Cardiometabolic Risk Among African American Women
A Pilot Study

Susan J. Appel, PhD, ACNP-BC, FNP-BC, CCRN; Robert A. Oster, PhD; Natalie A. Floyd, MSN, ANP-BC; Fernando Ovalle, MD, FACE

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 experience higher age-adjusted prevalence rates for obesity, hypertension, coronary heart disease, stroke, and type 2 diabetes than compared with any other group...
of US women.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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 arteriolosclerosis.

**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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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/m\textsuperscript{2} used for the diagnosis of metabolic syndrome.\textsuperscript{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

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

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

\textsuperscript{a}Central 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 m\textsuperscript{2}/kg.
hypertension, and stroke among US women.\textsuperscript{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.\textsuperscript{30} 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.\textsuperscript{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\textsuperscript{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.\textsuperscript{35} Acanthosis nigricans can also be found in all body folds (ie, back of neck, axillae, groin, elbows, or knees). Burke et al\textsuperscript{17} 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.\textsuperscript{37–39} Biomarkers, which represent inflammation and fibrinolysis, 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.\textsuperscript{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 definition\textsuperscript{17} alone for metabolic syndrome, especially among healthy younger to middle-aged African American women, often results in relatively low risk predictions.\textsuperscript{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.\textsuperscript{43,44}

The issues described above\textsuperscript{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.\textsuperscript{41,47} Ford\textsuperscript{41} 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 2 Categories of Abnormal Glucose Homeostasis\textsuperscript{36–39}

<table>
<thead>
<tr>
<th>Glucose Level</th>
<th>Terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 mg/dL</td>
<td>Euglycemia</td>
</tr>
<tr>
<td>100–125 mg/dL</td>
<td>Impaired fasting glucose (IFG)</td>
</tr>
<tr>
<td>≥126 mg/dL</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Glucose level after a 2-h post-oral glucose tolerance test (OGTT)</td>
<td></td>
</tr>
<tr>
<td>140–199 mg/dL</td>
<td>Impaired glucose tolerance (IGT)</td>
</tr>
<tr>
<td>≥ 200 mg/dL</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Prediabetes</td>
<td></td>
</tr>
<tr>
<td>100–125 mg/dL</td>
<td>Impaired fasting glucose (IFG)</td>
</tr>
<tr>
<td>140–199 mg/dL</td>
<td>Impaired glucose tolerance (IGT)</td>
</tr>
</tbody>
</table>

Source: American Diabetes Association.\textsuperscript{38}

### Box 3 Homeostatic Model of Assessment-Insulin Resistance (HOMA-ir)\textsuperscript{34} as a Measure of Insulin Resistance

HOMA-ir (mmol/L × μU/mL) = (fasting glucose (mmol/L) × fasting insulin (μU/mL))/22.5

HOMA-ir > 2.7 Insulin resistance

To convert glucose from mmol/L to μU/mL, multiply by 0.05551.
Results from the Jackson Heart Study, which included large numbers of African Americans, demonstrated that 37% of the 5,000 African American participants had metabolic syndrome. Insulin resistance may be one of the earliest components of the syndrome to be manifested when the individual is still euglycemic. 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. Impaired fasting glucose is a late sign of insulin resistance.

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 marker 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. 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.
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 HgA1c) 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 statistical 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.15

**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 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 both BMI (P < .0001, model R² = 0.63) or waist circumference (P < .0001, model R² = 0.59). The best model describing hs-CRP as an outcome variable seems to include 2-hour oral postglucose (P = .005, model R² = 0.31). The best models describing HOMA-ir as an outcome variable seem to include

### Table 1. Clinical Characteristics of the Cohort

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>33</td>
<td>31.24</td>
<td>7.25</td>
<td>20.0–46.0</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>33</td>
<td>91.94</td>
<td>14.48</td>
<td>70.90–45.70</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>33</td>
<td>30.99</td>
<td>6.52</td>
<td>23.08–50.55</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>33</td>
<td>122.58</td>
<td>14.48</td>
<td>100.67–153.67</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>33</td>
<td>73.42</td>
<td>10.13</td>
<td>54.67–100.67</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>33</td>
<td>88.55</td>
<td>10.86</td>
<td>72.0–126.0</td>
</tr>
<tr>
<td>2-h postglucose, mg/dL</td>
<td>33</td>
<td>116.39</td>
<td>38.76</td>
<td>73.0–241.0</td>
</tr>
<tr>
<td>Fasting insulin, µU/mL</td>
<td>33</td>
<td>20.67</td>
<td>11.64</td>
<td>7.0–59.0</td>
</tr>
<tr>
<td>HOMA-ir</td>
<td>32</td>
<td>4.70</td>
<td>3.44</td>
<td>1.39–18.21</td>
</tr>
<tr>
<td>PAI-1, ng/mL</td>
<td>29</td>
<td>24.10</td>
<td>20.83</td>
<td>1.77–83.14</td>
</tr>
<tr>
<td>CRP, ng/mL</td>
<td>32</td>
<td>0.564</td>
<td>0.62</td>
<td>0.03–2.65</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>33</td>
<td>112.23</td>
<td>34.19</td>
<td>62.40–174.4</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>33</td>
<td>75.51</td>
<td>28.69</td>
<td>37.00–152.0</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>33</td>
<td>52.55</td>
<td>15.80</td>
<td>31.0–101.0</td>
</tr>
</tbody>
</table>

**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.

*Log-transformed before statistical analysis.*
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
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 Ford 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 a higher 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. 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 endpoints 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. 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. 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, 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). 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). 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. These same racial differences in lipid profiles have also appeared in other large epidemiological studies such as the Charleston Heart Study and the Atherosclerosis Risk in Communities Study. Furthermore, because African Americans have both lower insulin sensitivity and higher circulating levels of insulin than whites do, the ATP III definition may be inappropriate for sole use within this...
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, Amowit and colleagues found metabolic syndrome to be the most powerful predictor of premature MI among racially diverse premenopausal women younger than 45 years. Similarly, Turkhan and colleagues 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


