Aerobic Exercise Training Improves Insulin Sensitivity Independent of Plasma Tumor Necrosis Factor-alpha Levels in Older Female Hypertensives

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The purpose of the present study was to determine if the improvement in insulin sensitivity following aerobic exercise training (AEX) is associated with a decline in plasma tumor necrosis factor-alpha (TNF-α) levels. Fourteen older hypertensive females (age, 62 ± 2 years) participated in a 6-month AEX program. Following AEX there was a significant increase in maximal aerobic capacity ($\dot{V}O_2$max) ($P = .0001$), and a significant decline in systolic ($P = .01$) and diastolic ($P = .006$) blood pressure. In addition, following AEX there was a significant decline in total body fat mass ($P = .005$), abdominal fat mass ($P = .048$), and percent body fat ($P = .006$). Insulin sensitivity, as assessed by the insulin-assisted frequently sampled intravenous glucose tolerance test (FSIVGTT), increased significantly following AEX ($P = .007$). Despite the increase in insulin sensitivity and the decline in body fat, plasma TNF-α levels were not altered by AEX ($P = .223$). No significant relationship existed among the changes in TNF-α levels and the changes insulin sensitivity or any measure of body composition following AEX. In conclusion, in this population of older hypertensive females, AEX improved insulin sensitivity and lowered blood pressure without a reduction in plasma TNF-α levels.

ADVANCING AGE is associated with the development of insulin resistance. Tumor necrosis factor–alpha (TNF-α) is a proinflammatory cytokine that is produced by adipocytes and is thought to play a role in the genesis of insulin resistance and type 2 diabetes.[1] TNF-α has been shown to induce insulin resistance in rodents, a phenomena that is reversed by the insulin-sensitizing drug troglitazone[2] or TNF-α neutralization.[3] Recently, Paolisso et al[4] demonstrated in humans that plasma TNF-α levels are elevated with advancing age (21 to 94 years) and that this increase is associated with insulin resistance. In this study,[4] plasma TNF-α levels were significantly related with age ($r = 0.64$), glucose disposal ($r = -0.51$), and adiposity ($r = 0.45$). Therefore, lowering plasma TNF-α levels may, in part, play a role in preventing the age-related decline in insulin sensitivity.

Hypertension is another disorder that is common in older individuals and associated with insulin resistance. The role TNF-α plays in hypertension is not as well defined. The observation that TNF-α increases the release of endothelin, a potent vasoconstrictor, in cultured vascular endothelial cells provides support for the idea that TNF-α is mechanistically linked to hypertension.[5] In obese subjects, plasma TNF-α and endothelin levels are positively correlated.[6] Genetic analysis indicates that obesity-associated hypertension is associated with the TNF-α gene locus in hypertensive French Canadians.[7]

Aerobic exercise training (AEX) has been shown to increase insulin sensitivity[8,9] and lower blood pressure in mild hypertensive individuals.[10,11] Although the precise mechanism of how AEX improves insulin action is not firmly established, it appears that an increase in skeletal muscle GLUT4 levels plays a major role.[9] The mechanism by which AEX lowers blood pressure is multifactorial and remains obscure. Since TNF-α is related to both insulin resistance[1,4] and hypertension,[7] it is not unreasonable to hypothesize that the increase in insulin sensitivity and the reduction in blood pressure that occur with AEX would be associated with a reduction in the levels of TNF-α. Therefore, the purpose of this study was to determine if TNF-α levels decrease in conjunction with the increase in insulin sensitivity and the reduction in blood pressure following AEX in older hypertensive females.

MATERIALS AND METHODS

Subjects

Fourteen female subjects (age, 62 ± 2 years) were recruited for the study. Subjects were recruited by advertisements in newspapers, from the University of Michigan Turner Geriatric Clinic, and from the University of Michigan Geriatric Center's Human Subjects Core. Prior to participation in the study, all subjects completed a medical history, physical examination, a complete blood cell count, routine blood chemistries, and urinalysis. Individuals were excluded from participation if they had clinically significant medical illness, were taking medications that could affect glucose metabolism, had a recent history of smoking or drug/alcohol abuse, or clinically relevant mental disorder. Subjects were also excluded from the study following a 2-hour, 75-g oral glucose tolerance test if they had the presence of diabetes mellitus, according to the World Health Organization criteria.[12]

General Study

Following a screening visit to determine their eligibility for participation as described above, subjects signed an informed consent form approved by the University of Michigan Institutional Review Board. Hypertensive subjects who were being treated with antihypertensive

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medications were tapered off their medications and were studied following a 4-week period during which no antihypertensive medications were taken. Subjects then underwent a maximal graded exercise test (Modified Bruce Protocol) to screen for coronary heart disease. During this test, oxygen consumption ($\dot{V}O_2$) and carbon dioxide (CO_2) production were measured continuously using a Collins CPX/Plus metabolic cart (Warren Collins, Braintree, MA).

Frequently Sampled Intravenous Glucose Tolerance Test

One week prior to the pretraining and post-training, frequently sampled intravenous glucose tolerance test (FSIVGTT), the subject consumed meals prepared by the University of Michigan General Clinical Research Center Metabolic kitchen. The caloric intake and percent of calories from carbohydrates (50% to 55%), fats (30% to 35%), and proteins (15% to 20%) was identical at pretraining and post-training. Forty-eight hours after the last bout of AEX, subjects had their insulin sensitivity assessed using the methodology described by Bergman.[13] Briefly, an intravenous catheter was inserted into an antecubital vein in one arm for the injection of insulin (Humulin-R, Eli Lilly, Indianapolis, IN) and glucose. Another catheter was inserted in a retrograde manner into a dorsal hand vein of the contralateral arm to sample blood for the measurement of glucose and insulin and TNF-α. Catheters were kept patent by a slow infusion of 0.45% saline (<50 mL/h). Beginning 20 minutes after the insertion of intravenous lines, 3 baseline blood samples for glucose, insulin, and TNF-α levels were obtained. Baseline values were calculated as the mean of these 3 measurements for each variable.

Fifty percent glucose (300 mg/kg) was given as an intravenous push over 30 seconds. Blood samples (3 mL) were collected at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 70, 80, 90, 100, 120, 140, 160, and 180 minutes after the glucose bolus. Insulin (0.02 U/kg) was given intravenously over 30 seconds, 20 minutes after the glucose injection to enhance precision of the estimates of insulin action.[14] The insulin sensitivity index (S_I) and glucose effectiveness (S_G) were calculated from a least squares fitting of the temporal pattern of glucose and insulin throughout the FSIVGTT using the MINMOD program (© R.N. Bergman, 1989). S_I is a measure of the effect of an increment in plasma insulin to enhance the fractional disappearance of glucose. The reproducibility for the minimal model approach for determining insulin sensitivity has been reported to be approximately 16%.[15,16]

Measurements of TNF-α, Glucose, and Insulin

Blood samples for plasma glucose, insulin, and TNF-α were collected into chilled glass tubes containing sodium heparin, stored on ice, and separated immediately following each study. Plasma was stored at -70°C until assay. Plasma glucose was measured by the autoanalyzer glucose oxidase method and plasma insulin by radioimmunoassay in the Core Laboratory of the Michigan Diabetes Research and Training Center. Baseline plasma samples were used for the assessment of TNF-α levels by an immunoenzymetric assay (Biosource, Nivelles, Belgium). Samples from each of the subjects' 2 studies were analyzed together in the same assay. The intra-assay and interassay coefficients of variation were 5.4% and 9.0%, respectively. The minimal detectable TNF-α concentration for this assay is estimated to be 3 pg/mL.

Measurement of Blood Pressure

Blood pressure was measured in triplicate using an oscillometric technique (Colin Electronics, Aichi, Japan) over the brachial artery. Subjects were seated comfortably for at least 15 minutes with the cuffed arm supported at heart level before measurements were taken. The mean of these 3 blood pressure measurements is reported.

Anthropometry

Body weight was measured to the nearest 0.1 kg using a medical scale. Height was measured to the nearest 0.5 cm using a stadiometer. Body mass index (BMI, kg/m^2) was determined by the subject's weight (kg) divided by the square of their height (m^2).

Dual-Energy X-Ray Absorptiometry

Subjects were scanned using a whole body dual-energy x-ray absorptiometry (DEXA) system (model DPX-IQ, Lunar Radiation Corp, Madison, WI; software version 4.5c) set at medium speed and medium collimation ratio. Subjects lay supine on the DEXA table with their arms adequately separated from their trunk and were instructed to remain still throughout the scanning procedure. After the completion of the whole body scan, a quadrilateral box was manually drawn around the L1-L4 region of interest (abdomen) bounded inferiorly by the horizontal line identifying the L4/L5 vertebral space and superiorly by the horizontal line identifying the T1 and T2 vertebral space. Scans were displayed with an adjustment of the gray scale, so that all of the soft tissue in the designated region was included.

Measurement of Maximal Aerobic Capacity

A maximal exercise test was performed at pretraining, after 3 months, and again after 6 months of AEX. The initial treadmill speed was set to elicit 75% of each subject's $\dot{V}O_2$max measured during their screening treadmill test. The treadmill elevation was increased every 2 minutes until the subject was exhausted and could not continue. $\dot{V}O_2$ and $\dot{V}CO_2$ were measured continuously and blood pressure and a 12-lead electrocardiogram were recorded every 3 minutes during the test. A true $\dot{V}O_2$max was considered to be attained if 2 of the following criteria were achieved: (1) respiratory exchange ratio greater than 1.10; (2) maximal heart rate of greater than 90% of age-predicted maximum (220 - age); or (3) a plateau in $\dot{V}O_2$ (change in $\dot{V}O_2 \leq 0.2$ L/min) with increasing workload.

Aerobic Exercise Training

All subjects participated in a 6-month supervised AEX training program that consisted of treadmill walking, stationary bicycling, and stair climbing. The intensity and duration of exercise was progressively increased so that subjects completed 40 minutes per session 3 days per week at 75% to 85% of their heart rate reserve for the last 3 months of training.

Statistical Analysis

Data were analyzed using Statview (Abacus Concepts, Berkeley, CA). An alpha level of 0.05 was accepted for statistical significance. The effects of AEX were assessed by paired *t* test. Simple regression analysis was used to assess the relationship between selected variables before AEX and the relationship between the changes in selected dependent variables following AEX.

RESULTS

Aerobic Capacity, Body Composition, and Blood Pressure

Six months of AEX produced a significant (15%) increase in $\dot{V}O_2$max, demonstrating that the exercise program was effective in increasing aerobic capacity. Systolic blood pressure, diastolic blood pressure, and mean arterial pressure all decreased significantly (5%) following AEX. AEX resulted in significant declines in body mass (3%), total fat (8%), abdominal fat (12%), and percent fat (4%). There was a trend for a lower body mass index following AEX, but this did not reach statistical significance ($P = .06$). Data are shown in Table 1.

Table 1. Subject Characteristics Before and After 6 Months of AEX

	Baseline	AEX	*P* Value
Age (yr)	62 ± 2	—	—
Body mass (kg)	80.8 ± 4.0	78.3 ± 4.2	.042
Body mass index (kg/m^2)	30.0 ± 1.4	29.1 ± 1.3	.056
Fat mass (kg)	35.5 ± 2.7	32.8 ± 2.8	.005
Abdominal fat mass (kg)	4.6 ± 0.1	4.3 ± 0.2	.048
Body fat percent (%)	44.7 ± 1.4	42.9 ± 1.5	.006
$\dot{V}O_2$max (mL/kg/min)	16.8 ± 0.9	19.3 ± 0.9	.0001
Systolic blood pressure (mm Hg)	151 ± 3	144 ± 4	.010
Diastolic blood pressure (mm Hg)	88 ± 2	84 ± 3	.006
Mean arterial pressure (mm Hg)	109 ± 3	104 ± 3	.001
Insulin (pmol/L)	88.6 ± 14.4	74.4 ± 11.5	.074
Glucose (mmol/L)	5.3 ± 0.1	5.2 ± 0.2	.741

Insulin Sensitivity Index

There was a 58% increase in insulin sensitivity ($P = .027$), as assessed by the FSIVGTT, following AEX (2.6 ± 0.6 *v* 4.1 ± 0.7 × 10^{-4}/min/μU/mL, Fig 1A). There was a trend for lower fasting plasma insulin levels after AEX ($P = .0741$), but this was not statistically significant (Table 1). Prior to the initiation of the AEX program, insulin sensitivity was not significantly correlated to any measures of body composition.

Plasma TNF-α Levels

Following AEX there was no significant change in plasma TNF-α levels (12.74 ± 1.93 *v* 11.38 ± 1.30 pg/mL, $P = .386$, Fig 1B). Plasma TNF-α levels were not related to insulin sensitivity before AEX ($r = 0.142$, $P = .644$) and the changes in plasma TNF-α levels following AEX were not related to the changes in insulin sensitivity ($r = 0.335$, $P = .264$, Fig 2). However, there was a trend for a relationship between the changes in plasma TNF-α levels and the changes in plasma insulin levels ($r = 0.504$, $P = .07$). Plasma TNF-α levels were not related to any measure of body composition prior to AEX. Following AEX, no significant relationship existed between changes in plasma TNF-α levels and total fat mass ($r = 0.336$, $P = .240$), abdominal fat mass ($r = 0.01$, $P = .983$), or percent body fat ($r = 0.174$, $P = .55$). Finally, prior to AEX no relationship existed between plasma TNF-α levels and systolic ($r = 0.050$, $P = .864$), diastolic ($r = 0.047$, $P = .874$), or mean arterial blood pressure ($r = 0.054$, $P = .853$). Following AEX, the changes in plasma TNF-α levels were not related to the changes in blood pressure.

DISCUSSION

The present study indicates that AEX increases insulin sensitivity and lowers blood pressure without any significant changes in plasma TNF-α levels in older hypertensive women. AEX also produced significant decreases in total fat mass, abdominal fat mass, and percent body fat, which were unrelated to changes in TNF-α. Therefore, in this population of older hypertensive females, it appears that AEX can improve insulin sensitivity, reduce blood pressure, and decrease body fat independent of changes in plasma TNF-α levels.

An extensive body of literature exists suggesting a link between TNF-α and insulin resistance.[1,17] Following weight loss[18,19] or troglitazone treatment,[2] insulin action improves and TNF-α levels decline, providing further in vivo evidence of a mechanistic link between these correlates. Furthermore, TNF-α–deficient mice are less susceptible to obesity-induced insulin resistance.[20] However, the present study demonstrates that 6 months of AEX significantly increased insulin sensitivity without a significant decline in plasma TNF-α levels. Studies that have implicated TNF-α as a contributor to insulin resistance have either treated animals with high doses of TNF-α[17] or produced dramatic weight loss (9 to 12 kg) in obese subjects.[18,19] One possible explanation of the differences between the present results and previous studies is the magnitude of the

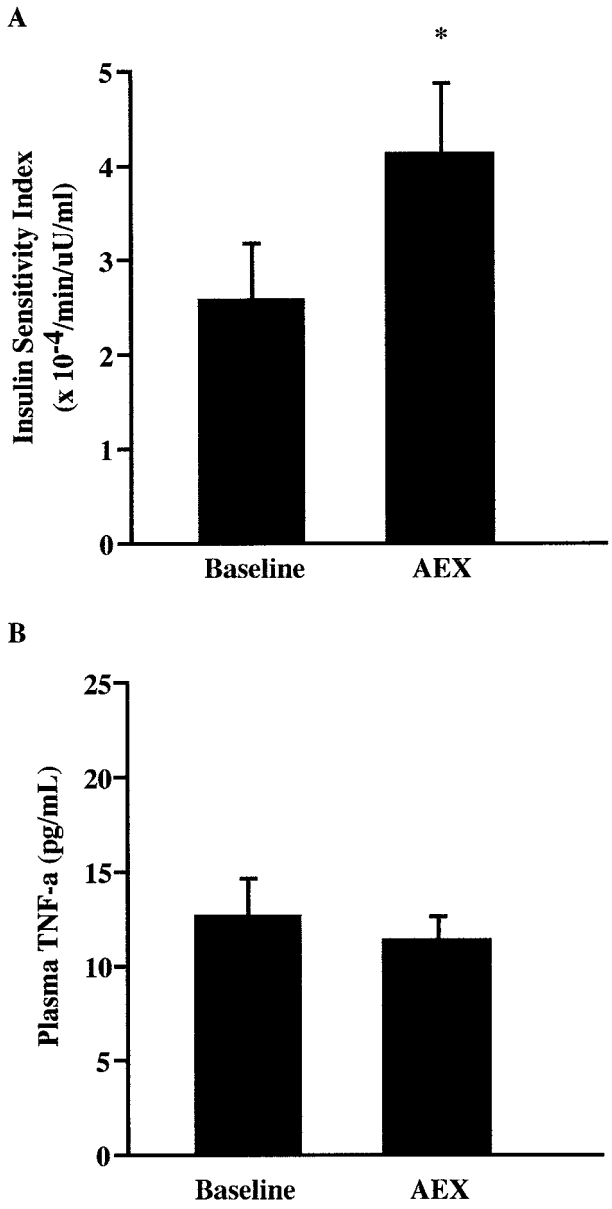

Fig 1. The effect of 6 months of AEX on (A) insulin sensitivity and (B) plasma TNF-α levels in older hypertensive women. *Significantly different from baseline, $P = .007$

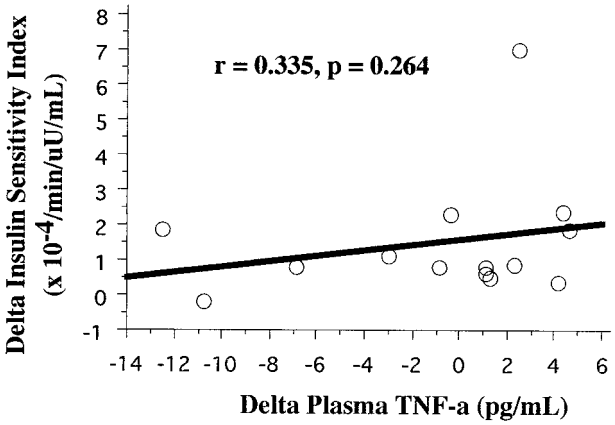

Fig 2. The relationship between the changes in insulin sensitivity and plasma TNF-α levels in older hypertensive women following 6 months of AEX.

weight loss. Although our subjects lost a significant amount of body mass (2.5 kg) following AEX, it may have not been enough to produce a significant decline in plasma TNF-α levels. Studies that report a significant decline in plasma TNF-α levels observed 3.5- to 5-fold greater declines in body mass[18,19] than the present study. However, another study demonstrated that AEX significantly decreased plasma TNF-α in conjunction with weight loss that was similar to the weight loss observed in the present study.[21] Another possible explanation for the differences between the present study and earlier studies may be that plasma TNF-α levels are a poor indicator of TNF-α action at the primary target tissues for insulin action. AEX may have reduced TNF-α production in skeletal muscle without altering plasma TNF-α levels. This idea is supported by a recent investigation that observed a reduction in skeletal muscle TNF-α expression following weight training in older individuals,[22] although plasma TNF-α was not assessed.

The present study did not observe a relationship between plasma TNF-α and insulin sensitivity or plasma TNF-α and adiposity prior to the initiation of AEX. The lack of a correlation before AEX may be due to the small range of insulin sensitivity and percent body fat values observed in our population of older female subjects. Unlike the present study, Paolisso et al[4] assessed glucose disposal and body compositions across a wide age range of individuals and uncovered significant relationships among plasma TNF-α, glucose disposal, and adiposity. Following AEX, the changes in plasma TNF-α levels were not related to the changes in insulin sensitivity or the changes in percent body fat. The lack of a relationship between these variables may be explained, in part, by the significant changes in insulin sensitivity and percent body fat without a significant change in plasma TNF-α levels following AEX.

The effect of AEX on plasma TNF-α levels has produced inconsistent results. In young healthy females, 3 months of AEX increased TNF-α.[23] Clapp and Kiess[24] examined the effect of AEX on TNF-α levels during late-term pregnancy-associated insulin resistance. AEX reduced plasma TNF-α levels compared to sedentary pregnant women. Upon cessation of AEX, TNF-α levels increased to levels similar to their pregnant sedentary peers. Similarly, Tsukui et al[21] demonstrated that 5 months of AEX lowered serum TNF-α levels in a group of healthy Japanese women. The reduction in TNF-α levels was correlated with a decline in plasma insulin levels and hemoglobin A_{1c}. Similar to Tsukui et al,[21] we demonstrated a trend for a relationship between changes in plasma insulin and TNF-α levels ($r = 0.504$, $P = .07$) following AEX. These findings suggest that TNF-α may play a role in regulating basal circulating insulin levels and possibly insulin-mediated glucose disposal. However, the present study observed a significant improvement in insulin sensitivity following AEX without a significant decline in plasma TNF-α levels. Accordingly, no relationship existed between changes in insulin sensitivity and changes in plasma TNF-α levels (Fig 2). The discrepancies between the present study and Tsukui et al[21] cannot be explained by the amount of weight loss, since we reported greater reductions in fat mass and body mass with no reduction in plasma TNF-α. It is possible that the timing of the plasma TNF-α measurements following the last bout of exercise might effect plasma TNF-α levels. In support of this hypothesis, Ostrowski et al[25] reported a 2- to 3-fold increase in TNF-α levels 1 to 3 hours following an acute bout of exercise. In the present study we assessed plasma TNF-α levels at 48 hours following the last bout of AEX and reported no change in plasma TNF-α levels following 6 months of AEX. Similarly, Horne et al[23] also assessed plasma TNF-α at 48 hours following the last bout of exercise training and reported a slight increase in plasma TNF-α. The timing of TNF-α measurements following the last bout of exercise is not reported by Clapp and Kiess[24] and Tsukui et al.[21] However, if plasma TNF-α levels were measured directly following a bout of exercise the reported changes may, in part, be due to the effects of an acute exercise bout rather than chronic exercise training. Because studies examining the effect of AEX on plasma TNF-α levels have involved pregnant subjects[24] or female Japanese subjects,[21] it is difficult to make comparisons to the present study of older female hypertensive. Additional studies are necessary to clearly establish the effects of AEX on plasma TNF-α levels.

In addition to an increase in insulin sensitivity, AEX has been shown to decrease blood pressure in hypertensive individuals.[11] Likewise, the present study demonstrates that AEX reduced systolic, diastolic, and mean arterial blood pressure. The association between hypertension and TNF-α has not been examined as thoroughly as its association with insulin resistance. The present finding that AEX reduced blood pressure but not plasma TNF-α indicates that the blood pressure–lowering effects of AEX are independent of plasma TNF-α levels. In addition, we observed no relationship between the changes in blood pressure and changes in plasma TNF-α levels.

In summary, the present study demonstrates that 6 months of AEX can improve insulin sensitivity and reduce blood pressure in older hypertensive females independent of changes in plasma TNF-α levels. It is possible that the lack of association between the changes in insulin sensitivity and TNF-α following AEX indicate that these 2 variables might not be mechanistically connected in this hypertensive population. Alternatively, it is possible that AEX increases insulin sensitivity by different mechanisms than dramatic weight loss[18,19] or treatment with troglitazone,[2] two interventions that appear to decrease plasma

TNF-α levels. In addition, the present results cannot rule out the possibility that a decline in skeletal muscle TNF-α levels might have contributed to the increased insulin sensitivity[22] following AEX. Nonetheless, aerobic exercise training improved insulin sensitivity without reducing TNF-α levels in older hypertensive females.

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