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Cardiometabolic Risk among African-American Women: A Pilot Study

Susan J. Appel, PhD, APRN, BC, CCRN[1], **Robert A. Oster, PhD**[2], **Natalie A. Floyd, MSN, APRN, BC**[3], and **Fernando Ovalle, MD, FACE**[4]

[1]Associate Professor and Option Facilitator for the Acute and Continuing Care Nurse Practitioner Program, School of Nursing, University of Alabama Birmingham, Alabama

[2]Associate Professor, Medical Statistics Section, Department of Medicine University of Alabama Birmingham, Birmingham, Alabama

[3]Doctoral Student School of Nursing, University of Alabama Birmingham and an Adult Nurse Practitioner at the Veterans Administration Hospital, Birmingham Alabama

[4]Associate Professor, Division of Endocrinology, Diabetes and Metabolism, School of Medicine, University of Alabama Birmingham, Alabama

Abstract

Objective—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 two of the commonly used definitions of the 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 (mean 31.24, +/- 7.25), 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%) of the 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 9 (27.3 %) by IDF criteria. Bivariate correlations showed associations between HOMA-$_{ir}$ and waist circumference, body mass index (BMI), acanthosis nigricans, the ATP III and IDF definitions for metabolic syndrome. PAI-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 HDL-C. $_{hs}$-CRP was significantly correlated with BMI and 2-hour post glucose.

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 the 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 CVD 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 is 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.

Keywords

metabolic syndrome; insulin resistance; inflammation; dysfibrinolysis; Plasminogen Activator Inhibitor-1 (PAI-1); high sensitivity C-reactive protein ($_{hs}$-CRP); Homeostatic Model of Assessment-insulin resistance (HOMA-$_{ir}$); health disparity

Recommendations from Healthy People 2010[1] emphasize the need to eradicate racial disparities in cardiovascular health. 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 U.S. 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).[2-4 5] African-American women typically have a higher body mass index (BMI), elevated levels of circulating insulin, lower levels of insulin sensitivity otherwise known as "insulin resistance" as well as a higher acute response of insulin to glucose when compared to Caucasian U.S. 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 Caucasian 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 Caucasians 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 athrothrombosis, 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.[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 elevated plasma inflammatory biomarkers and biomarkers of dysfibrinolysis exhibit vascular inflammation and are at greater risk for developing thrombi or plaque rupture. Biomarkers such as high-sensivity C-reactive protein ($_{hs}$-CRP) or plasminogen activator inhibitor-1 (PAI-1), when elevated 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 the abdominal adipocytes and foster excess release of plasminogen activator inhibitor-1 (PAI-1), which is indicative of impaired fibrinolysis. High $_{hs}$-CRP, insulin, 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 U.S. is from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) and consists of presence of 3 of the following 5 components: central (abdominal) obesity, hypertension, impaired fasting glucose, hypertriglyceridemia, or low HDL-C (see Box 1 for description of ATP III diagonistic criteria and Box 2 for categories of abnormal glucose homeostasis).[17] Recently, the International Diabetes Federation (IDF) relased a new definition of metabolic syndrome which has been used primarily in Europe and the Aisan Pacific Rim region which contains more strignet waist circumference measures, but only for Asians (See Box 1 for Comparison of 2 Common Definitions of the Metabolic Syndrome). However, the general IDFcriteria for metabolic syndrome offer a different combination of the same components plus use of BMI > 30 kg/m^2 used for diagnosis of metabolic syndrome.[27] Comparison of these two definitions potentially may assit in determining which one is more sentive 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 U.S. women even thought they posses the highest prevalence rates for type 2 diabetes, obesity, hypertension, and stroke among U.S. women.[28,29] The cardiovascular health disparity experienced by African-American women may relate to the findings that these women typically have a higher body mass index (BMI), elevated levels of circulating insulin, and lower levels of insulin sensitivity indicating a higher level of insulin resistance than their Caucasians counterparts.[9] However, non-diabetic African-American women also have a propensity for manifesting normal triglyceride and HDL-C levels until they develop type 2 diabetes. This benign lipid profile among non-diabetic African-American women lowers the sensitivity of the ATP III to identify them as manifesting the metabolic syndrome. Among other populations (i.e., Caucasian 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]

Box 1

Two Common Definitions of Metabolic Syndrome

National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[17]	**International Diabetes Federation (IDF)[65]**
Any 3 or more of the following:	
Abdominal obesity:	**Abdominal obesity**
Waist circumference >40 inches (102 cm) in men and 35 inches (88 cm) in women	Waist circumference for Asians (only) > 94 cm for men and > 80 cm for women *Must have either central obesity* or an elevated BMI + **2** of the following:*
Triglycerides ≥150 mg/dL	**Triglycerides** ≥150 mg/dl
HDL-C <40 mg/dL in men; <50 mg/dL in women	**HDL-C** < 40 mg/dl in men and <50 mg/dl in women
Blood pressure ≥130/85 mmHg	**Blood pressure** ≥130/85 mmHg
Fasting Glucose ≥100 mg/dL	**Fasting glucose** ≥100 mg/dL or previously diagnosed diabetes

Box 2

Categories of Abnormal Glucose Homeostasis

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- hour post oral glucose tolerance test (OGTT)	
140 - 199 mg/dL	Impaired Glucose Tolerance (IGT)
≥ 200 mg/dL	Diabetes Mellitus
Pre-diabetes	
100 - 125 mg/dL	Impaired Fasting Glucose (IFG)
140 - 199 mg/dL	Impaired Glucose Tolerance (IGT)

Sources: [66]

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 level of insulin sensitivity and its reverse insulin resistance with use of the intravenous glucose clamp measurement.[30-32](See Box 2: for Categories of Abnormal Glucose Homeostasis and Box 3: $HOMA\text{-}_{ir}$ as a measure of Insulin Resistance). 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.[33] Acanthosis nigricans can also be found in all body folds (i.e., back of neck, axillae, groin, elbows, or knees). Burke et al. 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 to any of the other sites. [33]

Box 3

HOMA-ir as a Measure of Insulin Resistance

Homeostatic Model of Assessment - insulin resistance (HOMA-ir)[32]	
HOMA-IR (mmol/L × μU/ml) = fasting glucose (mmol/L) × fasting insulin (μU/ml)/22.5	
Note: To convert glucose from **mmol/L** to **uU/ml** multiply by **0.05551**	
HOMA-ir > 2.7	Insulin Resistance

The presence of inflammation and a propensity toward thrombosis are stongly associated with metabolic syndrome.[37,38] Biomarkers, which represent inflammation and dysfibrinolysis, are elevated 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.[22,37] 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; further, these studies have not fully considered the impact of insulin resistance or race. In fact, using the ATP III definition[17] alone for metabolic syndrome, especially among healthy younger to middle aged African-American women, often results in relatively low risk predictions.[29,39-41] This is counterintuitive, since 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.[42,43]

The issues described above[40,41,44,45] suggest that metabolic syndrome may not describe risk accurately or early in the trajectory of CVD development the same for all populations and additional research is needed to better define the syndrome.[40,46] Ford[29] analyzed the National Health and Nutrition Examination Survey (NHANES) 1999-2002 data and found the prevalence of the 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 % respectively {adjusted age}; for ages 20-39: IDF 23.7 % and ATP III 22.0). However, Hispanic women had the highest prevelance rates for metabolic syndrome in NHANES.

Results from the Jackson Heart Study[6] which included large numbers of African-Americans demonstrated that 37% of the 5,000 Africans-Americans participants had the metabolic syndrome.[10] Insulin resistance may be one of the earliest components of the syndrome to be manifested when the individual is still euglycemic.[47] 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 due to their relative normal lipid profiles when in a non-diabetic state. The 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.[48-51] Therefore, further investigation of other markers of the 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 U.S. A total of 33 self-referred premenopausal African-American women age 20-46 years were screened in the fasting state for the metabolic syndrome using two common definitions (ATP III and IDF). Likewise, novel cardiovascular risk factors and non-invasive markers (waist circumference, BMI and identification of presence of acanthosis nigricans) were measured. The women had fasting glucose, insulin, lipids, PAI-1, $_{hs}$-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 (i.e., $_{hs}$-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, while HOMA-$_{ir}$ and acanthosis nigricans were used to indicate either degree and/or general presence of insulin resistance.

General procedures

Upon approval from the University Intuitional Review Board and research center's Scientific Advisory Committee, informational flyers were distributed at churches and beauty salons chosen randomly from the phone book. A recruitment advertisement was also placed in the local campus newspaper. The 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 and exclusion criteria consisted of the following: not pregnant, premenopausal, no recent use of steroids or oral contraceptives within the past three weeks, no treatment with injectable contraceptives in the last three months, 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 three generations and of main continent African decent (not from a Caribbean Island), and residing in the Southern U.S. This was to limit the amount of racial admixture within the population of interest.

The evening prior to 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. The blood pressure was measured prior to drawing of blood. Blood pressure was obtained by the same research assistant with an appropriate sized cuff, measured three times in the same arm, at least 5 minutes apart following AHA standards.[52] 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.

PAI-1 was measured in citrated plasma sensitive to free PAI-1 (both latent and active) but not PAI-1 in complex with t-PA. The analytical CV for the assay is 3.47%. The citrated samples were processed within 30 minutes of blood draw, and spun for a minimum of 3,000 g for 10 minutes to make sure 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 till all the samples were collected and ready to be shipped for analyses in one batch.[53]

Finally, each participant underwent a 2-hour oral glucose tolerance test. The laboratory examination was completed shortly after noon, 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 health care 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 were assisted by the PI's supervising physician who was an endocrinologist.

Statistical Analyses

Bi-variate 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 are shown in Table 3. Other models containing one or two 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 due to 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 the metabolic syndrome were compared using the two-group t-test. All serum variables, such as insulin, glucose, and cholesterol measures, were log-transformed prior to analysis to ensure normality of distribution. All statistical tests were two-sided and were performed using a significance level of 5%. Statistical analyses were performed with the use of SAS software.[54]

Results

Clinical characteristics of the sample are described in Table1. 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 %) of the women with central obesity. A total of 17 (51.5 %) of the women were overweight or obese based on their BMI. HOMA-$_{ir}$ identified 27 (81.8%) as having insulin resistance. Acanthosis nigricans was present in 16 (48 %) of the women.

The ATP III guidelines classified 7 (21.2 %) women as having metabolic syndrome, whereas the IDF criteria diagnosed 9 (27.3 %) 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-$_{ir}$, post-glucose was correlated. HOMA-$_{ir}$ was significantly correlated with BMI, waist circumference and PAI-1. HOMA-$_{ir}$ was significantly correlated to acanthosis nigricans.

Results of 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 ($p < 0.0001$, model $R^2 = 0.63$) or waist circumference ($p < 0.0001$, model $R^2 = 0.59$). The best model describing $_{hs}$-CRP as an outcome variable appears to include 2-hour oral post-glucose ($p = 0.005$, model $R^2 = 0.31$). The best models describing HOMA-$_{ir}$ as an outcome variable appear to include waist circumference ($p = 0.0045$, model $R^2 = 0.30$), ATP III definition of metabolic syndrome (yes [3 or more components] or no) ($p = 0.0016$, model $R^2 = 0.29$), or

ATP III (with central obesity as a required component) ($p = 0.0032$, model $R^2 = 0.26$). BMI is a statistically significant predictor in all models for the major outcome variables.

Discussion

The major findings of this study indicate that the simple non-invasive screening for acanthosis nigricans on the back of the neck coupled with the calculation of $HOMA_{-ir}$ are potentially useful and powerful interventions 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 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 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 elevated 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 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 U.S. 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 the 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 since much of the early risk reduction techniques are aimed at lifestyle modification. As 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 we found similar prevalence rates for the metabolic syndrome to those of a large epidemiological study conducted by Ford in the NHANES 1999-2002.[29] 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 adjust group 20-39 years was ATP III 22.0 % and IDF 23.7 % whereas our findings were ATP III 21.2% and 27.3 % for IDF. The similarity of our results to those found in the NHANES 1999-2002 may indicate 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 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.

Based on the literature we theorize if this population of African-American women had a higher prevalence of either hypertriglyceridemia or elevated $_{hs}$-CRP levels they would have manifested higher a degree of dysfibrinolysis. As elevated levels of triglycerides and/or $_{hs}$-CRP are known to stimulate the 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 elevated BMI or general level of adiposity. BMI explained 33% of the inflammation identified by $_{hs}$-CRP. This is a significant finding since 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 post glucose was strongly associated with inflammation explaining 31% of the variance related to $_{hs}$-CRP. Impaired glucose tolerance is commonly associated with development of type 2 diabetes and is worsened by generalized obesity.[55] Similar to inflammation and its relationship to an elevated BMI or enlarged waist circumference, it was found that dysfibrinolysis as indicated by circulating PAI-1 levels when regressed with BMI explained 63 % of the variance and waist circumference 59 % of the variance associated with circulating PAI-1 levels. Indicating that either an elevated 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 which did predict almost 14 % of the variance. These findings indicate that acanthosis nigricans may be an important clinical non-invasive 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 their 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 encouraging African-American women to optimize (i.e., decrease) both their weight and waist circumference in order 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 describe within the literature.[24,38,47] 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.[30] 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 four common definitions for metabolic syndrome,[17,26,56,57] the ATP III definition is most commonly used in the U.S. The ATP III definition, however, has been criticized for not including measurement of insulin resistance (i.e., elevated plasma insulin levels or acanthosis nigricans).[39-41,45,58,59] The ATP III definition relies heavily on

an abnormal lipid profile to meet the criteria for metabolic syndrome (elevated triglycerides and low HDL-C).[40] However, research has shown that non-diabetic African-American women do not manifest the abnormal lipid profiles commonly found among Caucasian and Hispanic populations. The Insulin Resistance Atherosclerosis Study found that African-Americans had significantly higher HDL-C ($p < 0.001$) and lower triglyceride levels ($p < 0.001$) than either Caucasians or Hispanics.[60] These same racial differences in lipid profiles have also appeared in other large epidemiological studies such as the Charleston Heart Study[61] and the Atherosclerosis Risk in Communities study.[62] Further, because African-American have both lower insulin sensitivity [11] and higher circulating levels of insulin than Caucasians the ATP III definition may be inappropriate for sole use within this population to determine cardiometabolic risk. Therefore, given non-diabetic African-American women's propensity 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 colleagues [63] found metabolic syndrome to be the most powerful predictor of premature myocardial infarction among racially diverse premenopausal women under age 45. Similarly, Turhan and colleagues found that women with premature coronary artery disease had a higher prevalence of metabolic syndrome than men (73% versus 31%, $p < 0.001$).[64] These two 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.

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Table 1

Clinical Characteristics of the Cohort

Variables	n	M	SD	Range
Age years	33	31.24	7.25	20.0-46.0
Waist cm	33	91.94	14.48	70.90-45.70
BMI kg/m^2	33	30.99	6.52	23.08-50.55
SBP mmHg	33	122.58	14.48	100.67-153.67
DBP mmHg	33	73.42	10.13	54.67-100.67
Fasting Glucose† mg/dL	33	88.55	10.86	72.0-126.0
2-hour post glucose mg/dL	33	116.39	38.76	73.0-241.0
Fasting Insulin uU/ml	33	20.67	11.64	7.0-59.0
HOMA-ir	33	4.70	3.44	1.39-18.21
PAI-1† ng/ml	29	24.10	20.83	1.77-83.14
CRP ng/ml	32	0.564	0.62	0.03-2.65
LDL† mg/dL	33	112.23	34.19	62.40-174.4
Triglycerides† mg/dL	33	75.51	28.69	37.00-153.0
HDL-C† mg/dL	33	52.55	15.80	31.0-101.0

†Log-transformed prior to statistical analysis.

Table 2

Correlations (Pearson) of physiologic variables

	Waist cm	**BMI kg/m^2**	**SBP mmHg**	**DBP mmHg**	**Fasting Glucose mg/dL**	**2-hr post Glucose mg/dL**	**Fasting Insulin uU/ml**	**HOMA -ir**	**PAI-1 ng/ml**	**CRP ng/ml**	**TG mg/dL**	**HDL-C mg/dL**	**ATPIII**	**IDF**	**AN**
HOMA-ir	0.527 0.002*	0.431 0.012*	0.119 0.507	0.030 0.866	0.763 <.0001*	0.201 0.278	0.988 <.0001*	1	0.409 0.027*	0.050 0.785	0.362 0.039*	-0.360 0.039*	0.455 0.008*	0.440 0.010*	0.424 0.014*
PAI-1† ng/ml	0.763 <.0001*	0.796 <.0001*	0.344 0.068	0.051 0.791	0.499 0.006*	0.359 0.065	0.354 0.059	0.409 0.027*	1	0.257 0.187	0.225 0.240	-0.471 0.009*	0.472 0.009*	0.338 0.072	0.330 0.080
CRP ng/ml	0.272 0.131	0.429 0.014*	0.030 0.866	-0.202 0.265	0.031 0.864	0.544 0.001*	0.051 0.781	0.050 0.785	0.257 0.187	1	0.221 0.222	0.130 0.475	0.039 0.832	-0.136 0.455	0.323 0.080

*statistically significant at 0.05

CRP = hs-C-Reactive Protein; TG = Triglycerides; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; AN= Acanthosis Nigricans

Table 3

Multiple Regression Models for Major Outcome Variables

Dependent Variable†	Independent Variables	Parameter Estimates ± SE	p	Model P	Model R^2
PAI-1	BMI	0.0483 ± 0.0074	0.0001	0.0001	0.63
	Age	- 0.0007 ± 0.0067	0.92		
PAI-1	Waist Circumference	0.0257 ± 0.0043	0.0001	0.0001	0.59
	Age	- 0.0057 ± 0.0074	0.45		
PAI-1	HOMA†	0.6595 ± 0.2886	0.031	0.063	0.19
	Age	0.0086 ± 0.0098	0.38		
PAI-1	HgA1c†	4.2558 ± 1.4239	0.0062	0.017	0.28
	Age	- 0.0043 ± 0.0098	0.67		
PAI-1	Fasting Glucose†	3.7871 ± 1.2769	0.0064	0.015	0.27
	Age	0.0086 ± 0.0098	0.35		
PAI-1	Fasting Insulin†	0.6679 ± 0.3469	0.065	0.12	0.15
	Age	0.0087 ± 0.0100	0.39		
PAI-1	HDL-C†	- 1.6084 ± 0.5263	0.0051	0.013	0.29
	Age	0.0141 ± 0.0093	0.14		
PAI-1	IDF (def. of M.S.)	0.5225 ± 0.1826	0.0082	0.019	0.26
	Age	- 0.0009 ± 0.0100	0.93		
PAI-1	ATP III (5 comp.)	0.4535 ± 0.1346	0.0023	0.0061	0.32
	Age	- 0.0034 ± 0.0097	0.73		
PAI-1	Acanthosis Nigricans	0.2678 ± 0.1461	0.078	0.14	0.14
	Age	0.0034 ± 0.0106	0.75		
PAI-1	ATP III (≥3 comp.)	0.4075 ± 0.1601	0.017	0.038	0.22
	Age	0.0027 ± 0.0099	0.79		
$_{hs}$-CRP	BMI	0.0349 ± 0.0156	0.033	0.038	0.20
	Age	0.0093 ± 0.0119	0.44		
$_{hs}$-CRP	2 hr post-glucose†	1.8800 ± 0.6102	0.0046	0.005	0.31
	Age	0.0088 ± 0.0106	0.41		
$_{hs}$-CRP	IGT	0.4107 ± 0.1957	0.045	0.040	0.21

Dependent Variable†	Independent Variables	Parameter Estimates ± SE	p	Model P	Model R^2
	Age	0.0129 ± 0.0112	0.26		
HOMA-$_{ir}$	BMI	0.0176 ± 0.0065	0.0014	0.038	0.20
	Age	-0.0035 ± 0.0059	0.55		
HOMA-$_{ir}$	Waist Circumference	0.0118 ± 0.0033	0.0011	0.0045	0.30
	Age	- 0.0057 ± 0.0056	0.31		
HOMA-$_{ir}$	HgA1c†	2.1413 ± 1.0335	0.0476	0.14	0.13
	Age	- 0.0052 ± 0.0071	0.47		
HOMA-$_{ir}$	Fasting Trig. †	0.5594 ± 0.2607	0.0401	0.12	0.13
	Age	0.0019 ± 0.0058	0.75		
HOMA-$_{ir}$	HDL-C†	- 0.7819 ± 0.3510	0.034	0.099	0.14
	Age	0.0040 ± 0.0059	0.50		
HOMA-$_{ir}$	ATP III (5 comp.)	0.2639 ± 0.0823	0.0032	0.012	0.26
	Age	- 0.0052 ± 0.0057	0.38		
HOMA-$_{ir}$	Acanthosis Nigricans	0.1916 ± 0.0881	0.0378	0.11	0.14
	Age	- 0.0034 ± 0.0062	0.59		
HOMA-$_{ir}$	ATP III (≥3 comp.)	0.3267 ± 0.0942	0.0016	0.0062	0.29
	Age	- 0.0034 ± 0.0062	0.59		

†Log-transformed prior to statistical analysis (PAI-1; $_{hs}$-CRP; HOMA-$_{ir}$; Fasting glucose; Fasting insulin; 2 hr post-glucose;HgA1c; Fasting Trig.;HDL-C)