neck had the highest sensitivity (93%) for insulin resistance, and it was found on the neck 99% of the time, compared with any other sites.

The presence of inflammation and a propensity toward thrombosis are strongly associated with metabolic syndrome.^{37–39} Biomarkers, which represent inflammation and dysfibrinolysis, are increased circulating levels of hs-CRP and/or PAI-1, respectively. These markers, along with components of metabolic syndrome, have been shown to be important early predictors of cardiac events.^{22,38} Most investigations of inflammation and fibrinolysis, however, have focused on American and/or European men and have studied women less often, particularly at middle age; furthermore, these studies have not fully considered the impact of insulin resistance or race. In fact, using the ATP III definition¹⁷ alone for metabolic syndrome, especially among healthy younger to middle-aged African American women, often results in relatively low risk predictions.^{31,40–42} This is counterintuitive because African American women have some of the highest prevalence rates for many of the cardiometabolic risk factors and suffer from extreme morbidity and mortality in association with obesity, type 2 diabetes, hypertension, and CVD. Thus, the ATP III definition, when used alone, may have serious shortcomings. Considering the components of metabolic syndrome along with other biomarkers may add to its prediction of cardiometabolic risk among African American women.^{43,44}

The issues described above^{41,42,45,46} suggest that metabolic syndrome may not describe risk accurately or early in the trajectory of CVD development the same way for all populations, and additional research is needed to better define the syndrome.^{41,47} Ford³¹ analyzed the National Health and Nutrition Examination Survey (NHANES) 1999–2002 data and found the prevalence of metabolic syndrome among African American women to be slightly higher when using the IDF versus ATP III definition (overall total: IDF, 38.8% and ATP III, 36.4%, adjusted for age; for ages 20–39 years: IDF, 23.7% and ATP III, 22.0). However, Hispanic women had the highest prevalence rates for metabolic syndrome in NHANES.

Box 3 Homeostatic Model of Assessment-Insulin Resistance (HOMA-ir)³⁴ as a Measure of Insulin Resistance

$$\text{HOMA-ir (mmol/L} \times \mu\text{U/mL)} = \frac{[\text{fasting glucose (mmol/L)} \times \text{fasting insulin (}\mu\text{U/mL)}]}{22.5}$$

HOMA-ir > 2.7 Insulin resistance

To convert glucose from mmol/L to $\mu\text{U/mL}$, multiply by 0.05551.

Results from the Jackson Heart Study,⁶ which included large numbers of African Americans, demonstrated that 37% of the 5,000 African American participants had metabolic syndrome.¹⁰ Insulin resistance may be one of the earliest components of the syndrome to be manifested when the individual is still euglycemic.⁴⁸ Unfortunately, the current ATP III definition likely identifies the syndrome among African Americans later rather than earlier by failing to capture the underlying and important pathology of insulin resistance because of their relative normal lipid profiles when in a nondiabetic state. Metabolic syndrome was identified among participants of the Jackson Heart Study primarily by the presence of central obesity, hypertension, and impaired fasting glucose.¹⁰ Impaired fasting glucose is a late sign of insulin resistance.^{49–52} Therefore, further investigation of other markers of metabolic syndrome among African American women may serve to further elucidate these issues.

Methods

This descriptive pilot study took place in the research center of a Southeastern medical center in the United States. A total of 33 self-referred premenopausal African American women aged 20 to 46 years were screened in the fasting state for metabolic syndrome using 2 common definitions (ATP III and IDF). Likewise, novel cardiovascular risk factors and noninvasive markers (waist circumference, BMI, and identification of presence of acanthosis nigricans) were measured. The women had fasting glucose, insulin, lipids, PAI-1, and hs-CRP levels drawn and then underwent a 2-hour oral glucose tolerance test. Various metabolic criteria were compared to determine the presence of metabolic syndrome, insulin resistance, and the association of other early cardiometabolic risk markers for type 2 diabetes and/or CVD (ie, hs-CRP, PAI-1, HOMA-ir, and acanthosis nigricans). High-sensitivity C-reactive protein was used as a marker of inflammation; PAI-1 was used as a maker for dysfibrinolysis, whereas HOMA-ir and acanthosis nigricans were used to indicate degree and/or general presence of insulin resistance.

General Procedures

Upon approval from the university institutional review board and research center's Scientific Advisory Committee, informational flyers were distributed at churches and beauty salons chosen randomly from a telephone book. A recruitment advertisement was also placed in the local campus newspaper. The principal investigator (PI) and her research assistant were available to provide oral presentations concerning the study to women's groups associated with the churches or beauty salons. Once a potential

participant responded, the research assistant made an initial telephone contact and interview to determine if the inclusion and exclusion criteria were met.

Inclusion criteria consisted of the following: not pregnant; premenopausal; no recent use of steroids or oral contraceptives within the past 3 weeks; no treatment with injectable contraceptives in the last 3 months; and never diagnosed or treated for an autoimmune disease, hypertension, dyslipidemia, or hyperglycemia. Additional criteria included English speaking, self-identified as an African American able to trace their maternal heritage back 3 generations and of main continent African decent (not from a Caribbean Island), and residing in the Southern United States. This was to limit the amount of racial admixture within the population of interest.

The evening before the study, the participant was contacted by the research assistant and reminded of the appointment and the need to be in a fasting state after 7:00 PM. Each of the participants reported by 7:00 AM to the research center. Written informed consent was obtained on the morning of the study. A demographic questionnaire was then completed. Subsequently, the following measures were obtained: blood pressure, height, weight, waist circumference, blood for fasting laboratory testing, 2-hour oral glucose tolerance test, and assessment for acanthosis nigricans. Blood pressure was measured before drawing of blood. Blood pressure was obtained by the same research assistant with an appropriate-sized cuff and was measured 3 times in the same arm, at least 5 minutes apart, following American Heart Association standards.⁵³ Waist circumference measurements were obtained on all the participants by the same nutritionist employed in the research center. The blood samples obtained in the fasting state were glucose, insulin, hs-CRP, lipid profile, and blood for the preparation of PAI-1 samples. Blood PAI-1 samples were prepared and sent to the University of Vermont. Numerous large epidemiological studies have consistently sent blood samples for determination of circulating PAI-1 levels to the Laboratory for Clinical Biochemistry Research at the University of Vermont.

Plasminogen activator inhibitor-1 was measured in citrated plasma sensitive to free PAI-1 (both latent and active) but not PAI-1 in complex with tissue plasminogen-activator. The analytical critical value for the assay is 3.47%. The citrated samples were processed within 30 minutes of blood draw and spun for a minimum of 3,000g for 10 minutes to make sure that there was no contamination from platelet PAI-1. The plasma samples were kept on ice and then stored in aliquots at -70°C at the research center's processing laboratory until all the samples were collected and ready to be shipped for analyses in one batch.⁵⁴

Finally, each participant underwent a 2-hour oral glucose tolerance test. The laboratory examination was completed shortly after noon, and data collection was then over. At the completion of the study, the participants were served a meal and given a coupon for free parking at the hospital parking deck and a \$75.00 gift certificate to a local grocery store. When the laboratory results of the study became available, participants received a copy and were free to share them with their personal healthcare provider. They were also given the PI's number for questions concerning the results along with a short written explanation of each test. If there were abnormal findings, the participant was sent a letter from the PI, and if a referral was indicated, the participant was assisted by the PI's supervising physician, who was an endocrinologist.

Statistical Analyses

Bivariate correlation analyses were used to examine the relationships between PAI-1, hs-CRP, HOMA-ir and all other continuous variables, and Spearman correlation analyses were used to examine the relationships between PAI-1, hs-CRP, HOMA-ir, and all other categorical variables (acanthosis nigricans, ATP III, and IDF).

Multiple linear regression analyses were used to model the relationships between PAI-1, hs-CRP, and HOMA-ir and other variables. All regression models contained either PAI-1, hs-CRP, or HOMA-ir as the dependent variable; one of the variables of interest (such as BMI or HgA_{1c}) as the independent predictor variable; and age as a covariate (as shown in Table 3). Other models containing 1 or 2 additional potential covariates were examined; however, the results of these models were not substantially different from the simpler models and, therefore, are not shown. It was not possible to put a large number of predictor variables and/or potential covariates into the models because of the limited sample size and a few missing data points for variables of interest.

The means of PAI-1, hs-CRP, and HOMA-ir for the ATP III and IDF definitions of metabolic syndrome were compared using the 2-group *t* test. All serum variables, such as insulin, glucose, and cholesterol measures, were log-transformed before analysis to ensure normality of distribution. All statistical tests were 2 sided and were performed using a significance level of 5%. Statistical analyses were performed with the use of SAS software.⁵⁵

Results

Clinical characteristics of the sample are described in Table 1. A mean HOMA-ir score of 4.7 indicates that the cohort was highly insulin resistant. Waist circumference was used to classify 18 (54.6%) women with

TABLE 1 Clinical Characteristics of the Cohort

Variables	n	Mean	SD	Range
Age, y	33	31.24	7.25	20.0–46.0
Waist circumference, cm	33	91.94	14.48	70.90–45.70
BMI, kg/m ²	33	30.99	6.52	23.08–50.55
SBP, mm Hg	33	122.58	14.48	100.67–153.67
DBP, mm Hg	33	73.42	10.13	54.67–100.67
Fasting glucose, ^a mg/dL	33	88.55	10.86	72.0–126.0
2-h postglucose, ^a mg/dL	33	116.39	38.76	73.0–241.0
Fasting insulin, ^a μU/mL	33	20.67	11.64	7.0–59.0
HOMA-ir ^a	33	4.70	3.44	1.39–18.21
PAI-1, ^a ng/mL	29	24.10	20.83	1.77–83.14
CRP, ^a ng/mL	32	0.564	0.62	0.03–2.65
LDL, ^a mg/dL	33	112.23	34.19	62.40–174.4
Triglycerides, ^a mg/dL	33	75.51	28.69	37.00–153.0
HDL-C, ^a mg/dL	33	52.55	15.80	31.0–101.0

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-ir, Homeostatic Model of Assessment-insulin resistance; LDL, low-density lipoprotein; PAI-1, plasminogen activator inhibitor-1; SBP, systolic blood pressure.

^aLog-transformed before statistical analysis.

central obesity. A total of 17 (51.5%) women were overweight or obese based on their BMI. HOMA-ir identified 27 (81.8%) women as having insulin resistance. Acanthosis nigricans was present in 16 (48%) women.

The ATP III guidelines classified 7 (21.2%) women as having metabolic syndrome, whereas the IDF criteria diagnosed 9 (27.3%) women as having metabolic syndrome.

Bivariate correlations are presented in Table 2. Pearson correlations revealed that BMI, waist circumference, and HOMA-ir were correlated to PAI-1. High-sensitivity CRP was significantly correlated to BMI. Although, hs-CRP was not significantly correlated to HOMA-ir, postglucose was correlated. HOMA-ir was significantly correlated with BMI, waist circumference, and PAI-1. HOMA-ir was significantly correlated to acanthosis nigricans.

The results of the multiple linear regression analyses performed on the major outcome variables PAI-1, hs-CRP, and HOMA-ir appear in Table 3. Results for models with statistically significant predictors or predictors that display a trend toward significance are displayed. The best models describing PAI-1 as an outcome variable appear to include either BMI ($P < .0001$, model $R^2 = 0.63$) or waist circumference ($P < .0001$, model $R^2 = 0.59$). The best model describing hs-CRP as an outcome variable seems to include 2-hour oral postglucose ($P = .005$, model $R^2 = 0.31$). The best models describing HOMA-ir as an outcome variable seem to include

TABLE 2 Correlations (Pearson) of Physiologic Variables

	Waist circumference, cm	BMI, kg/m ²	SBP, mm Hg	DBP, mm Hg	Fasting glucose, mg/dL	2-h postglucose, ^a mg/dL	Fasting insulin, ^a μ U/mL	HOMA-ir ^a	PAI-1, ^a ng/mL	CRP, ^a ng/mL	TG, ^a mg/dL	HDL-C, ^a mg/dL	ATP III	IDF	AN
HOMA-ir ^a	0.527	0.431	0.119	0.030	0.763	0.201	0.988	1	0.409	0.050	0.362	-0.360	0.455	0.440	0.424
	0.002 ^b	0.012 ^b	0.507	0.866	<.0001 ^b	0.278	<.0001 ^b		0.027 ^b	0.785	0.039 ^b	0.039 ^b	0.008 ^b	0.010 ^b	0.014 ^b
PAI-1, ^a ng/mL	0.763	0.796	0.344	0.051	0.499	0.359	0.354	0.409	1	0.257	0.225	-0.471	0.472	0.338	0.330
	<.0001 ^b	<.0001 ^b	0.068	0.791	0.006 ^b	0.065	0.059	0.027 ^b		0.187	0.240	0.009 ^b	0.009 ^b	0.072	0.080
CRP, ^a ng/mL	0.272	0.429	0.030	-0.202	0.031	0.544	0.051	0.050	0.257	1	0.221	0.130	0.039	-0.136	0.323
	0.131	0.014 ^b	0.866	0.265	0.864	0.001 ^b	0.781	0.785	0.187		0.222	0.475	0.832	0.455	0.080

Abbreviations: AN, acanthosis nigricans; ATP III, Adult Treatment Panel III; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-ir, Homeostatic Model of Assessment-insulin resistance; IDF, International Diabetes Federation; PAI-1, plasminogen activator inhibitor-1; SBP, systolic blood pressure; TG, triglycerides.

^aLog-transformed before statistical analysis.

^bStatistically significant at $P < 0.05$.

The values appearing below the correlations are P -values.

waist circumference ($P = .0045$, model $R^2 = 0.30$), ATP III definition of metabolic syndrome (yes [3 or more components] or no) ($P = .0016$, model $R^2 = 0.29$), or ATP III (with central obesity as a required component) ($P = .0032$, model $R^2 = 0.26$). Body mass index is a statistically significant predictor in all models for the major outcome variables.

Discussion

The major findings of this study indicate that the simple noninvasive screening for acanthosis nigricans on the back of the neck, coupled with the calculation of HOMA-ir, is a potentially useful and powerful intervention for clinical practice. The mere presence of acanthosis nigricans indicates the need for further investigation of the patient's cardiometabolic risk profile. Therefore, acanthosis nigricans should alert the clinician to the need for further evaluation of the individual for the presence of dysglycemia, dyslipidemia, inflammation, and frank insulin resistance. Once acanthosis nigricans is identified, the clinician should consider the need for obtaining fasting levels of glucose, insulin, hs-CRP, a lipid profile, and potentially a 2-hour oral glucose tolerance test. Consequently, a HOMA-ir should be calculated to determine the presence and/or degree of insulin resistance.

The women within this study were free living and had relatively few indicators of frank pathology. Hypertriglyceridemia and increased levels of hs-CRP are major stimuli for release of excessive circulating levels of PAI-1, and their normal to low levels in this sample may be one explanation for the lower degree of dysfibrinolysis found. These findings may indicate that these women were still early in their trajectory of risk toward possible development of type 2 diabetes and/or CVD. These findings even further emphasize the need to better understand the best use of early risk markers for insulin resistance, such as acanthosis nigricans and/or HOMA-ir.

As identified in the literature, African American women's risk for CVD is likely significantly underestimated based on the sole use of ATP III criteria within the United States. Clinicians should consider a broader definition of cardiometabolic risk than that is currently contained within the ATP III criteria when used alone to define metabolic syndrome. The inclusion of other definitions of metabolic syndrome, biomarkers of inflammation, and dysfibrinolysis, along with measures of insulin resistance, may add to earlier detection of cardiometabolic risk and ultimate reduction in cardiovascular health disparities among African American women. Screening among African American women for acanthosis nigricans may prove to be an exceptional early risk marker. This is especially true because much of the early risk reduction

TABLE 3 Multiple Regression Models for Major Outcome Variables

Dependent Variable ^a	Independent Variables	Parameter Estimates ± SE	P	Model P	Model R ²
PAI-1	BMI	0.0483 ± 0.0074	.0001	.0001	0.63
	Age	-0.0007 ± 0.0067	.92		
PAI-1	Waist circumference	0.0257 ± 0.0043	.0001	.0001	0.59
	Age	-0.0057 ± 0.0074	.45		
PAI-1	HOMA ^a	0.6595 ± 0.2886	.031	.063	0.19
	Age	0.0086 ± 0.0098	.38		
PAI-1	HgA _{1c} ^a	4.2558 ± 1.4239	.0062	.017	0.28
	Age	-0.0043 ± 0.0098	.67		
PAI-1	Fasting glucose ^a	3.7871 ± 1.2769	.0064	.015	0.27
	Age	0.0086 ± 0.0098	.35		
PAI-1	Fasting insulin ^a	0.6679 ± 0.3469	.065	.12	0.15
	Age	0.0087 ± 0.0100	.39		
PAI-1	HDL-C ^a	-1.6084 ± 0.5263	.0051	.013	0.29
	Age	0.0141 ± 0.0093	.14		
PAI-1	IDF (definition of MS)	0.5225 ± 0.1826	.0082	.019	0.26
	Age	-0.0009 ± 0.0100	.93		
PAI-1	ATP III (5 components)	0.4535 ± 0.1346	.0023	.0061	0.32
	Age	-0.0034 ± 0.0097	.73		
PAI-1	Acanthosis nigricans	0.2678 ± 0.1461	.078	.14	0.14
	Age	0.0034 ± 0.0106	.75		
PAI-1	ATP III (≥3 components)	0.4075 ± 0.1601	.017	.038	0.22
	Age	0.0027 ± 0.0099	.79		
hs-CRP	BMI	0.0349 ± 0.0156	.033	.038	0.20
	Age	0.0093 ± 0.0119	.44		
hs-CRP	2-h postglucose ^a	1.8800 ± 0.6102	.0046	.005	0.31
	Age	0.0088 ± 0.0106	.41		
hs-CRP	IGT	0.4107 ± 0.1957	.045	.040	0.21
	Age	0.0129 ± 0.0112	.26		
HOMA-ir	BMI	0.0176 ± 0.0065	.0014	.038	0.20
	Age	-0.0035 ± 0.0059	.55		
HOMA-ir	Waist circumference	0.0118 ± 0.0033	.0011	.0045	0.30
	Age	-0.0057 ± 0.0056	.31		
HOMA-ir	HgA _{1c} ^a	2.1413 ± 1.0335	.0476	.14	0.13
	Age	-0.0052 ± 0.0071	.47		
HOMA-ir	Fasting triglyceride ^a	0.5594 ± 0.2607	.0401	.12	0.13
	Age	0.0019 ± 0.0058	.75		
HOMA-ir	HDL-C ^a	-0.7819 ± 0.3510	.034	.099	0.14
	Age	0.0040 ± 0.0059	.50		
HOMA-ir	ATP III (5 components)	0.2639 ± 0.0823	.0032	.012	0.26
	Age	-0.0052 ± 0.0057	.38		
HOMA-ir	Acanthosis nigricans	0.1916 ± 0.0881	.0378	.11	0.14
	Age	-0.0034 ± 0.0062	.59		
HOMA-ir	ATP III (≥3 components)	0.3267 ± 0.0942	.0016	.0062	0.29
	Age	-0.0034 ± 0.0062	.59		

Abbreviations: ATP III, Adult Treatment Panel III; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HOMA-ir, Homeostatic Model of Assessment-insulin resistance; IDF, International Diabetes Federation; IGT, impaired glucose tolerance; MS, metabolic syndrome; PAI-1, plasminogen activator inhibitor-1.

^aLog-transformed before statistical analysis (PAI-1, hs-CRP, HOMA-ir, fasting glucose, fasting insulin, 2-hour postglucose, HgA_{1c}, fasting triglycerides, HDL-C).

techniques are aimed at lifestyle modification. Lifestyle modification is often one of the most difficult interventions to undertake and it also requires time.

Although this was a small pilot study, it is interesting to note that we found similar prevalence rates for metabolic syndrome to those of a large epidemiological study conducted by Ford³¹ in the NHANES 1999–2002. The mean age of the women who participated in this study was 31.24 years, and the prevalence rates found by Ford for the age-adjusted group (20–39 years) was 22.0% for ATP III and

23.7% for IDF, whereas our findings were 21.2% for ATP III and 27.3% for IDF. The similarity of our results to those found in the NHANES 1999–2002 may indicate that our population was very similar and not atypical to the population to which the NHANES might be generalized.

Limitations

The nature of a pilot study imposes numerous limitations, first of which is the small sample size and

limited geographic region from which the participants were recruited. Therefore, repeat of this study with a larger sample size and more diverse geographic regions is needed. A wider range of pathologies such as dyslipidemia and dysglycemia may have produced more varied results such as higher levels of inflammation and/or dysfibrinolysis. Although, we did screen the women for use of agents that alter insulin sensitivity, blood pressure, glucose, inflammation, and dysfibrinolysis as well as a diagnosis of CVD, diabetes, or autoimmune disorders, some may still have possessed these pathologies or have been taking medications before, which may have altered some of the variables of interest.

On the basis of the literature, we theorize that if this population of African American women had a higher prevalence of either hypertriglyceridemia or increased hs-CRP levels, they would have manifested higher a degree of dysfibrinolysis, as increased levels of triglycerides and/or hs-CRP are known to stimulate abdominal adipocytes to increase their release of circulating levels of PAI-1.

Clinical Implications

As a pilot study, the clinical implications are limited and need to be validated in a larger research study. However, there are numerous potentially important clinical implications that should be further investigated. For example, these African American women did experience mild to moderate levels of inflammation, which, in this study, was most closely associated with their increased BMI or general level of adiposity. Body mass index explained 33% of the inflammation identified by hs-CRP. This is a significant finding because the levels of inflammation were relatively low within this group of healthy and free-living women (hs-CRP levels, 0.03–2.65). Similarly, the categorical variable 2-hour postglucose was strongly associated with inflammation, explaining 31% of the variance related to hs-CRP. Impaired glucose tolerance is commonly associated with the development of type 2 diabetes and is worsened by generalized obesity.⁵⁶ Inflammation and dysfibrinolysis have both been found to be closely associated with an increased BMI or an enlarged waist circumference, as it was found that dysfibrinolysis, as indicated by circulating PAI-1 levels, explained 63% and 59% of the variance associated with circulating PAI-1 levels when regressed with BMI and waist circumference, respectively, indicating that either an increased BMI or an enlarged waist circumference may set up a metabolic environment, which may favor development of thrombosis.

Likewise, insulin resistance as indicated by HOMA-ir, when regressed with waist circumference,

explained 30% of the variance. HOMA-ir was significantly correlated with acanthosis nigricans and did predict almost 14% of the variance. These findings indicate that acanthosis nigricans may be an important clinical noninvasive screening tool. Identification of acanthosis nigricans in an otherwise seemingly low-risk African American woman may be of great clinical significance when used early to identify her risk trajectory toward cardiometabolic end points such as type 2 diabetes or CVD. These findings further highlight the importance of measuring body composition in clinical practice and the need to encourage African American women to optimize (ie, decrease) both their weight and waist circumference to minimize their cardiometabolic risk.

Both dysfibrinolysis (PAI-1 levels) and insulin resistance (HOMA-ir), when individually regressed on ATP III definition for metabolic syndrome, explained 32% and 29% of the respective variance. This may indicate the importance and association of both dysfibrinolysis and insulin resistance with metabolic syndrome within this population of women, as previously described within the literature.^{24,39,48} The major clinical implication here is that all African American women should routinely be assessed for insulin resistance using the presence of acanthosis nigricans and/ or HOMA-ir (when clinically feasible) even when they are euglycemic.³² HOMA-ir offers an early marker of insulin resistance that can be recognized long before diagnosis of metabolic syndrome is able to be made.

Although there are now 4 common definitions for metabolic syndrome,^{17,26,57,58} the ATP III definition is most commonly used in the United States. The ATP III definition, however, has been criticized for not including measurement of insulin resistance (ie, increased plasma insulin levels or acanthosis nigricans).^{37,40–42,46,59,60} The ATP III definition relies heavily on an abnormal lipid profile to meet the criteria for metabolic syndrome (increased triglyceride and low HDL-C levels).⁴¹ However, research has shown that African American women without diabetes do not manifest the abnormal lipid profiles commonly found among white and Hispanic populations. The Insulin Resistance Atherosclerosis Study found that African Americans had significantly higher HDL-C ($P < .001$) and lower triglyceride ($P < .001$) levels than did either whites or Hispanics.⁶¹ These same racial differences in lipid profiles have also appeared in other large epidemiological studies such as the Charleston Heart Study⁶² and the Atherosclerosis Risk in Communities Study.⁶³ Furthermore, because African Americans have both lower insulin sensitivity¹¹ and higher circulating levels of insulin than whites do, the ATP III definition may be inappropriate for sole use within this

Clinical Pearl

- Simple noninvasive screening can improve outcomes by identifying persons at-risk for type 2 diabetes or cardiovascular disease.
- Screening for acanthosis nigricans on the back of neck is one such screening approach to detect insulin resistance and increased cardiometabolic risk.
- The homeostasis model assessment of insulin resistance (HOMA-ir) is a screening tool useful on non-diabetic persons.

population to determine cardiometabolic risk. Therefore, given the propensity of African American women without diabetes to have normal HDL-C and triglyceride levels, coupled with their paradoxically high prevalence of morbidity and mortality from CVD, there is a need to elucidate the mechanisms involved in race-specific differences in the development of cardiometabolic risk leading to type 2 diabetes and CVD.

Metabolic syndrome has been identified as a predictor of the development of type 2 diabetes as well as nonfatal MI among premenopausal obese women. Indeed, Amowitz and colleagues⁶⁴ found metabolic syndrome to be the most powerful predictor of premature MI among racially diverse premenopausal women younger than 45 years. Similarly, Turhan and colleagues⁶⁵ found that women with premature coronary artery disease had a higher prevalence of metabolic syndrome than did their male counterparts (73% vs 31%, $P < .001$). These 2 studies found a higher prevalence of metabolic syndrome among young women with premature coronary heart disease. Further research on cardiometabolic risk among young, healthy women of diverse racial backgrounds may be valuable in guiding primary and secondary prevention and determining if these interventions should vary by race.

REFERENCES

1. US Department of Health and Human Services. *Healthy People 2010*. Conference edition [in two volumes]. Washington, DC: US Department of Health and Human Services; 2000.
2. American Heart Association. *American Heart Association, Heart and Stroke Statistical Update 2007*. Dallas, TX: American Heart Association; 2007.
3. Howard BV, Criqui MH, Curb JD, et al. Risk factor clustering in the insulin resistance syndrome and its relationship to cardiovascular disease in postmenopausal white, black, Hispanic, and Asian/Pacific Islander women. *Metabolism*. 2003;52:362–371.
4. Koro CE, L'italien GJ, Fedder DO. Major CHD risk factors predominate among African-American women who are eligible for lipid-lowering drug therapy under the new ATP III guidelines. *Eur J Cardiovasc Prev Rehabil*. 2004;11:376–381.
5. Sundquist J, Winkleby MA, Pudarc S. Cardiovascular disease risk factors among older black, Mexican-American, and white women and men: an analysis of NHANES III, 1988-1994. Third National Health and Nutrition Examination Survey. *J Am Geriatr Soc*. 2001;49:109–116.
6. Taylor HA Jr, Wilson JG, Jones DW, et al. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. *Ethn Dis*. 2005;15:S6–S17.
7. Appel SJ, Phadke P, Hunter G, et al. Racial differences in PAI-1 levels among healthy African-American and caucasian women. *Circ Suppl*. 2007;115(8):E290–E291.
8. Bergman RN, Zaccaro DJ, Watanabe RM, et al. Minimal model-based insulin sensitivity has greater heritability and a different genetic basis than homeostasis model assessment or fasting insulin. *Diabetes*. 2003;52:2168–2174.
9. Appel SJ, Harrell JS, Deng S. Racial and socioeconomic differences in risk factors for cardiovascular disease among Southern rural women. *Nurs Res*. 2002;51:140–147.
10. Gardner A. Metabolic syndrome hits Mississippi blacks hard. 2005. <http://www.forbes.com/lifestyle/health/feeds/hscout/2005/11/13/hscout529117.html>. Accessed December 1, 2005.
11. Gower B, Weinsier R, Jordan J, Hunter G, Desmond R. Effects of weight loss on changes in insulin sensitivity and lipid concentrations in premenopausal African American and white women. *Am J Clin Nutr*. 2002;76(5):923–927.
12. American Diabetes Association. The cardiometabolic risk initiative. 2006. <http://www.diabetes.org/for-health-professionals-and-scientists/cardiometabolic-risk.jsp>. Accessed August 11, 2007.
13. Haffner SM. The metabolic syndrome: inflammation, diabetes mellitus, and cardiovascular disease. *Am J Cardiol*. 2006;97:3A–11A.
14. Jeppesen J, Hansen TW, Rasmussen S, Ibsen H, Torp-Pedersen C. Metabolic syndrome, low-density lipoprotein cholesterol, and risk of cardiovascular disease: a population-based study. *Atherosclerosis*. 2006;189(2):369–374.
15. Lorenzo C, Williams K, Hunt KJ, Haffner SM. Trend in the prevalence of the metabolic syndrome and its impact on cardiovascular disease incidence: the San Antonio Heart Study. *Diabetes Care*. 2006;29:625–630.
16. Meigs JB, Wilson PW, Fox CS, et al. Body mass index, metabolic syndrome and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab*. 2006;91(8):2906–2912.
17. NCEP ATP III. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
18. Apetrei E, Ciobanu-Jurcut R, Rugina M, Gavrila A, Uscatescu V. C-reactive protein, prothrombotic imbalance and endothelial dysfunction in acute coronary syndromes without ST elevation. *Rom J Intern Med*. 2004;42:95–102.
19. Jaeger BR, Labarrere CA. Fibrinogen and atherothrombosis: vulnerable plaque or vulnerable patient?. *Herz*. 2003;28:530–538.
20. Juhan-Vague I, Pyke SD, Alessi MC, Jespersen J, Haverkate F, Thompson SG. Fibrinolytic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. ECAT Study Group. European Concerted Action on Thrombosis and Disabilities. *Circulation*. 1996;94:2057–2063.

21. Juhan-Vague I, Alessi MC, Morange PE. Hypofibrinolysis and increased PAI-1 are linked to atherothrombosis via insulin resistance and obesity. *Ann Med*. 2000;32(suppl 1): 78–84.
22. Juhan-Vague I, Alessi MC. PAI-1, obesity, insulin resistance and risk of cardiovascular events. *Thromb Haemost*. 1997;78:656–660.
23. Marchesi E, Martignoni A, Tinelli C, et al. Plasminogen activator inhibitor-1 and carotid intima-media thickening in patients with newly detected primary hypertension. *J Cardiovasc Risk*. 1999;6:363–369.
24. Mertens I, Verrijken A, Michiels JJ, Van der Planken M, Ruige JB, Van Gaal LF. Among inflammation and coagulation markers, PAI-1 is a true component of the metabolic syndrome. *Int J Obes (Lond)*. 2006;30:1308–1314.
25. Pradhan AD, Manson JE, Rossouw JE, et al. Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study. *JAMA*. 2002;288:980–987.
26. ACE. Proceedings of the American College of Endocrinology Insulin Resistance Syndrome Conference. Washington, DC, USA. August 25-26, 2002. *Endocr Pract*. 2003;9(suppl 2): 22–112.
27. Zimmet PZ, Alberti KG, Shaw JE. Mainstreaming the metabolic syndrome: a definitive definition. This new definition should assist both researchers and clinicians. *Med J Aust*. 2005;183:175–176.
28. American Diabetes Association. Position statement: screening. *Diabetes Care*. 2007;30:S93–S95.
29. Zimmet P, Magliano D, Matsuzawa Y, Alberti G, Shaw J. The metabolic syndrome: a global public health problem and a new definition. *J Atheroscler Thromb*. 2005;12:295–300.
30. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287:356–359.
31. Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care*. 2005;28:2745–2749.
32. Appel SJ. Calculating insulin resistance in the primary care setting: why should we worry about insulin levels in euglycemic patients? *J Am Acad Nurse Pract*. 2005;17:331–336.
33. Bonora E, Targher G, Alberiche M, et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. *Diabetes Care*. 2000;23:57–63.
34. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412–419.
35. Burke JP, Hale DE, Hazuda HP, Stern MP. A quantitative scale of acanthosis nigricans. *Diabetes Care*. 1999;22: 1655–1659.
36. Rexrode KM, Pradhan A, Manson JE, Buring JE, Ridker PM. Relationship of total and abdominal adiposity with CRP and IL-6 in women. *Ann Epidemiol*. 2003;13:674–682.
37. Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation*. 2004; 109:2818–2825.
38. Cook NR, Buring JE, Ridker PM. The effect of including C-reactive protein in cardiovascular risk prediction models for women. *Ann Intern Med*. 2006;145(1):21–29.
39. Reaven GM, Scott EM, Grant PJ, et al. Hemostatic abnormalities associated with obesity and the metabolic syndrome. *J Thromb Haemost*. 2005;3:1074–1085.
40. Appel SJ, Floyd NA, Giger JN, et al. African American women, metabolic syndrome, and National Cholesterol Education Program criteria: a pilot study. *Nurs Res*. 2005; 54:339–346.
41. Appel SJ. Metabolic syndrome: fact or fiction. *J Am Acad Nurse Pract*. 2006;18:255–257.
42. Liao Y, Kwon S, Shaughnessy S, et al. Critical evaluation of Adult Treatment Panel III criteria in identifying insulin resistance with dyslipidemia. *Diabetes Care*. 2004;27: 978–983.
43. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events. *Circulation*. 2003;107(3):391–404.
44. Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation*. 2004; 109:2818–2825.
45. Grundy SM. Metabolic syndrome scientific statement by the American Heart Association and the National Heart, Lung, and Blood Institute. *Arterioscler Thromb Vasc Biol*. 2005;25:2243–2244.
46. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2005;28:2289–2304.
47. Cheal KL, Abbasi F, Lamendola C, McLaughlin T, Reaven GM, Ford ES. Relationship to insulin resistance of the Adult Treatment Panel III diagnostic criteria for identification of the metabolic syndrome. *Diabetes*. 2004; 53:1195–1200.
48. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. *Endocrinol Metab Clin North Am*. 2004;33:283–303.
49. de Vegt F, Dekker JM, Jager A, et al. Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: the Hoorn Study. *JAMA*. 2001; 285:2109–2113.
50. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.
51. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343–1350.
52. Vendrame F, Gottlieb PA. Prediabetes: prediction and prevention trials. *Endocrinol Metab Clin North Am*. 2004;33:75–92, ix.
53. Grim C, Grim C. Blood pressure measurement. In: Izzo J, Blavk H, senior eds. *Hypertension Primer: The Essentials of High Blood Pressure*. 3rd ed. Dallas, TX: American Heart Association; 2003:321–324.
54. Macy EM, Meilahn EN, Declerck PJ, Tracy RP. Sample preparation for plasma measurement of plasminogen activator inhibitor-1 antigen in large population studies. *Arch Pathol Lab Med*. 1993;117:67–70.
55. SAS Institute I. *SAS/Stat 9 User's Guide*. Cary, NC: SAS Institute Inc; 2005.
56. Santaguida S, Janigro D, Hossain M, Oby E, Rapp E, Cucullo L. Side by side comparison between dynamic versus static models of blood-brain barrier in vitro: a permeability study. *Brain Res*. 2006;1109:1–13.
57. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for

- the Study of Insulin Resistance (EGIR). *Diabet Med*. 1999;16:442-443.
58. Zimmet P, Mm Alberti KG, Serrano Rios M. A new International Diabetes Federation worldwide definition of the metabolic syndrome: the rationale and the results. *Rev Esp Cardiol*. 2005;58:1371-1376.
59. Appel SJ. Metabolic syndrome: broadening the understanding of African-American women's risk for cardiovascular disease. *J Natl Black Nurses Assoc*. 2004;15:vii-ix.
60. Appel SJ, Moore TM, Giger JN. An overview and update on the metabolic syndrome: implications for identifying cardiometabolic risk among African-American women. *J Natl Black Nurses Assoc*. 2006;17:47-62.
61. Haffner SM, D'Agostino R Jr, Goff D, et al. LDL size in African Americans, Hispanics, and non-Hispanic whites: the insulin resistance atherosclerosis study. *Arterioscler Thromb Vasc Biol*. 1999;19:2234-2240.
62. Knapp RG, Sutherland SE, Keil JE, Rust PF, Lackland DT. A comparison of the effects of cholesterol on CHD mortality in black and white women: twenty-eight years of follow-up in the Charleston Heart Study. *J Clin Epidemiol*. 1992;45:1119-1129.
63. Metcalf PA, Sharrett AR, Folsom AR, et al. African American-white differences in lipids, lipoproteins, and apolipoproteins, by educational attainment, among middle-aged adults: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 1998;148:750-760.
64. Amowitz LL, Ridker PM, Rifai N, Loughrey CM, Komaroff AL. High prevalence of metabolic syndrome among young women with nonfatal myocardial infarction. *J Womens Health (Larchmt)*. 2004;13:165-175; discussion 175.
65. Turhan H, Yasar AS, Basar N, Bicer A, Erbay AR, Yetkin E. High prevalence of metabolic syndrome among young women with premature coronary artery disease. *Coron Artery Dis*. 2005;16:37-40.