Mitochondrial Respiration is Associated with Lower Energy Expenditure and Lower Aerobic Capacity in African American Women

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Objective: Reasons for the higher obesity prevalence in African American women (AAW) compared with Caucasian women (CW) are unknown. Energy expenditure and maximal aerobic capacity (VO₂max) are lower in AAW. It was hypothesized that these differences are explained by skeletal muscle characteristics, particularly mitochondrial content and function.

Methods: Multivariate regression analyses were used to examine the relationships between energy expenditure (resting and during a hyperinsulinemic-euglycemic clamp) and VO₂max versus body composition, physical activity, and skeletal muscle mitochondrial measurements in AAW and CW.

Results: In AAW, VO₂max was lower (P < 0.0001). Body-composition-adjusted energy expenditure during the clamp was lower in AAW (P < 0.002). Physical activity was similar in both groups. After adjusting for mitochondrial respiration, racial differences in energy expenditure and VO₂max were no longer present. Another novel finding was that a thermogenic response to the clamp was observed in CW (153 ± 62 kcal/d; P < 0.03) but not in AAW (219 ± 62 kcal/d; P = 0.43).

Conclusions: AAW and CW show differences in adjusted energy expenditure and aerobic capacity that are largely accounted for by differences in skeletal muscle mitochondrial oxidative characteristics. Further research is needed to determine whether lower mitochondrial respiration and lower thermogenesis are risk factors for obesity in AAW.

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Introduction

The prevalence of obesity and associated chronic diseases is higher in African American women (AAW) than in Caucasian women (CW) (1,2), but the reasons remain incompletely understood. Low resting energy expenditure (REE) and low 24-hour energy expenditure are associated with weight gain (3). Another risk factor for obesity is low aerobic capacity, which is determined by physical activity and genetic factors (4). In a parent-offspring study, the heritability of aerobic fitness was estimated as 40%, and the odds of having overweight or obesity were three- to tenfold lower in those with the highest level of aerobic fitness (4). These factors may play a role in the increased obesity risk in AAW.

A lower total energy expenditure (5-8) and lower REE have been consistently reported in AAW who are lean or who have overweight or obesity compared with CW (5-9). Whether these differences play a role in the higher risk for obesity in AAW is unknown, but we recently demonstrated that lower energy expenditure explained the lower weight loss achieved by AAW during a behavioral intervention (7). The primary determinant of REE is fat-free mass (FFM) (10) with gender, race, age, body fat, and genetics contributing to variation (10-12). However, the mechanisms responsible for the lower energy expenditure in AAW are not completely understood.

In addition to lower energy expenditure, AAW have lower maximal aerobic capacity (VO₂max) (8,13). Physical activity plays a major role in aerobic capacity, but a limitation of most studies in AAW is that an objective assessment of free-living physical activity is not obtained. Differences in hemoglobin levels and skeletal muscle aerobic capacity were shown to be associated with lower VO₂max in AAW, but they did not fully explain the racial difference (13).
Skeletal muscle, although having a low relative energy expenditure (on a per unit basis), is the largest component of FFM and accounts for approximately 20% to 30% of oxygen uptake at rest (14). We suggest that differences in skeletal muscle characteristics related to oxidative capacity might play a role in the lower energy expenditure and VO₂max in AAW. Previous observations support the rationale for pursuing this hypothesis. Skeletal muscle fiber type composition, capillary density, and mitochondrial volume density have been associated with obesity, muscle respiratory capacity, and VO₂max (15-19). A lower percentage of type I fibers (16,20) and lower oxidative capacity have been observed in skeletal muscle in AAW (13,20). Support for mitochondrial metabolism playing a role in racial differences in energy expenditure comes from the observation that African mitochondrial DNA haplogroups are associated with lower REE (21). Furthermore, we previously showed that mitochondrial respiration was lower and was associated with lower peripheral glucose uptake in AAW compared with CW (20).

Based on these observations, the primary goal of this report is to determine whether skeletal muscle characteristics, particularly mitochondrial content and function, explain the racial differences in energy expenditure and VO₂max. A secondary goal is to examine whether AAW have a blunted thermogenic response to infused insulin and glucose.

**Methods**

Participants in this study also participated in a study of differences in glucose metabolism, and a detailed description has been reported (20). Briefly, 22 young AAW and 22 CW without obesity who were matched for BMI, body weight, and age were enrolled. We chose to study women without obesity to examine metabolic disturbances before the onset of obesity and avoid the potential confounder of metabolic disturbances that occur after increased adiposity is established. Inclusion criteria included age > 18 and ≤ 36 years, stable body weight over the previous 3 months, not pregnant or lactating, and sedentary (<20 minutes of activity, three times a week). Exclusion criteria included significant disease or unstable medical condition, diabetes mellitus, and any drug treatment that alters glucose metabolism. The protocol was approved by the University of Pittsburgh Institutional Review Board. All research participants gave written informed consent.

**Whole body measures**

Body composition, including the amount of FFM in the trunk region and the amount of appendicular FFM, was assessed by dual-energy x-ray absorptiometry (GE Lunar iDXA; GE Healthcare, Chicago, Illinois). Maximal aerobic capacity was measured by graded exercise testing using an incremental modified Astrand protocol on an electronically braked cycle ergometer. Free-living physical activity was assessed for 6.1 ± 1.4 days, within 12.7 ± 7.4 days of the VO₂max testing, by using multisensor activity monitors (Sensewear MF Armband; BodyMedia, Pittsburgh, Pennsylvania), which have been shown to perform as well or better than other activity monitors (22-24). An inpatient overnight stay was scheduled (at least 3 days after exercise test). Energy expenditure was measured, and a muscle biopsy was performed the following morning.

Participants were admitted to a Clinical Research Unit at approximately 5 pm for an overnight stay, where they received a standardized meal (10 kcal/kg; 50% carbohydrate, 15% protein, 35% fat) and then fasted until completion of study procedures. The following morning, REE was determined by indirect calorimetry (Parvo Medics TrueOne 2400; Parvo Medics, Sandy, Utah), as previously described (7). Energy expenditure measurements were repeated during the steady state (SS; final 30 minutes) of each step of a two-step hyperinsulinemic-euglycemic clamp (SS1: 15 mU/m²/min; SS2: 40 mU/m²/min) implemented to assess insulin sensitivity (20).

**Muscle biopsies**

A percutaneous muscle biopsy (vastus lateralis) was cleared of blood and adipose and partitioned for analyses, as previously described (20,25). From the total biopsy sample, a fresh sample was placed into buffer (BIOPS) for high-resolution respirometry (20), a portion was placed in mounting medium for histochemical analysis (25), and a portion was prepared for transmission electron microscopy (20).

Muscle fiber type and capillary density were measured by using standard histochemical methods (20,25). Mitochondrial volume density, or the fraction of cell volume occupied by mitochondria, was assessed from transmission electron microscopy images by using digital morphometry and the point-sampling technique of classical stereology (26,27).

As previously reported (20), muscle fibers (1.5-2.5 mg) were permeabilized with saponin (50 μg/mL in BIOPS buffer) for 20 minutes and treated with blebbistatin (25 μM) to inhibit contraction before insertion into the chamber of the Oxygraph system (Oxygraph-2k; Oroboros Instruments, Innsbruck, Austria) with Mir05 buffer at 37°C. State 4 respiration was determined with 5 mM glutamate, 2 mM malate, 10 mM succinate, and 25 μM palmitoyl carnitine. Maximal coupled or State 3 respiration was subsequently measured with stepwise ADP titration (manual injection, 37.5-4,000 μM). Vmax and Kₘ were determined using standard Michaelis-Menten kinetics. Maximal uncoupled or State U respiration was assessed with the subsequent addition of p-trifluoromethoxy carbonyl cyanide phenylhydrazone (2 μM × 3 additions). In quality control testing, there was no significant effect of adding cytochrome c (10 μM) on respiration.

**Data analysis**

Analysis of variance (ANOVA) (Proc GLM, SAS 9.4 for Windows; SAS Institute Inc., Cary, North Carolina) was used for group comparisons, with and without adjusting for appropriate variables included as covariates (e.g., FFM, proportion of type I fibers, mitochondrial density). Two-way repeated-measures ANOVA (Proc Mixed; covariance structure: unstructured), with and without covariates, was used for the analysis of the three energy expenditure measurements (before and during the clamp). The thermogenic response to the clamp was calculated by subtracting the REE from the energy expenditure during the clamp (average of SS1 and SS2).

Based on Shapiro-Wilk tests, all variables except minutes of physical activity were normally distributed. The square root of minutes of physical activity was normally distributed and was used in the model for VO₂max. Homogeneity of variance for all variables was confirmed by using Levene’s test.

To investigate whether relationships (e.g., between REE or VO₂max and mitochondrial respiration) were different between races, tests of
slopes and intercepts were carried out by using regression analysis (Proc GLM). Stepwise multiple regression was used to model energy expenditure and VO_{2max}, with race, FFM, fat mass, proportion and amount of FFM in the trunk, minutes of physical activity, hemoglobin and thyroid-stimulating hormone levels, proportion of type I and type II muscle fibers, capillary density, mitochondrial density, and mitochondrial respiration as potential parameters. The default significance level for a parameter to enter and stay in the model was set at $P = 0.15$. To examine the parameter effect of race in the final models for REE and energy expenditure during the clamp, the significance level for a parameter to enter and stay in the model was increased (to force race in the model); for REE, each was increased to 0.8, and for the energy expenditure during the clamp, each was increased to 0.6. The total sample size included 22 AAW and 22 CW. However, three energy expenditure values for AAW are missing because of equipment malfunction, values for fiber typing are missing for two AAW and two CW, and values for mitochondrial density and respiration are missing for one AAW and two CW. Values are presented as mean ± SD, except in analyses including covariates, in which we report least squares mean ± SEM and graphical presentation of data (mean ± SE).

Results

Participant characteristics

As previously reported (20), the AAW and CW were matched for BMI (22.7 ± 3.1 kg/m$^2$ vs. 22.7 ± 3.1 kg/m$^2$), weight, and age (22.8 ± 4.0 years vs. 24.3 ± 5.5 years). The AAW had a lower percentage of body fat (27.1% ± 6.7% vs. 32.1% ± 6.8%; $P < 0.02$). The amount of FFM in the trunk region was similar in AAW and CW (19.8 ± 2.6 kg vs. 19.7 ± 2.5 kg), while the amount of appendicular FFM was higher in AAW (21.0 ± 3.1 kg vs. 19.1 ± 2.6 kg; $P < 0.04$). The proportion of FFM within the trunk area was lower in AAW (44.3% ± 1.7% vs. 46.3% ± 1.6%; $P < 0.001$), and conversely, the proportion of appendicular FFM was higher in AAW (46.8% ± 2.0% vs. 45.0% ± 1.5%; $P < 0.002$). Serum thyroid-stimulating hormone levels were similar in AAW and CW (1.78 ± 0.33 mIU/L vs. 1.91 ± 0.62 mIU/L; $P = 0.55$). Blood hemoglobin levels were lower in AAW compared with CW (12.7 ± 1.0 mg/dL vs. 13.4 ± 0.8 mg/dL; $P < 0.02$).

Energy expenditure and thermogenesis

Replicate measures of energy expenditure obtained at baseline and during each SS phase of a fasting, two-step hyperinsulinemic-euglycemic clamp demonstrated a lower energy expenditure in AAW compared with CW (unadjusted, $P < 0.05$; Figure 1A; $P < 0.0002$ adjusting for FFM; $P < 0.002$ adjusting for FFM and fat mass). There was a suggestion of an effect of the insulin and glucose infusion associated with the clamp on energy expenditure ($P = 0.062$) and a difference in response by race ($P = 0.081$). The change in energy expenditure during the clamp (average and SS1 and SS2) compared with baseline energy expenditure (REE) was significant only in CW ($P < 0.03$) and was different between AAW and CW (Figure 1B; $-19 ± 88$ kcal/d vs. $53 ± 119$ kcal/d; $P < 0.04$).

VO\textsubscript{2}max

During the VO\textsubscript{2}max tests, AAW and CW achieved nearly identical maximal respiratory exchange ratio (1.10 ± 0.06 vs. 1.12 ± 0.07; $P = 0.57$) and rating of perceived exertion (17.3 ± 1.4 vs. 17.4 ± 1.4; $P = 0.86$). Even though objective (respiratory exchange ratio) and subjective (rating of perceived exertion) measures confirmed that the AAW and CW provided a maximal effort, VO\textsubscript{2}max was 12.9% lower in AAW (2,020 ± 410 mL/min vs. 2,320 ± 491 mL/min; $P = 0.04$). This difference became more pronounced (18.3% lower) when adjusting for FFM as a covariate (AAW: 1,951 ± 70 mL/min vs. CW: 2,389 ± 70 mL/min; $P < 0.0001$) or when dividing by FFM (45.1 ± 6.9 mL/min/kg vs. 54.4 ± 7.8 mL/min/kg; $P < 0.0001$).

As shown in Table 1, objectively assessed free-living physical activity could not explain the racial difference in VO\textsubscript{2}max. Activity energy expenditure (AEE), time spent in total, vigorous, or very vigorous activity, time spent in sedentary behavior, and steps per day were similar for AAW and CW.

Mitochondrial content and respiration

Mitochondrial content was lower in AAW (3.7% ± 1.2% vs. 4.8% ± 1.6%; $P < 0.02$). As previously reported, high-resolution respirometry of permeabilized muscle fibers revealed a lower oxidative capacity in AAW (20). After adjusting for mitochondrial content as

| Parameter     | AAW (n = 22) | CW (n = 22) | $P$   |
|---------------|--------------|-------------|-------|
| AEE, kcal/d   | 631 ± 278    | 594 ± 518   | 0.77  |
| PA, min/d     | 126 ± 52     | 116 ± 89    | 0.64  |
| Vigorous PA, min/d | 23 ± 19 | 27 ± 43 | 0.72 |
| Very vigorous PA, min/d | 3 ± 4 | 4 ± 7 | 0.65 |
| Sedentary, h/d | 14.3 ± 1.2   | 14.1 ± 1.6  | 0.55  |
| Steps/d       | 9,958 ± 4472 | 8,721 ± 3,452 | 0.31 |

PA defined as ≥ 3 METs, vigorous PA as 6-9 METs, and very vigorous PA as > 9 METs. AEE, activity energy expenditure; METs, metabolic equivalents; PA, physical activity.
a covariate, AAW still showed significantly lower State 4 (67 ± 6 6 4 pmol/s/mg vs. 80 ± 6 6 4 pmol/s/mg dry weight; \( P < 0.04 \)), State 3 (324 ± 6 6 17 pmol/s/mg vs. 418 ± 6 6 18 pmol/s/mg dry weight; \( P < 0.001 \)), and State U (365 ± 6 6 15 pmol/s/mg vs. 486 ± 6 6 17 pmol/s/mg dry weight; \( P < 0.0001 \)) mitochondrial respiration. The respiratory control ratio (State 3 divided by State 4 respiration) was not significantly different between AAW and CW (4.9 ± 6 6 0.9 vs. 5.3 ± 6 6 0.7; \( P = 0.21 \)). The ADP concentration at half maximum respiration (\( K_m \)) was similar in AAW and CW (256 ± 6 6 80 m\( \mu \)M vs. 277 ± 6 6 79 m\( \mu \)M; \( P = 0.41 \)).

**TABLE 2** Correlations with REE and VO\(_{2\max}\)

| Variable          | REE       | VO\(_{2\max}\), L/min | VO\(_{2\max}\), mL/min/kg FFM |
|-------------------|-----------|------------------------|-------------------------------|
|                   | \( r \)   | \( P \)                | \( r \)                       | \( P \)                   |
| FFM               | 0.52      | 0.0005                 | 0.58                         | 0.00001                 |
| Trunk FFM         | 0.46      | 0.003                  | 0.61                         | 0.0001                  |
| Appendicular FFM  | 0.54      | 0.0003                 | 0.52                         | 0.0003                  |
| Trunk FFM, %      | −0.20     | 0.20                   | 0.09                         | 0.55                    |
| Fat               | 0.59      | 0.0001                 | 0.25                         | 0.10                    |
| Minutes physical activity | −0.20     | 0.19                   | 0.29                         | 0.053                   |
| Sedentary minutes | 0.11      | 0.51                   | −0.28                        | 0.069                   |
| Hemoglobin        | 0.17      | 0.28                   | 0.22                         | 0.16                    |
| TSH               | −0.24     | 0.13                   | 0.00                         | 0.99                    |
| Type I fibers, %  | 0.13      | 0.45                   | 0.39                         | 0.02                    |
| Type II fibers, % | −0.13     | 0.45                   | −0.39                        | 0.02                    |
| Mitochondrial density | 0.41      | 0.009                  | 0.62                         | 0.0001                  |
| State 4 respiration | 0.41     | 0.02                   | 0.54                         | 0.0003                  |
| State 3 respiration | 0.29     | 0.08                   | 0.48                         | 0.002                   |
| State U respiration | 0.35     | 0.04                   | 0.48                         | 0.003                   |

\( n = 22 \) AAW and 22 CW, with the following exceptions: REE values for 3 AAW are missing; for fiber typing, values are missing for 2 AAW and 2 CW; for mitochondrial density and respiration, values are missing for 1 AAW and 2 CW. FFM, fat-free mass; TSH, thyroid-stimulating hormone.

Modeling energy expenditure

When all subjects were combined, REE was significantly correlated with total, trunk, and appendicular FFM and fat mass (Table 2). Mitochondrial density and mitochondrial respiration were also correlated with REE. Many of the correlations tended to be stronger against the energy expenditure during the clamp, particularly mitochondrial parameters. For example, the correlations with mitochondrial density (\( r = 0.50; P < 0.0009 \)), State 3 respiration (\( r = 0.42; P < 0.009 \)), and State U respiration (\( r = 0.54; P < 0.007 \)) tended to be stronger compared with the correlations shown in Table 2 for REE. Although REE and State 4 respiration were lower in AAW, there was no racial difference in the relationship between REE and State 4 respiration (Figure 2A; slopes: \( P = 0.73 \); intercepts: \( P = 0.75 \)).

We next modeled energy expenditure including subject characteristics and race. The first parameters to enter the model for REE were body fat and FFM (Table 3, Model 1). Although race explained 3% of the variance in REE, it was not significant (\( P = 0.12 \)). When also including skeletal muscle parameters, State 4 respiration was the only variable to enter the model (Table 3, Model 2; \( r^2 = 0.66; P < 0.0001 \)). No other body composition or blood variables entered either model.

The same subject characteristics, including race (\( P < 0.002 \)), entered the model when examining the energy expenditure during the clamp (average of SS1 and SS2; Table 3, Model 3). The final model for the energy expenditure during the clamp was similar to the final model for REE and included fat mass, FFM, and State U respiration, explaining 75% of the variance (Table 3, Model 4). No additional parameters, including race, entered either model.
TABLE 3 Stepwise multiple regression models for energy expenditure and VO₂max

| £²/P  | Intercept | Variable 1 | Variable 2 | Variable 3 |
|-------|-----------|------------|------------|------------|
|       | REE, kcal/d |           |            |            |
| Model 1 | 0.56 0.0001 | 341 | 14.3 × fat | 16.8 × FFM | −74 × race |
| Model 2 | 0.66 0.0001 | 264 | 17.9 × fat | 11.9 × FFM | 2.4 × State 4 |
| Model 3 | 0.68 0.0001 | 284 | 12.1 × fat | 20.4 × FFM | −162 × race |
| Model 4 | 0.75 0.0001 | 80  | 16.4 × fat | 14.5 × FFM | 0.68 × State U |
| Model 5 | 0.62 0.0001 | −498 | 56 × FFM | −474 × race | 42 × PAI/×, min |
| Model 6 | 0.65 0.0001 | −874 | 94 × mito density | 41.6 × FFM | 2.2 × State 3 |

Energy expenditure Models 1 and 3 include 19 AAW and 22 CW, Model 2 includes 18 AAW and 20 CW, and Model 4 includes 18 AAW and 17 CW. VO₂max Model 5 includes 22 AAW and 22 CW, while Model 6 includes 20 AAW and 19 CW.

When forcing race in the model for REE (Model 2), the parameter estimate for race was eliminated (14 ± 49 kcal/d; £ = 0.78) compared with that observed in Model 1 (−74 ± 46 kcal/d; £ = 0.12).

Forcing race in the model for the energy expenditure during the clamp (Model 4) eliminated the significant race effect (−28 ± 50 kcal/d; £ = 0.60) observed in Model 3 (−162 kcal/d; £ < 0.0002).

Modeling VO₂max

When all subjects were combined, hemoglobin levels, hours being sedentary, proportion of type I and type II muscle fibers, mitochondrial density, State 4 respiration, maximal State 3 respiration, and State U respiration were significantly correlated with VO₂max adjusted for FFM (Table 2). There was no significant racial difference in the relationship between VO₂max and State 3 respiration between AAW and CW (Figure 2B; slopes: £ = 0.70; intercepts: £ = 0.93).

To identify the most important contributing factors to the racial difference in VO₂max, we conducted regression analyses. When including race, body composition, hemoglobin levels, and physical activity variables in a stepwise multiple regression, FFM was the first variable to enter the model, explaining 33% of the variance (£ < 0.0001), followed by race, explaining 21%, and daily minutes of physical activity, which explained 7% of the variance (Table 3, Model 5). None of the other potential variables entered the model.

When also including skeletal muscle characteristics, mitochondrial density was the first parameter to enter the model, followed by FFM and then maximal State 3 respiration (Table 3, Model 6). Physical activity did not enter this model, and there was no longer a significant race effect (£ = 0.13). When also including race in Model 6, the parameter estimate for race was reduced by 64% (−171 ± 110 mL vs. −474 ± 49 mL oxygen per minute compared with that observed in Model 5).

Parameters associated with thermogenic response

We found that the only parameter significantly correlated with the increase in energy expenditure during the clamp was peripheral insulin sensitivity (£ = 0.40; £ < 0.01) (20). There was a suggestion of a relationship with nonoxidative glucose disposal (20), but this association did not quite reach significance (£ = 0.30; £ = 0.061). There was no significant association between mitochondrial respiration and the increase in energy expenditure during the clamp (State 3, £ = 0.13; £ = 0.42; State U, £ = 0.22; £ = 0.21).

Discussion

A lower energy expenditure and VO₂max have been consistently reported in AAW compared with CW (5-9,13), but the reasons for these differences have not been entirely understood. We have previously demonstrated that lower mitochondrial respiration was associated with lower peripheral glucose uptake in the AAW in this study (20). The primary goal of the present report was to examine whether
skeletal muscle oxidative capacity explains the lower energy expenditure and VO₂max in AAW. We demonstrate that it does. Racial differences in body-composition-adjusted energy expenditure and VO₂max were no longer present when also adjusting for mitochondrial respiration.

A strength of our study is that we measured energy expenditure both at rest (at which individuals spend only a fraction of their day) and during an insulin and glucose infusion (hyperinsulinemic-euglycemic clamp), which provided interesting insights. For example, the racial difference in adjusted (FFM and fat mass) energy expenditure during the clamp (−162 ± 40 kcal/d; P < 0.0001) was more than twofold greater than observed with the preclamp REE (−74 ± 46; P = 0.12). The racial differences in energy expenditure were eliminated after the inclusion of mitochondrial respiration in the models.

One parameter that we explored regarding the racial difference in VO₂max is the level of habitual physical activity. However, objectively assessed physical activity was similar in AAW and CW and, therefore, could not explain this racial difference. Another parameter that we explored was the mitochondrial oxidative capacity of skeletal muscle, which has previously been shown to be highly correlated with VO₂max (18,19,28,29). The present work now demonstrates that the racial difference in VO₂max disappears after adjusting for mitochondrial content and respiration. Furthermore, after adjusting for FFM and mitochondrial content, a racial difference was still evident (P < 0.01). However, when also including mitochondrial respiration (explaining 17% of the variance, Model 6), the significant racial difference in VO₂max was eliminated.

The etiology of the lower mitochondrial respiration in AAW is yet to be elucidated. One possibility is that this is due to genetic differences. A substantial portion of the variability in REE has been attributed to genetic influences independent of body composition, age, and gender (30,31). European ancestry admixture in African Americans has been shown to be strongly associated with higher REE (32). Furthermore, differences in mitochondrial DNA may play a role. Common African mitochondrial DNA haplogroups have been associated with lower REE (21). Mitochondrial DNA sequence variation has also been shown to be associated with free-living activity energy expenditure (33). These observations suggest that genetic factors might explain the lower mitochondrial oxidative capacity and, indirectly, the lower VO₂max and REE in AAW.

An additional novel finding from our study is that a thermogenic response to insulin and glucose infusion during the course of a hyperinsulinemic-euglycemic clamp was observed in CW but not in AAW. A thermogenic response has been reported in Caucasians without obesity by using a similar insulin infusion rate (34-36). However, in Pima Indians without obesity, no thermogenic response was observed (35), showing considerable similarity with our findings in AAW. At least part of the increase in energy expenditure during a clamp has been attributed to glucose storage as glycogen, an energy requiring process (34-36). We have previously shown that lean AAW had lower insulin sensitivity and lower nonoxidative glucose disposal than CW (20). We now show that insulin sensitivity was significantly correlated with the increase in energy expenditure during the clamp. Therefore, at least part of the blunted response in energy expenditure observed in AAW may be a consequence of insulin resistance in skeletal muscle.

A limitation of our study is that we included only women. This deliberate choice was because women show a greater racial disparity for the prevalence of obesity (odds ratio 2.26 in women vs. 1.13 in men) (37) and diabetes incidence (2.4-fold in women vs. 1.5-fold in men) (38). Our data cannot be unequivocally extended to men, but it is worth noting that a lower REE has been reported in African American men (39). Whether African American men share similar mitochondrial characteristics needs further research.

In summary, the lower energy expenditure and VO₂max observed in AAW compared with CW are at least partially explained by differences in the mitochondrial oxidative capacity of skeletal muscle. In addition, we report the novel finding that the thermogenic effect of infused insulin and glucose that is observed in CW is not observed in AAW. Additional research is needed to determine whether low skeletal muscle mitochondrial respiration and decreased thermogenesis are predisposing risk factors for weight gain in AAW.

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