# Resistance Training Enhances Insulin-Mediated Glucose Disposal With Minimal Effect on the Tumor Necrosis Factor-Alpha System in Older Hypertensives

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**The purpose of the present study was to determine if the improvement in insulin sensitivity after resistance training (RT) is associated with a decline in plasma levels of tumor necrosis factor-alpha (TNF-$\alpha$), soluble TNF-$\alpha$ receptor 1 (sTNF R1), and soluble TNF receptor 2 (sTNF R2). Eleven older hypertensives (5 men/6 women, 67 ± 2 years) participated in a 4-month RT program. Following RT there was a significant increase in upper body ($P = .029$) and lower body strength ($P = .001$), assessed by the bench press 1-repetition maximum (1RM) and leg press 1RM, respectively. The RT program produced a significant increase in lean body mass (LBM) ($P = .029$), a trend for a decline in percent body fat ($P = .083$), and no change in total body mass ($P = .958$). Insulin-mediated glucose disposal, assessed by the hyperinsulinemic euglycemic clamp procedure, significantly increased following RT ($P = .026$). Despite the increase in insulin action, plasma levels of TNF-$\alpha$, sTNF R1, and sTNF R2 were not significantly altered by RT (TNF-$\alpha$: $P = .118$, sTNF R1: $P = .184$, sTNF R2: $P = .168$). In conclusion, a 4-month RT program significantly increased insulin-mediated glucose disposal and LBM without a significant reduction in plasma levels of TNF-$\alpha$, sTNF R1, and sTNF R2 in older hypertensive subjects.**


INSULIN RESISTANCE is a metabolic and cardiovascular disorder that is common in older individuals. Tumor necrosis factor-alpha (TNF-$\alpha$) 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-$\alpha$ has been shown to induce insulin resistance in rodents, a phenomena that is reversed by the insulin-sensitizing drug troglitazone[2] or TNF-$\alpha$ neutralization.[3] In human subjects, Paolisso et al[4] demonstrated that plasma TNF-$\alpha$ levels are elevated with advancing age (21 to 94 year) and are associated with decreased insulin-mediated glucose disposal ($r = -.51$) and increased adiposity ($r = .45$). Precisely how TNF-$\alpha$ promotes insulin resistance is not known, but evidence suggests that TNF-$\alpha$ inhibits critical steps in insulin signal transduction.[5-7]

TNF-$\alpha$ action is initiated when the cytokine binds to its 2 cell surface receptors, soluble TNF receptor 1 (sTNF R1) and soluble TNF receptor 2 (sTNF R2). Following receptor binding an extracellular soluble portion of each receptor is cleaved, remaining in the circulation longer than TNF-$\alpha$ and possibly reflecting previous TNF-$\alpha$ action.[8] Therefore, assessing soluble TNF receptors might provide a more sensitive measure of TNF-$\alpha$ action than measuring plasma TNF-$\alpha$ levels alone.[8-10] Recently, the ratio of sTNF R2: sTNF R1 was negatively related to maximal oxygen uptake ($\dot{V}O_{2max}$),[11] the hallmark measure for cardiorespiratory fitness. Because $\dot{V}O_{2max}$ is an excellent predictor of insulin sensitivity,[12] it is not surprising that the ratio of sTNF R2: sTNF R1 is greater in type 2 diabetics.[11] Furthermore, the increase in insulin sensitivity following aerobic exercise training was associated with a decrease in plasma sTNF R2 levels,[13] suggesting that a reduction in TNF-$\alpha$ levels might mediate the increase in insulin sensitivity.

Advancing age is associated with an increased prevalence of hypertension, a disease that is common in insulin-resistant and type 2 diabetic individuals. Recently, Demirbas et al[14] demonstrated that hypertensive individuals are insulin resistant and have higher plasma TNF-$\alpha$ levels than normotensive controls. Plasma TNF-$\alpha$ levels appear to be independently associated with systolic blood pressure across a wide range of adiposity (4.1% to 57.8% body fat, 16.6 to 38.0 kg/m$^2$ body mass index [BMI]).[15] In hypertensive French Canadians, obesity-related hypertension is associated with the TNF-$\alpha$ gene locus.[16] A potential mechanism linking TNF-$\alpha$ to hypertension is the potent vasoconstrictor, endothelin. In cultured vascular endothelial cells TNF-$\alpha$ increases the release of endothelin[17] and in obese human subjects plasma TNF-$\alpha$ and endothelin levels are positively correlated.[18]

It is well-established that aerobic exercise training enhances insulin sensitivity[19] and lowers blood pressure in mild hypertensive individuals.[20,21] To date, only 2 studies have examined the effects of resistance training (RT) on insulin sensitivity.[22,23] Similar to insulin sensitivity, the effects of RT on blood pressure in hypertensive individuals have not been well studied. Therefore, one purpose of this study was to determine the effects of RT on insulin-mediated glucose disposal and blood pressure in older hypertensive subjects. Because the effect of RT on plasma TNF-$\alpha$ levels is not known, a second purpose of the present study was to determine if the changes in insulin-mediated glucose disposal following RT were associated with reciprocal changes in plasma levels of TNF-$\alpha$, sTNF R1, and sTNF R2. Our primary hypothesis is that RT will increase

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insulin-mediated glucose disposal and lower blood pressure in older hypertensive subjects. Our secondary hypothesis is that the changes in insulin-mediated glucose disposal following RT will be inversely related to the changes in plasma levels of TNF-$\alpha$, sTNF R1, and sTNF R2.

## MATERIALS AND METHODS

### *Subjects*

Eleven subjects (5 men, 6 women, 67 $\pm$ 2 year) 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 Subject Research Participant Core. Prior to participation in the study, all subjects completed a medical history, physical examination, a complete blood 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.[24]

### *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 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 ($\dot{V}CO_2$) production were measured continuously using a Collins CPX/Plus metabolic cart (Warren Collins, Braintree, MA).

### *Hyperinsulinemic Euglycemic Clamp Studies*

Insulin sensitivity before and after 4 months of RT was assessed by the hyperinsulinemic euglycemic glucose clamp technique.[25] Following RT, the clamp procedure was performed at 24 hours following the last bout of resistance exercise. Briefly, an intravenous (IV) catheter was inserted into an antecubital vein for infusion of insulin and glucose. A second catheter was inserted into a brachial artery for blood sampling for glucose and insulin. Beginning 20 minutes after the insertion of IV lines, 3 baseline arterial blood samples for plasma levels of glucose, insulin, TNF-$\alpha$, sTNF R1, and sTNF R2 were obtained. Baseline values were calculated as the mean of these 3 measurements for each variable. Insulin (Humulin-R, Eli Lilly, Indianapolis, IN) was administered at a primed infusion rate of 100 pmol/m$^2$/min for 180 minutes. During the clamp, plasma glucose levels were measured at 5-minute intervals using the glucose oxidase method (Beckman Instruments, Fullerton, CA) and 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 in the Core Laboratory of the Michigan Diabetes Research and Training Center. Mean glucose infusion rates were normalized for lean body mass (LBM) and averaged over the last 30 minutes of the insulin infusion. Steady-state plasma insulin levels were calculated over the same interval.

### *Measurements of TNF-$\alpha$ and TNF Receptors*

Plasma levels of TNF-$\alpha$, sTNF R1, and sTNF R2 were assessed at baseline and 24 hours following the last bout of RT. Briefly, blood samples 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 was conducted. The average of 3 baseline plasma samples was used for the assessment of TNF-$\alpha$, sTNF R1, and sTNF R2 levels by immunoenzymetric assays (Biosource, Nivelles, Belgium). Samples from each of the subjects' 2 studies (baseline and post-training) were analyzed together in the same assay. The intra-assay and interassay coefficient of variation for TNF-$\alpha$ was 5.9% and 8.5%, respectively. The intra-assay and interassay coefficient of variation for sTNF R1 was 4.1% and 7.3%, respectively. The intra-assay and interassay coefficient of variation for sTNF R2 was 4.9% and 7.9%, respectively. The minimal detectable TNF-$\alpha$, sTNF R1, and sTNF R2 concentrations for each assay are estimated to be 0.5 pg/mL, 50 ng/mL, and 100 pg/mL, respectively.

### *Measurement of Blood Pressure*

Resting blood pressure was assessed 24 hours following the last bout of RT just prior to the euglycemic hyperinsulinemic clamp procedure. Systolic, diastolic, and mean arterial blood pressure were assessed by placing a 20-gauge 1.25-in Insyte catheter into the brachial artery of the nondominant arm. The catheter was connected to a pressure transducer (Hewlett-Packard 1290A quartz transducer; Hewlett-Packard, Andover, MA). Blood pressure was measured while the subject was in the supine position, following a 20-minute resting period. Systolic, diastolic, and mean arterial blood pressures were determined from the electronically integrated area under the intra-arterial blood pressure curve from the Marquette telemetry system (Marquette Electronics Series 7700; Marquette Electronics, Milwaukee, WI).

### *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 at baseline and during the last week of RT (model DPX-IQ; Lunar Radiation, Madison, WI; software version 4.5c). The DEXA system was 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 Oxygen Uptake ($\dot{V}O_{2max}$)*

A maximal exercise test was performed at baseline and at the end of the 4-month RT program (72 to 96 hours after to hyperinsulinemic euglycemic clamp). The initial treadmill speed was set to elicit 75% of the 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% 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.

**Table 1. Subject Characteristics at Baseline and Following 4 Months of Resistance Training**

| | Baseline | Resistance Trained | *P* Value |
|---|---|---|---|
| Age (yr) | 67 ± 2 | — | — |
| Body mass (kg) | 77.63 ± 4.0 | 77.7 ± 4.1 | .958 |
| Body mass index (kg/m$^2$) | 29.1 ± 1.4 | 29.0 ± 1.3 | .637 |
| Lean body mass (kg) | 46.0 ± 3.3 | 47.0 ± 3.1 | .029 |
| Fat mass (kg) | 27.2 ± 2.9 | 26.6 ± 3.1 | .396 |
| Abdominal fat mass (kg) | 2.9 ± 0.3 | 2.9 ± 0.4 | .527 |
| Percent body fat (%) | 37.1 ± 3.1 | 35.7 ± 3.1 | .083 |
| Glucose disposal rate (mg/kg$_{LBM}$/min) | 11.08 ± 0.4 | 12.67 ± 0.1 | .026 |
| $\dot{V}O_2$max (mL/kg/min) | 21.2 ± 1.1 | 22.1 ± 1.4 | .463 |
| Systolic blood pressure (mm Hg) | 163 ± 4 | 170 ± 5 | .093 |
| Diastolic blood pressure (mm Hg) | 82 ± 3 | 82 ± 2 | .915 |
| Mean arterial blood pressure (mm Hg) | 114 ± 3 | 116 ± 2 | .367 |
| Bench press 1RM (kg) | 41 ± 5 | 45 ± 4 | .029 |
| Leg press 1RM (kg) | 106 ± 11 | 131 ± 10 | .001 |
| Glucose (mmol/L) | 5.6 ± 0.1 | 5.9 ± 0.1 | .016 |
| Insulin (pmol/L) | 78.8 ± 7.7 | 74.1 ± 7.8 | .606 |

*RT*

All subjects participated in a 4-month supervised RT program on Cybex machines that consisted of the bench press, leg press, shoulder press, lateral row, bicep curls, tricep extension, leg extensions, and leg curls. Prior to the initiation of the RT program, the subject's 1-repetition maximum (1-RM) was determined on the leg press and bench press exercises. This was accomplished by progressively increasing the resistance on subsequent sets until only one repetition could be completed. To allow for adequate recovery, 2 minutes of rest was allowed between each set. The initial RT intensity for each exercise was progressively increased so that by the end of the second week the subjects completed 2 sets of 10 to 12 repetitions of each exercise 3 days per week. The resistance was increased by ~ 5 kg when the subject could complete12 repetitions on a particular exercise.

*Statistical Analysis*

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

## RESULTS

*Strength, Body Composition, $\dot{V}O_{2max}$, and Blood Pressure*

RT significantly increased bench press 1RM (41 ± 5 *v* 45 ± 4 kg, $P = .029$) and leg press 1RM (106 ± 11 *v* 131 ± 10 kg, $P = .001$). The increase in upper and lower body strength was accompanied by a significant increase in LBM (46.0 ± 3.3 *v* 47.0 ± 3.1 kg, $P = .029$) (Table 1). Following the 4-month RT program there were no significant changes in percent body fat (37.1 ± 3.1 *v* 35.7 ± 3.1%, $P = .083$), total fat mass (27.2 ± 2.9 *v* 26.6 ± 3.1 kg, $P = .396$), or abdominal fat mass (2.9 ± 0.3 *v* 2.9 ± 0.4 kg, $P = .527$). There was no effect of RT on systolic ($P = .093$), diastolic ($P = .915$), or mean arterial blood pressure ($P = .367$). Finally, 4 months of RT did not alter $\dot{V}O_{2max}$ ($P = .463$).

*Insulin Sensitivity*

The insulin infusion rate produced similar plasma insulin levels during the last 30 minutes of insulin infusion at baseline and following 4 months of RT (7.15 ± 0.43 *v* 7.51 ± 0.42 pmol/L, $P = .110$). There was a significant 15% increase in the glucose disposal rate following 4 months of RT, as assessed by the hyperinsulinemic euglycemic clamp procedure (Table 1). Fasting plasma insulin levels were not significantly altered by RT, but plasma glucose increased significantly following RT (Table 1).

*Plasma Levels of TNF-$\alpha$, sTNF R1, and sTNF R2*

Following RT there was a 16% decline in plasma TNF-$\alpha$ levels (7.23 ± 0.59 *v* 6.23 ± 0.56, Fig 1), but this did not reach statistical significance ($P = .118$). The plasma levels of sTNF R1 (1.73 ± 0.16 *v* 1.96 ± 0.24 ng/mL, $P = .184$, Fig 2), sTNF R2 (3.10 ± 0.16 *v* 2.99 ± 0.496 ng/mL), $P = .143$, Fig 3), and the sTNF R2: sTNF R1 ratio (1.96 ± 0.17 *v* 1.77 ± 0.70 ng/mL, $P = .159$, Fig 4) were not significantly altered by RT. Plasma TNF-$\alpha$ levels were not associated with insulin-medi-

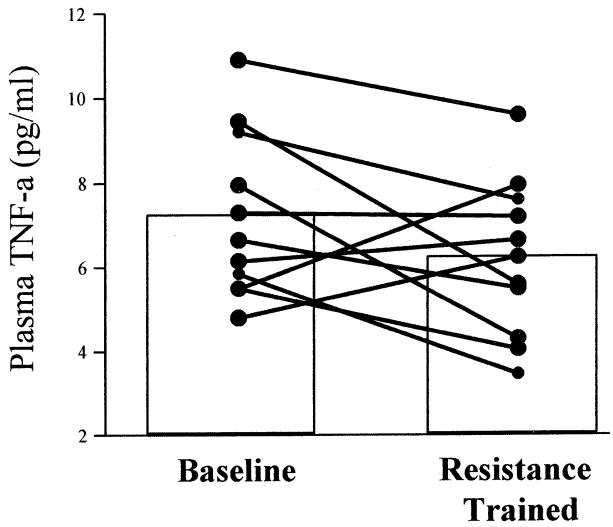


**Fig 1. The effect of 4 months of RT on plasma TNF-$\alpha$ levels in older hypertensives.**

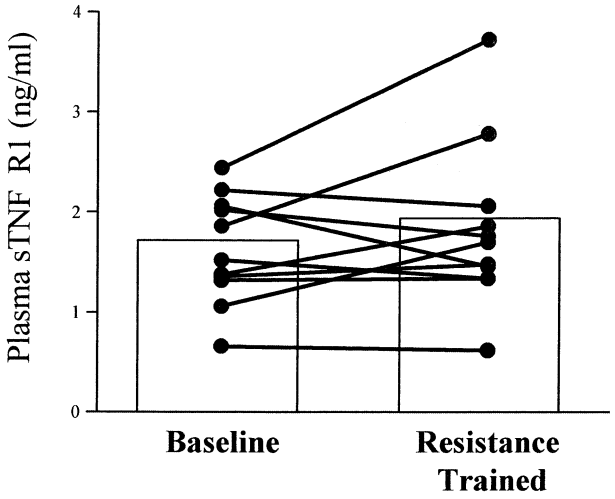


**Fig 2. The effect of 4 months of RT on plasma levels of sTNF R1 in older hypertensives.**

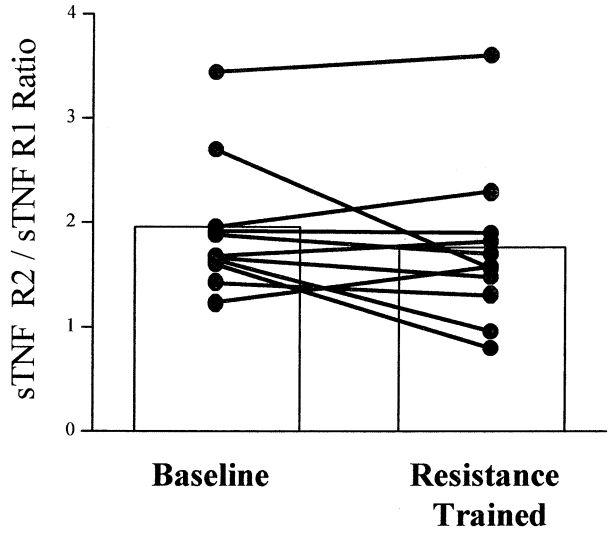


**Fig 4. The effect of 4 months of RT on the ratio of plasma levels of sTNF R2 and sTNF R1 in older hypertensives.**

ated glucose disposal at baseline ($r$ = .118, $P$ = .713), and the changes in plasma TNF-$\alpha$ following RT were not associated with the changes in insulin-mediated glucose disposal ($r$= .194, $P$ = .567). There was no association between either sTNF R1 and insulin-mediated glucose disposal ($r$ = 200, $P$ = .533) or sTNF R2 and insulin-mediated glucose disposal ($r$ = .262, $P$ = .410) at baseline. Following RT changes in sTNF R1 and sTNF R2 were not associated with changes in insulin-mediated glucose disposal (sTNF R1: $r$ = .111, $P$ = .732; sTNF R2: $r$ = .416, $P$ = .179). There was a trend for an association between plasma TNF-$\alpha$ levels and percent body fat at baseline ($r$ = .560, $P$ = .073), however, the changes in plasma TNF-$\alpha$ and the changes in percent body fat following RT were not related ($r$ = .147, $P$ = .665). No other measure of body composition was related to plasma levels of TNF-$\alpha$, sTNF R1, or sTNF R2 at baseline or following RT. Systolic, diastolic, and mean arterial blood pressure were not related to plasma levels of TNF-$\alpha$, sTNF R1, or sTNF R2 at baseline or following RT.

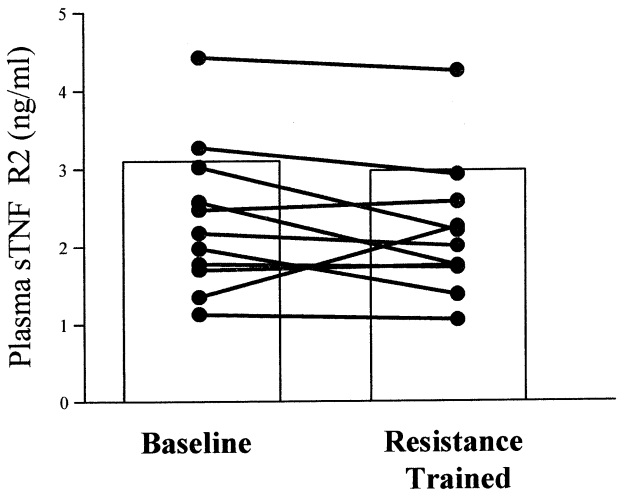


**Fig 3. The effect of 4 months of RT on plasma levels of sTNF R2 in older hypertensives.**

## DISCUSSION

The present study indicates that RT increases insulin-mediated glucose disposal and LBM without a decrease in blood pressure or a significant reduction in plasma levels of TNF-$\alpha$, sTNF R1, and sTNF R2 in older hypertensives. Therefore, it appears that RT can improve insulin sensitivity, without reducing blood pressure or decreasing TNF-$\alpha$ levels.

Although aerobic exercise training is well established to enhance insulin's ability to stimulate glucose uptake, only 2 studies have examined the effect of RT on insulin sensitivity.[22,23] Initial studies reported that RT lowers the insulin responses to an oral glucose challenge in young[26,27] and older[22,26,28] males, indicating an increase in insulin action. Miller et al[22] directly assessed insulin sensitivity before and after 4 months of RT in a group of middle-aged normotensive men and observed a significant increase in insulin sensitivity. Similar to the results of Miller et al,[22] the present study also observed an increase in insulin-mediated glucose disposal in a group of older hypertensive individuals. However, Ryan et al[23] reported only a trend for an increase in insulin sensitivity following 4 months of RT that was not statistically significant ($P$ = .06). Based on the studies that demonstrated a decreased insulin response to an oral glucose challenge following RT,[26-28] as well as the present results and the results of Miller et al,[22] it appears that RT is a useful intervention for reducing insulin resistance in older individuals.

The possibility of a mechanistic link between TNF-$\alpha$ and insulin resistance has received considerable attention (see Hotamisligil and Spiegelman[1] and Hotamisligil et al[29]). Interventions that improve insulin action appear to lower plasma TNF-$\alpha$ levels. For example, both weight loss[30,31] and troglitazone treatment[2] enhance insulin action and lower plasma levels of TNF-$\alpha$. Although aerobic exercise training is well established to increase insulin sensitivity, its effect on plasma

TNF-$\alpha$ levels has produced inconsistent results.[32-35] Similar to aerobic exercise training, RT improves insulin sensitivity,[22,23] but whether or not the improvement in insulin sensitivity following RT is associated with a decline in plasma TNF-$\alpha$ levels is not known. The present study demonstrates that the improvement in insulin-mediated glucose disposal following 4 months of RT occurs without a significant decline in plasma TNF-$\alpha$ levels. Horne et al[33] examined the effect of 3 months of RT on plasma TNF-$\alpha$ and demonstrated no significant effect. In a group of frail elderly individuals (81 $\pm$ 1 years), 3 months of RT decreased TNF-$\alpha$ mRNA and protein levels in skeletal muscle biopsies.[36] Although plasma TNF-$\alpha$ levels were not assessed, these findings indicate that RT can decrease TNF-$\alpha$ expression in skeletal muscle, the primary site for insulin-mediated glucose disposal. Therefore, the increase in insulin-mediated glucose disposal following RT or aerobic exercise training may be due to a reduction in skeletal muscle TNF-$\alpha$ levels, which is not reflected in plasma levels of TNF-$\alpha$.

Assessing soluble forms of TNF receptors is thought to provide a better indication of TNF-$\alpha$ system activation than plasma levels of TNF-$\alpha$ alone.[8-10] The effect of aerobic exercise training or RT on sTNF R1 and sTNF R2 has not been studied extensively. Tsukui et al[35] demonstrated a significant decrease in sTNF R1 and sTNF R2 following 5 months of aerobic exercise training in healthy Japanese women. Straczkowski et al[13] observed a significant decline in plasma levels of TNF-$\alpha$ and sTNF R2, without a significant decline in sTNF R1 following aerobic exercise training. Interestingly, only the changes in sTNF R2 were significantly related to the changes in insulin sensitivity following the aerobic exercise training program.[13] Fernandez-Read et al[11] demonstrated that the ratio of sTNF R2: sTNF R1 decreased following 3 months of aerobic exercise training, and the sTNF R2: sTNF R1 ratio was inversely related to $\dot{V}O_{2max}$. Because $\dot{V}O_{2max}$ is an excellent predictor of insulin sensitivity,[12] the investigators suggested that changes in the sTNF R2: sTNF R1 ratio may reflect changes in insulin sensitivity.[11] The present study demonstrates that RT does not alter plasma levels of sTNF R1, sTNF R2, or the sTNF R2: sTNF R1 ratio, but significantly increases insulin-mediated glucose disposal in a group of older hypertensives. Furthermore, we found no relationship between changes in the sTNF R2: sTNF R1 ratio and changes in insulin-mediated glucose disposal following RT. The discrepancy between our present results and the results of Fernandez-Read et al[11] may be due, in part, to differences in the population studied. Fernandez-Read et al[11] examined individuals with long standing type 2 diabetes (8.2 years), while our study examined nondiabetic hypertensive individuals with normal or impaired glucose tolerance. However, Straczkowski et al[13] demonstrated a significant relationship between changes in sTNF R2 and changes in insulin sensitivity following aerobic exercise training in subjects with normal and impaired glucose tolerance. Another potential explanation for the differences in the present results, the results of Straczkowski et al[13] and the results of Fernandez-Read et al[11] is the mode of exercise training. We utilized a RT program that resulted in a significant increase in LBM with no change in either fat mass or body weight; whereas Straczkowski et al[13] utilized an aerobic exercise training program that resulted in a significant decline in body weight. Perhaps the association between insulin action and the TNF-$\alpha$ system is somewhat dependent on the degree of adiposity and the extent of fat loss following a particular intervention.

The present study observed a trend for a relationship between plasma TNF-$\alpha$ and adiposity prior to the initiation of RT ($r$ = .560, $P$ = .073) and no relationship between plasma TNF-$\alpha$ and insulin-mediated glucose disposal. The changes in TNF-$\alpha$ levels following RT were not associated with the changes in either adiposity or insulin-mediated glucose disposal. Furthermore, neither sTNF R1 nor sTNF R2 were correlated to adiposity or glucose disposal at baseline or following RT. The lack of a correlation among the TNF-$\alpha$ system, adiposity, and glucose disposal before RT may be due to the small range of insulin sensitivity and percent body fat values observed in a relatively small number of older hypertensive subjects. Studies that have revealed strong relationships among the TNF-$\alpha$ system, adiposity, and insulin sensitivity have investigated a wide age-range of individuals with varied degrees of adiposity and insulin action.[4,11]

One limiting factor to the present investigation is the relatively small number of hypertensive subjects studied (n = 11). Therefore, we cannot rule out the possibility that an insufficient number of subjects were studied to detect a significant reduction in plasma TNF-$\alpha$ levels following RT. Although we did not observe any significant changes in plasma levels of TNF-$\alpha$, sTNF R1, and sTNF R2, one cannot rule out the possibility that a decline in skeletal muscle TNF-$\alpha$ levels might have contributed to the increase in insulin sensitivity following RT.[36]

In summary, the present study demonstrates that 4 months of RT can improve insulin-mediated glucose disposal and LBM in older hypertensive individuals independent of significant changes in plasma levels of TNF-$\alpha$, sTNF R1, and sTNF R2. Furthermore, we observed no relationship between the changes in insulin-mediated glucose disposal and the changes in the TNF-$\alpha$ system following RT. It is possible that the lack of association between the changes in insulin action and the TNF-$\alpha$ system following RT indicates that these variables might not be mechanistically connected in this population of older hypertensive individuals. Alternatively, it is possible that RT increases insulin sensitivity by mechanisms distinct from dramatic weight loss[30,31] or troglitazone treatment,[2] 2 interventions that appear to decrease plasma TNF-$\alpha$ levels. We conclude 4 months of RT improved insulin-mediated glucose disposal without significantly reducing plasma levels of TNF-$\alpha$, sTNF R1, sTNF R2 in a small group of older hypertensive subjects.

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