Effective Exercise Modality to Reduce Insulin Resistance in Women With Type 2 Diabetes

Darcye J. Cuff, MSC1,2
Graydon S. Meneilly, MD3
Alan Martin, PhD2
Andrew Ignaszewski, MD, FRCP1
Hugh D. Tildesley, MD1
Jiri J. Frohlich, MD, FRCP1

OBJECTIVE — The purpose of this study was to evaluate whether a combined resistance and aerobic training program would improve insulin sensitivity compared with aerobic training alone in postmenopausal women with type 2 diabetes. A second objective was to relate the improved insulin sensitivity to changes in abdominal adipose tissue (AT) and thigh muscle density.

RESEARCH DESIGN AND METHODS — A total of 28 obese postmenopausal women with type 2 diabetes were randomly assigned to one of three 16-week treatments: control, aerobic only training (Ae only), or aerobic plus resistance training (Ae + RT). Pre- and posttreatment outcome measures included glucose disposal by hyperinsulinemic-euglycemic clamp and computed tomography scans of abdominal AT and mid-thigh skeletal muscle.

RESULTS — Glucose infusion rates increased significantly (P < 0.05) in the Ae + RT group. Both exercise groups had reduced abdominal subcutaneous and visceral AT and increased muscle density. The Ae + RT training group exhibited a significantly greater increase in muscle density than the Ae only group. Improved glucose disposal was independently associated with changes in subcutaneous AT, visceral AT, and muscle density. Muscle density retained a relationship with glucose disposal after controlling for abdominal AT.

CONCLUSIONS — Adding resistance training to aerobic training enhanced glucose disposal in postmenopausal women with type 2 diabetes. The improved insulin sensitivity is related to loss of abdominal subcutaneous and visceral AT and to increased muscle density.

Diabetes Care 26:2977–2982, 2003

Aerobic exercise training is an effective intervention for the prevention and treatment of insulin resistance and type 2 diabetes (1–4). Several important issues remain unclear regarding exercise, insulin action, and obesity. Little data are available on women with diabetes, on the most effective components of an exercise program including resistance training, or on the interaction of body composition changes and improvements in insulin action as a result of exercise training. This study addresses these areas by evaluating the addition of resistance training to an aerobic program in postmenopausal women with diabetes and by relating body composition changes to insulin sensitivity improvements.

Resistance training may induce beneficial changes in insulin sensitivity via muscle mass development, effectively increasing glucose storage, facilitating glucose clearance from the circulation, and reducing the amount of insulin required to maintain a normal glucose tolerance (5). Muscle mass is lost with aging; therefore, resistance training may be particularly important in older women. Limited data suggest that improvements in insulin sensitivity after resistance training are similar to those achieved with aerobic exercise training (6–9). Yet, training programs that combine the two modalities (aerobic and resistance training) may be most advantageous because they combine different mechanisms of action (10). This suggests that a combined program may have greater potential to reduce insulin resistance than either exercise regime alone. The primary objective of this study was to evaluate whether adding resistance training to an aerobic training program further improves insulin sensitivity in postmenopausal women with type 2 diabetes.

Exercise training may improve insulin action via changes in regional adipose tissue (AT) deposition, a recognized predictor of risk for type 2 diabetes and cardiovascular disease (11), and more recent evidence suggests that intramuscular lipid is an early contributor to the pathogenesis of insulin resistance (12,13). Currently, there is insufficient evidence to determine whether regularly performed exercise is associated with preferential reductions in abdominal AT, from either subcutaneous or visceral components (14). It is also unclear how aerobic or resistance training affects intramuscular lipid accumulation. The second objective of this study was to evaluate changes in abdominal subcutaneous, visceral, and skeletal muscle AT after exercise training and to relate these changes to changes in insulin sensitivity in obese postmenopausal women with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Subjects

Subjects were recruited from the St. Paul’s Hospital Diabetes Teaching and Training Center and by newspaper advertisement. Inclusion criteria were as follows: postmenopausal status, type 2 diabetes con-
Exercise to reduce insulin resistance

Table 1—Initial subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Ae+RT</th>
<th>Ae only</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.0 ± 2.9</td>
<td>63.4 ± 2.2</td>
<td>59.4 ± 1.9</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>4.7 ± 1.2</td>
<td>3.7 ± 0.9</td>
<td>3.2 ± 0.6</td>
</tr>
<tr>
<td>Number of participants treated with:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet only</td>
<td>2</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Single oral agent</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Two or more oral agents</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>95.6 ± 6.5</td>
<td>89.5 ± 3.9</td>
<td>81.2 ± 3.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>36.7 ± 2.0</td>
<td>33.3 ± 1.5</td>
<td>32.5 ± 1.4</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>119.0 ± 2.1</td>
<td>111.1 ± 2.1</td>
<td>106.1 ± 2.3</td>
</tr>
<tr>
<td>Glycosylated hemoglobin (%)</td>
<td>1.75 ± 0.12</td>
<td>1.64 ± 0.10</td>
<td>1.68 ± 0.11</td>
</tr>
<tr>
<td>Glucose infusion rate (mg · kg⁻¹ · min⁻¹)</td>
<td>2.29 ± 0.46</td>
<td>2.36 ± 0.33</td>
<td>2.78 ± 0.49</td>
</tr>
<tr>
<td>CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total abdominal AT (L4–L5) (cm²)</td>
<td>808.4 ± 68.0</td>
<td>720.0 ± 42.0</td>
<td>616.8 ± 41.9</td>
</tr>
<tr>
<td>Subcutaneous (cm²)</td>
<td>549.3 ± 50.8</td>
<td>468.9 ± 26.9</td>
<td>401.2 ± 42.9</td>
</tr>
<tr>
<td>Visceral (cm²)</td>
<td>259.1 ± 34.4</td>
<td>251.1 ± 22.9</td>
<td>215.7 ± 25.8</td>
</tr>
<tr>
<td>Midthigh skeletal muscle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional area (cm²)</td>
<td>225.8 ± 8.9</td>
<td>208 ± 10.1</td>
<td>224.1 ± 15.8</td>
</tr>
<tr>
<td>Low-density muscle (cm²)</td>
<td>50.6 ± 4.2</td>
<td>51.3 ± 6.7</td>
<td>49.4 ± 7.3</td>
</tr>
<tr>
<td>Normal-density muscle (cm²)</td>
<td>175.3 ± 7.5</td>
<td>156.6 ± 12.8</td>
<td>174.8 ± 11.1</td>
</tr>
</tbody>
</table>

Data are n or means ± SE.

trolled by diet or oral agents, central obesity (waist circumference >90 cm), and an inactive lifestyle (<20 min of moderately vigorous activity, twice per week, over the last year). Eligible subjects underwent a physical examination and a maximal graded exercise tolerance test with electrocardiogram monitoring to exclude individuals with subjective or objective evidence of coronary artery disease. Subjects were then randomly assigned to one of three groups: usual care, aerobic plus resistance training (Ae+RT), or aerobic only training (Ae only). A total of 28 women completed the study; their descriptive characteristics are outlined in Table 1. Their initial age, years since diagnosis of diabetes, glycosylated hemoglobin levels, weight, BMI, level of fitness, or computed tomography (CT) measures did not differ between the groups (P > 0.05), although subcutaneous AT areas displayed a trend to statistical difference across groups (P = 0.057). Distribution of diabetic therapy is outlined in Table 1.

All subjects gave their written informed consent to participate in the study, which was conducted according to the ethical guidelines of the University of British Columbia and St. Paul’s Hospital.

Exercise training protocols

Ae+RT. A total of 10 women participated in a supervised 16-week structured aerobic and resistance training program, three times per week. Each class consisted of a warm-up, an aerobic phase, a resistance training phase, and a cooldown to total a class time of 75 min. The aerobic phase involved individually prescribed exercise at 60–75% of heart rate reserve (based on the initial maximal graded exercise tolerance test), using treadmills, stationary bicycles, recumbent steppers, elliptical trainers, and rowing machines. The resistance training program consisted of five exercises (leg press, leg curl, hip extension, chest press, and latissimus pull down) for two sets of 12 repetitions using stack weight equipment. Resistive training began with light loads and thereafter progressed as technique permitted. Training loads were monitored during the program, with strength improvements reported from the third week of training (to allow for learning) as compared with the last week.

Ae only. Nine women participated in a supervised aerobic training program lasting 16 weeks, three times per week, with 75-min structured exercise classes. Each class consisted of a warm-up, an aerobic phase, and a cooldown. Aerobic exercise intensity was individually prescribed as for the Ae+RT group, and the equipment used was the same. Low-impact low-intensity dynamic movement replaced the resistance training component of the Ae+RT group; therefore, the warm-up and cooldown phases were somewhat longer than in the combined training group. Published values for low-impact aerobic movement are estimated to be ~0.1 kcal · min⁻¹ · kg⁻¹ (15,16), similar to the estimated energy cost of resistance training (17,18). These class designs were used to minimize potential differences in energy expenditure between the exercise training groups.

Peak VO₂ determination

Peak VO₂ was determined before entering the study and at the end of the 16 weeks. Respiratory gas analyses were carried out during a progressive Naughton protocol treadmill test to voluntary exhaustion. Oxygen uptake (VO₂) was determined using a Beckman metabolic cart (SensorMedics Yorba Linda, CA). The 12-lead electrocardiogram analyses were ongoing throughout the test.

Dietary assessment

Subjects were asked to continue with their current diet and physical activity patterns outside of the study protocol. Dietary patterns were analyzed by 3-day food records before and after the study and were analyzed with the Nutritionist IV software (First Data Bank, San Bruno, CA).

Regional AT and skeletal muscle by CT imaging

CT imaging was performed on a General Electric CT/i scanner (General Electric Medical Systems, Milwaukee, WI) before and after the treatment. An initial lateral scout, centered at the level of the iliac crest, allowed accurate positioning of a single non-angled axial image at the L4/L5 vertebral disc space. A 10-mm single-image scan was taken using the parameters of 120 kVp, 300 mA, with 1 s duration, with a 512 by 512 matrix. This image was used to assess cross-sectional areas of subcutaneous and visceral AT. A second anterior-posterior scout covered the iliac crest to just below the knee to allow accurate positioning of a second image at the midpoint of the femur, from the superior rim of the femoral head to the
in the euglycemic clamp study was to measure basal insulin and glucose. At their repeat glucose clamp at 48

subjects in the exercise groups underwent fast, as previously described (19). Sub-

cuticular laboratory after a 12-h overnight

Subjects were asked to report to the hos-

ter the 16 weeks of training, the exercise
groups improved their
ter the 16 weeks of training, the exercise
groups improved their

Hypermuscular-eryglicemic clamp

Subjects were asked to report to the hos-

ter the 16 weeks of training, the exercise
groups improved their

Results are reported as group means ±

Statistical analysis

Results are reported as group means ±

Blood work

Venous blood samples were analyzed for fasting glucose, glycosylated hemoglobin, total cholesterol, LDL, HDL, triglyceride, and apolipoprotein B. Sampling was done after a 14-h fast, with no alcohol for the preceding 3 days. All measures were con-
ducted in the St. Paul’s Hospital, accred-

tance of

Blood work

Venous blood samples were analyzed for fasting glucose, glycosylated hemoglobin, total cholesterol, LDL, HDL, triglyceride, and apolipoprotein B. Sampling was done after a 14-h fast, with no alcohol for the preceding 3 days. All measures were con-
ducted in the St. Paul’s Hospital, accred-

RESULTS — Both exercise groups lost

Fitness and dietary measures

Attendance for the exercise sessions averaged 92% across both training groups. After the 16 weeks of training, the exercise
groups improved their O2peak by an average of 11.4% versus the control group (P < 0.05). The two exercise groups did

tance of

Blood work

Analyses of fasting venous blood samples for glycosylated hemoglobin (Table 2), total cholesterol, LDL, HDL, triglyceride, and apolipoprotein B did not reveal any significant changes between groups after the intervention (lipid data not shown).
Euglycemic-hyperinsulinemic clamp

Initial values of steady-state glucose disposal did not differ across groups. Comparisons of change in steady-state glucose infusion demonstrated a statistically significant difference between the Ae+RT group and the control group (increase of 1.82 ± 0.52 vs. 0.07 ± 0.28 mg·kg⁻¹·min⁻¹, P < 0.05) and a trend to increase compared with the Ae only group (0.55 ± 0.36 mg·kg⁻¹·min⁻¹, P = 0.10) (Table 2).

CT scans

Adipose tissue areas. The loss in total abdominal AT cross-sectional area was greater in the Ae + RT group than the control group (−48.3 ± 18.4 vs. 17.1 ± 18.0 cm², P < 0.05) (Table 2). The change in the other AT area compartments did not achieve statistical significance. When the two exercise groups were combined for analyses, the change in subcutaneous abdominal AT and in total abdominal AT were greater in the exercise groups compared with the control group (total abdominal AT: −33.5 ± 11.2 vs. 17.1 ± 18.0 cm², P < 0.05; subcutaneous abdominal AT: −15.5 ± 9.2 vs. 17.4 ± 9.0 cm², P < 0.05).

Muscle cross-sectional areas. Muscle cross-sectional area displayed a trend to increase across the three groups (Ae + RT group, 5.9 ± 2.0 cm²; Ae only group, 0.9 ± 2.1 cm²; control group, 0.7 ± 1.6 cm², P = 0.110) (Table 2). After training, low-density muscle area was decreased in both the Ae + RT (−4.1 ± 2.5 cm², P < 0.05) and Ae only group (−1.4 ± 1.3 cm², P < 0.05) compared with the control group (3.2 ± 1.0 cm²), whereas the amount of normal-density muscle tissue was increased. The increase in the normal-density tissue in the Ae + RT training group (10.5 ± 2.0 cm²) was greater than both control (−3.5 ± 1.7 cm²) and Ae only (2.3 ± 1.8 cm²) groups’ changes (P < 0.05, Table 2).

Relationship of regional body composition with glucose disposal

The change in abdominal subcutaneous AT (r = −0.64, P < 0.001), visceral AT (r = −0.32, P < 0.05), muscle cross-sectional area (r = 0.43, P < 0.05), and normal-density muscle (r = 0.52, P < 0.01) were all correlated with the change in glucose infusion rates during the euglycemic clamp. After control for the change in subcutaneous abdominal AT, both muscle cross-sectional area (r = 0.47, P < 0.01) and area of normal-density muscle (r = 0.46, P < 0.01) retained significant relationships with glucose disposal, but visceral AT did not.

CONCLUSIONS — We tested the effect of adding resistance training to an aerobic training program on insulin sensitivity and changes in abdominal obesity and skeletal muscle characteristics in postmenopausal women with type 2 diabetes. The principal finding is that a combined aerobic plus resistance training program elicited significant improvements in insulin sensitivity compared with the control group. Both training regimes resulted in reductions in body weight and total abdominal obesity, specifically from the subcutaneous component of abdominal AT. Training reduced the low-density component of thigh muscle, with a concomitant increase in the normal-density component, with an incremental effect seen with aerobic plus resistance training. The change in insulin resistance was related to changes in abdominal subcutaneous and visceral adipose and muscle cross-sectional area and density.

Exercise training modality and glucose disposal

The addition of resistance training to an aerobic program resulted in an improved glucose disposal, which was not evident in this study after aerobic training alone. This supports the initial hypothesis that the addition of resistance training would prove effective in improving insulin sensitivity. Resistance training alone has been seen to exert a beneficial effect on glucose disposal in young nonobese women (20), men with impaired glucose tolerance (8), and healthy postmenopausal women (7). This work indicates that the outcome of a combined aerobic plus resistance training program may be more successful in improving insulin resistance than a program with aerobics alone.

Improvement in insulin sensitivity was seen in the Ae + RT group but was not evident in the Ae only group. Other work has demonstrated improved insulin sensitivity in response to aerobic only training programs in nonobese, obese, or impaired glucose tolerant subjects. Subjects with established diabetes may be more insulin resistant, perhaps requiring a longer timeframe to respond to an aerobic training stimulus. It appears that using a more effective exercise stimulus, i.e., one that includes resistance training, may bring about changes within the timeframe investigated.

Beneficial improvements in insulin sensitivity brought about by exercise training attenuate within 3–6 days after the last exercise session (21–23). Our results may reflect the impact of the most recent exercise session, or a training adaptation or an interaction of both. In clinical application, this suggests the value of consistent exercise frequency to maintain the beneficial effects on carbohydrate metabolism.

No change was seen in this study in glycosylated hemoglobin levels. Recent reviews of the response of glycosylated hemoglobin levels to exercise training found a modest response (0.5–1.0%) or no response to training interventions (24,25). Variable findings have been attributed to small sample sizes and the complex pathophysiology of type 2 diabetes, which could have contributed to the lack of findings in this study.

Our finding of improved insulin sensitivity in response to a combined aerobic plus resistance training program suggests that resistance training may be a valuable aspect of exercise programming. This may be particularly true in light of the lack of significant response to an aerobic training only program in this study population. These are the first data demonstrating the effectiveness of resistance training in older women with type 2 diabetes and the effectiveness of a combined training program.

Regional body composition changes

In the combined exercise group, total abdominal AT was decreased, with the loss more apparent from the subcutaneous depot than from the visceral depot. These findings differ from reports in which exercise training without weight loss resulted in decreases in both abdominal AT areas in diabetic men (2) or decreased visceral but not subcutaneous abdominal depot in nonobese postmenopausal women (26). In studies where exercise training is accompanied by substantial weight loss, decreases in both abdominal regions have been documented in obese women (27,28) and obese men (18,29). The variable differences across studies may be attributable to small adiposity changes (in studies with no weight
change), small sample sizes, and large variability in these depots seen in most studies. This study group was characterized by abdominal obesity (BMI of $\sim 34$ kg/m$^2$ and waist circumference of $\sim 112$ cm) by selection criteria, but considerable heterogeneity in abdominal adipose patterning was apparent. Two studies with large sample sizes have shown changes in both visceral and subcutaneous abdominal AT after exercise training with small weight loss in obese postmenopausal women (30) or no weight loss in normal-weight premenopausal women (31).

The method of expressing changes in adiposity may affect study conclusions. If the change is expressed relative to initial levels (i.e., as a percentage), it may lead to the conclusion that visceral adipose losses are greater than abdominal subcutaneous losses. But if evaluated as an absolute change value, losses from abdominal subcutaneous AT are equal to or greater than that from the visceral area (18,27,28,31).

Cross-sectional associations have demonstrated a stronger relationship of subcutaneous abdominal AT with insulin resistance (32,33). Subcutaneous abdominal AT has been identified as the source of free fatty acids (34), which are thought to be involved in the negative health impacts of increased abdominal obesity. These data, taken in conjunction with the data from our study indicating a greater loss of subcutaneous abdominal AT after exercise training, support the suggestion that visceral AT is not of singular importance (32,33,35) but that subcutaneous abdominal AT also plays a role.

Muscle cross-sectional area and muscle density

Low-density muscle tissue is thought to contain greater amounts of inter- and intracellular lipid and has been linked to insulin resistance. It has been unclear how exercise training affects this aspect of muscle composition. An endurance training effect could include depletion of intramuscular lipid, and the addition of resistance training could stimulate muscle mass development and possibly lipid depletion.

Muscle cross-sectional area did not change after aerobic training but displayed a trend to increase after aerobic plus resistance training. This confirms other findings of no change with aerobic training, with muscle hypertrophy after resistance training (18,20,26,29,36).

In both training groups, low-density muscle area decreased and normal-density muscle area increased. The increment in normal-density muscle was greater in the aerobic plus resistance training group. Others have reported similar changes in muscle composition after aerobic training with (27) or without (20) weight loss and after resistance training (20,36). These findings indicate that exercise training reduces the proportion of low-density muscle and increases the proportion of normal-density muscle, changes that are thought to reflect changes in intermuscular lipid content. Results from magnetic resonance imaging studies have also demonstrated a reduction in intermuscular fat after either aerobic or resistance training, although these studies have involved larger weight losses (28). Our results extend these findings and suggest that using both exercise modalities is additive in the effects on muscle composition change. Furthermore, muscle composition characteristics, linked to insulin resistance, can thus be ameliorated in postmenopausal women with type 2 diabetes.

Relationship of changes in body composition to changes in insulin sensitivity

Our results suggest that improvements in glucose disposal after exercise training are independently related to changes in subcutaneous abdominal obesity and to muscle cross-sectional area and muscle density in obese postmenopausal women with type 2 diabetes. Change in visceral adipose did not show a relationship with glucose disposal independent of subcutaneous abdominal AT. Few published reports are available that directly assess insulin sensitivity relative to changes in body composition after a training program. One study reported a significant association between glucose disposal and changes in visceral AT in obese men, although possible relationships to subcutaneous AT were not reported (29).

The independent relationship of muscle characteristics to glucose disposal after exercise training is a new finding. One study was unable to relate muscle mass (assessed by magnetic resonance imaging) to insulin sensitivity after aerobic training (29). The difference may be due to the added effectiveness of muscular strength training. The improvement in glucose disposal in young nonobese women seen after strength training disappeared when indexed for whole-body fat-free mass (20), suggesting that the increase in lean body tissue (including skeletal muscle) was responsible for the improvement. An endurance-trained group in the same study retained insulin sensitivity improvements after accounting for fat-free mass. These authors were not able to demonstrate a relationship between increased attenuation value and glucose disposal in either the endurance- or resistance-trained groups. Muscle density or intramuscular lipid may play a more significant role in the older diabetic group of this study than in the healthy younger normal-weight group.

Summary

Enhanced glucose uptake was seen in postmenopausal women with type 2 diabetes after a combined aerobic plus resistance training program. This improvement was related to losses of AT area from abdominal subcutaneous depot and to increases in thigh muscle cross-sectional area and thigh muscle attenuation characteristics. We conclude that a combined endurance plus resistance training program is most effective in improving insulin sensitivity in these women and that the improvements are associated with changes in muscle characteristics brought about by strength training.

Acknowledgments — This research was supported by a grant from the Heart and Stroke Foundation of British Columbia and the Yukon (J.J.F., principal investigator). D.J.C. is a PhD candidate.

We are indebted to the participants who donated blood, sweat, and laughter; to Ellen Bjornson for her exceptional exercise leadership; and to Chris Lockhart and Rosemary Torresani for their expertise and care during the euglycemic clamp studies.

This study is published in abstract form in Diabetes, June 2003.

References


Exercise to reduce insulin resistance


34. Guo ZK. Regional postprandial fatty acid metabolism in different obesity phenotypes. *Diabetes* 48:1586-1592, 1999
