

Effects of Aerobic and Resistive Exercise Training on Glucose Disposal and Skeletal Muscle Metabolism in Older Men

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Background. Aging is associated with insulin resistance, primarily as a result of physical inactivity and increased abdominal obesity. We hypothesized that aerobic (AEX) or resistive (RT) exercise training would result in comparable improvements in glucose disposal in older men, but that there would be different metabolic adaptations in skeletal muscle.

Methods. Thirty-nine older (63 ± 1 years, mean \pm standard error of the mean), overweight and obese (body mass index = 30.3 ± 0.4 kg/m²) men were assigned to AEX (treadmill walking and/or jogging, $n = 19$) or RT (upper and lower body, $n = 20$) programs 3 d/wk for 6 months, with 9 completing AEX and 13 completing RT. Testing before and after the exercise programs included body composition, euglycemic–hyperinsulinemic clamps, and vastus lateralis muscle biopsies.

Results. Maximal oxygen consumption ($\text{VO}_{2\text{max}}$) increased by 16% after AEX ($p < .01$), while leg and arm muscle strength increased by $45 \pm 5\%$ and $27 \pm 5\%$ after RT ($p < .0001$). Although participants were monitored to maintain their body weight during the exercise program, body weight decreased by 2% after AEX ($p < .05$), and increased by 2% after RT ($p < .05$). Whole-body glucose disposal, determined during the last 30 minutes of a 2-hour 480 pmol/m²/min euglycemic–hyperinsulinemic clamp, increased comparably by 20%–25% after AEX (51 ± 5 to 61 ± 5 $\mu\text{M/kg fat-free mass/min}$, $p < .05$) and RT (49 ± 3 to 58 ± 3 $\mu\text{M/kg fat-free mass/min}$, $p < .05$). The increase in vastus lateralis muscle glycogen synthase fractional activity in response to insulin stimulation was significantly higher after AEX compared to after RT ($279 \pm 59\%$ compared to $100 \pm 28\%$ change, $p < .05$). Neither AEX nor RT altered muscle glycogen synthase total activity, glycogen content, or levels of phosphatidylinositol 3-kinase.

Conclusion. These results suggest that AEX and RT result in comparable improvements in glucose metabolism in older men, whereas an increase in insulin activation of glycogen synthase occurred only with AEX. These improvements in insulin sensitivity could reduce the risk of metabolic syndrome and type 2 diabetes and attenuate the development of cardiovascular disease.

AGING is associated with a deterioration of glucose tolerance and insulin resistance, primarily as a result of physical deconditioning, increased abdominal obesity (1,2), and impaired insulin action in the skeletal muscle (3,4). Increased abdominal obesity with aging is a direct result of poor dietary habits and reduced physical activity, as well as genetic and hormonal factors. Metabolic changes in the skeletal muscle may contribute to the development of insulin resistance in older individuals via reduced glycogen synthase (GS) activity (5), reduced oxidative capacity (6), and reduced activation of proteins involved in insulin signaling and glucose transport (7,8).

Regular aerobic (AEX) and resistive (RT) exercise training are often recommended to older individuals as a means to improve insulin sensitivity and glucose homeostasis (9–13), thereby preventing the development of the metabolic syndrome and type 2 diabetes mellitus and reducing the risk for cardiovascular disease. Both AEX and RT improve insulin sensitivity in part by reducing total and abdominal body fat (14–18). Increased basal GS total activity (19,20), glycogen synthesis (21), and GLUT4 levels (11,22–26) also contribute to the improvements in insulin sensitivity with AEX and RT. AEX increases the activity of insulin signaling proteins insulin receptor substrate

(IRS1) and phosphatidylinositol (PI) 3-kinase in young persons (27,28), but not in older persons (29), whereas RT does not affect the activity of IRS1 or PI 3-kinase (19). Although one study has examined the effect of exercise training on in vivo insulin activation of skeletal muscle GS in middle-aged, insulin-resistant persons (20), the effects of exercise training in older, insulin-resistant persons has not been previously reported. In addition, the effects of RT on GS activation during a euglycemic–hyperinsulinemic clamp are not known.

To our knowledge, no studies have made a direct comparison of whether AEX and RT differ in the nature and/or the magnitude of the mechanisms by which both types of exercise improve glucose disposal in older, obese adults. We hypothesized that regular exercise, whether AEX or RT, will improve glucose disposal in older, obese men, but the nature and magnitude of changes in skeletal muscle metabolism will differ between the two types of exercise training because of differences in the exercise stimulus to the muscle. A better understanding of the mechanisms contributing to the improvement in insulin action with either AEX or RT will permit the development of more effective exercise regimens in the treatment and prevention of insulin resistance and its health consequences in older, obese adults.

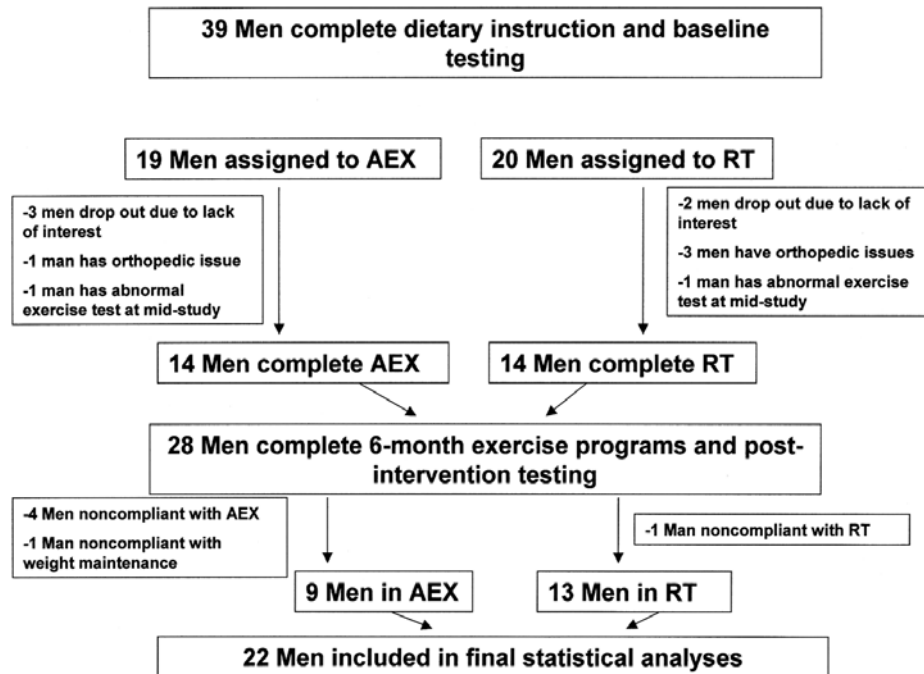


Figure 1. Flow chart of participant enrollment and completion of the 6-month intervention. AEX = aerobic exercise; RT = resistive exercise.

MATERIALS AND METHODS

Participants

We enrolled 39 healthy nonsmoking, sedentary, overweight (body mass index [BMI] 25–29.9 kg/m²) and obese (BMI 30–40 kg/m²) middle-aged and older (50–79 years) men from a group of 97 men from the Baltimore–Washington area. All potential participants were weight-stable (<2 kg weight change) and sedentary (<20 minutes of aerobic exercise 2 times/wk) for the previous 6 months. Written informed consent was obtained from all individuals according to the guidelines of the University of Maryland Institutional Review Board for Human Research.

All participants underwent initial screening evaluations that included a medical history, physical examination, fasting blood profile, and 12-lead resting electrocardiogram. Individuals with untreated hypertension (blood pressure >160/90 mmHg) or hyperlipidemia (triglycerides ≥4.5 mM, cholesterol >6.2 mM, low-density lipoprotein cholesterol >4.3 mM) were referred to their doctor for therapy and allowed to enter if they were treated with an antihypertensive or lipid-lowering drug that did not affect glucose metabolism. Men with heart disease, cancer, or liver, renal, or hematological disease were excluded from participation. In addition, all participants underwent a screening Bruce graded treadmill test to exclude those men with asymptomatic coronary artery disease. Those participants with positive tests were excluded, unless they underwent further cardiovascular evaluation and were found to have false-positive tests by thallium scintigraphy ($n = 4$ participants).

Study Protocol

Participants received instruction in maintaining a weight-stable, American Heart Association Step I diet, by a reg-

istered dietitian 1 d/wk for 10–12 weeks, prior to baseline testing (30). Participants were weight-stable on the Step I diet prior to baseline testing, and were instructed to maintain the Step I diet throughout the study. Participants were weighed on a weekly basis to confirm weight stability, and calories were adjusted to keep body weight stable during exercise training.

After completion of the dietary instruction, the participants were assigned to either AEX ($n = 19$) or RT ($n = 20$), 3 d/wk for approximately 6 months. Six men (two from AEX, four from RT) dropped out of the exercise program due to orthopedic injuries ($n = 4$) or subsequent abnormal treadmill test at midstudy testing ($n = 2$), five (three from AEX, two from RT) dropped out due to lack of interest and time commitment, and six (five from AEX, one from RT) were dropped from the final study analyses due to noncompliance to exercise (did not maintain prescribed frequency, intensity, or duration of exercise, as described below, $n = 5$) or weight maintenance compliance issues (lost >4 kg during the study, $n = 1$) (Figure 1). Thus, nine men successfully completed AEX and 13 men successfully completed RT programs. The baseline characteristics of those participants who dropped out due to lack of interest or noncompliance issues did not differ from those of the men who completed the study (data not shown).

The AEX included 5-minute warm-up and cool-down periods, followed by treadmill walking or running, with a gradual increase in duration and intensity over the first 9 weeks to a final duration and intensity of 45–50 min/d at 75%–80% maximal heart rate reserve (31) for the remainder of the exercise program. After 3 months of exercise training, a midstudy maximal oxygen consumption (VO_{2max}) test was performed (data not shown), and the training intensity was adjusted based on improvements in aerobic capacity. The

RT included both upper (one set) and lower body (two sets) exercises, using pneumatic (resistive) machines (leg press, chest press, leg curl, latissimus pull down, leg extension, military press). Participants alternated the upper and lower body exercises to minimize fatigue. The resistance was set at 80% of the 1 repetition maximum (1 RM), with the participant performing 8–12 repetitions per set. When participants reached 12 repetitions, the amount of resistance was increased by 5% at the next exercise session. After 3 months of exercise, a midstudy 1 RM strength test was performed (data not shown), and resistance levels for each exercise were adjusted accordingly. Participants also performed one set (8–12 repetitions) of free weight biceps and triceps curls and one set of abdominal crunches (25–30 repetitions) during each exercise session. For both exercise programs, blood pressures and heart rates were recorded before warm-up and after completion of the exercise session. Exercise compliance (attendance and adherence to the exercise program) was documented each week of the study.

Metabolic Testing

All participants were weight-stable within 1 kg for at least 2 weeks before testing. All postexercise training measures were performed at least 24 hours (but not longer than 36 hours) after the last exercise session.

Oral Glucose Tolerance Test

An oral glucose tolerance test was performed after a 12-hour fast. Blood samples were drawn before and at 30-minute intervals for 2 hours after ingestion of 75 g of glucose. Plasma glucose concentrations were measured using the glucose oxidase method (Beckman Instruments, Fullerton, CA). Results of the oral glucose tolerance test were used to document baseline glucose tolerance status in the participants (32).

Body Composition Measurements

Height (in centimeters) and weight (in kilograms) were measured to calculate BMI. Circumference measurements of the waist (at the narrowest point superior to the hip) and the hip (at the greatest gluteal protuberance) were measured in duplicate. All participants underwent a total body scan using dual energy x-ray absorptiometry (DXA; Lunar Corp., Madison, WI) to determine percent body fat, fat mass, and fat-free mass (FFM; total body bone mineral content plus lean tissue mass). A single-slice computed tomography scan taken midway between L₄ and L₅ was performed using a PQ6000 scanner (General Electric, Milwaukee, WI) to measure visceral abdominal adipose tissue (VAT), subcutaneous abdominal adipose tissue (SAT), and sagittal diameter (determined at the level of the umbilicus and the fourth lumbar intervertebral disk; 33). A single-slice computed tomography scan was also taken at the midthigh level to quantify muscle area (Hounsfield units [HU]: 30 to 80), subcutaneous fat area of the thigh (HU: −190 to −30), and low-density lean tissue (HU: 0 to 29). Because there were no differences between muscle areas of the right and left thigh, the right thigh muscle area was used for all analyses.

Measurement of $\dot{V}O_{2\max}$

A treadmill $\dot{V}O_{2\max}$ test was performed by each participant to determine his cardiorespiratory fitness. A true $\dot{V}O_{2\max}$ was considered to be attained if two of the following three criteria were met: (i) respiratory exchange ratio at maximal exercise >1.10, (ii) maximal heart rate >90% of age-predicted maximum (220–age), and (iii) a plateau in $\dot{V}O_2$ (<200 ml/min change in the $\dot{V}O_2$) with an increase in workload. If the criteria for a true $\dot{V}O_{2\max}$ were not met, the test was repeated. $\dot{V}O_{2\max}$ is expressed in liters per minute.

Muscle Strength

Strength testing was performed on Keiser K-300 equipment (Keiser Corp., Fresno, CA), using a protocol previously described (13). Participants were familiarized with the equipment at least two times with low-intensity exercise sessions prior to the initial strength evaluation. The strength testing determined a participant's 1 RM, defined as the maximum amount of weight that can be moved through the full range of motion successfully one time. Strength was measured in both upper and lower body using the following exercise machines: leg press, leg extension, chest press, and latissimus pull down.

Hyperinsulinemic–Euglycemic Glucose Clamp and Muscle Biopsies

For 2 days prior to the clamp study, participants were provided with an American Heart Association weight-maintaining Step I diet (30). The composition of the diet was 50%–55% carbohydrate, 15%–20% protein, <30% fat, and 300–400 mg of cholesterol per day and a polyunsaturated-to-saturated fat ratio of 0.6–0.8. The number of calories allowed for each participant was estimated from the 7-day food records and from estimates of energy expenditure (34). The glucose clamp was performed in the morning after a 12-hour overnight fast.

Whole-body glucose disposal was measured after a 12-hour overnight fast using the hyperinsulinemic–euglycemic glucose clamp technique (35). Briefly, an intravenous catheter was inserted into an antecubital vein for infusion of insulin and glucose, and a second catheter was inserted into a dorsal hand vein for blood sampling. The hand was then placed in a warming box thermostatically controlled at 70°C to arterialize the blood. After a priming dose of insulin, Humulin insulin (Eli Lilly, Indianapolis, IN) was infused at a constant rate of 240 and 480 pmol/m²/min for 2 hours at each insulin dose. Plasma glucose levels were measured at 5-minute intervals using the glucose oxidase method (Beckman Instruments, and were maintained at basal levels with a variable infusion of 20% glucose, which was adjusted according to a computerized algorithm. Samples were obtained at 10-minute intervals during the clamp for subsequent measurement of plasma insulin levels by radioimmunoassay (Linco Research, Inc., St. Charles, MO).

Indirect Calorimetry

Continuous indirect calorimetry was performed for 30 minutes prior to the start of the glucose clamp and during the last 30 minutes of each insulin infusion by the open

Table 1. Body Composition at Baseline (Pre) and After 6 Months of Aerobic or Resistive Exercise Training (Post)

Variables	Aerobic Exercise (N = 9)		Resistive Exercise (N = 13)	
	Pre	Post	Pre	Post
Body weight, kg	92.1 ± 3.8	90.4 ± 3.6*	91.8 ± 3.2	93.2 ± 3.1*
Body mass index, kg/m ²	29.9 ± 0.7	29.4 ± 0.5*	29.4 ± 0.8	29.8 ± 0.8
Waist, cm	102 ± 2	102 ± 3	103 ± 3	103 ± 2
% body fat	31.7 ± 1.7	30.1 ± 1.5*	29.0 ± 1.1	29.6 ± 1.1
Fat mass, kg	29.6 ± 2.3	27.5 ± 1.8*	27.1 ± 1.8	27.8 ± 1.8
Fat-free mass, kg	62.9 ± 2.4	63.9 ± 2.8	65.4 ± 1.6	66.3 ± 1.3
Mid thigh muscle area, cm ²	121 ± 8	119 ± 6	122 ± 6	130 ± 5
Mid thigh low-density lean tissue area, cm ²	20 ± 3	20 ± 2	21 ± 3	23 ± 2
Visceral adipose tissue area, cm ²	166 ± 24	150 ± 22	154 ± 17	160 ± 15
Subcutaneous adipose tissue area, cm ²	291 ± 13	270 ± 19*	278 ± 18	277 ± 14
Sagittal diameter, cm	25 ± 1	24 ± 1*	25 ± 1	25 ± 1

Notes: Values are means ± standard error of the mean.

* $p < .05$, Pre versus Post.

circuit dilution technique using a SensorMedics DeltaTrac cart (Yorba Linda, CA) to quantitate rates of glucose and fat oxidation with correction for protein oxidation based on 24-hour urinary urea nitrogen, as previously described (33). Nonoxidative glucose metabolism is the difference between total glucose uptake and glucose oxidation.

Calculations

The mean plasma glucose level was computed for each individual participant and expressed as a percentage of the desired goal. The plasma glucose levels were 5.8 ± 0.1 and 5.9 ± 0.2 mM/L (mean ± standard error of the mean, p = not significant [NS], pre- vs postexercise training for AEX and RT groups together), which was $98.3 \pm 0.3\%$ (baseline) and $98.1 \pm 0.3\%$ (6 month) of the desired goal, with a coefficient of variation of $5.5 \pm 0.4\%$ and $6.0 \pm 0.2\%$, respectively. Values of mean glucose disposal (M; $\mu\text{M}/\text{kg}_{\text{FFM}}/\text{min}$) were calculated at 5-minute intervals, and were averaged over the last 30 minutes of each insulin dose. Steady-state plasma insulin levels were averaged from 10–120 minutes and 130–240 minutes for the lower and higher insulin doses, respectively.

Muscle Biopsies and Analysis

Prior to the start of the clamp procedure, a vastus lateralis muscle biopsy was taken from each participant under local anesthesia ($n = 6$ for AEX, $n = 11$ for RT). Muscle tissue was used for the measurement of the p85 subunit of PI 3-kinase protein levels (UBI; Lake Placid, NY; 8,36), citrate synthase activity (37), and glycogen content (38). Insulin-stimulated muscle biopsies were performed during the glucose clamp after the $240 \text{ pmol}/\text{m}^2/\text{min}$ insulin dose in a subset of men ($n = 5$ for AEX, $n = 6$ for RT) to determine basal and insulin-stimulated GS fractional, independent, and total activities. The frozen muscle samples were lyophilized and microdissected before assay (39). The concentrations of

glucose-6-phosphate used to determine GS total and independent activities were 10 mmol/L and 0.1 mmol/L, respectively (40).

Statistical Analyses

Data were analyzed using standard statistical software packages (Statview for Windows; SAS Institute, Cary, NC). Differences between groups and pre- versus post-testing were determined using nonparametric statistical tests (Mann-Whitney and Wilcoxon signed rank tests). Spearman rank correlations were calculated between variables of interest. All data are presented as mean ± standard error of the mean. Statistical significance was set at $p < .05$.

RESULTS

The study included 9 men (5 AEX, 4 RT) with normal glucose tolerance, 7 men (1 AEX, 6 RT) with impaired fasting glucose (fasting plasma glucose >5.5 mM and <7.0 mM) or impaired glucose tolerance (2-hour postprandial glucose ≥ 7.8 mM and <11.1 mM), and 6 men ($n = 3/\text{group}$) with unconfirmed diabetes (fasting plasma glucose ≥ 7.0 mM or 2-hour postprandial glucose ≥ 11.1 mM; 32). The glucose tolerance status of the men did not affect the changes with exercise training or the relationships between M, body composition, and $\text{VO}_{2\text{max}}$ (data not shown). There were no initial differences in age, body composition, $\text{VO}_{2\text{max}}$, or M between the exercise groups, and the age of the men did not affect the overall results of the study. The average attendance rate was similar between the groups and averaged $75 \pm 4\%$ versus $74 \pm 5\%$ for AEX and RT, respectively ($p = \text{NS}$), despite the fact all participants were encouraged to attend 85% or more of the exercise sessions.

Body Composition (Table 1)

Participants in the AEX group lost a small but significant amount of weight, fat mass, and percent body fat ($-1.8 \pm 0.6\%$, $-6.1 \pm 2.6\%$, and $-4.8 \pm 1.9\%$ change, respectively, $p < .05$). The participants in the RT group gained a small but significant amount of weight ($1.6 \pm 0.6\%$, $p < .05$), but there were no significant changes in fat mass or percent body fat. SAT and sagittal diameter decreased significantly by $-7 \pm 3\%$ and $-5 \pm 2\%$ ($p < .05$) in AEX, but did not change in RT. Waist circumference, FFM, VAT, mid thigh muscle and subcutaneous fat areas, and mid thigh low-density lean tissue did not change significantly after either AEX or RT. Those participants who completed the 6-month intervention, but were not included in the final analyses due to noncompliance with the AEX exercise program had responses to exercise training for percent changes in body weight, fat mass, FFM, and VAT similar to those of the compliant exercisers. A significant difference between compliant and noncompliant exercisers was observed in the percent change in SAT after the 6-month exercise program, with an increase in SAT observed in the noncompliant exercisers compared to a significant decrease observed in the compliant exercisers. A similar analysis was not possible in the RT group, because only one man was noncompliant with the exercise program.

Table 2. Aerobic Capacity and Muscle Strength at Baseline (Pre) and After 6 Months of Aerobic or Resistive Exercise Training (Post)

Variables	Aerobic Exercise (N = 9)		Resistive Exercise (N = 13)	
	Pre	Post	Pre	Post
VO _{2max} , L/min	2.6 ± 0.2	3.0 ± 0.3*	2.6 ± 0.1	2.8 ± 0.1
Leg press, lbs	666 ± 48	686 ± 55	737 ± 45	1052 ± 80*†
Leg extension, lbs	134 ± 9	150 ± 10*	150 ± 8	213 ± 11*†
Chest press, lbs	115 ± 9	131 ± 7*	138 ± 11	176 ± 13*†
Latissimus pull down, lbs	153 ± 7	163 ± 7*	166 ± 7	202 ± 9*†

Notes: Values are means ± standard error of the mean. VO_{2max} = maximal oxygen consumption.

**p* < .05, Pre versus Post; †*p* < .05, aerobic versus resistive.

Aerobic Capacity and Muscle Strength (Table 2)

There was a 16% increase in VO_{2max} with AEX (*p* < .01), which was greater than the 7% increase in the RT group (*p* < .05). Relative increases in muscle strength in the RT group were significantly greater than with AEX for the leg press (48 ± 9% vs 8 ± 11%, *p* < .05), the leg extension (43 ± 5% vs 13 ± 4%, *p* < .001), and the latissimus pull down (19 ± 4% vs 7 ± 3%, *p* < .05), but not for the chest press, despite a 2-fold difference in the percent increase in muscle strength (33 ± 7% vs 17 ± 8%, *p* = NS). There was no relationship between the change in VO_{2max} or muscle strength with age or the initial level of VO_{2max} or muscle

strength. Those participants who completed the 6-month intervention, but were not included in the final analyses due to noncompliance with the AEX exercise program had responses to exercise training for percent changes in VO_{2max} similar to those of the compliant exercisers.

Fasting Glucose and Insulin Levels and Glucose Disposal (M) (Figure 2)

There were no significant changes in fasting glucose (5.8 ± 0.3 to 5.7 ± 0.3 mM and 5.6 ± 0.2 to 5.9 ± 0.2 mM, AEX and RT, respectively; *p* > .05) and insulin (73 ± 13 to 68 ± 15 pmol/L and 109 ± 21 to 98 ± 13 pmol/L, AEX and RT, respectively; *p* > .05) concentrations after AEX and RT. Insulin concentrations during the glucose clamp did not differ between groups, and did not change with exercise training (514 ± 38 to 543 ± 60 pmol/L and 579 ± 30 to 626 ± 49 pmol/L for 240 pmol/m²/min, and 1124 ± 125 to 1152 ± 71 pmol/L and 1214 ± 85 to 1227 ± 54 pmol/L for 480 pmol/m²/min for AEX and RT, pre- vs postexercise training, respectively). Glucose disposal increased by 23 ± 16% after AEX (23.5 ± 3.6 to 27.2 ± 4.2 μM/kg_{FFM}/min) and 13 ± 10% after RT (22.7 ± 3.8 to 24.6 ± 3.8 μM/kg_{FFM}/min) during the 240 pmol/m²/min insulin infusion, but these changes in M did not reach statistical significance. The increase in M during the 480 pmol/m²/min insulin infusion was significant by 23 ± 8% after AEX

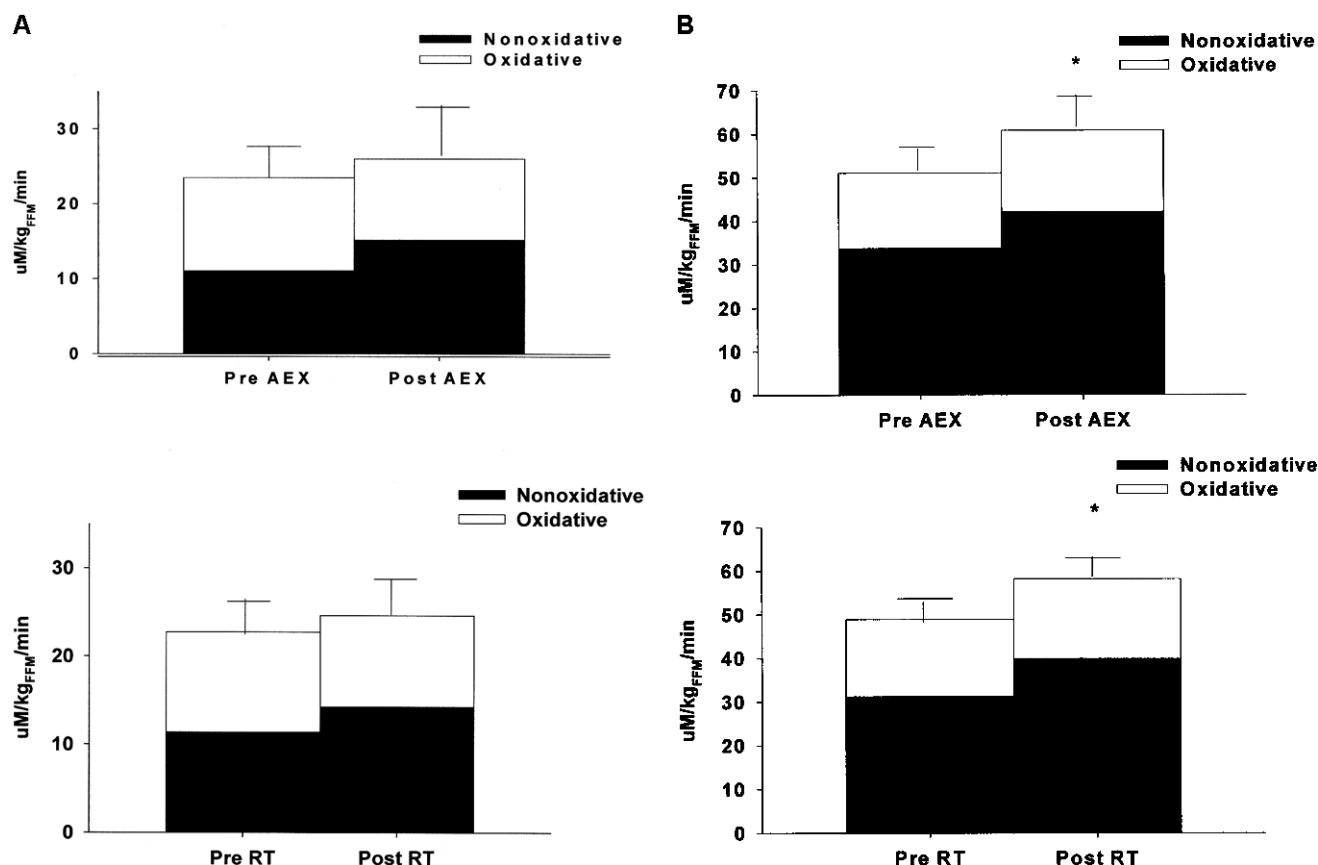


Figure 2. Nonoxidative and oxidative glucose disposal (μM/kg_{FFM}/min) in the aerobic (AEX, *n* = 9) and resistive (RT, *n* = 13) groups during 240 pmol/m²/min (A) and 480 pmol/m²/min (B) at baseline and after 6 months of exercise training (mean ± standard error of the mean; **p* < .05, pre- vs postexercise).

Table 3. Skeletal Muscle Basal and Insulin-Stimulated Glycogen Synthase Activities at Baseline (Pre) and After 6 Months of Aerobic or Resistive Exercise Training (Post)

Glycogen Synthase Activity, nmol/min · mg protein	Aerobic Exercise (N = 5)				Resistive Exercise (N = 6)			
	Pre		Post		Pre		Post	
	Basal	Insulin	Basal	Insulin	Basal	Insulin	Basal	Insulin
Total	11.7 ± 2.4	14.4 ± 3.6	13.8 ± 3.4	11.8 ± 2.7	16.6 ± 4.2	18.0 ± 4.1	15.7 ± 3.4	15.9 ± 4.2
Independent	0.46 ± 0.19	1.28 ± 0.68	0.52 ± 0.21	1.40 ± 0.44*	0.98 ± 0.43	1.54 ± 0.54*	0.72 ± 0.25	1.41 ± 0.42*
Fractional, %	3.4 ± 1.0	7.5 ± 2.2*	3.6 ± 1.0	12.2 ± 3.6*	4.9 ± 1.3	8.5 ± 2.4	4.6 ± 1.7	7.7 ± 1.6*

Notes: Values are means ± standard error of the mean.

* $p < .05$, basal versus insulin values.

(51.1 ± 5.1 to 60.8 ± 5.2 $\mu\text{M/kg}_{\text{FFM}}/\text{min}$; $p < .05$) and by 21 ± 6% after RT (48.8 ± 3.2 to 58.1 ± 3.5 $\mu\text{M/kg}_{\text{FFM}}/\text{min}$; $p < .05$). Similar changes in M were observed in the noncompliant AEX exercisers compared to the compliant AEX exercisers. Nonoxidative carbohydrate metabolism increased after RT (31.3 ± 2.7 to 40.0 ± 3.5 $\mu\text{M/kg}_{\text{FFM}}/\text{min}$; $p < .01$) and showed a trend for an increase in nonoxidative carbohydrate metabolism after AEX (33.8 ± 4.5 to 42.1 ± 4.7 $\mu\text{M/kg}_{\text{FFM}}/\text{min}$; $p = .10$). Carbohydrate and fat oxidation values at rest and during each insulin infusion did not change with AEX or RT (data not shown).

The change in M during the 480 pmol/ m^2/min insulin infusion was significantly related to the change in resting fat oxidation in both exercise groups ($r=0.72$ and $r=0.59$, AEX vs RT, respectively; $p < .05$). The changes in M, fat oxidation, and nonoxidative carbohydrate metabolism at either insulin dose did not correlate with changes in body composition measures, $\text{VO}_{2\text{max}}$, or muscle strength in either exercise group.

Skeletal Muscle Metabolism (Table 3)

Citrate synthase activity increased in 4 out of 6 AEX and 6 out of 11 RT participants, but the changes were not statistically significant (35 ± 13 to 48 ± 10 $\mu\text{mol}/\text{mg}$ protein/min and 26 ± 4 and 29 ± 4 $\mu\text{mol}/\text{mg}$ protein/min, AEX and RT, respectively; $p > .05$). Levels of skeletal muscle PI 3-kinase protein was also not altered significantly by either AEX (1.0 ± 0.3% to 1.0 ± 0.2% standard; $p > .05$) or RT (0.9 ± 0.1% to 0.8 ± 0.1% standard; $p > .05$).

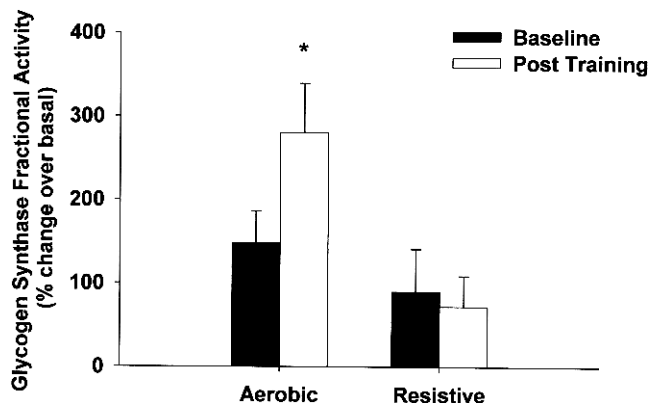


Figure 3. Percent change in glycogen synthase fractional activity in response to insulin stimulation at baseline and after 6 months of aerobic ($n = 5$) or resistive training ($n = 6$) (mean ± standard error of the mean; * $p < .05$, aerobic [AEX] vs resistive [RT] exercise).

Skeletal muscle glycogen content did not change after AEX (64 ± 7 to 66 ± 15 mmol/kg wet weight) or RT (73 ± 10 to 66 ± 7 mmol/kg wet weight). There were no differences between noncompliant and compliant exercisers in the AEX group for measures of muscle metabolism. GS fractional activity increased significantly after insulin stimulation before exercise training in the AEX group only. After exercise training, GS fractional activity increased significantly after insulin stimulation in both AEX and RT (Table 3, $p < .05$). However, the effect of insulin to increase GS fractional activity over basal activity was significantly greater after AEX (279 ± 59%) than after RT (100 ± 28%) (Figure 3, $p < .05$). Independent GS activity increased significantly after insulin stimulation before exercise training in the RT group only. After exercise training, independent GS activity increased significantly after insulin stimulation in both groups ($p < .05$). In contrast, total GS activity was not affected by insulin or by exercise. The changes in M at either insulin dose did not correlate with changes in GS in response to insulin stimulation in AEX or RT.

DISCUSSION

The purpose of this study was to test the hypothesis that both AEX and RT would improve insulin sensitivity in older, obese men, but the nature and magnitude of the changes in skeletal muscle metabolism would differ between the two groups, due to inherent differences in the exercise stimulus with each type of exercise. To our knowledge, our study is the first study to specifically compare the effects of AEX versus RT on both glucose disposal and GS activity. Our results suggest that AEX and RT result in comparable improvements in glucose disposal. Although there was a significant increase in insulin-stimulated GS fractional activity after both AEX and RT, the magnitude of the increase was 2.5-fold greater after AEX than after RT. These results have clinical relevance, as they corroborate the efficacy of both AEX and RT in reducing the insulin resistance associated with aging, obesity, and a sedentary lifestyle in older men.

The results of this study suggest that AEX training is associated with a greater increase in insulin activation of GS fractional activity than is RT in older men. Neither AEX nor RT affected GS total activity. Similar findings are observed with acute exercise. Both acute exercise and insulin increased GS fractional activity without an effect on GS total activity in healthy sedentary individuals (41). In addition, the increase in GS fractional activity induced by

acute exercise was significantly greater than the increase induced with insulin (41). In a different study of acute exercise (one-legged exercise for 30 minutes) in young healthy men, GS total activity was not different between the exercised leg and the rested leg under basal conditions or during the euglycemic-hyperinsulinemic clamp (42). It is interesting that athletes do not have higher basal GS fractional activity, higher total GS activity, or higher glycogen content compared to healthy nonathletes under basal conditions (22). Lastly, acute glycogen-depleting (knee extension) exercise did not affect GS total activity in healthy men (43). The results from our study and from other studies suggest that aerobic exercise training, acute exercise, and in vivo insulin do not affect GS total activity. Furthermore, acute exercise in healthy participants, aerobic exercise training in middle-aged, insulin-resistant participants, and aerobic exercise training in older insulin-resistant participants all improve the effect of in vivo insulin to increase GS fractional activity.

The only published study to examine GS activity after RT reported significant increases in basal total GS activity in older healthy men and in men with type 2 diabetes after one-legged RT (19), but insulin-stimulated GS activity was not determined. Glycogen content was significantly increased after training when both groups of men were combined (19). The present study in older insulin-resistant nondiabetic participants did not observe a significant increase in basal or insulin-stimulated total GS activity or in glycogen content after RT. Differences in the characteristics of the participants; the design, intensity, and frequency of the exercise training programs; weight and dietary stability at the time of testing; dietary influences; or some other undetermined factor may account for the differences in the results between the two studies.

Neither of the training programs in the present study resulted in significant increases in skeletal muscle PI 3-kinase protein levels. Few studies have examined the effects of exercise training on PI 3-kinase protein levels in older participants; they opted to evaluate changes in insulin-stimulated PI 3-kinase activity. Our study suggests that increased PI 3-kinase protein levels do not contribute to the increase in glucose disposal with exercise training. Other studies confirm that changes in PI 3-kinase protein levels are not necessary to improve glucose disposal (44).

There are some strengths and limitations that should be considered with respect to the design and outcomes of this study. To our knowledge, this is the first study to examine whether there are differential metabolic effects of AEX and RT on glucose disposal and muscle metabolism in a comparable population of healthy, obese, older men. Additional strengths of the study include weight and dietary stability of the participants prior to all testing, the significant improvements in $\text{VO}_{2\text{max}}$ and strength with the training programs, consistent timing of the muscle biopsies within 24–36 hours of the last exercise session, and the comparable levels of muscle glycogen at the time of the clamp and muscle biopsies, a factor that eliminates the possibility of glycogen depletion as a mechanism for the increase in glucose disposal and GS fractional activity (45, 46). Limitations of the study include the small but significant

changes in body weight in both groups, the lack of significant increase in FFM with RT, and the relatively small sample size in each group, especially for the muscle specimens. Although we encouraged all participants to maintain body weight (and monitored weight) during the study, both groups had a small but significant change in body weight, with participants in AEX losing a small amount of body weight, and those in RT gaining a small amount of body weight. These changes did not appear to affect the improvements in glucose disposal. The reasons for the lack of an increase in FFM and muscle area following RT in the present study are not known, but may be related to the age, deconditioned status, or testosterone status of the study participants, as the improvements in muscle strength are similar to those observed in previous studies (19,47). The relatively small sample sizes in both groups and limited mass of the muscle biopsy samples probably reduced our ability to detect significant changes in skeletal muscle metabolism, and prevented us from measuring other proteins and enzymes that might have increased in skeletal muscle after training. Additional research studies are needed to examine the effects of AEX and RT on other enzymes and proteins that regulate glucose metabolism in the skeletal muscle (activity, absolute levels, and gene expression).

Conclusion

The results of this study show that AEX and RT improve glucose disposal to a comparable degree in older, obese men, and suggest that AEX is associated with a greater increase in insulin activation of GS fractional activity when compared to RT. Further studies are needed to generalize these findings to an ethnically diverse population of men and women.

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