Postprandial endothelial function does not differ in women by race: an insulin resistance paradox?

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Muniyappa R, Sachdev V, Sidenko S, Ricks M, Castillo DC, Courville AB, Sumner AE. Postprandial endothelial function does not differ in women by race: an insulin resistance paradox? Am J Physiol Endocrinol Metab 302: E218–E225, 2012. First published November 1, 2011; doi:10.1152/ajpendo.00434.2011.—Insulin resistance is independently related to cardiac and vascular function and augments CV risk in African Americans with hypertension (13). Because African-American women are insulin-resistant compared with white women, they are highly susceptible to develop CVD.

Endothelial dysfunction characterized by reduced nitric oxide (NO)-dependent vascular activity mediates the initiation and progression of atherosclerosis and predicts CV events (19). Diabetes, obesity, the metabolic syndrome, and their CV complications cluster together due, in part, to reciprocal relationships between insulin resistance and endothelial dysfunction (35). Racial differences in endothelial function have been well documented, with African Americans demonstrating impaired postprandial function compared with whites (3, 6, 8–11, 14, 21, 24, 26, 29, 31, 32, 34, 42, 48, 49). However, in many of these studies, the African-American population included a disproportionate number of individuals with diabetes, hypertension, and dyslipidemia, confounders known to affect endothelial dysfunction. Moreover, insulin resistance/sensitivity was not specifically characterized in these studies. Thus, these studies were unable to ascertain the independent contribution of insulin resistance to racial differences in endothelial dysfunction.

Insulin resistance is associated with exaggerated postprandial excursions of lipidemia, glycemia, insulinemia, oxidative stress, and inflammatory markers, each known to independently and negatively affect endothelial function (35). Considering that a substantial amount of time of the day is spent in the postprandial state, in theory, these cumulative detrimental effects on the endothelium could be significant. Moreover, these postprandial changes are particularly accentuated following a high-fat meal in insulin-resistant individuals (25). Although previous studies have reported differences in baseline endothelial function, whether racial differences in postprandial endothelial function exist is not known. In addition, whether reduced insulin sensitivity predisposes African Americans to develop endothelial dysfunction has also not been clarified. Therefore, we sought to evaluate the contribution of insulin resistance to endothelial function in African Americans. In the present study, we hypothesized that age- and body mass index (BMI)-matched African-American women have impaired postprandial endothelial function compared with the more insulin-sensitive white women. To test this hypothesis, we evaluated postprandial endothelial function following a typical American breakfast in age- and BMI-matched African-American and white women.

African American women suffer disproportionately from greater cardiovascular (CV) morbidity and mortality when compared with white women (15). In addition to differences in cultural issues, socioeconomic status, and access to health care, traditional cardiometabolic risk factors such as hypertension, diabetes, obesity, smoking, and physical inactivity disproportionately affecting African-American women contribute to the increased cardiovascular disease (CVD) risk (1, 15). Insulin resistance is independently related to cardiac and vascular function and augments CVD risk in African Americans with hypertension (13). Because African-American women are insulin-resistant compared with white women, they are highly susceptible to develop CVD.

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MATERIALS AND METHODS

Study Design and Study Subjects

This study was conducted at the National Institutes of Health (NIH) Clinical Center, Bethesda, MD. The study protocol was approved by the Institutional Review Board of the National Institute of Diabetes, Digestive, and Kidney Diseases. Signed informed consent was provided by all subjects before participation. Women between 21 and 60 years of age and not taking medication or nutritional supplements known to affect insulin sensitivity or vascular reactivity were recruited from the local community through newspaper advertisements. Exclusion criteria were pregnancy, diabetes, liver disease, pulmonary disease, renal insufficiency, coronary heart disease, heart failure, peripheral vascular disease, coagulopathy, or other systemic disease.

Each subject completed the study in 4 to 6 wk. After the screening visit, participants returned for a second visit during which an insulin-modified frequently sampled intravenous glucose tolerance test (IM-FSIVGTT) was performed. A week later, participants were placed on a 7-day equilibration diet. For seven consecutive mornings (excluding weekends), the participant arrived fasting to the Clinical Center to be weighed and eat breakfast under supervision. Lunch and dinner were provided in insulated containers to be eaten off-site. Weekend meals were provided for the subject with breakfast on Friday morning. On day 8, the subject returned at 7:00 A.M. to the Clinical Center. An intravenous catheter was placed in the right antecubital vein. A standardized breakfast (detailed below) was consumed in 10–15 min. Endothelial function testing using flow-mediated dilation (FMD) was assessed before eating breakfast and at 2, 4, and 6 h following the meal. Blood samples were obtained at 0, 2, 4, and 6 h.

Meal composition and macronutrient distribution. Energy needs were estimated using the Mifflin St. Jeor equation with a physical activity factor that best represented the subject’s self-reported daily activity level. Subjects were instructed to continue customary physical activity during the 7-day diet. Dietary energy content was adjusted by the research dietitian for weight fluctuations beyond ±1.5 kg to ensure weight maintenance while consuming the equilibration diet. The macronutrient distribution of the diet was designed to approximate the “typical American diet” with a macronutrient distribution of 15% protein, 33% fat, and 52% carbohydrate (41). The subjects consumed the same foods every day. However, the diet for each subject was individualized. During the dietary period, subjects were allowed to consume additional water, zero-calorie beverages, salt, pepper, and spices, but alcohol was not permitted.

Standardized breakfast. Each subject consumed a breakfast that contained 30% of the calories given on the last day of the 7-day equilibration period. The macronutrient distribution of the standardized breakfast was 20% protein, 40% fat, and 40% carbohydrate. All subjects received the same foods in the standardized breakfast, which consisted of an egg and cheddar cheese omelet cooked in butter, a plain bagel with cream cheese, and orange juice.

Endothelial Function Testing Using FMD

Assessment of endothelial function was conducted in the fasting state in a quiet temperature-controlled room maintained at 22°C using standardized procedures and at 2, 4, and 6 h following consumption of the standardized breakfast. Endothelium-dependent vasodilator function was assessed as previously reported (47). Briefly, subjects lay supine on a bed and were allowed to rest for at least 30 min. Next, the left brachial artery was visualized 2–15 cm proximal to the antecubital fossa with a 15L8 transducer (Acuson Sequoia, Mountain View, CA). After baseline images and flow measurements were obtained, a pressure cuff applied on the forearm was inflated to 200–250 mmHg for 5 min. Blood flow was measured during the 15 s following cuff release (reactive hyperemia), and arterial images that measured diameter were acquired between 60 and 90 s after cuff deflation. Additionally, pulsed-wave Doppler measurements were obtained before and immediately after cuff deflation to determine hyperemic shear stress (HSS). FMD was calculated as the increase in poststimulus diameter as a percentage of the baseline diameter. For FMD, arterial diameter was measured from the anterior to posterior endothelial lumen interface at end diastole, which was coincident with the R wave on the electrocardiogram. Velocity time integral (VTI) in reactive hyperemia was determined by measuring three consecutive tracings of the velocity envelope obtained at peak flow immediately following cuff release and averaging them. Assuming conditions of laminar flow and constant viscosity, HSS in reactive hyperemia was calculated by the equation: HSS (dyn/cm²) = 8 × 0.035 (dyn·s·cm⁻²) × VTI (cm) × (heart rate/60)/[baseline brachial artery diameter (mm)/10] (33). Off-line analyses of coded images were analyzed by an investigator blinded to the image sequence and subject’s ethnicity.

Insulin Resistance and Secretion

The insulin sensitivity index (SI) was determined from the minimal model using data from the IM-FSIVGTT as previously described (version 6.02; MinMOD Millenium, Los Angeles, CA) (52). The acute insulin response to glucose (AIRg), a surrogate marker of β-cell function, was calculated as the area under the curve (AUC) for plasma insulin between 0 and 10 min for the insulin concentration above basal.

Dual-Energy X-Ray Absorptiometry

Whole body composition measurements were performed with a QDR 4500A dual-energy X-ray absorptiometer (Hologic, Bedford, MA) in the array mode with the use of software version 5.71A as previously described (51).

Measurement of Visceral Adipose Tissue Content

Visceral adipose tissue was measured at lumbar levels (L2–L3) using a HiSpeed Advantage CT/1 scanner (GE Medical Systems, Milwaukee, WI) and analyzed on a SUN workstation using the MEDx image analysis software package (Sensor System, Sterling, VA) (51).

Laboratory Assays

Routine assays for serum lipids, plasma glucose and insulin, and HbA1C (A1C) were performed in the Department of Laboratory Medicine at the Clinical Center, NIH.

Statistical Analyses

Data from participants were analyzed according to a preestablished statistical analysis plan. The primary outcome measure for this study was prospectively designated as the difference in postprandial hyperemic response between age- and BMI-matched African-American and white women. All other comparisons were considered secondary. A sample size of n = 36, with 18 African-American women and 18 white women was deemed sufficient to provide 80% power in detecting a difference of 2.0% or greater in FMD with α = 0.05 based on previous studies (45). The presence of skewed data was evaluated by visual inspection of Q-Q plots, stem and leaf plots, or box plots and verified by the Shapiro-Wilk test for normal distribution. After testing data for normality, we used Student’s paired t or Wilcoxon signed-rank test for evaluation of baseline characteristics between the racial groups. Variables measured at baseline and 2, 4, and 6 h were evaluated by repeated-measures ANOVA, and interactions were tested between time and racial group. Relationships between changes in FMD and independent predictors of endothelial dysfunction were assessed by univariate regression analysis. Because of the exploratory nature of this study, no adjustments were made for multiple comparisons, and values of P < 0.05 were considered to represent statistical significance. The statistical software StatsDirect version 2.7.2 (Cheshire, UK) was used for data analysis.
Baseline characteristics of African-American and white women in the study. Values shown are unadjusted means ± SD or median (25th–75th percentile); n, no. of subjects. LDL, low-density lipoprotein; HDL, high-density lipoprotein; SHBG, sex hormone-binding globulin. P values indicate significance for comparisons between African-American and white women with Student’s t or Wilcoxon’s signed-rank test, as appropriate. ¶P values indicate significance for comparisons between groups after adjustment for percent total body fat.

RESULTS

Baseline Clinical Characteristics of Study Subjects

This study included age- and BMI-matched African-American women (n = 18) and white women (n = 18). Baseline clinical characteristics of 36 women who completed our study are reported in Table 1. In addition to being age- and BMI-matched, abdominal total, subcutaneous, and visceral fat content were not significantly different between the groups (Table 1). As expected, African-American women were less insulin sensitive than white women (Table 1). The reduced insulin sensitivity in African-American women was accompanied by an enhanced pancreatic β-cell function as evident by the robust insulin response to intravenous glucose load (AIRg). Consistent with these findings, fasting plasma glucose and insulin as well as a measure of glycemic control, A1C, were comparable between the groups. Consistent with prior reports (50), even with the lower insulin sensitivity, African-Americans had higher high-density lipoprotein (HDL) cholesterol and lower triglycerides (TG) levels compared with whites (Table 1). However, the fasting concentrations of total cholesterol, low-density lipoprotein (LDL) cholesterol, and free fatty acids (FFA) did not differ by race. Levels of estradiol and total testosterone did not differ by race, but African-Americans had lower sex hormone-binding globulin concentrations (Table 1). In addition, the median annual income and education levels were similar in both racial groups (data not shown).

Baseline Vascular Parameters of Study Subjects

African Americans had a higher systolic blood pressure than whites (Table 2). Baseline brachial artery diameter, magnitude of HSS (the stimulus inducing FMD), and brachial artery FMD were equivalent in both groups (Table 2). Similarly, circulating levels of vascular inflammatory markers such as high-sensitivity C-reactive protein (hsCRP), fibrinogen, and homocysteine were similar in the racial groups (Table 2).

Table 1. Clinical characteristics of African-American and white women in the study

<table>
<thead>
<tr>
<th>Variables</th>
<th>African American (n = 18)</th>
<th>White (n = 18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>35 ± 9</td>
<td>38 ± 12</td>
<td>0.40</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31 ± 6</td>
<td>29 ± 6</td>
<td>0.38</td>
</tr>
<tr>
<td>Lean body mass, kg</td>
<td>49 ± 7</td>
<td>48 ± 8</td>
<td>0.92</td>
</tr>
<tr>
<td>Total body fat, %</td>
<td>37 ± 9</td>
<td>38 ± 8</td>
<td>0.68</td>
</tr>
<tr>
<td>Abdominal total fat, cm²</td>
<td>343 ± 210</td>
<td>346 ± 198</td>
<td>0.72†</td>
</tr>
<tr>
<td>Abdominal visceral fat, cm²</td>
<td>78 ± 70</td>
<td>102 ± 67</td>
<td>0.22‡</td>
</tr>
<tr>
<td>Abdominal subcutaneous fat, cm²</td>
<td>265 ± 158</td>
<td>244 ± 142</td>
<td>0.24¶</td>
</tr>
<tr>
<td>Metabolic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dl</td>
<td>88 ± 7</td>
<td>89 ± 8</td>
<td>0.62</td>
</tr>
<tr>
<td>Fasting plasma insulin, µU/ml</td>
<td>5.2 (3.5–6.7)</td>
<td>4.2 (1.9–8.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hemoglobin A1C, %</td>
<td>5.4 ± 0.4</td>
<td>5.4 ± 0.4</td>
<td>0.65</td>
</tr>
<tr>
<td>Insulin sensitivity index, min⁻¹·µU·mL⁻¹</td>
<td>3.6 ± 1.5</td>
<td>5.2 ± 2.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Acute insulin response, µU·mL⁻¹·min⁻¹</td>
<td>680 ± 345</td>
<td>227 ± 174</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipids, mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>165 ± 34</td>
<td>175 ± 38</td>
<td>0.39</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>94 ± 28</td>
<td>105 ± 31</td>
<td>0.28</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>59 ± 15</td>
<td>49 ± 10</td>
<td>0.03</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>56 ± 37</td>
<td>97 ± 49</td>
<td>0.01</td>
</tr>
<tr>
<td>Free fatty acids, µEq/l</td>
<td>518 ± 136</td>
<td>544 ± 154</td>
<td>0.61</td>
</tr>
<tr>
<td>Hormonal measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol, pg/ml</td>
<td>73 (43–138)</td>
<td>97 (52–173)</td>
<td>0.48</td>
</tr>
<tr>
<td>Total testosterone, ng/dl</td>
<td>44 ± 19</td>
<td>41 ± 18</td>
<td>0.53</td>
</tr>
<tr>
<td>SHBG, nmol/l</td>
<td>34 ± 14</td>
<td>50 ± 20</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Baseline vascular parameters and inflammatory markers in African-American and white women in the study. Values shown are mean ± SD or median (25th–75th percentile). P values indicate significance for comparisons between African-American and white women with Student’s t or Wilcoxon’s signed-rank test, as appropriate.

Table 2. Vascular parameters and inflammatory markers in African-American and white women in the study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>African American (n = 18)</th>
<th>White (n = 18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>122 ± 12</td>
<td>114 ± 10</td>
<td>0.03</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>75 ± 8</td>
<td>73 ± 8</td>
<td>0.57</td>
</tr>
<tr>
<td>Baseline brachial artery diameter, mm</td>
<td>3.10 ± 0.39</td>
<td>3.11 ± 0.44</td>
<td>0.99</td>
</tr>
<tr>
<td>Baseline flow-mediated dilatation, %</td>
<td>8.65 ± 4.64</td>
<td>7.78 ± 4.17</td>
<td>0.56</td>
</tr>
<tr>
<td>Hyperemic shear stress, dyn/cm²</td>
<td>65 ± 18</td>
<td>65 ± 19</td>
<td>0.89</td>
</tr>
<tr>
<td>Inflammatory markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-sensitivity C-reactive protein, mg/l</td>
<td>0.37 (0.04–1.50)</td>
<td>0.68 (0.19–3.04)</td>
<td>0.28</td>
</tr>
<tr>
<td>Fibrinogen, ng/dl</td>
<td>319 ± 63</td>
<td>310 ± 45</td>
<td>0.64</td>
</tr>
<tr>
<td>Homocysteine, µM/l</td>
<td>6.89 ± 1.64</td>
<td>7.22 ± 1.11</td>
<td>0.48</td>
</tr>
</tbody>
</table>
Meal-associated changes in metabolic parameters are shown in Fig. 1. There was a significant rise in postprandial glucose and insulin concentrations following the meal in both groups of women, but the magnitude of these changes were not significantly different between the groups. Similarly, 2 h postprandial glucose, glucose area under curve (AUC0–360 min), and insulin AUC0–360 min were comparable between the racial groups (data not shown). Plasma FFA levels decreased following the meal, with maximal suppression occurring at 2 h that was followed by a gradual return of FFA to baseline levels (Fig. 1). The degree of FFA suppression tended to be lower in African-American women (69 ± 21 vs. 79 ± 11%, 2-sided P = 0.07). Postprandial concentrations of plasma TG increased with time in both groups (P < 0.05), but the magnitude of the increase was significantly lower in African-American compared with white women (TG AUC0–360 min: 279 ± 190 vs. 492 ± 255 mg·dl⁻¹·min⁻¹·10⁻², P < 0.01) (Fig. 1).

In the postprandial phase, brachial artery FMD increased significantly in both groups (Fig. 2). However, there was no significant difference in FMD between the groups. Similarly, there were no significant racial differences in meal-related increases in preocclusion brachial artery diameter and HSS (data not shown).

**Relationships Between Metabolic Parameters and Endothelial Function**

Associations between FMD and metabolic parameters were evaluated by linear regression. The interactions between race and metabolic parameters for FMD were examined. None of the interaction terms reached significance at the 0.05 level, except the relationship between baseline TG concentration and FMD. Therefore, we examined these relationships (FMD and metabolic parameters, except TG) in the combined cohort. At baseline, in all women combined, age (r = −0.40, P = 0.01) and fasting glucose (r = −0.35, P = 0.04) were negatively related to FMD. There were no significant relationships between FMD and insulin sensitivity, AIRg, fasting levels of insulin, FFA, cholesterol, sex steroids (estradiol, total testosterone), hsCRP, total body fat, or abdominal visceral fat content. TG levels were positively associated with FMD in African-American women (r = 0.49, P = 0.04) but negatively related to FMD in white women (r = −0.58, P = 0.01). Similar relationships were observed between postprandial TG levels and FMD at 4 h (African-Americans: r = 0.79, P = 0.001; whites: r = −0.52, P = 0.03). No other postprandial metabolic parameters were related to FMD following a meal.

**DISCUSSION**

In the present study, we demonstrated that, even though African-American women were insulin-resistant compared with age- and BMI-matched white women, there were no racial differences in baseline or postprandial FMD. This observation suggests that shear stress-induced endothelial release and action of NO are not impaired by postprandial glycemia or lipemia in insulin-resistant African-American women compared with a more insulin-sensitive group of white women. Our study results suggest that insulin sensitivity may not be a
principal determinant of endothelial dysfunction, a vascular feature typically observed in African-American women.

**Endothelial Dysfunction and Insulin Resistance**

Endothelial dysfunction and reduced NO-dependent vascular activity is a consistent feature of insulin-resistant states (35). Consequently, it is frequently hypothesized that the high prevalence of insulin resistance contributes to the racial predisposition to endothelial dysfunction and the higher CVD burden in African Americans. However, none of the studies demonstrating racial differences in endothelial function were designed to evaluate the independent contribution of insulin resistance (3, 6, 8–11, 14, 21, 24, 26, 29, 31, 32, 34, 42, 48, 49).

**Study Design and Clinical Characteristics of Study Participants**

There are two strengths of our study design that merit discussion. First, the study design ensures comparison of endothelial function in a well-matched, biracial group of women for various confounders that may affect endothelial function. African-American and white women in this study were well-matched for age, physical activity, BMI, total body fat, and visceral fat content. In addition, the levels of sex steroids and circulating concentrations of biomarkers of inflammation and CV risk such as hsCRP, fibrinogen, and homocysteine were similar in both groups of women. Moreover, fasting insulin and glucose, A1C, total cholesterol, LDL cholesterol, and FFA levels were also not different between the groups. Second, studies have suggested that variation in meal frequency and dietary composition may predict postprandial lipemia to a high-fat meal (36). To control for any such variation, all of our study participants were placed on a standard equilibration diet for 7 days before consuming the standardized breakfast.

We used FSIVGTT and minimal modeling to assess insulin sensitivity in our study. The minimal model has been used in hundreds of studies, including the frequently cited multicenter Insulin Resistance Atherosclerosis Study, which reported lower insulin sensitivity among African Americans vs. whites (18). In addition, there are many other studies that have reported that insulin sensitivity as measured by the minimal model is 40–50% lower in African Americans (2, 16, 20, 23, 27, 39, 40, 46). To compare our findings with previous studies, we performed a pooled analysis of studies that included women or predominantly women (2, 16, 18, 20, 23, 27, 39, 40, 46). S1 mean [95% confidence interval (CI)] in African Americans was lower than whites [African Americans: 3.1 (2.3–3.7), n = 848; whites: 5.1 (3.6–6.5), n = 1,164]. The pooled weighted mean difference in S1 between African Americans and whites was \(-1.47 (95\% \text{ CI} = -2.0 \text{ to } -0.94, P < 0.0001)\). In our study, African-American women were less insulin-sensitive \([S_1 (\text{mean } \pm \text{SD})]: 3.6 \pm 1.5 \text{ vs. } 5.2 \pm 2.6, P = 0.02\) than white women. Accordingly, the mean values and the magnitude of the differences in S1 between the races observed in our study are in accordance with published studies. Impaired postprandial FFA suppression, an early indicator of insulin resistance, was also lower in African-American women (69 ± 21 vs. 79 ± 11%, \(P = 0.03\), 1-sided \(P\)), a finding observed in other studies as well (44). Taken together, African-American women in our study are less insulin-sensitive than the age- and BMI-matched white women and ideal to test our hypothesis.

**Racial Differences in Baseline Endothelial Function**

Previous studies report reduced vasodilator response to various stimuli, including ischemia, exercise, acetylcholine, isoproterenol, and mental stress in African Americans compared with whites (3, 6, 8–11, 14, 21, 24, 26, 29, 31, 32, 34, 42, 48, 49). Techniques used to assess endothelial function in these studies included forearm perfusion technique that measures changes in forearm blood flow in response to ischemia or intra-arterial infusion of a pharmacological agent, FMD technique that measures changes in brachial artery diameter using a high-resolution ultrasound following transient ischemia, or acetylcholine-induced and flow-mediated changes in coronary artery diameter by angiography. Differences in study design and the techniques/stimuli to assess endothelial function preclude direct comparison of our results with these studies. However, some (9, 29, 42) but not all studies (17) evaluating racial differences in FMD have shown impaired endothelium-dependent vasodilation to hyperemia in African Americans. Our current study demonstrated no differences in baseline FMD between the racial groups. This is in agreement with the study by Gokce et al. (17) but contrasts findings from Perregaux et al. (42), Campia et al. (9), and Loehr et al. (29). The apparent inconsistencies in these study findings may reflect differences in characteristics of the study population such as age, presence of other comorbidities, concomitant use of medications, menopausal status, and brachial artery size. In our study, there were no differences in baseline HSS, suggesting that the magnitude of the stimulus for FMD was similar between the groups and that there may not be racial differences in microvascular function either. Also, in each of these studies, there were baseline differences in BMI, with African Americans having a greater BMI compared with whites (9, 29, 42). Thus, the contribution of body fat content to the variance in the findings of these studies cannot be definitively ascertained. Finally, the mean age of subjects in the study by Perregaux et al. (42) were lower (~30 yr), whereas those by Loehr et al. (29) were higher (~78 yr) than in our study. Studying a different vascular bed,
the coronary vasculature, Houghton et al. (22) failed to observe racial differences in acetylcholine-induced (endothelium-dependent) vasodilation in normotensive women. Notwithstanding these disparate findings, our study findings are robust, since none of the previous studies rigorously matched the two racial groups for total body and visceral fat content, metabolic parameters, inflammation, and sex steroid levels as performed in our current study.

Racial Differences in Postprandial Endothelial Function

Insulin-resistant states are characterized by inappropriately high circulating levels of FFA, TG, and glycemia. Considering that a typical human spends a substantial part of the day in the postprandial state, the adverse effects of these metabolic abnormalities on the endothelium can be significant. Many (5, 12, 43, 53, 54), but not all (4, 45), studies have shown that postprandial lipemia induces endothelial dysfunction. Increased oxidative stress associated with postprandial lipemia, in part by decreasing NO bioavailability, has been suggested to play a key causal role in this process (54). In a study of South African blacks, postprandial AUC for TG was associated with the presence of coronary artery disease (37). Thus, postprandial lipemia may play a role in the increased CVD in individuals of African origin. However, to our knowledge, there are no studies examining racial differences in postprandial endothelial function. Therefore, we hypothesized that postprandial lipemia following a meal would impair endothelial function to a greater degree in insulin-resistant African-American women than their well-matched white cohort. Postprandial increases in glucose, insulin, and FFA were similar in magnitude in both racial groups (Fig. 1). However, consistent with other reports, despite being insulin-resistant, African-American women have lower levels of fasting and postprandial TG than whites (Fig. 1). In both groups, breakfast induced a significant increase in endothelial function, but, despite being insulin-resistant, African-American women did not show any significant differences in postprandial vascular reactivity compared with their insulin-sensitive white counterparts.

Interpretation of our study finding necessitates consideration and discussion of a few relevant issues. First, the neutral finding observed in our study is unlikely to result from a type 2 statistical error because our study was abundantly powered for this end-point. A sample size of \( n = 36 \) was deemed sufficient to provide 80% power in detecting a difference of 2.0% or greater in FMD with \( \alpha = 0.05 \). A post hoc analysis for repeated-measures ANOVA for the interaction effect (racial group \( \times \) time) showed that our study sample (\( n = 36 \)) had sufficient power (0.93) to detect an effect size of 0.15 (Cohens \( f \)). A posteriori comparison of FMD values at 4 h following the meal in the groups revealed a higher FMD in African-American women compared with white women (adjusted mean: 12.7 ± 1.3 vs. 9.1 ± 1.2%, \( P = 0.008 \); ANCOVA with FMD differences in the racial group is adjusted for age, baseline FMD, and racial group). Similar analyses at 2 and 6 h revealed a greater but a nonsignificant trend (\( P < 0.20 \)) toward higher FMD values in African Americans compared with whites. This finding of a higher FMD response at 4 h in African-American women rejects our proposed hypothesis in favor of the alternative. In addition, these observations also suggest that African-American women appear to be more tolerant to the detrimental effects of a lipid load on the endothelium.

Second, another potential explanation for the lack of racial differences in postprandial endothelial function may be the lower levels of TG and markers of oxidative stress following a meal in African-American compared with white women (7). However, correlation analyses in our study suggest that race differentially affects the relationship between TG and FMD both at baseline and postprandially. FMD was positively related with TG in African-American women, whereas these variables were negatively correlated in white women. While many studies (reviewed in Ref. 54) show a negative correlation between TG levels and FMD, other studies report a positive relationship as observed in African-American women in our current report (4, 45). However, the mechanistic basis for this novel finding is unclear and needs to be confirmed in a larger study. Third, it is conventional notion that insulin resistance is associated with various components of the metabolic syndrome. However, the associations among insulin resistance and CV risk factors such as blood pressure, HDL-to-TG ratio, visceral adiposity, and carotid artery intimal thickness are rather weak in African Americans (38). Consistent with these findings, insulin resistance is associated with impaired endothelial function and increased levels of biomarkers of endothelial dysfunction in whites but not in African Americans (28, 30). Our study results show that endothelial function as measured by FMD is not impaired in young insulin-resistant African-American women. These findings together suggest that the link between insulin resistance and endothelial dysfunction in African Americans is rather weak.

Study Limitations

This study has several limitations. First, the study is cross-sectional in nature and, although adequately powered, our findings need to be confirmed in a larger study. Second, since our study included only middle-aged healthy premenopausal women, our results may not be applicable to men, older postmenopausal women, or women with other comorbidities. Third, insulin sensitivity was assessed by minimal modeling of FSIVGTT data. Although, FSIVGTT has been used to assess insulin sensitivity in many large clinical studies, euglycemic-hyperinsulinemic clamp studies are preferable to confirm racial differences in insulin sensitivity. Fourth, postischemic hyperemia was used as a stimulus to evaluate endothelial function in our study, and whether a different measurement method using other stimuli would impact the findings is not known and needs to be examined in future studies.

In conclusion, in this study, we have shown that, in well-matched young African-American and white women, despite being insulin-resistant, baseline and postprandial endothelial function as measured by FMD is comparable in both racial groups. These results imply that insulin sensitivity may not be a significant determinant of racial differences in endothelial function. The dissociation between insulin resistance and endothelial function suggests that there is an “insulin resistance paradox” as it relates to endothelial dysfunction in African Americans. Similar inconsistency has been observed with other features of the insulin-resistant phenotype such as lower TG levels and hepatic and visceral fat content in African Americans. Additional investigations are warranted to assess the
mechanisms underlying this insulin resistance paradox and identify the factors that contribute to racial differences in CV risk.

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DISCLOSURES

None

REFERENCES


