Relationship between insulin sensitivity and in vivo mitochondrial function in skeletal muscle

Bovon Sirikul,1 Barbara A. Gower,1 Gary R. Hunter,1 Dawnine E. Larson-Meyer,1 and Bradley R. Newcomer2

1Departments of Human Studies and Nutrition Sciences; 2Department of Diagnostic and Therapeutic Sciences, University of Alabama at Birmingham, Birmingham, Alabama; and 3Department of Family and Consumer Sciences (Human Nutrition), University of Wyoming, Laramie, Wyoming

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Sirikul, Bovorn, Barbara A. Gower, Gary R. Hunter, Dawnine E. Larson-Meyer, and Bradley R. Newcomer. Relationship between insulin sensitivity and in vivo mitochondrial function in skeletal muscle. Am J Physiol Endocrinol Metab 291: E724–E728, 2006.—Recent data have shown that individuals with low insulin sensitivity (SI) also have reduced whole body maximal oxygen uptake. The objectives of this study were to determine 1) whether muscle mitochondrial function was independently related to SI after being adjusted for known determinants of SI and 2) whether lower SI among African-American (AA) vs. Caucasian-American (CA) women was due to lower muscle mitochondrial function among AA women. Subjects were 37 CA and 22 AA premenopausal women (age: 33.6 ± 6.3 yr). Mitochondrial function [time constant of ADP (ADPtc)] was assessed during a 90-s unilateral isometric contraction using 31P magnetic resonance spectroscopy, SI with an intravenous glucose tolerance test, body composition by dual-energy X-ray absorptiometry, and visceral adipose tissue (VAT) with computed tomography. ANOVA was used to compare CA and CA groups, and multiple linear regression modeling was used to identify independent predictors of SI. Between-race comparisons indicated that muscle oxidative capacity was lower among AAs vs. CAs (ADPtc: 25.6 ± 9.8 vs. 21.4 ± 9.9 s). Multiple linear regression models for the dependent variable SI contained VAT and race and ADPtc. Significant independent effects for all predictor variables were observed in both the first (r2 = 0.345) and second (r2 = 0.410) models. The partial correlation for race was lower in the second model (−0.404 vs. −0.300), suggesting that muscle mitochondrial function contributed to the racial difference in SI. Lower muscle mitochondrial function among AAs may in part explain lower SI among them.

AN ASSOCIATION between mitochondrial dysfunction and reduced insulin sensitivity (SI) has been observed in cross-sectional studies (18, 30). Biopsy evidence indicates that oxidative capacity at the muscle level has an important impact upon SI with reduced oxidative enzyme activity in muscle, including smaller mitochondria and reduced electron transport chain activity, correlating with severity of decreased SI (35). Simoneau and Kelley (36) found that impaired mitochondrial function might contribute to the reduction in the activity of oxidative pathway marker enzymes seen in individuals with insulin resistance and obesity. Reduced oxidative enzyme activity has been found to be related to the severity of decreased SI in skeletal muscle (14, 35).

The higher incidence of type 2 diabetes among African Americans (AAs) compared with Caucasian Americans (CAs) may be due, in part, to lower SI among AAs vs. CAs (12, 13, 29). The physiological explanation for the observed lower SI in AAs compared with CAs is not known. Racial differences in muscle mitochondrial function may contribute to racial differences in SI. Although it has been demonstrated that AA women have lower muscle mitochondrial function than CA women (16), it is not known whether the difference in mitochondrial function explains the racial difference in SI. Understanding the physiological basis for racial differences in SI will become important as race-specific type 2 diabetes prevention strategies are developed and implemented.

Several clinical conditions often accompany decreased SI, such as obesity and deposition of visceral adipose tissue (VAT) (5). Fat distribution, especially increased fat in the intra-abdominal or visceral depot, is thought to play an important role in decreased SI. However, cross-sectional studies have shown that AA women have lower levels of VAT, both absolute and relative to total body fat mass, than do CAs (23, 39). The paradoxical observation of AAs having both lower VAT and lower SI suggests that VAT may be serving as a surrogate for other body fat compartments with which it is highly correlated, and/or lower SI may be due to factors unrelated to and independent of VAT (10). Thus factors other than VAT must be invoked to explain lower SI among AAs. We examined the possibility that lower muscle mitochondrial function might contribute to lower SI among AAs.

Several studies (33, 35, 36) have shown greater whole body oxidative capacity to be associated with greater SI. Measures of in vivo mitochondrial function using 31P magnetic resonance spectroscopy (31P-MRS) have been correlated with whole body aerobic capacity (24). The recovery rate of calculated free ADP, or the time constant of ADP (ADPtc), has been used as a marker of mitochondrial function, one that is independent of pH (1, 2). Shorter recovery time constants denotes higher rates of ATP synthesis via oxidative phosphorylation.

The purpose of the present study was to examine the relationship between in vivo muscle mitochondrial function (as measured by ADPtc) and whole body SI. Analysis of in vivo activity of skeletal muscle mitochondrial function will help to enhance our understanding of the role muscle mitochondrial function in glucose metabolism and insulin sensitivity.
function plays in $S_I$. Even though associations between $S_I$ and mitochondrial function have been documented in at-risk individuals (e.g., offspring of type 2 diabetics) (30), to our knowledge, a statistically significant correlation between in vivo MRS measurements of mitochondrial function and $S_I$ has not been documented in a general population of healthy premenopausal women. A secondary aim was to determine whether differences in muscle mitochondrial function explain the difference in $S_I$ between AAs and CAs.

METHODS

Fifty-nine (37 CA, 22 AA) premenopausal women between the ages of 20 and 46 yr were studied in a “normal-weight” state, defined as a body mass index (BMI) of $<25$ kg/m$^2$. Of the 59 women, 34 (58%) were whites with at least one first-degree relative. Overweight women subsequently participated in a supervised weight loss program, during which they lost weight to achieve a “normal” BMI of $<25$ kg/m$^2$. For the present study, these subjects were tested in an energy balance state after 4 wk of carefully supervised weight maintenance. The 34 postoverweight women included 14 AA and 20 CA women. The 34 postoverweight women were then group matched on the basis of age, race, and BMI, with 25 control subjects who reported never having been overweight or obese and not having had overweight or obese first-degree relatives. The control group included 9 AA and 16 CA women. For all subjects, race was based on self reports.

Subjects were not taking medications known to affect body composition, energy metabolism, fuel utilization, $S_I$, heart rate, or thyroid status and did not smoke. The involvement of human subjects was approved by the Institutional Review Board of The University of Alabama, Birmingham, and all subjects provided written informed consent. Subjects were assessed during the follicular phase of the menstrual cycle. All volunteers were screened and briefed about the experimental protocol, and informed consent was obtained prior to any testing.

Study variables were assessed under weight-stable, diet-controlled conditions through the General Clinical Research Center (GCRC). Before each evaluation, all subjects were maintained in a weight-stable state for 4 wk, during which all food was provided through the GCRC to maintain macronutrient intake within the range of 20–22% of energy as fat, 16–23% as protein, and 55–64% as carbohydrate. No alcohol intake was permitted. Dietary adherence and body weight loss to achieve a “normal” BMI of $<25$ kg/m$^2$. For the present study, these subjects were tested in an energy balance state after 4 wk of carefully supervised weight maintenance. The 34 postoverweight women included 14 AA and 20 CA women. The 34 postoverweight women were then group matched on the basis of age, race, and BMI, with 25 control subjects who reported never having been overweight or obese and not having had overweight or obese first-degree relatives. The control group included 9 AA and 16 CA women. For all subjects, race was based on self reports.

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Maximum aerobic capacity was assessed as maximal whole body aerobic capacity relative to total body mass ($V_O_{2\text{max}}$) during a maximal modified Bruce-graded treadmill protocol and expressed relative to body weight and to fat-free mass (FFM). Consumption of oxygen and production of carbon dioxide were measured continuously via open-circuit spirometry and analyzed with the use of a metabolic cart (model 2900; SensorMedics, Yorba Linda, CA). Standard criteria for heart rate, respiratory quotient, and plateauing achieved ensured achievement of $V_{O_{2\text{max}}}$, as previously described (17). Collection of sera and tolbutamide-modified, frequently sampled, intravenous glucose tolerance test. At $\sim$0700 after the subjects had fasted for 12 h, flexible intravenous catheters were placed in the antecubital spaces of both arms. Three blood samples were drawn over a 40-min period, and the sera were subsequently separated and pooled for analysis of lipids. Three additional blood samples were taken over a 20-min period for determination of basal glucose and insulin (the average of the values was used for basal fasting concentrations). At time 0, glucose (50% dextrose, 11.4 g/m$^2$) was administered intravenously. Blood samples (2.0 ml) were then collected at the following times (min) relative to glucose administration at 0 min: 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180. Tolbutamide (125 mg/m$^2$) was injected intravenously at 20 min. Serum samples were analyzed for glucose and insulin, and values were entered into the MINMOD computer program (version 3.0, Richard N. Bergman; Department of Physiology and Biophysics, University of Southern California, Los Angeles, CA) for determination of $S_I$ (3, 41).

Assay of glucose and insulin. Glucose was measured in 10 μl of serum by using an Ektachem DT II System (Johnson & Johnson Clinical Diagnostics, Rochester, NY). In our laboratory, this analysis has a mean intra-assay coefficient of variation (CV) of 0.61% and a mean interassay CV of 1.45%. Insulin was assayed in duplicate 200-μl aliquots with Diagnostic Products (Los Angeles, CA) Coat-A-Count kits. According to the supplier, the cross-reactivity of this assay with proinsulin is $\sim$40% at mid-curve; C-peptide is not detected. In our laboratory, this assay has a sensitivity of 11.4 pmol/l (1.9 μU/ml), a mean intra-assay CV of 5%, and a mean interassay CV of 6%. Commercial, quality control serum samples of low, medium, and high insulin concentration (Lyphochek; Bio-Rad, Anaheim, CA) were included in every assay to monitor variation over time, as described by Gower et al. (11).

Analysis of skeletal muscle metabolism. $^1$H-MRI and $^{31}$P-MRS were conducted on a 4.1-T whole body imaging and spectroscopy system as previously described (24, 25, 26, 28). Each subject was requested to fast and abstain from caffeinated beverages for $\geq 6$ h and from exercise for $\geq 24$ h prior to testing. The subjects performed unilateral isometric plantar flexion exercises using a lab-constructed exercise bench that attached to the patient table of the spectrometer. Isometric plantar flexion force was measured with this device, as previously described (24, 26, 27, 28). After a warm up, in-magnet exercise periods consisted of a 90-s isometric plantar flexion at 100% of maximum voluntary contraction. A 7-cm $^1$H-$^{31}$P surface coil was used to collect 2 s of time-resolved $^{31}$P-MRS data during 60 s of rest, 90 s of exercise, and 7.5 min of recovery (24, 25, 28). The coil was fastened to the underbelly of the calf muscle, centered about its maximum circumference. $^{31}$P-MRS data were collected using the following parameters: TR = 2,000 ms, 4 dummy pulses, one average, and a half-passage adiabatic excitation pulse.

Skeletal muscle mitochondrial function by ADP$_c$ was determined using the model of Argov et al. (1). Specifically, ADP$_c$ was determined by fitting the recovery of each metabolite to a monoexponential curve, using Sigma Plot (Jandel Scientific; SPSS, Chicago, IL). A previous study (24) reported that recovery of ADP data obtained every 2 s is closely approximated by a mono-exponential curve. The ADP$_c$ corresponded to the time required to lose $\sim$63% of end-exercise ADP concentration. The CV of ADP$_c$ is 3.3% for exercise at this intensity (20).

Body composition evaluation. Body composition was determined by dual-energy X-ray absorptiometry (DEXA) (DPX-L; Lunar Radiation, Madison, WI) with the use of software version 1.33 (Lunar Radiation). Cross-sectional areas of VAT and subcutaneous abdominal adipose tissue (SAAT) were determined by computed tomography (CT) with the use of a HiLight/HTD Advantage scanner (General Electric, Milwaukee, WI) set at 120 kVp (peak kilovoltage) and 40 mA. Subjects were examined in the supine position with their arms stretched above their heads, with a 5-mm scan taken for 2 s at the level of the umbilicus. With the use of procedures established by Kiwist et al. (22), the attenuation range for adipose tissue was $\sim$30 to $\sim$90 Hounsfield units. Cross-sectional areas of adipose tissue were determined by using a computerized fat tissue-highlighting technique. VAT and SAAT were measured by separating adipose tissue areas by encircling the muscle wall surrounding the abdominal cavity with a cursor. Tissue cross sections between $\sim$30 and $\sim$90 Hounsfield units in the respective areas were considered to be VAT and SAAT. Both intra- and interobserver test-retest reliability had an r value of 0.99 with a CV of $<2\%$ on the basis of reevaluation of 20 scans.
Table 1. Descriptive statistics and metabolic outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>AA (n = 22)</th>
<th>CA (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>33.4±6.1</td>
<td>33.7±6.6</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>64.8±9.9</td>
<td>64.6±5.7</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163.8±7.2</td>
<td>164.7±5.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.0±2.4</td>
<td>23.8±1.3</td>
</tr>
<tr>
<td>VAT, cm²</td>
<td>44.9±17.4</td>
<td>59.6±26.8</td>
</tr>
<tr>
<td>ADP_c, s⁻¹</td>
<td>25.6±9.8</td>
<td>21.4±9.9</td>
</tr>
<tr>
<td>( V_\text{O}_2 \text{max} ) ml/kg⁻¹/min⁻¹</td>
<td>97.2±10.6</td>
<td>92.4±10.7</td>
</tr>
<tr>
<td>( V_\text{O}_2 \text{max-FFM} ) ml/kg FFM⁻¹/min⁻¹</td>
<td>49.9±7.7</td>
<td>56.8±8.5</td>
</tr>
<tr>
<td>( S \text{I} \times 10^{-4} ) min⁻¹/(μIU/ml)</td>
<td>5.7±3.5</td>
<td>7.8±4.3</td>
</tr>
</tbody>
</table>

Values are means ± SD. AA, African American; CA, Caucasian American; BMI, body mass index; VAT, visceral adipose tissue; ADP_c, time constant of ADP (lower values denote higher mitochondrial function); \( V_\text{O}_2 \text{max} \), maximal whole body aerobic capacity relative to total body mass; \( V_\text{O}_2 \text{max-FFM} \), maximal whole body aerobic capacity relative to fat-free mass; \( S \text{I} \), insulin sensitivity. *AA vs. CA, P < 0.05.

Statistical analysis. Statistical analyses were performed with the use of SPSS software, version 11.0 (SPSS). Descriptive statistics are given as means ± SD. For all analyses, values for \( S \text{I} \) were log transformed to eliminate skewness. Correlations between \( S \text{I} \) and morphological and mitochondrial variables were assessed using Pearson correlation coefficients. Multiple linear regression analysis was used to model the relationship between \( S \text{I} \) (dependent variable) and mitochondrial function and body composition (independent variables). The best multivariate model was selected on the basis of preliminary analysis using independent variables, with the largest simple correlations with \( S \text{I} \) and maximum \( R^2 \). Two different models were tested. In the first model, race (AA vs. CA) and VAT were examined as predictors of \( S \text{I} \). In the second model, race, VAT, and ADP_c were examined as predictors of \( S \text{I} \). For all analyses, a P value <0.05 was deemed statistically significant.

RESULTS

The unadjusted descriptive statistics by race are presented in Table 1. AAs had lower \( S \text{I} \) and VAT and higher ADP_c (indicating lower muscle mitochondrial function) than did CA. The univariate relationships among the variables of interest are shown in Table 2. \( S \text{I} \) was inversely correlated to ADP_c (\( r = -0.360 \)) and VAT (\( r = -0.342 \)). VAT was more strongly related to \( S \text{I} \) than any other fat compartment measure, and thus the fat compartment was included in the multiple linear regression models. The association between ADP_c and VAT was not significant.

The mean \(^{31}\)P data curves depicting depletion and recovery of ADP for each group are presented in Fig. 1. This represents the ADP concentration data for the last exercise data point (at 90 s) through the first 260 s of recovery (i.e., until the ADP levels return to baseline values) and allows for visualization of the differences in oxidative phosphorylation between the two groups. An initial multiple linear regression model for the dependent variable \( S \text{I} \) using race (AA vs. CA) and VAT as independent variables is shown in Table 3. Race and VAT were significant and independent predictors of \( S \text{I} \). This first model explained ~34% of the variance of \( S \text{I} \). \( V_\text{O}_2 \text{max adjusted} \) for FFM was not a significant predictor of \( S \text{I} \) when included with race and VAT (Table 4). However, with the inclusion of ADP_c into a model with race and VAT, all variables were significant and independent predictors of \( S \text{I} \) (Table 5). The variance explained by this second model was 41%. The partial correlation for race decreased from model 1 to model 2 (~0.404 vs. ~0.300) with the inclusion of ADP_c, suggesting that mitochondrial function explained part of the difference observed between AAs and CAs in \( S \text{I} \).

DISCUSSION

This study was the first to test the hypothesis that mitochondrial function, measured in vivo, may contribute to the observed lower \( S \text{I} \) among healthy AAs compared with CAs. The results of this study indicated that, among premenopausal women, race, mitochondrial function, and VAT were independent predictors of \( S \text{I} \). These results support the hypothesis that lower mitochondrial function might contribute to decreased \( S \text{I} \) in skeletal muscle (18, 19, 30), and furthermore, racial differences in mitochondrial function may contribute to lower \( S \text{I} \) among AA vs. CA women.

Table 2. Pearson correlation coefficients between \( S \text{I} \) and predictor variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \text{ADP}_c )</th>
<th>( \text{VO}_2 \text{max, ml/kg}^{-1}\text{min}^{-1} )</th>
<th>( \text{VO}_2 \text{max-FFM, ml/kg FFM}^{-1}\text{min}^{-1} )</th>
<th>VAT</th>
<th>Body Fat, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{VO}_2 \text{max} ) ml/kg⁻¹/min⁻¹</td>
<td>-0.274*</td>
<td>-0.376*</td>
<td>-0.237</td>
<td>-0.0236</td>
<td></td>
</tr>
<tr>
<td>( \text{VO}_2 \text{max-FFM} ) ml/kg FFM⁻¹/min⁻¹</td>
<td>-0.376*</td>
<td>0.928*</td>
<td>-0.164</td>
<td>0.371*</td>
<td></td>
</tr>
<tr>
<td>VAT</td>
<td>0.027</td>
<td>-0.340*</td>
<td>-0.237</td>
<td>-0.404*</td>
<td></td>
</tr>
<tr>
<td>Body fat, %</td>
<td>0.003</td>
<td>-0.510*</td>
<td>-0.164</td>
<td>0.371*</td>
<td></td>
</tr>
<tr>
<td>( S \text{I} \times 10^{-4} ) min⁻¹/(μIU/ml)</td>
<td>-0.316*</td>
<td>0.438*</td>
<td>0.388*</td>
<td>0.316*</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05.
In agreement with other studies (6, 34), we found that VAT was an independent predictor of $S_I$. Losses of VAT through diet-induced weight loss (8, 11), and diet combined with 16 wk of moderate-intensity exercise, have been associated with increased $S_I$ (7). The mechanisms thought to be responsible for the modulation of insulin action by VAT include increased portal release of free fatty acids (4, 40) and/or abnormal expression and secretion of fat-derived peptides, such as resistin (37), leptin, ACRP30, and tumor necrosis factor-α (15).

ADP$_{tc}$ emerged as a significant independent predictor of $S_I$ in this study. This is consistent with the hypothesis that mitochondrial function is related to, and may be a contributing factor to, $S_I$. In fact, ADP$_{tc}$ might even underestimate the contribution of mitochondrial function to $S_I$. This could be because our measurements were confined to a single muscle group (gastrocnemius and soleus). The inclusion of measurements at other sites (e.g., latissimus dorsi, quadriceps) may strengthen the relationship we observed. Our observation that $\dot{V}O_2\text{max}$ adjusted for FFM was not independently related to $S_I$ strengthens the relationship we observed. Our observation that $\dot{V}O_2\text{max}$ adjusted for FFM was not independently related to $S_I$

Table 3. Multiple linear regression for the dependent variable $S_I$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model $R^2$</th>
<th>Estimate</th>
<th>SEE</th>
<th>Partial $R$</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.345</td>
<td>1.048</td>
<td>0.081</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>VAT</td>
<td>$-0.001$</td>
<td>0.001</td>
<td>$-0.427$</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>$-0.189$</td>
<td>0.063</td>
<td>$-0.404$</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

SEE, standard error of the estimate; partial $R$, partial correlation for the variable adjusting for other variables.

The finding that race was a significant predictor of $S_I$ in both models was expected. Several studies (10, 11, 12, 13, 29) have found that AA had lower $S_I$ than CA; however, the physiological basis for lower $S_I$ among AA is still not clear. Lower VAT among AA suggests that differences in central vs. peripheral fat distribution do not explain lower $S_I$ among AA (12). Furthermore, multiple linear regression analysis supported the notion that VAT does not account for the racial difference in $S_I$.

Table 4. Multiple linear regression for the dependent variable $S_I$

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Partial $R$</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.410</td>
<td>1.376</td>
<td>0.101</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>VAT</td>
<td>$-0.002$</td>
<td>0.001</td>
<td>$-0.461$</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>$-0.060$</td>
<td>0.065</td>
<td>$-0.300$</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>$\dot{V}O_2\text{max}$</td>
<td>0.002</td>
<td>0.003</td>
<td>$-0.328$</td>
<td>0.034</td>
<td></td>
</tr>
</tbody>
</table>

Lower values denote higher mitochondrial function.

Table 5. Multiple linear regression for the dependent variable $S_I$ with ADP$_{tc}$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model $R^2$</th>
<th>Estimate</th>
<th>SEE</th>
<th>Partial $R$</th>
<th>$P$ Value</th>
</tr>
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<tbody>
<tr>
<td>Intercept</td>
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<td>$-0.300$</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>ADP$_{tc}$</td>
<td>$-0.002$</td>
<td>0.003</td>
<td>$-0.328$</td>
<td>0.034</td>
<td></td>
</tr>
</tbody>
</table>

The addition of ADP$_{tc}$ into the multiple linear regression model decreased the partial correlation for race, suggesting that lower $S_I$ among AAs may be partially explained by lower muscle mitochondrial function. Lower whole body oxidative capacity in AAs compared with CAs has been observed in children (31, 38) and premenopausal women (16, 17). Thus lower oxidative capacity, which has been associated with mitochondrial function (24), may contribute to lower $S_I$ among AAs.

Taken together, our results suggest that muscle mitochondrial function plays a role in maintaining $S_I$ that is independent of fat distribution and race. These results are applicable only to normal-weight healthy premenopausal women, and we cannot speculate on the role that muscle mitochondrial function might play on $S_I$ in other groups. Furthermore, muscle mitochondrial function may explain, in part, the observed racial differences in $S_I$. In this study, it was not possible to determine whether low $S_I$ was caused by impaired mitochondrial function or whether mitochondrial function was downregulated due to a decreased muscle energy demand (e.g., low physiological function and activity).

Although mitochondrial function has been previously studied in a resting basal state (30), we measured muscle under exercise conditions. This allowed us to measure the mitochondrial function capacity, which would be more representative of activated muscle. It would have been interesting to see the differences between the muscle’s basal and perturbed conditions. Future studies should be done to measure both basal and perturbed mitochondrial function to get a more complete picture of the relationship between mitochondrial function and $S_I$.

One of the limitations of our study was that we did not measure intramuscular lipids (IMCLs) in our subjects. Measures of IMCL would have considerably strengthened this study, because increased IMCL has been associated with type 2 diabetes (14) and decreased $S_I$ (9, 21). Furthermore, measuring both resting and maximal mitochondrial function via MRS in conjunction with IMCL measures would allow a more complete insight into the interplay between $S_I$ and metabolism and should be considered in future studies. Future studies should also use a combination of MRI methods to measure blood flow and capillarization to thoroughly assess the role of mitochondrial function in determining $S_I$. Finally, future studies should extend these experiments to determine whether acute or chronic exercise training improves mitochondrial function and $S_I$.

GRANTS

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