Exercise and improved insulin sensitivity in older women: evidence of the enduring benefits of higher intensity training

Loretta DiPietro,1,2 James Dziura,1,2 Catherine W. Yeckel,1,3 and P. Darrell Neufer1,4

1 The John B. Pierce Laboratory, and the Departments of 2Epidemiology and Public Health, 3Internal Medicine, and 4Cellular and Molecular Physiology, Yale University School of Medicine, New Haven, Connecticut

Submitted 25 April 2005; accepted in final form 29 August 2005

DiPietro, Loretta, James Dziura, Catherine W. Yeckel, and P. Darrell Neufer. Exercise and improved insulin sensitivity in older women: evidence of the enduring benefits of higher intensity training. J Appl Physiol 100: 142–149, 2006. First published September 1, 2005; doi:10.1152/japplphysiol.00474.2005.—Few studies have compared the relative benefits of moderate- vs. higher intensity exercise training on improving insulin sensitivity in older people while holding exercise volume constant. Healthy older (73 ± 10 yr) women (N = 25) who were inactive, but not obese, were randomized into one of three training programs (9-mo duration): 1) high-intensity (80% peak aerobic capacity (V\text{O}_2\text{peak}; T_H) aerobic training; 2) moderate-intensity (65% V\text{O}_2\text{peak}; T_M) aerobic training; or 3) low-intensity (stretching) placebo control (50% V\text{O}_2\text{peak}; C_TB). Importantly, exercise volume (300 kcal/session) was held constant for subjects in both the TH and the TM groups. V\text{O}_2\text{peak} was determined by using a graded exercise challenge on a treadmill. Total body fat and lean mass were determined with dual-energy X-ray absorptiometry. The rate of insulin-stimulated glucose utilization as well as the suppression of lipolysis were determined ~72 h after the final exercise bout by using a two-step euglycemic-hyperinsulinemic clamp. We observed improved glucose utilization at the higher insulin dose with training, but these improvements were statistically significant only in the T_H (21%; P = 0.02) compared with the T_M (16%; P = 0.17) and C_TB (8%; P = 0.37) groups and were observed without changes in either body composition or V\text{O}_2\text{peak}. Likewise in the T_H group, we detected a significant improvement in insulin-stimulated suppression (% of adipose tissue lipolysis at the low-insulin dose (38–55%, P < 0.05). Our findings suggest that long-term higher intensity exercise training provides more enduring benefits to insulin action compared with moderate- or low-intensity exercise, likely due to greater transient effects.

While there are data suggesting some degree of mandatory decline in insulin sensitivity and glucose tolerance with aging (8, 19, 28, 35), the extent of these pathophysiologic alterations is likely modulated by several other potentially confounding factors that also change with age, namely, increased adiposity, decreased lean mass, and reduced physical activity (26, 31, 34, 39, 40). Older people who exercise regularly appear to be protected from the development of insulin resistance and glucose intolerance (4, 5, 24, 30, 33), and this protection may be independent of exercise-related changes in body composition (6, 9, 38). However, the magnitude of improvement in insulin-stimulated glucose disposal with exercise training (performed at the same relative intensity) may be attenuated in older compared with younger people (31). This blunted response may be dependent on the absolute exercise intensity, as well as the volume (i.e., energy expenditure) of each training bout. The initial degree of insulin resistance also may influence the degree of responsiveness to exercise training, such that older people with the greatest degree of impairment may demonstrate the greatest improvement.

In younger people, transient improvements in insulin sensitivity correlate positively with the intensity of the training bout (29); however, untrained older people may not be capable of performing higher intensity activity due to the loss of aerobic capacity, to chronic disease, or to fear of injury (1). Moderate-intensity exercise may be an effective strategy in older people, if it is performed daily and for a long enough duration to result in a sufficient volume of energy expenditure. Few studies have compared the relative benefits of moderate- vs. higher intensity training while holding exercise volume constant. This makes it difficult to distinguish between the unique contributions of exercise intensity and of exercise volume to improved metabolic function and to the consequent decay in these functional improvements between exercise bouts.

We proposed that a 9-mo aerobic training program (comprising an energy expenditure of ~300 kcal/bout) would provide for both the extreme opportunity to alter body composition, as well as the chance to determine whether long-term training could extend the acute benefits of exercise beyond 24–48 h in inactive older women. Moreover, given the same absolute exercise volume (i.e., 300 kcal), we hypothesized that the greatest training-related improvements in metabolic function would occur with higher compared with moderate-intensity exercise and, consistent with our previous findings, would occur independent of changes in body composition.

METHODS

Subjects. Older (≥60 yr) women were recruited by advertisement from private older adult residential communities in Connecticut and from local community senior centers. Eligible study subjects included those who reported no regular physical activity for the previous 6 mo, were nonsmokers and not on hormone replacement therapy or glucose-lowering medication, and without class I obesity (i.e., body mass index <30 kg/m\textsuperscript{2}). Older volunteers were screened by their personal physician for cardiovascular disease, neuroendocrine disorders, and other uncontrolled chronic disease. In addition, all eligible study subjects successfully completed an exercise tolerance test performed in the Department of Cardiology at Yale University-New Haven Hospital. Use of a medically screened study population ensured a sample of older subjects healthy enough to participate in such a training study, but with a wide range of insulin sensitivity. Following these screening assessments, volunteers meeting all inclusion criteria.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
(N = 27) completed all baseline assessments before being randomized; however, data analysis was conducted on only those subjects with complete data at follow-up (n = 25; 73 ± 10 yr; age range 62–84 yr). The protocol was approved by the Human Investigations Committee of Yale University School of Medicine, and all eligible study subjects gave written, informed consent before their participation.

Exercise training protocol. Subjects were randomized into one of three groups: I) a higher intensity [V̇O₂peak; 80% peak aerobic capacity (V̇O₂peak) or 2) moderate-intensity (TM; 65% V̇O₂peak) aerobic training group; or 3) a lower intensity placebo control (CTB; 50% V̇O₂peak) group. Exercise intensity in these groups was based on a heart rate (HR) necessary to achieve this relative intensity during the graded exercise challenge. Thus the average (range) HR targets for the three groups were 123 beats/min (107–134 beats/min) for the TH group, 104 beats/min (97–110 beats/min) for the TM group, and 81 beats/min (75–90 beats/min) for the CTB group. Volunteers in the TH and TM groups exercised under supervision in small groups of five persons primarily on treadmills. To provide some variability in training mode and to avoid injury, subjects were allowed to “jog” on mini-trampolines, use rowing ergometers, or perform step aerobics for 5 min after each 15- to 20-min interval of treadmill walking, while maintaining their target HR. Subjects in the placebo control group participated together in a supervised exercise program of stretching and strengthening using Thera-bands, Thera-balls, and balance boards. The training and control groups were identical with regard to exercise frequency (4 days/wk) throughout the 9-mo intervention. After an initial 4- to 6-wk lead-in period, exercise volume was held constant for subjects in both the TH and the TM groups. Therefore, subjects randomized to the two aerobic training groups exercised for a duration necessary to expend 300 kcal/session (estimated from V̇O₂peak and body weight) (1). If we assume a V̇O₂peak of 1.40 l/min (20 ml·kg⁻¹·min⁻¹ for a 68-kg older women), this required ~55 and 65 min of exercise for TH and TM groups, respectively. Subjects in the CTB group exercised for 45 min/session. HR was monitored continuously during exercise (Polar Electro) and was recorded every 10 min during each exercise session. Because we were interested in the independent effects of exercise on glucose metabolism, subjects were instructed to maintain their usual dietary intake throughout the 9-mo period.

Determination of VO₂peak. VO₂peak was determined on a treadmill with the use of a modified Balke and Ware protocol (3). Subjects were tested to volitional exhaustion, and all subjects met two of three criteria for determining maximum O₂ consumption (V̇O₂): a respiratory exchange ratio ≥1.15; plateauing of the VO₂; or HR > age-predicted maximum [220 – age (yr)]. HR was continuously recorded (Polar Electro), while blood pressure was measured by auscultation. VO₂ was determined by sampling expired gas fractions of CO₂ and O₂ from a mixing chamber (Sensormedics, 2900; Sensormedics, Anaheim, CA). These measurements were corrected to standard conditions and used to determine VO₂ at 20-s intervals throughout the test. VO₂peak was determined by averaging values over the final minute of testing.

Euglycemic-hyperinsulinemic clamp. Whole body insulin-stimulated glucose utilization was determined by using a two-step euglycemic-hyperinsulinemic clamp, according to methods described by DeFronzo and colleagues (7). For 3 days before the study, subjects were asked to avoid sustained moderate or vigorous activity and were provided a weight-standardized diet (~30 kcal·kg⁻¹·day⁻¹) comprising 60% carbohydrate and 20% fat. Body weight was assessed during this 3-day period to ensure that subjects remained weight stable. Following a 12-h overnight fast, an indwelling catheter was placed in an antecubital vein for infusion of insulin and glucose. Samples of arterialized blood were obtained from a second catheter placed retrograde in the distal portion of a dorsal hand vein, with the hand kept in a box warmed to ~70°C for the duration of the clamp procedure. To measure hepatic glucose production (HGP), a [6,6-²H]glucose (99% enriched; Tracer Technology, Somerville, MA) prime (18 μmol/kg) was given for 5 min at the beginning of a 2-h basal (equilibrium) period, followed by a constant infusion (0.22 μmol/kg), which was maintained throughout the baseline and remainder of the clamp procedure. To determine changes in peripheral lipolysis, a continuous infusion of [³H₂]glycerol (0.2 μmol·kg⁻¹·min⁻¹) (99% enriched; Tracer Technology) was given during the basal period and during the clamp to measure glycerol turnover. The infusion rate was chosen to ensure ~5% plasma enrichment. Following the baseline period, regular human insulin (Squibb-Nov, Princeton, NJ) was infused as a primed continuous low-dose infusion (10 mU·m⁻²·min⁻¹) for 120 min followed by a higher dose infusion (40 mU·m⁻²·min⁻¹) for 120 min. Simultaneously, a primed variable infusion of glucose (20% dextrose) was started, and the rate was adjusted to maintain plasma glucose at ~100 mg/dl during hyperinsulinemia. Blood samples for determining HGP and glycerol turnover were collected before the tracer infusions and at 10-min intervals during the last 30 min of the basal period and last 30 min of each step of hyperinsulinemia. Plasma insulin, glycerol, and free fatty acid (FFA) concentrations were determined at baseline and every 30 min throughout the study. Plasma glucose concentrations were determined every 5 min. All clamps were performed in the General Clinical Research Center of Yale University-New Haven Hospital under medical supervision. We were interested in capturing the more enduring aspects of chronic training on insulin sensitivity and in knowing whether long-term training could extend the acute benefits of exercise past 24 or 48 h. Thus, to distinguish transient effects of exercise on insulin sensitivity from more chronic adaptations occurring with long-term training, the clamps at 9 mo were performed ~72 h following the last training session.

Oral glucose tolerance test. A 3-h, 75-g oral glucose tolerance test (OGTT) was performed at baseline, and at 3, 6, and 9 mo, according to the guidelines of the American Diabetes Association (2). Plasma glucose and insulin concentrations were determined before (~15 and 0 min) and at 30-min intervals during the test. All subjects were instructed to eat a diet containing 150 g or more of carbohydrates per day for 3 days before the OGTT, and all testing was performed within 48 h of exercise.

Blood analysis. All blood samples were placed in prechilled test tubes. Samples were centrifuged at 4°C, and the plasma was stored at ~70°C until analyzed in the Core Laboratory of the General Clinical Research Center. Pre- and postraining samples for each subject were analyzed in duplicate within a single assay. Plasma glucose concentrations were analyzed by using the glucose oxidase method (YSI 2300; Yellow Springs Instruments, Yellow Springs, OH). Plasma immunoreactive insulin concentrations were determined with a double antibody radioimmunoassay (Diagnostic, Webster, TX). Plasma concentrations of FFA were determined by standard microfluorimetric procedures (Sigma, St. Louis, MO). Blood samples for the determination of glucose kinetics (20) and glycerol turnover (25) were analyzed by standard procedures at the Diabetes Endocrinology Research Center of Yale University School of Medicine.

Calculations. The rate of whole body insulin-stimulated glucose utilization (M value; mg·kg⁻¹·min⁻¹) under low- and higher dose insulin infusion was calculated from the average glucose infusion rate during the final 60 min of each step and was corrected for changes in the glucose pool sizes, according to methods described by DeFronzo et al. (7). The M value divided by insulin concentrations during the final 30 min of the clamp (M/I) was calculated and used as an indicator of insulin sensitivity in the muscle. The glucose appearance rate (Rg) was calculated from plasma [³H₂]glucose enrichments, and the rate of tracer infusion by the equation \( R_g = [(APE \text{ infused/} APE \text{ plasma glucose}) - 1] \cdot F \), where APE is atoms percent excess and F represents the isotope infusion rate (μg·kg⁻¹·min⁻¹). HGP was then calculated as the difference between Rg and the glucose infusion rate. Glycerol turnover was calculated from plasma [³H₂]glyceraldehyde and the rate of tracer infusion by the equation \( R_g = [(APE \text{ infused/} APE \text{ plasma glyceraldehyde}) - 1] \cdot F \).
Body composition. Height and weight were measured on a balance-beam scale, and the abdominal circumference (cm) was measured in triplicate at the umbilicus by the same examiner before and after training. We have observed a strong correlation ($r = 0.80; P < 0.001$) between the abdominal circumference and the visceral fat area measured by computed tomography in our older populations (10). Overall body composition [whole body muscle (kg) and fat mass (kg)] scans were obtained by dual-energy x-ray absorptiometry.

Physical activity. To quantify volitional activity performed outside the laboratory, as well as activity being performed as part of the formal training program, self-reported habitual physical activity was assessed at baseline and at 3, 6, and 9 mo using the Yale Physical Activity Survey (YPAS) (11). The YPAS was designed specifically for older populations and assesses common work, exercise, and recreational activities performed during a typical week in the past month. The YPAS also provides a method for adjusting for seasonal variation. In that regard, it is quite useful for tracking activity over a 9-mo period.

Analysis. Univariate statistics (means $\pm$ SD) first were generated on all study variables. Simple correlations among the study variables were tested by using the Spearman rank order correlation coefficient. Cross-sectional differences at baseline in the levels of all study variables before and after the exercise training intervention were tested by using paired $t$-tests and two-way repeated-measures analysis of covariance, respectively. Statistical significance was set at an alpha-level of 0.05. Data were analyzed by using SAS WINDOWS 8.04 (SAS Institute, Cary, NC).

RESULTS

Tables 1 and 2 present the subject characteristics at baseline and at follow-up. Retention to the 9-mo training program (144 sessions) and adherence to the prescribed training HR (i.e., intensity) and training duration per session were high in all three groups (Table 1). There were no baseline differences among the three treatment groups with regard to age or $V_{O2peak}$. Subjects in the $C_{TB}$ group reported less physical activity than women in the other two groups, although these differences did not achieve statistical significance (Table 1). Reported physical activity tended to increase at 9 mo in all three groups, although not significantly so. More importantly, however, this reported increase in estimated total weekly energy expenditure was not sufficient to account for the 1,200 kcal/wk training stimulus in the $T_M$ group, thereby suggesting some compensatory decrease in energy expenditure outside of the training sessions in the women performing moderate-intensity training, perhaps due to their longer training duration compared with women in the $T_H$ group. Body composition was also similar among the study groups at baseline (Table 2). The 9-mo training program did not increase $V_{O2peak}$ or alter body composition in any of the three treatment groups.

Although these older women were considered healthy enough to participate in a long-term training study based on physician screening, approximately one-half of the subjects (52%) met the criterion for impaired glucose tolerance, based on a 2-h glucose value from the baseline OGTT $\approx 140$ mg/dl. At baseline, the M value at the 40 mU insulin dose (M value$_{40}$) was inversely correlated with the 2-h glucose value from the OGTT ($r = -0.54; P < 0.02$). In addition, we observed a wide range in the degree of insulin sensitivity at baseline as determined from the higher insulin dose (M value$_{40}$: 1.4–11.3 mg·kg lean$^{-1}$·min$^{-1}$). For comparison purposes, the average M value$_{40}$ observed in the present study (7.1 $\pm$ 3.4 mg·kg lean$^{-1}$·min$^{-1}$) was lower than that reported by Hughes et al. (17) (9.7 $\pm$ 4.2 mg·kg lean$^{-1}$·min$^{-1}$) among slightly younger (64 $\pm$ 2 yr) glucose-intolerant men and women of similar adiposity (37% fat) and determined by identical procedures.

Fasting metabolic characteristics before the start of the clamp procedure did not change significantly under any exercise training condition (Table 3). In contrast, however, we observed increases in the M value$_{40}$ in all three training groups (Table 4). These improvements in glucose utilization were statistically significant only in the $T_H$ group (21%; $P < 0.02$) and not in the $T_M$ (16%; $P = 0.17$) and $C_{TB}$ (8%; $P = 0.37$) training groups.

<table>
<thead>
<tr>
<th>Table 1. General characteristics of the study population before and after training</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Age, yr</td>
</tr>
<tr>
<td>$V_{O2peak}$, ml·kg$^{-1}$·min$^{-1}$</td>
</tr>
<tr>
<td>Activity*, kcal/wk</td>
</tr>
<tr>
<td>Retention, %</td>
</tr>
<tr>
<td>Adherence, %</td>
</tr>
<tr>
<td>Time</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SD; $n$, no. of subjects. $V_{O2peak}$, peak aerobic capacity; HR, heart rate. *Self-reported physical activity from the Yale Physical Activity Survey and adjusted for seasonal variation.

<table>
<thead>
<tr>
<th>Table 2. Anthropometric characteristics of the study population before and after training</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
</tr>
<tr>
<td>Lean mass*, kg</td>
</tr>
<tr>
<td>Body fat*, %</td>
</tr>
<tr>
<td>Abdominal circumference, cm</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SD; $n$, no. of subjects. BMI, body mass index. *Based on dual-energy X-ray absorptiometry.
groups, but did appear to follow a dose-response trend with regard to exercise intensity. When normalized for the level of circulating insulin during the final 30 min of the clamp, glucose uptake improved significantly only in the TH group (25%; \( P = 0.05 \)) (Table 4). Individual data on training-related changes in M value at 40 mg U/ml are displayed in Fig. 1. These data suggest a greater proportion of responders in the TH group compared with the TM or CTB groups and a weak correlation between degree of initial impairment in insulin sensitivity and the magnitude of response. Overall, neither the M value at 40 mg U/ml (\( r = -0.24; P = 0.28 \)) nor the 2-h glucose value from the OGTT (\( r = 0.11; P = 0.63 \)) at baseline correlated significantly with the absolute magnitude of change in the M value at 40 mg U/ml with training.

The data then were stratified further by insulin resistance status at baseline (i.e., M value at 40 mg U/ml \( \geq 4.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)) and examined within the treatment groups. On average among older women in the TH group, the absolute change in glucose utilization was similar between those with and without insulin resistance (1.52 vs. 1.60 mg U/ml \( \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)). Among women in the TM group, those who were characterized as resistant experienced a greater mean absolute improvement in glucose utilization compared with their more sensitive counterparts (1.22 vs. 0.23 mg U/ml \( \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)); however, this is likely explained by one extreme response (Fig. 1) and should be viewed cautiously.

Low-dose insulin was used to determine hepatic and adipose tissue insulin sensitivity. Basal rates of HGP were similar at baseline among all three groups, and, across all treatments, low-dose insulin infusion induced a very robust suppression of HGP (>50%; Table 4). The degree of HGP suppression improved significantly in the TM group (\( P < 0.05 \)), presumably due to the slightly lower pretraining rate of suppression in this group. Rates of HGP were negligible at the higher insulin dose in all three groups, suggesting complete suppression of HGP with insulin stimulation in these older women.

Glycerol isotopic enrichment data during low- and higher dose insulin infusion are presented in Fig. 2 and indicate that, in general, subjects achieved steady state with regard to glycerol enrichment within each stage of the clamp procedure. The glycerol Ra was calculated from only steady-state enrichment data, in which case the Ra is equivalent to the rate of disappearance (25). Insulin suppression of adipose tissue lipolysis improved significantly only in the TH group, indicated by the decrease in Ra at the low insulin dose (Table 5). Insulin-stimulated suppression of plasma glycerol also improved significantly at both insulin doses in the TH group (47–58% at low dose, \( P < 0.05 \); and 64–74% at higher dose insulin, \( P < 0.01 \)), whereas significant improvements were observed in the TM group only at the higher insulin dose (61–71%, \( P < 0.05 \)). FFA concentrations during hyperinsulinemia reached nadir values of <0.10 \( \mu \text{mol} / \text{l} \) during the final stage of the clamp in all three groups; however, improvements in FFA suppression were observed only in the TM group at the low insulin dose (25–14 \( \mu \text{mol} / \text{l} ; P < 0.05 \)).

**DISCUSSION**

Recent cross-sectional data support an age-related decline in insulin sensitivity of ~8% per decade (35). Although older trained athletes have markedly higher insulin sensitivity compared with their sedentary peers, the level of insulin-stimulated glucose uptake, nonetheless, remains blunted in these older compared with younger athletes (5), suggesting that there may be some functional decline in glucose metabolism that is attributable to mandatory aging. Several studies provide evidence, however, that the contribution of aging per se to this decline in metabolic function is trivial after adjusting for age-related differences in physical activity and body composition (26, 31, 34, 39, 40).

### Table 3. Fasting metabolic characteristics of the study population, before and after training

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 7)</th>
<th>9 mo</th>
<th>Baseline (n = 9)</th>
<th>9 mo</th>
<th>Baseline (n = 9)</th>
<th>9 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mg/dl</td>
<td>104.5 ± 7.0</td>
<td>97.5 ± 3.2</td>
<td>100.0 ± 7.4</td>
<td>101.6 ± 6.8</td>
<td>99.5 ± 5.0</td>
<td>100.8 ± 8.8</td>
</tr>
<tr>
<td>Insulin, μU/ml</td>
<td>13.6 ± 2.8</td>
<td>11.6 ± 4.0</td>
<td>15.1 ± 8.5</td>
<td>15.3 ± 7.1</td>
<td>13.4 ± 2.9</td>
<td>14.5 ± 4.9</td>
</tr>
<tr>
<td>FFA, μmol/l</td>
<td>0.68 ± 0.08</td>
<td>0.65 ± 0.06</td>
<td>0.72 ± 0.12</td>
<td>0.68 ± 0.10</td>
<td>0.70 ± 0.18</td>
<td>0.59 ± 0.17</td>
</tr>
<tr>
<td>Glycerol, μmol/l</td>
<td>72.0 ± 29.4</td>
<td>81.5 ± 26.2</td>
<td>65.6 ± 16.2</td>
<td>68.8 ± 13.9</td>
<td>62.3 ± 14.5</td>
<td>71.7 ± 8.5</td>
</tr>
</tbody>
</table>

Values are means ± SD; \( n \), no. of subjects. FFA, free fatty acids.

### Table 4. Metabolic characteristics of the study population during the euglycemic-hyperinsulinemic clamp, before and after training

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 7)</th>
<th>9 mo</th>
<th>Baseline (n = 9)</th>
<th>9 mo</th>
<th>Baseline (n = 9)</th>
<th>9 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>M value at 10 mU, mg/kg lean (^{-1}) min(^{-1})</td>
<td>2.1 ± 1.56</td>
<td>2.5 ± 2.08</td>
<td>1.4 ± 1.21</td>
<td>1.7 ± 1.53</td>
<td>1.9 ± 1.22</td>
<td>2.2 ± 1.22</td>
</tr>
<tr>
<td>M value at 40 mU, mg/kg lean (^{-1}) min(^{-1})</td>
<td>7.5 ± 2.08</td>
<td>8.1 ± 3.38</td>
<td>6.2 ± 3.31</td>
<td>7.1 ± 2.73</td>
<td>7.5 ± 3.62</td>
<td>9.0 ± 3.60*</td>
</tr>
<tr>
<td>( \Delta )HGP, μU/ml</td>
<td>0.09 ± 0.03</td>
<td>0.08 ± 0.03</td>
<td>0.08 ± 0.06</td>
<td>0.07 ± 0.03</td>
<td>0.08 ± 0.03</td>
<td>0.10 ± 0.03*†</td>
</tr>
<tr>
<td>Basal HGP, mg/kg (^{-1}) min(^{-1})</td>
<td>1.70 ± 0.31</td>
<td>1.72 ± 0.26</td>
<td>1.89 ± 0.30</td>
<td>1.63 ± 0.27*</td>
<td>1.65 ± 0.30</td>
<td>1.73 ± 0.27</td>
</tr>
<tr>
<td>HGP at 10 mU, mg/kg (^{-1}) min(^{-1})</td>
<td>0.57 ± 0.70</td>
<td>0.23 ± 0.81</td>
<td>0.82 ± 0.42</td>
<td>0.41 ± 0.30*</td>
<td>0.37 ± 0.69</td>
<td>0.27 ± 0.48</td>
</tr>
</tbody>
</table>

Values are means ± SD; \( n \), no. of subjects. HGP, hepatic glucose production; M value, whole body glucose metabolism rate, both low (10 mU·min\(^{-2}\)·kg\(^{-1}\)) and high (40 mU·min\(^{-2}\)·kg\(^{-1}\)); \( \Delta \)HGP, M value at 40 mU·min U/ml plus insulin concentrations over the last 30 min of the clamp. *Within-group improvement, \( P < 0.02 \). †\( P < 0.05 \) vs. moderate-intensity training or lower intensity placebo control group.
The impact of endurance exercise training as an effective countermeasure for improving insulin sensitivity in sedentary older women has received little attention. Our study is unique in comparing the effects of exercise of similar caloric expenditure, but varying intensity, on insulin sensitivity in older people. Indeed, we demonstrate long-term training-related improvements in insulin sensitivity in previously inactive older women that remained evident even 72 h after exercise and appeared to follow a dose-response trend with regard to relative exercise intensity. A greater magnitude of improvement was observed among older women performing higher intensity aerobic training compared with women performing a similar volume of aerobic exercise at moderate intensity and compared with women performing low-intensity, light-resistance exercise. Moreover, these training-related improvements in insulin sensitivity were observed without coincident improvements in overall body composition or \( V\dot{O}_2\) peak (primary factors with regard to the observed decline in metabolic resiliency common among older people). Insulin-stimulated suppression of adipose tissue lipolysis also improved with higher intensity training.

There are few longitudinal data on aerobic exercise training and insulin sensitivity in older people, and our results are of similar magnitude to those reported by others (13, 17, 21, 35, 38). In contrast to our findings are those recently reported by Goulet et al. (14) of no sustained effect of higher intensity aerobic training on insulin sensitivity in healthy older women. This latter study used methods very similar to ours; however, the training period was 6 mo in duration, and, perhaps more importantly, insulin sensitivity was determined 96 h following exercise. It also must be emphasized that there is sound evidence of exercise training-related improvements in insulin sensitivity that are achieved with far shorter training periods than in our study, ranging from 7 days to 6 mo (6, 16, 17, 21, 38).

Differences between younger and older people in the magnitude of response in peripheral insulin sensitivity to exercise training may be explained in part by aging-related loss of muscle mass and decrements in a number of key factors related to muscle oxidative capacity in older people (6, 15, 23, 28). Recently, Short et al. (35) reported moderate-intensity (70% maximum HR), training-related improvements in insulin sensitivity that were inversely related to age, improving by 72% \((P < 0.001)\) among younger (20–39 yr) subjects and by 20% \((P = \text{not significant})\) among middle-aged (40–59 yr) subjects, but decreasing by 5% \((P = \text{not significant})\) among people aged 60 yr or older. In contrast, the glucose transport capacity (GLUT-4 protein content), oxidative enzyme activity, and the mitochondrial content of the muscle (all measured 96–120 h after exercise) increased equally across all age groups in response to training. On the other hand, Cox et al. (6) report similar absolute improvements in insulin action (determined by an intravenous glucose tolerance test) between inactive younger (22 ± 1 yr) and older (61 ± 1 yr) women after only
Table 5. Glycerol turnover during hyperinsulinemia before and after training

<table>
<thead>
<tr>
<th></th>
<th>Thera-band (n = 7)</th>
<th>Moderate Intensity (n = 9)</th>
<th>Higher Intensity (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>9 mo</td>
<td>Baseline</td>
</tr>
<tr>
<td>Basal R/Rd, mg·kg⁻¹·min⁻¹</td>
<td>0.29±0.05</td>
<td>0.26±0.08</td>
<td>0.28±0.09</td>
</tr>
<tr>
<td>R/Rd 10 mU, mg·kg⁻¹·min⁻¹</td>
<td>0.16±0.05</td>
<td>0.13±0.05</td>
<td>0.15±0.06</td>
</tr>
<tr>
<td>R/Rd 40 mU, mg·kg⁻¹·min⁻¹</td>
<td>0.14±0.05</td>
<td>0.10±0.05</td>
<td>0.12±0.03</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of subjects. Glycerol turnover data were obtained during steady-state conditions, in which the rate of appearance (Ra) is equal to the rate of disappearance (Rd). *Within-group improvement, P < 0.05. †P < 0.05 compared with moderate-intensity training.

7 days of endurance training on a bicycle ergometer that employed a similar relative intensity and volume of exercise as in our study (1 h at 75% maximum V̇O₂). These improvements in insulin action (measured 15–17 h after exercise) were accompanied by similar relative increases in muscle GLUT-4 protein concentrations, regardless of age, and were independent of changes in body composition. These important findings suggest that aging-related differences in the ability to improve insulin sensitivity with exercise training may be related to more functional impairments (e.g., insulin signaling and/or actual defects in the trafficking of GLUT-4 to the sarcolemma in response to insulin) that may not be easily altered by exercise in older people (especially after decades of disuse).

Recovery from exercise, even just a single bout, is associated with an increase in muscle insulin sensitivity that persists for several hours, presumably to facilitate the rapid replenishment of glycogen reserves in muscle. To emphasize the more enduring chronic effects of exercise training, we performed follow-up measurements of peripheral insulin sensitivity ~72 h after the last training session to avoid any acute effects from the final exercise session. That a 21% improvement in insulin action (glucose uptake and suppression of lipolysis) remained after 72 h in our study subjects exercising at 80% V̇O₂peak emphasizes the more enduring nature of higher intensity training. These enduring benefits are more likely attributable to a greater transient response, which, even so, may be lost by 96 h (14). In further support of this notion, our pre- and posttraining OGTT data (obtained within 48 h of exercise) suggest that the long-term metabolic impact of moderate- and higher intensity exercise is likely distinct. In the T_H group, 50% of the women experienced improvements in 2-h stimulated glycerol values that were coincident with improvements in the M value_0 (r = −0.81; P = 0.02). In contrast, none of the women in the T_M group experienced coincident improvements in 2-h glucose values, despite the observed improvements in the M value_0 in 50% of these women (r = 0.12; P = 0.78).

Our strategy to wait 72 h, however, may have resulted in an attenuation of the true training effect due to the decay in specific training adaptations [e.g., GLUT-4 expression (18) and/or translocation] that may have occurred over this time period in these older women. Other studies that measured insulin sensitivity within 15–48 h of the last exercise bout (6, 13, 16, 21) observed greater relative improvements compared with ours at a similar exercise volume and/or intensity. Therefore, if we had used a shorter time interval between exercise and measurement of insulin sensitivity, we may have observed greater improvements in metabolic function with moderate- and higher intensity exercise and would not have missed the acute effects realized by daily exercise.

Interestingly, Goulet et al. (14), Hughes et al. (17), and Short et al. (35) all used a very protracted time interval between the cessation of exercise training and evaluation of insulin sensitivity in their older study subjects. Taken together with those findings, our own data indicate that the exercise training effect on insulin sensitivity may decay more rapidly in older people. Furthermore, this may be especially so after moderate- compared with higher intensity training, since we observed a 16% increase in insulin sensitivity with moderate-intensity exercise (65% V̇O₂peak) at 72 h, compared with an 11% increase reported by Hughes et al. (17) (50–75% HR reserve) at 96 h and a 5% decrease reported by Short et al. (35) (70% HRmax) at 96–120 h. In any case, it is not clear whether older women have an acute response to exercise that is similar in magnitude to a long-term training response, especially given that we observed favorable alterations in insulin sensitivity in the absence of corresponding changes in fitness or body composition. More carefully controlled experimental work is necessary in older people to determine the specific mechanisms underlying both transient (e.g., GLUT-4 content and translocation, oxidative enzyme activity, etc.) and chronic (e.g., body composition, muscle fiber alterations, mitochondrial content, etc.) improvements in insulin sensitivity with exercise training and the specific timing of their consequent decay with detraining.

This study had several strengths; namely, it was a randomized controlled intervention involving 9 mo of supervised aerobic exercise of two different intensities (but similar caloric load) with a placebo control group performing low-intensity exercise training of a completely different mode. Overall retention to the 9-mo intervention was high (>90%), and adherence to the prescribed intensity and duration of training was 85% or greater. Therefore, we are confident that the training stimulus was applied appropriately. In addition, our study sample of older women was over a decade older than subjects described in other studies of exercise training and aging (6, 13, 17) and had a wide range of both glucose tolerance and insulin sensitivity, thereby enhancing the external validity of the data to the general population of older people. That we observed no improvement in V̇O₂peak after 9 mo of endurance training is, indeed, contrary to other studies of older people. Given the low levels of aerobic fitness (i.e., 20 ml O₂·kg⁻¹·min⁻¹) in our study subjects and others (22), however, even a relative stimulus of 80% V̇O₂peak translates into an absolute stimulus of only 4.5 metabolic equivalents, which may not be sufficient to improve maximal aerobic capacity in robust older women not on hormone replacement therapy (36, 37).

Several studies have observed improvements in insulin sensitivity with training that may have been further modulated by
significant improvements in body composition (13, 21, 35). Consistent with our previous findings after 4 mo of training (9), behavioral compensation outside of training either by decreased volitional physical activity or by increased caloric intake in the T_M and T_H groups may explain our inability to observe any change in body composition in these older women. On the other hand, the abdominal circumference may have underestimated the actual change in abdominal fat mass in the present study. Nonetheless, that we observed no such changes in overall body fat or lean mass after training helps to emphasize that the overall improvement in insulin sensitivity was likely due to the exercise training stimulus per se.

In conclusion, we observed that, compared with long-term low- or moderate-intensity exercise training, higher intensity training provides more enduring benefits to ameliorating the aging- and disuse-related decline in peripheral insulin sensitivity observed in otherwise healthy older women. Clinically, these findings suggest that higher intensity exercise that expends ~300 kcal at a time can be performed every 2 days without losing benefits. This level of exercise can be achieved by the majority of older people by gradually incorporating 45–50 min of brisk walking (HR of 115–125 beats/min) on 4 days/week into their lifestyle. Because the acute benefits of moderate-intensity exercise may decay more rapidly than those derived from higher intensity exercise, the same volume of moderate exercise (HR of 100–110 beats/min) may need to be performed daily to be effective in improving metabolic function.

ACKNOWLEDGMENTS

We thank Jodi L. Criminis, Anne Marie Cheatham, Jennifer Fawcett, and the nursing and technical staffs of the Yale University-New Haven General Clinical Research Center and the Yale University Diabetes Endocrinology Research Center for technical expertise, and the study staffs for commitment to this research. J. Dziura currently holds the position of Associate Research Scientist at the Yale University-New Haven General Clinical Research Center.

GRANTS

This work was supported by National Institutes of Health Grants RO1 AG-17163 (L. DiPietro), MO1 RR-00125, P30 AR-46032, and P30 DK-45735.

REFERENCES


