Resistive Training Increases Insulin Action in Postmenopausal Women

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Background. This study examined the effects of 4 months of resistive training in postmenopausal women on glucose metabolism and peripheral tissue sensitivity to endogenously released insulin.

Methods. Thirteen moderately obese (30–49% body fat) postmenopausal women (50–65 years) participated in the study. The six more obese women were enrolled in the resistive training with weight loss (RT&WL) program, while the remainder participated in resistive training alone (RT). β-cell sensitivity to glucose and peripheral tissue sensitivity to endogenously released insulin were examined during hyperglycemic clamps (7.9 mmol/L above basal) before and after the intervention(s).

Results. The RT program resulted in a significant improvement in upper and lower body strength (p < .01) in all subjects. Body weight, fat mass, and percent body fat decreased with RT&WL (p < .001), but did not change with RT alone. There was no change in fat-free mass or maximal oxygen consumption after the intervention(s). Insulin response during the last 20 min of the 2 hr hyperglycemic clamps (7.9 mmol/L above basal plasma glucose levels) decreased after the intervention(s) in the entire group by 29% (p < .01), but decreased more in the group that lost weight (43%, p < .05) than in women who remained weight stable (16%, p = .05). Glucose utilization did not change.

Conclusion. RT alone, or in combination with WL, increases insulin action and reduces hyperinsulinemia in postmenopausal women. This suggests that RT has the potential to ameliorate and perhaps prevent the development of insulin resistance and non-insulin-dependent diabetes mellitus (NIDDM) in postmenopausal women.

Reduced physical activity is a consequence of normal aging. A sedentary life style is associated with increased obesity and a loss of fat-free mass, conditions which promote insulin resistance and hyperinsulinemia. Endurance training reduces hyperinsulinemia and improves insulin action in older men and women (1,2). Resistance training, without changes in body weight, increases insulin sensitivity in older men (3). Increased body fat is also associated with reduced rates of insulin-mediated glucose disposal (4–6). Modest weight reduction improves glucose disposal and glycemic control in obese diabetic patients (7–10) as well as in normal subjects (11). Increases in body fat and insulin resistance are associated with the menopause, and are major risk factors for non-insulin-dependent diabetes mellitus (NIDDM) and cardiovascular disease (CVD) in older women. Interventions such as exercise and weight loss, which would reduce these risk factors for disease, have obvious health implications for women.

To our knowledge, the effects of a resistive training regime alone or with weight loss on endogenous insulin secretion and peripheral tissue sensitivity to insulin are not known in older women. We hypothesized that these interventions would improve glucose homeostasis. To test this hypothesis we enrolled sedentary postmenopausal women in either a resistive training program (RT), or a combined resistive training and weight loss intervention (RT&WL). Our results indicate that RT improves insulin action in postmenopausal women, and this effect is magnified when RT is accompanied by WL.

Methods

Subjects

Thirteen postmenopausal women between the ages of 50–65 years were recruited for participation in the study. All methods and procedures were approved by the Institutional Review Board of the University of Maryland, and all subjects provided written informed consent. Six women who had a BMI > 27 kg/m² were enrolled in the RT&WL intervention according to obesity recommendations of the National Diabetes Data Group (12), and the remaining seven women (BMI < 27 kg/m²) entered the RT alone program (Table 1). Subjects were screened by medical history, physical examination, fasting blood profile, 2 hr oral glucose tolerance test, and a graded exercise treadmill test. All subjects were nonsmokers, free of diabetes (13) and CVD, and were not on any medications. One woman in each group had an impaired glucose tolerance test. All women were at least 2 years postmenopausal and none were on hormone-replacement therapy. Only persons who were weight stable and had not participated in a regular exercise program for a minimum of 6 months prior to the study were included.

Diet

To minimize any effect that differences in diet might have on the measured metabolic variables, all subjects were instructed on the American Heart Association Step I (14) diet by a registered dietitian for 4 weeks before the initiation of...
the exercise program. All subjects were asked to maintain the composition of this diet throughout the study’s duration. Compliance was monitored by review of food records taken every 4 weeks throughout the study. On the average, subjects consumed a diet consisting of 50–55% carbohydrate, 15–20% protein, ≤30% fat, and ≤300 mg of cholesterol per day. After the initial metabolic assessments, RT was started. During the training period, the RT&WL group underwent weekly individualized dietary counseling and caloric restriction to induce approximately 0.25–0.5 kg weight loss per week. During the last 2 weeks of the 4-month program, all subjects were instructed to continue training but maintain a constant weight on diets similar in composition to their baseline diet before repeat testing.

Strength Tests
A dynamometer was used to assess upper and lower body torque before and after training (Kin-Com 125 E Plus, Chat-tex Co., Chattanooga, TN). Muscular strength is defined as the amount of torque exerted voluntarily at various speeds. Leg extension and flexion were tested at 30°/sec with the lever arm from the Kin-Com attached to the tibia and its axis of rotation aligned with the rotation axis of the knee joint. Support straps around the chest, pelvis, and thigh were used to stabilize the trunk, hip joint, and thigh. Elbow extension and flexion were tested at 30°/sec while subjects were in a seated position and stabilized with straps around the hips, chest, and biceps. The rotational axis of the lever arm was aligned with the rotational axis of the elbow adjacent to the lateral epicondyle of the humerus. Prior to maximal testing, subjects were given two warm-up trials at a submaximal effort and one maximal effort for practice. Three maximal efforts were then performed and recorded for both extension and flexion. All subjects received verbal encouragement to exert maximal force. The highest value obtained for these three trials was recorded as the final peak torque score. The Kin-Com 125 E Plus was calibrated on each testing day using the precision of the DPX-L program for body composition analyses. The precision of the DPX-L for the ratio of soft tissue attenuation (Rst) and percent fat measurements was assessed by scanning an aluminum spine phantom, followed by a plastic container filled with 9 cm of water and 6 cm of 100% vegetable oil to simulate 40% fat. This setup was scanned 5 times prior to the start of the study and 5 times after the training period to yield identical values for Rst (CV = 0.1%) and percent fat (CV = 0.9%). The in vivo reproducibility for this method is approximately 1% (16).

Maximal Oxygen Consumption (\(V\text{O}_{2}\text{max}\))
\(V\text{O}_{2}\text{max}\) was measured before and after training to confirm that subjects were untrained prior to the study and that they did not engage in regular aerobic exercise during the study. A continuous treadmill test protocol was performed (15). Validation that \(V\text{O}_{2}\text{max}\) had been reached was established if two of the following three criteria were met: (a) a plateau in oxygen uptake with an increased work load as evidenced by a difference in oxygen uptake of <2 ml·kg\(^{-1}\)·min\(^{-1}\); (b) a respiratory exchange ratio >1.10; and (c) a maximal heart rate within 10 beats/min of the age-predicted maximal value.

Hyperglycemic Clamps
All subjects were weight- and activity-stabilized for at least 2 weeks prior to metabolic testing performed before and after training. Peripheral tissue sensitivity to endogenously secreted insulin and \(\beta\)-cell sensitivity to glucose were measured before the initiation of the intervention and 24 hours after the last exercise session using the hyperglycemic clamp technique (17). For the assessment of basal glucose and insulin levels, three arterialized blood samples were taken from the dorsal hand vein at 10-min intervals starting at ~30 minutes. With the start of the clamp at time 0, blood samples were obtained every 2 min from 0 to 10 min and every 5 and 10 min thereafter for the determination of plasma glucose and insulin levels. Plasma glucose concentrations were measured by the glucose oxidase method (Beckman Glucose Analyzer Instruments, Fullerton, CA), and the rate of glucose infusion was adjusted every 5 min to maintain the desired level of glycemia (+7.9 mmol/L above basal) for 2 hours. The plasma glucose levels were well maintained and stable during the 120-minute clamp period and averaged 99.8 ± 1.7% (SD) of the desired goal. The CV of plasma glucose levels during all clamps \((n = 26)\) was 5.8 ± 2.0 (SD). The actual concentration of the glucose solution measured 1.020 ± 0.003 mmol/L, which was 90% of its stated concentration. Plasma levels of insulin were measured by radioimmunoassay, which has an insulin-specific antibody (cross-reactivity with pro-insulin less than 0.2%) (Linco, St. Louis, MO). All determinations were run in duplicate. All plasma insulin levels were measured in a single assay to minimize interassay variation.

Statistical Analyses
The mean concentration of glucose and insulin was calculated for each sample time point. The trapezoidal rule was used to calculate the integrated response of the first phase insulin release (0–10 min) and over subsequent 20-min intervals from 20–120 min for each subject. The integrated
response was divided by its time interval to compute mean concentrations. Insulin leaves the plasma compartment to exert its action at the tissue level; this concentration of insulin at the tissue level was estimated using the previously described model where the insulin concentration at the tissue level is referred to as I₃, (compartment 3) (18). Glucose utilization (M) for 20-min intervals was calculated from the amount of glucose infused after correction for both glucose equivalent space (glucose space correction) and the amount of urinary glucose loss, as previously described (19). Differences within and between studies were evaluated using one or more of the following tests as appropriate: paired and unpaired t-test, repeated analysis of variance, and Pearson correlation coefficients. A "backward" stepwise procedure was employed where all independent variables are first placed in the regression model and then sequentially eliminated if not significantly related to the dependent variable. All statistical tests were two-tailed. Data are expressed as mean ± standard error of the mean (SEM), and significance was set at the .05 level. All analyses were performed utilizing Statview 512* (BrainPower Inc., CA) or SAS (20) software.

RESULTS

Subject Characteristics
The 13 women recruited to participate in this RT study were of similar average age (range 50–65 years). Due to the study design, the six women who were enrolled in the RT&WL group were of significantly higher weight, percent body fat, fat mass, FFM, and BMI than the seven women who remained weight stable (p < .05, Table 1). The former group lost weight, body fat mass, and percent body fat (p < .001) but not FFM, while the RT group did not change body composition. While waist circumference decreased only in the RT&WL group (p < .05), waist-hip ratio (WHR) did not change. There was a small tendency to increase FFM in the entire group, while total BMC (data not shown) did not change. There was no change in V̇O₂max (L/min) in either group.

Dietary Analysis
The analysis of two sets of seven-day food records, one obtained before and one obtained after the intervention, in the RT group revealed no changes in total caloric intake or kcal/kg between initial and final evaluations (1636 ± 84 vs 1572 ± 108 kcal/d), or percent calories from carbohydrate (61 ± 3 vs 61 ± 4%), fat (21 ± 2 vs 23 ± 3%), and protein (19 ± 1 vs 18 ± 1%). Although total 24 hr caloric intake significantly decreased in the RT&WL group after the weight loss program (1666 ± 193 vs 1432 ± 83 kcal/d, p < .05), there was no change in kcal/kg per day, and percent calories from carbohydrate, fat, and protein also remained constant (56 ± 1 vs 59 ± 1%; 25 ± 1 vs 25 ± 2%; 22 ± 1 vs 21 ± 1%).

Muscular Strength
Training improved muscular strength, as indicated by increases in biceps flexion, triceps extension, leg extension, and leg flexion in both groups (Table 2, all p < .01). Muscular strength assessed by three repetition maximum (3RM) of the leg press, leg extension, latissimus pulldown, and upper back using the Keiser equipment also increased significantly in both groups (p < .01) (data not shown). These improvements in strength were similar in both groups.

Glucose Metabolism
Fasting plasma glucose and insulin concentrations were similar in the RT and RT&WL groups and did not change after either intervention (Table 1). First phase insulin response (0–10 min) did not change in either group following the interventions (Figure 1). The second phase insulin response (10–120 min) increased continuously during the 2-hour clamp procedure (p < .05). In addition, the insulin response during each succeeding 20-min period during the second phase of the hyperglycemic clamp as well as the mean 20–120 min insulin response were all significantly higher in the RT&WL group than the RT group before the interventions. The entire second phase insulin response decreased 9% (n.s.) after the intervention in the RT group and 32% in the RT&WL group (p < .05). The 100–120 min

Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Initial (n = 7)</th>
<th>Final</th>
<th>Initial (n = 6)</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>58 ± 2</td>
<td>—</td>
<td>58 ± 2</td>
<td>—</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.8 ± 3.0†</td>
<td>61.9 ± 3.0†</td>
<td>78.5 ± 2.5</td>
<td>74.3 ± 2.4**</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.2 ± 0.9†</td>
<td>23.2 ± 0.9†</td>
<td>30.3 ± 1.3</td>
<td>28.7 ± 1.2</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>36.8 ± 1.9†</td>
<td>35.6 ± 2.3</td>
<td>42.8 ± 1.4</td>
<td>39.3 ± 1.5**</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>22.3 ± 2.3‡</td>
<td>21.8 ± 2.4</td>
<td>33.1 ± 2.2</td>
<td>28.6 ± 1.9**</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>37.6 ± 0.9†</td>
<td>38.4 ± 1.2†</td>
<td>43.7 ± 0.4</td>
<td>44.2 ± 0.6</td>
</tr>
<tr>
<td>V̇O₂max (L/min)</td>
<td>1.5 ± 0.1†</td>
<td>1.5 ± 0.1</td>
<td>1.9 ± 0.1</td>
<td>1.7 ± 0.1</td>
</tr>
<tr>
<td>Basal glucose (mmol/L)</td>
<td>5.2 ± 0.1</td>
<td>5.2 ± 0.1†</td>
<td>5.4 ± 0.1</td>
<td>5.3 ± 0.2</td>
</tr>
<tr>
<td>Basal insulin (pmol/L)</td>
<td>70 ± 6</td>
<td>65 ± 5</td>
<td>88 ± 16</td>
<td>78 ± 7</td>
</tr>
</tbody>
</table>

Values are means ± SEM.
**p < .001, Final vs Initial.
†p < .05 Initial RT vs Initial RT&WL.
‡p < .05 Initial RT&WL vs Initial RT.
§p < .05 Final RT vs Final RT&WL.
insulin response decreased 16% ($p = .05$) in the RT group and 43% ($p < .05$) in the RT&WL group. Furthermore, due to a larger decrease in insulin response in the RT&WL group after the interventions, there were no significant differences in insulin response between the two groups for each sequential 20-min intervals or for the 20–120 min response. Glucose utilization, $M$, which increased over the 2 hours of hyperglycemia ($p < .05$), was similar in both groups and did not change with the interventions (Figure 2).

A progressive increase in insulin and glucose utilization occurs from 20–120 min during the clamp. This creates an endogenous dose-response system in which $I_3$ (insulin concentration in compartment 3) is the dose and $M$ (glucose utilization) is the physiological response. The relationship of total glucose utilization during each succeeding 20-min interval to the concentration of $I_3$ quantifies the temporal association between these two variables. The slopes of the curves represent the sensitivities of tissues to insulin and are estimates of insulin-dependent glucose utilization. The slope of the relationship between glucose utilization ($M$) and insulin ($I_3$) was significantly lower in the RT&WL group than the RT group ($b = .095$) at baseline (Figure 3), indicating that the RT&WL group metabolized less glucose at each insulin concentration, consistent with a greater degree of insulin resistance. After the intervention, the slope of $M$ vs $I_3$ for the RT&WL group increased by 52%, while the slope of $M$ vs $I_3$ for the RT group did not change; thus, there was no longer a difference in the slope of the relationship between $M$ and $I$ between the two groups (Figure 2).

The 100–120 min insulin response correlated with the initial weight ($r = .62$), BMI ($r = .68$), fat mass ($r = .63$), percent fat ($r = .60$), and waist circumference ($r = .56$), ($n = 13$; all $p < .05$). Using a backward stepwise multiple regression analysis with BMI, percent fat and waist circumference as the independent variables in the model, only BMI remained at the $p < .05$ level to predict the insulin response. The change in insulin response from 100–120 min during the clamp correlated with the change in body weight ($r = .66$), change in fat mass ($r = .63$), and the change in waist circumference ($r = .56$), (all $p < .05$) in all 13 subjects.

**DISCUSSION**

Physical inactivity leads to a deterioration in insulin sensitivity. The increase in body fat associated with the menopausal state exacerbates this, and may predispose older women to an insulin-resistant state. With increased inactivity and obesity, the insulin resistance may predispose older women to develop NIDDM. Results of this study demonstrate that RT, alone or in combination with WL, improves peripheral tissue sensitivity to endogenously released insulin in postmenopausal women. This was demonstrated by either an improvement in the slope of glucose utilization vs insulin concentration or from an equivalent amount of glucose utilization with a reduction in insulin levels. Furthermore, when RT is combined with WL in obese postmenopausal women, the effect is magnified. This suggests that RT and WL may be useful to ameliorate the decline in insulin action that occurs with aging, obesity, and the associated sedentary life style.

The decrease in insulin response after the intervention in the RT&WL group was of sufficient magnitude to enable the relationship of glucose utilization to endogenously released insulin comparable in the two groups. Plausible explanations for this similarity in insulin response after the intervention are the muscular adaptations achieved due to training, along with the similarity in levels of percent body fat in both groups obtained after the interventions. Furthermore, the

### Table 2. Strength Values

<table>
<thead>
<tr>
<th>Kin-Com (Newton meter)</th>
<th>Resistive Training (Initial)</th>
<th>Resistive Training and Weight Loss (Initial)</th>
<th>Resistive Training (Final)</th>
<th>Resistive Training and Weight Loss (Final)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicep flexion</td>
<td>$18 \pm 4$</td>
<td>$25 \pm 4$</td>
<td>$36 \pm 6^*$</td>
<td>$37 \pm 6$</td>
</tr>
<tr>
<td>Tricep extension</td>
<td>$34 \pm 4$</td>
<td>$34 \pm 4^*$</td>
<td>$52 \pm 4^*$</td>
<td>$54 \pm 4^*$</td>
</tr>
<tr>
<td>Leg extension</td>
<td>$63 \pm 3$</td>
<td>$63 \pm 10$</td>
<td>$95 \pm 9^*$</td>
<td>$97 \pm 9^*$</td>
</tr>
<tr>
<td>Leg flexion</td>
<td>$34 \pm 4$</td>
<td>$34 \pm 4^*$</td>
<td>$40 \pm 6$</td>
<td>$64 \pm 6^*$</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

* $p < .01$, Final vs Initial.

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**Figure 1.** Plasma insulin concentrations during the hyperglycemic clamp of the RT (A) and RT&WL (B) groups pretraining (open circles) and posttraining (closed circles). Values are means ± SE. $+p = .05$ and $^*p < .05$ posttraining vs pretraining.
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Figure 2. Glucose metabolized (M) during the hyperglycemic clamp in the RT (A) and RT&WL (B) groups pretraining (open circles) and posttraining (closed circles). Values are means ± SE.

Figure 3. The relationship of glucose utilization to insulin concentration in the extracellular space (compartment 3) in the RT and RT&WL groups pretraining (A) and postraining (B).

A training program allowed the RT&WL group to maintain FFM despite weight loss, thereby maintaining the mass of metabolically active tissue available to utilize glucose. Other possible explanations for the improvement in insulin action observed in the present study include changes in muscle capillarization and an increase in the level of glucose transporters, specifically GLUT-4 protein, the major isoform in skeletal muscle responsible for insulin-stimulated glucose uptake (21).

The benefits of aerobic training on glucose metabolism are well appreciated, with reported improvements in insulin sensitivity ranging between 11–36% (1,2,22,23). Few studies have examined the effect of RT on glucose metabolism. Glucose tolerance may either improve (24,25) or not change (26) with RT. We previously reported that RT in weight-stable men increased glucose disposal over 20% at both physiological and supraphysiological levels of hyperinsulinemia (3). The improvements in insulin sensitivity with RT in postmenopausal women are similar to those achieved with aerobic exercise or with RT in older men.

Although weight loss is difficult to maintain, it results in increased insulin action (27). Weight loss alone improves glucose tolerance in obese subjects (11) as well as in patients with impaired glucose tolerance and NIDDM (10,28,29).
Although the WL in the RT&WL group was only 4 kg, the reduction in insulin response was substantial (43%). We have demonstrated that WL alone of 11 kg (~3 x as in the present study) results in a similar reduction of insulin response (40%) in obese older men (29). This suggests that the combination of RT&WL has a potentiating effect on insulin action. As demonstrated in the present study, changes in body weight, composition, and distribution improve glucose homeostasis. The decreases in insulin response in these subjects after the intervention were correlated to changes in body weight, and could be attributed in large part to the decrease in body fat. The significant correlation between the changes in insulin response and waist circumference is compatible with the concept that fat mass loss from the abdominal depot is associated with an improvement in insulin sensitivity.

Dietary intake could affect glucose homeostasis. A high carbohydrate diet without substantial weight loss does not improve insulin sensitivity (30). However, a high-carbohydrate, high-fiber diet does increase insulin sensitivity in young and older healthy individuals (31). In our study, dietary composition was carefully controlled both before all metabolic testing and during the intervention. Thus, we do not believe that changes in dietary composition influenced our results. The small number of subjects is a limitation of this study. Furthermore, a long-term follow-up of the metabolic parameters is warranted to ascertain whether compliance and these metabolic adaptations are maintained.

In conclusion, resistive training improves muscular strength and insulin action in postmenopausal women. When RT is combined with weight loss, there is a greater reduction in insulin response to hyperglycemia than with RT alone. These results suggest that in obese, sedentary postmenopausal women, RT with and without WL improves glucose homeostasis and thus has the potential to prevent the development of diabetes mellitus.

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REFERENCES


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