High-intensity interval training without weight loss improves exercise but not basal or insulin-induced metabolism in overweight/obese African American women

Avigdor D. Arad, Fred J. DiMenna, Naketa Thomas, Jacqueline Tamis-Holland, Richard Weil, Allan Geliebter, and Jeanine B. Albu

1The New York Obesity Nutrition Research Center, Mt. Sinai St. Luke's Hospital, New York, New York; and 2Teachers College, Department of Biobehavioral Sciences, Columbia University, New York, New York

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DURING FASTING AND OTHER CONDITIONS where blood glucose concentration must be protected, glucose oxidation is reduced and fat oxidation is increased to provide sufficient acetyl-CoA for the tricarboxylic acid cycle (49). Conversely, during postprandial conditions or when hyperglycemic stimuli are experimentally induced, carbohydrate utilization increases and fat catabolism is suppressed (37). This ability to shift between carbohydrate and fat as fuel (i.e., “metabolic flexibility”) is an important characteristic of healthy function that requires sensitivity to the actions of insulin. Consequently, it is not surprising that metabolic flexibility is reduced when insulin resistance is present with obesity (37). For example, the fasting rate of fat oxidation is lower in skeletal muscle of obese compared with lean subjects (37), and obese subjects also lack the ability to shift to the appropriate fuel after imposition of a eucaloric high-fat diet (59, 62) and during insulin-stimulated conditions (i.e., when rate of fat oxidation should increase and decrease, respectively) (37). There is growing research interest in this “metabolic inflexibility” because of its link to weight gain (65) and the pathogenesis of insulin resistance and Type 2 diabetes (37, 62).

Weight loss by dietary and/or surgical intervention increases insulin sensitivity in obese subjects with or without diabetes (25, 27, 34, 37, 47). However, the flexibility required to increase fat catabolism during fasting or when dietary fat intake is increased is not restored by weight loss (2, 37). Furthermore, compared with matched controls, formerly obese subjects exhibit lower rates of fat oxidation at rest and during recovery from moderate-intensity exercise despite similar rates of fat mobilization (50). Collectively, these findings are consistent with the contention that a mitochondrial defect might be responsible for dysfunctional fat metabolism that is associated with obesity and the pathophysiology of insulin resistance (37, 56).

The chronic performance of endurance exercise (i.e., “endurance training”) increases the activity of mitochondrial enzymes and genes involved in mitochondrial biogenesis (59). These adaptations imply an enhanced ability for muscle mitochondria to oxidize fat, and indeed for healthy subjects, endurance training improves insulin sensitivity in untrained healthy young adults (58) and ameliorates age- and disease-related declines in healthy elderly subjects (54) and individuals with impaired glucose tolerance and/or obesity (9, 12, 15), respectively. Furthermore, Goodpaster et al. (26) found that in conjunction with caloric reduction, endurance training increases the fasting rate of fat oxidation in obese subjects with the favorable change being the strongest predictor of improved insulin sensitivity. Similarly, endurance training improves fasting fat oxidation in older obese subjects with impaired glucose tolerance (57) and nonobese subjects with Type 2 diabetes (61). However, the ability of endurance training to increase fasting fat utilization might depend upon the intensity/volume of exercise, the severity of pathological progression, and/or whether caloric restriction and weight loss accompany training (26, 43).
From a traditional standpoint, endurance training involves rhythmic contractions of a significant portion of the body’s large muscle groups at a sustainable percentage of the maximal voluntary contraction (i.e., “aerobic exercise”). However, endurance training has recently been redefined by a “new” protocol comprising relatively short bouts of high-intensity exertion interspersed with periods of low-intensity exercise or rest. This “high-intensity interval training” (HIIT), which has typically been reserved for athletes, has been shown to also be appropriate for untrained individuals because of its time efficient nature and ability to improve cardiorespiratory fitness, for example, increase the maximal rate of oxygen consumption ($V_{O2max}$), the standard index of cardiorespiratory fitness (4), and lactate threshold (LT), the threshold that demarcates the moderate and heavy exercise intensity domains (13). There is also a growing body of research which suggests that HIIT is both safe and effective in the clinical setting (28, 41). Interestingly, HIIT-induced cardiorespiratory adaptations appear to be specifically attributable to increased muscle mitochondrial capacity (23, 42); therefore, it is not surprising that HIIT improves insulin sensitivity in normal-weight individuals (3). However, findings regarding the effect of HIIT on insulin sensitivity in overweight/obese subjects have been mixed (14, 24, 31), and the effects of HIIT on metabolic flexibility in overweight/obese subjects has not been investigated.

The purpose of the present randomized controlled clinical trial was to determine the effect of a 14-wk HIIT intervention with weight stability on metabolic flexibility, insulin sensitivity, and cardiorespiratory fitness in sedentary, premenopausal, nondiabetic, overweight/obese African American (AA) women. We chose this subject population because AA women have a higher incidence of obesity (39) and metabolic inflexibility (7) and lower cardiorespiratory fitness (e.g., $V_{O2max}$ and LT) (40, 52), peripheral insulin sensitivity, and mitochondrial capacity (17) compared with their white counterparts. AA women are also less physically active, with time constraints being the most frequently cited reason (18). Collectively, these distinctions make this subject population appropriate candidates for an intervention that halts the progression of the diabetic pathophysiology, improves cardiorespiratory fitness, and is both time efficient and more enjoyable to perform (5). We hypothesized that compared with control subjects only exposed to pre/post testing, HIIT-trained subjects would exhibit 1) improved metabolic flexibility due to increased postabsorptive fat oxidation and insulin-stimulated fat suppression, 2) improved insulin sensitivity, and 3) increased $V_{O2peak}$ gas exchange threshold (GET), a noninvasive measurement that approximates LT, and exercise tolerance.

METHODS

Subjects. After initial screening and assessment, 28 healthy, premenopausal (age, 20-40 yr), sedentary (exercise frequency/duration, ≤3 times/wk, 60 min/session), nondiabetic (fasting blood glucose, <110 mg/dl), overweight/obese (BMI, >25 kg/m²) AA women volunteered to participate in this randomized controlled clinical trial. Experimental procedures were submitted to and approved by the St. Luke’s Roosevelt Institute for Health Science Institutional Review Board, and all subjects gave their written informed consent prior to commencement of the study after procedures, associated risks, and potential benefits of participation had been explained. Subjects were considered for inclusion only if they self-reported that all four grandparents were AA. Initial screening required subjects to complete a comprehensive medical history and physical activity questionnaire. Exclusion criteria included 1) weight change >±2 kg within the past 3 mo, 2) taking any medications that might affect insulin or fat metabolism (including oral contraceptives), 3) smoking within the past 6 mo, 4) consuming ≥2 oz ethanol per day, and/or 5) having irregular menstrual cycles (e.g., skipping >2 monthly cycles per year). Subjects who passed this initial screening underwent a full physical examination, which included blood work, resting ECG, and oral glucose tolerance test (OGTT) to ensure absence of diabetes (2-h OGTT plasma glucose, <140 mg/dl), hyperlipidemia (fasting plasma triglycerides, <350 mg/dl and total cholesterol <300 mg/dl), and other chronic illnesses that might affect their capacity to exercise. Eligible subjects were then required to perform a step-incremental cycling test (see below), and ECG was recorded so that subjects displaying an abnormal exercise response could also be excluded from participation. The flow of participants throughout this process is depicted in Fig. 1.

Experimental design. Subjects performed a step-incremental cycling test for determination of $V_{O2peak}$, GET, and limit of tolerance ($T_{max}$) prior to the intervention phase of the study. All subjects completed the same incremental test following the intervention phase, and in both cases this test and measurement of resting metabolic rate (RMR) was done prior to a 10-day controlled feeding period (see below). A timeline depicting this series of events is presented in Fig. 2. Pre- and postintervention testing following the 10-day controlled feeding period included measurements of body composition, insulin sensitivity, and substrate utilization. Upon completion of this testing prior to the intervention phase, subjects were randomly assigned to a HIIT or a control group (CON). The intervention phase lasted ~14 wk, during which HIIT completed a supervised endurance training intervention (see below) while CON maintained their normal level of physical activity. Both groups received careful monitoring and dietary counseling by a registered dietician to ensure weight stability throughout the course of the study. With respect to the controlled feeding period, subjects completed the Paffenbarger Physical Activity Questionnaire both prior to and following the intervention phase to account for differences in physical activities of daily living (48). Pre- and postintimal sensitivity was assessed during the follicular phase of the menstrual cycle.

Resting metabolic rate. Following screening and prior to the step-incremental test, subjects had their RMR measured by indirect calorimetry. Subjects reported to the laboratory between 7:00 and 9:00 AM after a 12-h overnight fast and remained stationary in a supine position for 20 min. Exhaled air was then continuously sampled for 40 min with a ventilated hood system (Vmax Encore, VIASYS Healthcare, Yorba Linda, CA) to determine the rates of oxygen consumption ($V_{O2}$) and carbon dioxide production ($V_{CO2}$). $V_{O2}$ and $V_{CO2}$ were averaged for the final 30 min of testing, and these averages were used to determine RMR, fat oxidation rate (FO), and carbohydrate oxidation rate (CO) with the following stochiometric equations (11, 19):

$$\text{RMR} = \left[ (3.58 \times V_{O2}) + (1.448 \times V_{CO2}) - 0.002 \right] \times 4.184 \times 1440 \quad (1)$$

$$\text{FO} = (1.67 \times V_{O2}) - (1.67 \times V_{CO2}) \quad (2)$$

$$\text{CO} = (4.55 \times V_{CO2}) - (3.21 \times V_{O2}) \quad (3)$$

where $V_{O2}$ and $V_{CO2}$ are expressed in liters/min, RMR is expressed in kJ/day, and FO and CO are expressed in g/min. For postintervention RMR, this procedure was repeated on week 12 of the intervention period ≥48 h following an exercise session.

Step-incremental cycling test. Before and after the intervention phase, subjects performed a step-incremental cycling test to limit of tolerance on an electronically braked cycle ergometer (Monarch, 828E, Hasbro, Sweden). For HIIT postintervention, this test took place at least 48 h following an exercise session. After 3 min of
unloaded “warm-up” cycling, work rate (WR) was increased to 25 W and subjects cycled for 2 min at a self-selected cadence (50–70 rpm), after which WR was increased by 15 W per 2-min stage until the limit of tolerance. During these tests, pulmonary gas exchange and ventilation were measured breath by breath with open-circuit spirometry (same system as RMR measurement; see above). The gas analyzers were calibrated before each test with gases of known concentration, and the turbine volume transducer was calibrated with a 3-liter syringe. Gas exchange and ventilatory data were collected continuously and averaged over consecutive 10-s periods. Heart rate and cardiac function were also recorded continuously via electrocardiogram (Marquette Electronics, MAC VU, Milwaukee, WI), and blood pressure was measured every 2 min to ensure normal physiological responses.

Exercise performance parameters. \( \dot{V}O_{2peak} \) was defined as the highest 30-s rolling mean \( \dot{V}O_2 \) value attained prior to termination of the incremental test. The WR attained during the final stage (WR\(_{peak}\)) and time to limit of tolerance (T\(_{lim}\)) was recorded. We also determined the time for which \( \dot{V}O_2peak \) could be maintained (t\(_{\dot{V}O_{2peak}}\)) by calculating the duration for which 10-s mean \( \dot{V}O_2 \) values lying within one standard deviation (in relation to the corresponding 30-s rolling mean) of \( \dot{V}O_{2peak} \) appeared consistently (i.e., with \( \leq 1 \) value not satisfying the criterion appearing consecutively). GET was determined by consensus from a panel of independent reviewers experienced at making the determination from a cluster of measurements, including 1) the first disproportionate increase in \( \dot{V}CO_2 \) from visual inspection of individual plots of \( \dot{V}CO_2 \) vs. \( \dot{V}O_2 \), 2) an increase in expired ventilation (\( \dot{VE}/\dot{V}O_2 \)) with no increase in \( \dot{VE}/\dot{V}CO_2 \), and 3) an increase in end-tidal O\(_2\) tension with no fall in end-tidal CO\(_2\) tension. Once determined, GET was expressed as a metabolic rate both in absolute (i.e., \( \dot{V}O_2 \) in liters/min) and relative (to \( \dot{V}O_{2peak} \)) terms. Finally, \( \dot{V}O_2 \) and \( \dot{V}CO_2 \) were averaged over the final 20 s of each 2-min stage, and these \( \dot{V}O_2 \) values were used to determine the \( \dot{V}O_2/WR \) slope via linear regression with the fitting window constrained to all stages that were completed.

Controlled feeding period. The pre- and postintervention RMR estimates for each subject (see above) were used to construct a weight-maintaining high-fat diet (50% fat, 35% carbohydrate, 15% protein) with energy content = RMR \( \times \) 1.5 (NDSR software) \( ^{1} \). This diet was designed to promote maximal stimulation of fat oxidation with weight maintenance \( ^{7} \). A Registered Dietician devised the diet for each subject with consideration given to food preferences, allergies and intolerances and all food was provided free of charge for participants. Following the incremental cycling test before and after the intervention phase, subjects ingested this diet during a 10-day controlled feeding period that preceded insulin sensitivity and substrate utilization measurements (see below). The subjects were provided with the foods needed to eat at home for 8 days. On day 9, subjects reported to the Clinical Research Center and, beginning at 7:00 AM, had their 24-h energy expenditure (TEE\(_{24}\)) measured by wholebody room calorimetry (metabolic chamber, St. Luke’s-Roosevelt Obesity Research Center, New York, NY). To ensure eucaloric energy balance and, therefore, weight stability, dietary modifications were made in accordance with this measured value prior to subsequent measurements. Because of concerns regarding “detraining” of the chronic adaptive response for HIIT subjects, postintervention insulin sensitivity and substrate utilization measurements were performed 72 h following the final training session. Consequently, subjects began the 10-day controlled feeding period 7 days prior to the final training session so that the measurement of TEE\(_{24}\) on day 9 (see above) was

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**Fig. 1.** CONSORT diagram depicting the flow of participants through the various stages of this randomized controlled clinical trial. HIIT, high-intensity interval training group; CON, no-exercise control group.

**Fig. 2.** Pre- and postintervention testing protocol that was employed in this study. RMR, measurement of resting metabolic rate; INC, incremental cycling test to limit of tolerance; TEE\(_{24}\), measurement of 24-h energy expenditure; DXA, measurement of body composition by dual X-ray absorptiometry; MRI, measurement of body composition by whole multislice MRI; Clamp, measurement of insulin sensitivity and substrate utilization by euglycemic-hyperinsulinemic clamp.
done 48 h following the final training session. CON subjects were tested according to the same timeline, which is depicted in Fig. 2.

**Body composition measurements.** Prior to the 10-day controlled feeding period, subjects had their body mass (Weight Tronix, New York, NY) and height (Holtain Stadiometer, Crosswell, UK) measured to the nearest 0.1 kg and 0.5 cm, respectively. Subjects wore a hospital gown and undergarments for this assessment. Subjects were instructed to carefully monitor their body mass throughout the feeding period and report any changes that they experienced. Dietary adjustments were made for changes more than ±2 kg. Measurements on day 9 of the controlled feeding period also included fat mass, fat-free mass and percent body fat [dual X-ray absorptiometry (DXA)], and total body skeletal muscle and site-specific adipose tissue (wholebody multislice MRI) (1). Body mass was also measured weekly throughout the intervention phase.

**Insulin sensitivity measurement.** Following the controlled feeding period after an overnight fast, subjects were assessed before (i.e., in the postabsorptive state) and during a 3-h euglycemic-hyperinsulinemic clamp. During this procedure, blood samples were collected at 10-min intervals during the postabsorptive and steady-state conditions, and these samples were immediately centrifuged, aliquoted, and frozen at −80°C. Plasma insulin concentration was measured by radioimmunoassay (Linco Research, St. Charles, MO), glucose concentration was assessed by the glucose-oxidase method (Beckman Glucose Analyzer, Fullerton, CA), and the concentration of free fatty acids (FFA) was determined by the enzymatic colorimetric method (Wako Chemicals USA, Richmond, VA). FFA suppression was calculated as the difference between FFA at hyperinsulinemic steady state and FFA during the postabsorptive condition expressed as a percent change relative to the latter. Insulin clearance (IC) was calculated as the ratio of the difference in insulin concentration between hyperinsulinemic steady-state and postabsorptive conditions vs. the rate of insulin infusion during the procedure (80 mU·m⁻²·min⁻¹) (16). Wholebody glucose disposal rate was determined and expressed relative to FFM (M), after which insulin sensitivity index (i.e., M adjusted for steady-state plasma insulin level; M/I) was calculated.

**Substrate utilization measurements.** As was the case for RMR, the ventilated hood system was used to perform indirect calorimetry during the postabsorptive and hyperinsulinemic steady-state conditions of the euglycemic clamp. For both conditions, subjects were supine and awake. 

<table>
<thead>
<tr>
<th>Work Interval</th>
<th>75% HRR</th>
<th>80% HRR</th>
<th>85% HRR</th>
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<tr>
<td>30 s</td>
<td>45 s</td>
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<tr>
<th>Rest Interval</th>
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<th>5</th>
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**High-intensity interval training intervention.** For the experimental group, the intervention phase involved HIIT sessions performed three times per week for ~14 wk. (Note: to ensure that postintervention testing was done during the follicular phase of a subject’s menstrual cycle, the intervention phase was shortened to 13 wk or extended to 15 wk if necessary.) All sessions were supervised by an exercise physiologist. The total duration of each session was 24 min. Intensity of training was monitored via heart rate response based on a percentage of heart rate reserve (HRR), the difference between the maximal and resting heart rates that were measured during the preintervention incremental test. Each HIIT session began with 6 min of warm-up cycling at 50% HRR after which four work intervals (30–60 s at 75–90% HRR) were performed with recovery intervals (180–210 s at 50% HRR) interspersed. Following the final work interval, 5 min of “cool-down” cycling was performed. Progressive overload was applied over the course of the intervention by manipulating both work interval intensity and work/recovery ratio (see Fig. 3).

**Statistical analysis.** An independent t-test was used to assess differences between HIIT and CON prior to the intervention phase. A 2 × 2 (time by group) repeated-measures ANOVA was employed to determine the effects of the training intervention on the parameters of interest. Significant effects were further evaluated by post hoc t-tests with the alpha level adjusted via a Fisher’s LSD correction. Data are presented as means ± SD. Statistical significance was accepted when P < 0.05.

**RESULTS**

Fourteen subjects were assigned to HIIT and fourteen subjects were assigned to CON; however, five members of HIIT and three members of CON did not complete the study (see Fig. 1). The data of these subjects, therefore, were excluded from analysis. Reasons for these dropouts were 1) the disruption caused by Hurricane Sandy (HIIT, n = 2), 2) an inability to satisfy time commitments (HIIT, n = 3; CON, n = 1), 3) dissatisfaction with the no-exercise/weight management requirements for the group (CON, n = 1), and 4) relocation (CON, n = 1). Preintervention data for the subjects that did complete the study for HIIT (age, 29 ± 4 yr; fasting blood glucose, 88 ± 13 mg/dl; 2-h OGTT, 104 ± 28 mg/dl; n = 9) and CON (age, 30 ± 7 yr; fasting blood glucose, 93 ± 7 mg/dl; 2-h OGTT, 106 ± 15 mg/dl; n = 11) are presented in Tables 1–3. Physical activities of daily living (Paffenbarger scale) were similar between groups prior to the intervention phase and the values were consistent with what would be expected...
for sedentary subjects (HIIT, 831 ± 389 kcal/wk; CON, 679 ± 466 kcal/wk). There were also no significant differences in age, fasting blood glucose, 2-h OGTT, RMR, TEE24, body mass or measures of body composition, exercise performance (except for \( V_{\text{O2peak}} \) in liters/min and \( V_{\text{O2peak}} \), \( P < 0.05 \); see Table 3), insulin sensitivity, or substrate utilization (\( P > 0.05 \); Tables 1–3). All subjects fully complied with dietary consultations and weekly weighing throughout the course of the study, and all nine members of HIIT completed 100% of the training that was prescribed (eight in an uninterrupted manner, one with a 3-wk hiatus interspersed). However, two subjects in CON did not undergo pre- or postintervention clamp testing (veins inaccessible for infusion), two subjects in HIIT did not undergo postintervention MRI testing (discouraged because of discomfort experienced during pretest), and one subject in HIIT did not undergo postintervention exercise testing (ill the day the test was scheduled and subsequently left the country). Furthermore, because of poor data collection, the exercise-testing data of another HIIT subject could not be used. Consequently, data presented for measurements derived during these tests are based on \( n = 9 \) for CON (MRI and clamp testing) and \( n = 7 \) for HIIT (exercise testing).

**Body composition.** Group means ± SD for body composition measurements are presented in Table 1. As per the experimental design, body mass did not change in either group during the course of the study. Fat mass, fat-free mass and percent body fat also did not change significantly in either group. The volume of visceral adipose tissue was decreased in the HIIT group (\( P < 0.05 \)); however, neither the volume of skeletal muscle or subcutaneous, intramuscular, or total adipose tissue was altered by training. There was no change in any tissue volume measures in CON.

**Table 2.** Insulin-sensitivity and substrate utilization measurements pre- and postintervention for the HIIT and CON groups

<table>
<thead>
<tr>
<th></th>
<th>HIIT Pre</th>
<th>HIIT Post</th>
<th>CON Pre</th>
<th>CON Post</th>
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<tr>
<td>Insulin sensitivity</td>
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<tr>
<td>IC, m(\text{ml} \cdot \text{BSA}^{-1} \cdot \text{min}^{-1})</td>
<td>368 ± 42</td>
<td>355 ± 36</td>
<td>404 ± 73</td>
<td>393 ± 92</td>
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<td>M, mg(\text{min}^{-1} \cdot \text{kg}^{-1} \cdot \text{FFM})</td>
<td>14.1 ± 2.5</td>
<td>16.6 ± 4.3</td>
<td>15.2 ± 2.7</td>
<td>16.8 ± 4.4</td>
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<tr>
<td>M/L, mg(\text{min}^{-1} \cdot \text{kg}^{-1} \cdot \text{FFM} \cdot \text{mU} \cdot \text{ml}^{-1})</td>
<td>0.06 ± 0.01</td>
<td>0.07 ± 0.03</td>
<td>0.08 ± 0.02</td>
<td>0.08 ± 0.02</td>
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<tr>
<td>FFA suppression, %</td>
<td>96.5 ± 1.4</td>
<td>96.8 ± 1.9</td>
<td>96.5 ± 1.9</td>
<td>94.9 ± 3.7</td>
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<tr>
<td>Postabsorptive substrate utilization</td>
<td></td>
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<tr>
<td>NPRER(_{PA})</td>
<td>0.79 ± 0.02</td>
<td>0.80 ± 0.04</td>
<td>0.81 ± 0.04</td>
<td>0.80 ± 0.03</td>
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<tr>
<td>FO(_{PA}), mg(\text{min}^{-1} \cdot \text{kg}^{-1} \cdot \text{FFM})</td>
<td>1.36 ± 0.25</td>
<td>1.34 ± 0.35</td>
<td>1.39 ± 0.43</td>
<td>1.45 ± 0.39</td>
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<tr>
<td>CO(_{PA}), mg(\text{min}^{-1} \cdot \text{kg}^{-1} \cdot \text{FFM})</td>
<td>1.60 ± 0.39</td>
<td>1.69 ± 0.64</td>
<td>1.92 ± 0.53</td>
<td>1.75 ± 0.56</td>
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<tr>
<td>Hyperinsulinemic substrate utilization</td>
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<td></td>
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<tr>
<td>NPRER(_{IS})</td>
<td>0.93 ± 0.04</td>
<td>0.95 ± 0.07</td>
<td>0.93 ± 0.05</td>
<td>0.93 ± 0.05</td>
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<tr>
<td>FO(_{IS}), mg(\text{min}^{-1} \cdot \text{kg}^{-1} \cdot \text{FFM})</td>
<td>0.49 ± 0.26</td>
<td>0.37 ± 0.43</td>
<td>0.47 ± 0.37</td>
<td>0.49 ± 0.37</td>
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<tr>
<td>CO(_{IS}), mg(\text{min}^{-1} \cdot \text{kg}^{-1} \cdot \text{FFM})</td>
<td>4.27 ± 0.82</td>
<td>4.75 ± 1.16</td>
<td>4.49 ± 2.18</td>
<td>4.78 ± 1.28</td>
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<td>Metabolic flexibility</td>
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<td>(\Delta\text{NPRER})</td>
<td>0.14 ± 0.04</td>
<td>0.15 ± 0.06</td>
<td>0.13 ± 0.05</td>
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<tr>
<td>Exercise substrate utilization</td>
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<tr>
<td>NPRER(_{40})</td>
<td>0.93 ± 0.08</td>
<td>0.84 ± 0.06*</td>
<td>0.85 ± 0.06</td>
<td>0.91 ± 0.08</td>
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<td>FO(_{40}), mg(\text{min}^{-1} \cdot \text{kg}^{-1} \cdot \text{FFM})</td>
<td>2.18 ± 2.66</td>
<td>4.42 ± 2.82</td>
<td>2.81 ± 1.13</td>
<td>1.81 ± 2.17</td>
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<tr>
<td>CO(_{40}), mg(\text{min}^{-1} \cdot \text{kg}^{-1} \cdot \text{FFM})</td>
<td>16.33 ± 8.12</td>
<td>10.01 ± 5.65*</td>
<td>8.49 ± 5.14</td>
<td>12.74 ± 7.75</td>
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</table>

Values are means ± SD. IC, insulin clearance; M, wholebody glucose disposal rate adjusted for FFM; M/L, wholebody glucose disposal rate adjusted for steady-state plasma insulin level; FFA, free fatty acid; \(\Delta\text{NPRER}\), difference in nonprotein respiratory exchange ratio between postabsorptive and insulin-stimulated conditions of the euglycemic-hyperinsulinemic clamp; FO, fat oxidation; CO, carbohydrate oxidation; subscript PA, postabsorptive; subscript IS, insulin stimulated; subscript 40, cycling at 40 W. *Significant group-by-time interaction for reduction in HIIT (\( P < 0.05 \)).
Insulin sensitivity. Group means ± SD for insulin sensitivity measurements are presented in Table 2, and individual subject responses are depicted in Fig. 4A. There was no group-by-time interaction for the increase in insulin sensitivity that occurred during the intervention phase. IC and FFA suppression during the insulin-stimulated condition were not significantly altered during HIIT or CON.

Substrate utilization measurements. Group means ± SD for substrate utilization estimates during both conditions of the hyperinsulinemic clamp (postabsorptive and insulin stimulated, respectively) and the 40-W stage of the incremental test (i.e., the highest WR for which all subjects were exercising below GET) are provided in Table 2. During the clamp procedure, there were no significant pre/post differences in either postabsorptive or insulin-stimulated NPRER, FO, or CO for either group. Consequently, metabolic flexibility (i.e., ΔNPRER) was unaltered by training (see Table 2 and Fig. 4B). However, during the exercise condition, there was a significant group-by-time interaction for NPRER and CO for the 40-W work rate (P < 0.05), and follow-up analysis revealed that NPRER and CO were reduced in HIIT, but not in CON. FO at 40 W posttraining was unaltered by HIIT (P = 0.06).

Exercise performance. Exercise performance parameters are provided in Table 3. A significant group-by-time interaction was observed for WRpeak and Tlim (Fig. 5) and also for tV̇O2peak, GET absolute and GET relative (P < 0.05). Follow-up analysis revealed that these exercise performance parameters were significantly increased in HIIT, but not in CON (Table 3). Conversely, there was no significant group-by-time interaction for V̇O2peak stated in absolute terms (Fig. 5) or when stated relative to total body or fat-free mass. There was also no change in either group for V̇O2/WR slope.

Table 3. Exercise performance parameters pre and postintervention in the HIIT and CON groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HIIT Pre</th>
<th>HIIT Post</th>
<th>CON Pre</th>
<th>CON Post</th>
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<tbody>
<tr>
<td>V̇O2peak, liters/min</td>
<td>2.18 ± 0.47†</td>
<td>2.30 ± 0.45</td>
<td>1.68 ± 0.49</td>
<td>1.78 ± 0.48</td>
</tr>
<tr>
<td>V̇O2peak, ml·min⁻¹·kg⁻¹</td>
<td>23.1 ± 4.9</td>
<td>24.9 ± 5.5</td>
<td>19.7 ± 6.3</td>
<td>20.9 ± 6.6</td>
</tr>
<tr>
<td>V̇O2peak, ml·min⁻¹·kg⁻¹·FFM</td>
<td>42.1 ± 7.1</td>
<td>45.1 ± 9.1</td>
<td>35.1 ± 10.3</td>
<td>37.6 ± 9.9</td>
</tr>
<tr>
<td>WRpeak, W</td>
<td>139 ± 15</td>
<td>156 ± 26*</td>
<td>137 ± 18</td>
<td>133 ± 22</td>
</tr>
<tr>
<td>Tlim, s</td>
<td>987 ± 146</td>
<td>1124 ± 202*</td>
<td>972 ± 146</td>
<td>931 ± 173</td>
</tr>
<tr>
<td>tV̇O2peak, s</td>
<td>41 ± 12†</td>
<td>86 ± 40*</td>
<td>76 ± 35</td>
<td>58 ± 25</td>
</tr>
<tr>
<td>GET absolute, liters/min</td>
<td>0.97 ± 0.23</td>
<td>1.29 ± 0.34*</td>
<td>0.87 ± 0.35</td>
<td>0.91 ± 0.37</td>
</tr>
<tr>
<td>GET relative, %V̇O2peak</td>
<td>45 ± 6</td>
<td>56 ± 7*</td>
<td>51 ± 15</td>
<td>50 ± 12</td>
</tr>
<tr>
<td>V̇O2/WR slope, ml·min⁻¹·W⁻¹</td>
<td>12.9 ± 2.6</td>
<td>13.3 ± 3.7</td>
<td>10.4 ± 5.0</td>
<td>9.9 ± 3.5</td>
</tr>
</tbody>
</table>

Values are means ± SD. V̇O2peak, peak rate of oxygen consumption; WRpeak, peak rate of work; Tlim, limit of tolerance; tV̇O2peak, time for which the peak rate of oxygen consumption could be maintained; GET, gas exchange threshold; V̇O2/WR slope, the slope of the relationship between rate of oxygen consumption and rate of work during incremental cycling. *Significant group-by-time interaction for increase in HIIT (P < 0.05). †Significant difference for preintervention values between groups (P < 0.05).
DISCUSSION

The main findings from this investigation are that a 14-wk HIIT intervention without body-weight loss improved metabolic performance during exercise, but not during basal and insulin-stimulated states, in sedentary, premenopausal, nondiabetic, overweight/obese AA women. Specifically, compared with control subjects who performed no-exercise training, HIIT subjects experienced reduced CHO oxidation and NPRER at the same absolute submaximal work rate and increased metabolic rate at GET after training. However, fuel oxidation and NPRER under basal and insulin-stimulated conditions during a euglycemic-hyperinsulinemic clamp were unaltered by HIIT, which means that the index we used to assess metabolic flexibility ($\Delta$NPRER) was not influenced by training. HIIT also improved exercise tolerance; however, $V_O^2_{peak}$ was unaffected. These results suggest that compared with the exercise condition, there is greater complexity associated with the metabolic characteristics of fasting and insulin stimulation as assessed in the present study, i.e., basal fat oxidation and insulin-stimulated glucose metabolism/FFA suppression at a saturating insulin dose, respectively. Consequently, these characteristics might only be altered when body-weight loss is also present.

Contrary to our hypothesis, HIIT did not improve insulin sensitivity in at-risk subjects who were not yet diabetic. This contrasts previous reports of improved insulin sensitivity after endurance training in overweight/obese subjects; however, a number of aspects of the present methodology might explain this discrepancy. For example, DeFronzo et al. (15) found increased insulin-mediated glucose metabolism in obese women with normal OGTT after 6 wk of traditional endurance training; however, posttraining clamp measurements were performed 48–72 h following the final training session. An acute effect of exercise on glucose disposal persists for ~72 h (38); therefore, this timing raises concerns that the observed effect might not reflect a chronic adaptation (55). However, it is also important to ensure that testing is performed prior to dissipation of a chronic effect; hence, in the present study, we chose to perform postraining measurements 72 h following the final training session in an attempt to avoid the former and include the latter. Questions have also been raised regarding the degree to which improvements are attributable to exercise training per se, as opposed to altered energy balance and subsequent weight loss that often accompanies it (54). Consequently, we rigorously controlled energy balance to ensure weight stability throughout the training intervention. Our results, therefore, are consistent with the notion that body-weight loss is a critical component that is required to induce a chronic improvement in insulin sensitivity. In support of this contention, Schenk et al. (53) report that reductions in systemic fatty acid mobilization/uptake due to weight loss play a primary role in increased insulin sensitivity, as the improvement is not amplified when exercise training that enhances the ability to oxidize fat is also part of the intervention.

The exercise program employed in the present investigation might also explain our findings. Most studies that have assessed the effect of exercise on insulin sensitivity have used traditional endurance training (i.e., sustainable exercise at a constant work rate for an extended period). However, heretofore, exercise program variables (e.g., intensity, duration, and volume of training) that optimize benefits have not been well defined. For example, a cross-sectional analysis across a wide range of ethnicities, ages, and glucose-metabolizing capacities revealed similar effects of nonvigorous and vigorous habitual...
activity on insulin sensitivity when energy expenditure was accounted for (44). This implicates total energy expenditure as opposed to intensity per se as the critical stimulus. Similarly, Houmard et al. (33) found that intensities ranging from 40 to 80% $V_\text{o2peak}$ are all sufficient to elicit an improvement; however, regardless of intensity, a training duration of $\sim 170$ min/wk induced a greater effect compared with $\sim 115$ min/wk. In contrast, Kang et al. (35) reported that when energy expenditure was matched, insulin sensitivity was improved following seven exercise sessions performed at 70% $V_\text{o2peak}$ for 50 min, but not 50% $V_\text{o2peak}$ for 70 min. The reason(s) for these discrepant findings is/are unclear, but might include lack of differentiation between acute and chronic effects and/or the method used to determine insulin sensitivity and/or characteristics of the subjects.

In the present investigation, we showed that a low-volume (3 sessions/wk $\times$ 4 work-bouts/session $\times$ 30–60 s/work-bout), high-intensity (75–90% HRR) interval training program did not improve insulin sensitivity in overweight/obese subjects using the clamp, which is the “gold standard” means of assessment (8). This contrasts previous reports of a “chronic” (i.e., at 72 h) improvement in insulin sensitivity in healthy normal-weight subjects after six sessions of SIT (sprint interval training), i.e., HIIT with work intervals performed with “all-out” effort using the clamp (51) and OGTT (3). However, for overweight/obese men, a similar SIT protocol elicited an acute effect at 24 h that was no longer present 48 h later (64). Previous investigations of the influence of HIIT on insulin sensitivity in overweight/obese subjects have also returned equivocal findings (14, 24, 31). Lack of effect in this case has been suggested to reflect a blunted response in females (24) and/or the influence of the diet that accompanied the training (21). Consequently, either of these factors alone or the two in concert might explain why our HIIT protocol did not improve insulin sensitivity in overweight/obese females who had their diets controlled so that they did not lose body weight during the intervention. However, with respect to the latter, it is interesting to note that HIIT subjects did experience an $\sim 16\%$ reduction in visceral adipose tissue, which should be linked to improved insulin sensitivity regardless of whether body-weight loss is also present (46). The reason(s) it was not is/are unclear, but might be related to our subject population as greater insulin resistance in AA compared with white women is not related to differences in any of the adipose tissue compartments, including the visceral region (1). Consequently, it is possible that a HIIT program like the present one without weight loss might benefit insulin sensitivity when a more “typical” profile is present (i.e., in populations where visceral adipose tissue plays a predominant role in insulin resistance).

In addition to assessing insulin sensitivity according to glucose disposal rate (both the absolute value and the absolute value adjusted for steady-state insulin level; i.e., $M$ and $M/I$, respectively), we also assessed insulin’s regulatory influence by measuring the metabolic flexibility observed when switching between conditions where fat and carbohydrate oxidation are preferred. We chose to quantify this capacity by calculating the difference in NPRER between postabsorptive and insulin-stimulated conditions of the clamp ($\Delta$NPRER) and, contrary to our hypothesis, no training-related improvement was observed. Indeed, neither postabsorptive nor insulin-stimulated substrate utilization were favorably altered by HIIT (see Table 2 and Fig. 4). This contrasts previous reports by Goodpaster et al. (26) who found that the combination of exercise training and body-weight loss for obese subjects increased both the insulin-stimulated capacity for glucose utilization and the ability to oxidize fat in the basal state. Importantly, improvement of the latter was associated with increased insulin sensitivity, which highlights the critical influence of insulin action with regard to functional fuel switching.

There are a number of differences between our methodology and that employed in the study of Goodpaster et al. (26) that might explain the discrepant findings regarding postabsorptive and insulin-stimulated substrate oxidation. As previously mentioned, Goodpaster et al. (26) combined exercise with weight loss induced by dietary intervention. This is important because Solomon et al. (56) found that after 12 wk of moderate-intensity endurance training, postabsorptive fat oxidation was increased when accompanied by a hypocaloric, but not a eucaloric diet. Similarly, there is no acute effect of eucaloric exercise on fat oxidation (45). Therefore, the lack of effect of HIIT on postabsorptive fat oxidation in the present study might be related to the weight stability aspect of our methodology. However, it is important to note that the obese subjects trained by Solomon et al. (57) had impaired glucose tolerance, which was not the case for our subjects. Moreover, both interventions employed in that study improved insulin sensitivity; therefore, body-weight loss was not required in addition to exercise to elicit an effect. Collectively, this suggests that the pretraining status of our subjects might have also played a role in our findings. For example, given that impaired postabsorptive fat oxidation predicts the severity of insulin resistance (37) and subjects with low rates of postabsorptive fat oxidation improve to a greater extent because of training (26), it is possible that the “window for adaptation” was not sufficiently large for our subjects to benefit from training. Indeed, postabsorptive NPRER for the HIIT group prior to the training intervention in our study ($\sim 0.79$) was lower than that which was present pretraining for the subjects of Goodpaster et al. (26) and that which has been reported for obese metabolically inflexible individuals (37, 43). Consequently, it appears as if metabolic flexibility in our at-risk subjects was quite high prior to training (e.g., $\Delta$NPFRER = 0.14), which means that the present findings cannot be used as conclusive proof that HIIT without body-weight loss does not improve metabolic flexibility in metabolically inflexible subjects. We also found high rates of insulin-induced FFA suppression pretraining (e.g., $\sim 97\%$ in both groups), which further suggests that our subjects had sufficient metabolic flexibility prior to the intervention. However, the high rates of FFA suppression during the pretraining clamp assessment might also reflect the high rate of insulin infusion that we used during the procedure (see below). Finally, with respect to the smaller window for adaptation that was available for our subjects prior to training, it is important to note that the high-fat controlled diet we had subjects consume might have decreased postabsorptive NPRER, causing the “normal” values we observed pretraining and consequent lack of training effect. However, if our subjects were metabolically inflexible because of dysfunctional fat regulation during the postabsorptive state, it should also manifest as an inability to adjust to high-fat intake (60, 62). Indeed, it has been shown that AA women lack metabolic flexibility in response to a high-fat diet regardless of body composition (7).
Much like insulin sensitivity, the HIIT protocol we employed might also explain the disparate findings regarding the effect of training on postabsorptive and insulin-stimulated metabolism. The methodology of Goodpaster et al. (26) resulted in considerable variation in both intensity and duration of exercise during the traditional endurance training that was performed, and the authors report that intensity and volume were each positively correlated with the reduced postabsorptive NPRER. Given the nature of HIIT, our subjects performed a much lower volume compared with subjects in that study, and while intensity was much higher, traditional endurance training at a sustainable work rate should allow for a greater absolute contribution of fat as fuel. While this might be compensated for by increased energy turnover during the postexercise recovery period after HIIT (29), it is also possible that sustained exercise at the intensity that elicits the maximal rate of fat oxidation (i.e., “FATmax”) might provide a specific stimulus that is appropriate for obese and/or insulin-resistant subjects (10, 36). Independently or in concert, these unique aspects of HIIT might render it less effective for improving dysfunctional fat metabolism compared with the more traditional approach where a volume threshold is surpassed, but an intensity ceiling is not. Finally, Goodpaster et al. reported an ~20% increase in V̇O₂max due to training, whereas in the present study V̇O₂peak was unaffected by HIIT even though subject adherence to training was high. It is, therefore, possible that the endurance training effect experienced by our subjects was not sufficient to improve postabsorptive fat reliance. However, the possibility that a type II error masked an effect of HIIT on V̇O₂peak in our study cannot be discounted (see below and Fig. 5).

Despite no change in substrate utilization at the extremes that were assessed during the clamp procedure, HIIT did result in more favorable fuel selection during exercise at the same absolute submaximal work rate (i.e., 40 W; see Table 2). This is important because use of clamp-derived ΔNPRER as an index of metabolic flexibility is not universally accepted, and, indeed, it has been suggested that the flexibility required to adapt to physiological challenges like exercise or meal-to-meal dynamics might provide a better indicator (6, 20). A HIIT-induced reduction in exercise NPRER is also important if traditional endurance training at a work rate that requires a high rate of fat oxidation should be incorporated into a HIIT regimen (22). Assessment of metabolic flexibility using postabsorptive NPRER has also been questioned because this value is influenced by acute energy balance and dietary macronutrient consumption (20). To control for these factors, we implemented a 10-day controlled feeding period prior to testing during which subjects ingested a high-fat eucaoric diet designed to promote maximal fat oxidation with weight maintenance (7). This diet likely allowed for a consistent comparison across time points.

In addition to fuel utilization at 40 W, a number of other aspects of exercise performance were improved by HIIT. In partial support of our third hypothesis, the metabolic rate at GET was increased in both absolute and relative terms (Table 3). Importantly, this threshold defines a range of metabolic rates for which V̇O₂ achieves a rapid steady state at the lowest possible oxidative cost and blood lactate concentration is not elevated above resting level (63). Consequently, while not the maximum sustainable metabolic rate, GET does dictate the highest effort that can be sustained with minimal discomfort (i.e., within the “moderate-intensity domain”). This means that it likely represents a more relevant measure of “functional capacity” for subjects like those in the present study. For example, an increased metabolic rate at GET can support greater functionality during physical activities of daily living and also allow for a higher work rate to be sustained during constant work rate “fat-reliant” exercise that might be required for overweight/obese subjects (10, 22).

In further support of our hypothesis, exercise tolerance was increased by HIIT, as six of seven subjects exercised for a longer period of time and reached a higher work rate after training (Fig. 5A). However, contrary to our hypothesis, V̇O₂peak was unchanged (Fig. 5B). One explanation for a higher maximum rate of work with unchanged maximum rate of oxygen consumption is improved exercise economy; however, the V̇O₂/WR slope during the incremental protocol was not decreased by training. Training might also improve the ability to persist once V̇O₂peak is attained, and indeed we found an approximate two-fold increase in V̇O₂peak for HIIT that supports this explanation. Finally, it is possible that a type II error masked the significant improvement in V̇O₂peak that is typically reported following a HIIT intervention (4). In this regard, V̇O₂peak was increased in six of seven HIIT subjects (Fig. 5B).

Unfortunately, statistical power had been reduced because we only had exercise-test data for seven out of the nine HIIT participants (see above).

A number of methodological aspects of the present study warrant mention. We chose a 14-wk training period despite the fact that a number of HIIT studies have shown remarkable training-induced adaptations after much shorter interventions (23). However, given the population we were working with, we were unsure regarding the degree to which we would be able to achieve a sufficient intensity during our work intervals at the beginning of the intervention, when subjects were unaccustomed to training. This is why we allowed 7 wk before subjects worked at the highest intensity that was required. We also felt that this gradually progressing approach might increase the likelihood that subjects would adhere to the program. Finally, we wanted to compare HIIT to the traditional endurance training interventions that have proven successful at altering metabolic flexibility (26); hence, we felt a similar intervention length would better allow us to isolate the effects of the HIIT approach per se. Our HIIT protocol involving “submaximal” exercise during work intervals was also different from many of the ones that have been successfully used in healthy subjects where work intervals are performed with all-out effort (i.e., SIT) (23, 51). The insulin infusion rate we chose is also of note. Insulin resistance in AA women appears to be attributable to lower peripheral insulin sensitivity, as hepatic insulin sensitivity is not different between AA women and their white counterparts (17). Consequently, to isolate this specific aspect of metabolic control, we used a saturating dose that would ensure complete suppression of hepatic glucose production and a blood glucose “steady state” during the procedure (16). However, this infusion rate is relatively high, which might explain the near-maximal values of FFA suppression that were observed pretraining and, by extension, the lack of training-induced change elicited by HIIT. Similarly, sufficient insulin responsiveness relative to the saturating dose might have masked improvements in insulin sensitivity (i.e., a leftward
shift of the insulin dose-response curve) that occurred because of the training intervention. Finally, as previously mentioned, it is important to recognize that the weight maintenance aspect of our methodology likely influenced our findings. Consequently, it is important to extend this research by investigating the effects of HIIT protocols with weight loss allowed in overweight/obese at-risk subjects.

In conclusion, a 14-wk HIIT intervention improved metabolic performance during exercise, but did not improve insulin sensitivity or metabolic flexibility assessed between basal and insulin-stimulated states during a euglycemic-hyperinsulinemic clamp with saturating insulin dose in sedentary, premenopausal, nondiabetic AA women. With respect to metabolic flexibility, the lack of effect was due to unaltered fat utilization and fat suppression during postabsorptive and insulin-stimulated conditions, respectively. These lack of improvements likely reflect the fact that body-weight loss did not accompany the intervention. Furthermore, while this subject population is at high risk, future research should explore the degree to which a similar HIIT intervention might improve these dysfunctional aspects of metabolism in overweight/obese subjects with greater disease progression and, therefore, a larger window for adaptation. Future research might also investigate ways in which HIIT can be enhanced for overweight/obese subjects, for example, by combining it with traditional endurance training that relies on fat as fuel to a greater extent. HIIT also improved exercise tolerance, metabolic rate at GET, and exercise fat utilization. These changes have both functional importance and implications regarding supplemental training that might be required in addition to HIIT to restore fuel-regulating capacity in metabolically inflexible individuals.

**GRANTS**

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


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