

Reductions in Plasma Cytokine Levels With Weight Loss Improve Insulin Sensitivity in Overweight and Obese Postmenopausal Women

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OBJECTIVE — The purpose of this study was to determine whether improvements in insulin sensitivity with weight loss are mediated by changes in inflammation in obese, postmenopausal women.

RESEARCH DESIGN AND METHODS — We studied 58 sedentary, overweight, and obese (BMI 33 ± 1 kg/m², means \pm SEM) postmenopausal (58 ± 1 year) women at baseline and 37 women who completed 6 months of weight loss induced by diet and exercise. The women underwent 3-h hyperinsulinemic-euglycemic clamps (40 mU \cdot m⁻² \cdot min⁻¹) to determine glucose utilization (*M*). Insulin sensitivity was determined as *M/I*, the amount of glucose metabolized per unit of plasma insulin (*I*). Visceral adipose tissue (VAT) and plasma concentrations of C-reactive protein (CRP), cytokines interleukin (IL)-6, and tumor necrosis factor (TNF)- α , as well as their soluble receptors, were measured.

RESULTS — At baseline, CRP concentration was a predictor of both glucose utilization and insulin sensitivity, independent of adiposity, race, and aerobic fitness (*M*: partial $r = -0.30$, $P = 0.03$, and *M/I*: partial $r = -0.32$, $P = 0.02$). Weight loss resulted in significant reductions in body weight, fat mass, VAT, and fasting glucose and insulin levels ($P < 0.05$). Both glucose utilization and insulin sensitivity increased by 16% ($P < 0.05$). CRP, IL-6, and soluble TNF receptor (sTNFR)-1 concentrations decreased ($P < 0.05$), but concentrations of TNF- α , sTNFR-2, and soluble IL-6 receptor (IL-6sR) did not change. In stepwise regression models to predict changes in glucose homeostasis, changes in VAT and sTNFR-1 independently predicted changes in glucose utilization ($r = -0.49$ and cumulative $r = -0.64$, $P < 0.01$), while changes in VAT and IL-6 were both independent predictors of changes in insulin sensitivity ($r = -0.57$ and cumulative $r = -0.68$, $P < 0.01$).

CONCLUSIONS — Improvements in glucose metabolism with weight loss programs are independently associated with decreases in cytokine concentrations, suggesting that a reduction in inflammation is a potential mechanism that mediates improvements in insulin sensitivity.

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Abbreviations: CRP, C-reactive protein; FFM, fat-free mass; IL, interleukin; IL-6sR, soluble IL-6 receptor; SAT, subcutaneous adipose tissue; TNF, tumor necrosis factor; sTNFR, soluble TNF receptor; VAT, visceral adipose tissue.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Elevated circulating concentrations of C-reactive protein (CRP) and interleukin (IL)-6 predict the development of type 2 diabetes in middle-aged women (1) and in elderly adults (2,3). These inflammatory markers are also increased in obesity (4,5) and associated with features of the insulin resistance syndrome (4,6). Another proinflammatory cytokine, tumor necrosis factor (TNF)- α , is also increased in obesity and type 2 diabetes (7). These data suggest that the inflammatory process may play a critical role in the pathogenesis of insulin resistance.

In the few studies that examined the associations between plasma cytokine levels and insulin sensitivity assessed via the glucose clamp, negative correlations are reported between soluble TNF receptor (sTNFR)-2 and glucose utilization in obese young women (8) and between CRP and glucose utilization in obese postmenopausal women (9). In addition, glucose utilization is negatively associated with plasma concentrations of IL-6 in the Pima Indians (10), but this relationship disappears after adjustment for obesity. Thus, inflammation may be involved in the causal pathway between obesity and insulin resistance.

Emerging evidence shows that behavioral treatments, such as weight loss and exercise, that improve glucose metabolism (11–13) also decrease inflammatory markers. Dietary-induced weight loss results in decreases in CRP, IL-6, and TNF- α concentrations in obese women (14–17). It is also postulated that physical activity plays a role in inflammation, such that more active individuals have lower concentrations of IL-6 and CRP (18), and exercise training decreases several markers of inflammation (19,20). In other studies, the combined effects of weight loss and increased physical activity result in decreases in CRP and/or IL-6 levels in obese premenopausal women (21,22).

These previous studies suggest that

Table 1—Metabolic characteristics and inflammatory markers of postmenopausal women (n = 58)

	Mean ± SD	Range
Age (years)	58 ± 6	50–70
Weight (kg)	87.0 ± 13.1	61.4–121.8
Body fat (%)	46.7 ± 4.7	30.7–56.6
Fat mass (kg)	40.3 ± 8.8	23–63
FFM (kg)	45.3 ± 5.6	32–57
VAT (cm ²)	155.4 ± 55.3	73–293
SAT (cm ²)	468.2 ± 107.4	273–802
VO _{2max} (l/min)	1.68 ± 0.33	1.01–2.39
Plasma glucose (mmol/l)	5.5 ± 0.4	4.6–6.7
Plasma insulin (pmol/l)	63 ± 9	18–173
Glucose utilization		
μmol · kg ⁻¹ · min ⁻¹	24.7 ± 7.91	10.6–47.3
μmol · kg _{FFM} ⁻¹ · min ⁻¹	47.3 ± 14.0	19.7–78.8
Insulin sensitivity		
μmol · kg ⁻¹ · min ⁻¹ /pmol/l	0.051 ± 0.019	0.015–0.095
μmol · kg _{FFM} ⁻¹ · min ⁻¹ /pmol/l	0.098 ± 0.003	0.025–0.182
CRP (μg/ml)	7.01 ± 5.74	0.51–35.1
TNF-α (pg/ml)	1.93 ± 2.6	0.2–14.9
sTNFr-1 (pg/ml)	803 ± 201	303–1,483
sTNFr-2 (pg/ml)	1,868 ± 441	734–3,035
IL-6 (pg/ml)	2.29 ± 1.47	0.45–10.0
IL-6sR (μg/ml)	23.3 ± 6.3	9.7–41.5

Data are means ± SEM. Units are ml · m⁻² · min⁻¹ for 120–180 min of clamp.

improvements in insulin sensitivity after weight loss may be mediated by changes in inflammation. Therefore, the purpose of this study was to test our hypotheses that improvements in insulin sensitivity with diet- and exercise-induced weight loss will be associated with reductions in inflammation in obese postmenopausal women and that this association will be independent of decreases in total and regional body fat.

RESEARCH DESIGN AND METHODS

The women in this study were postmenopausal (had not

menstruated for at least 1 year and had plasma follicle-stimulating hormone levels >30 mIU/ml) and were 50–70 years old, healthy, overweight, and obese (BMI >25 kg/m², range 25–41). Only women who were weight stable (<2.0-kg weight change in previous year) and sedentary (<20 min of aerobic exercise twice a week) were recruited to participate. Women were screened by medical history questionnaire, physical examination, fasting blood profile, and a graded exercise treadmill test in an attempt to exclude those with cardiovascular disease. The women underwent a 2-h 75-g oral glu-

cose tolerance test during screening to exclude women with diabetes (23). All women were nonsmokers and showed no evidence of cancer, liver, renal, or hematological disease, or other medical disorders. The Institutional Review Board of the University of Maryland approved all methods and procedures. Each participant provided written informed consent to participate in the study.

Sixty-two women met the study inclusion/exclusion criteria and were enrolled. Fifty-eight of these women (46 Caucasians and 12 African Americans) had complete baseline data, including completion of a 3-h glucose clamp. Nineteen of these women were on hormone replacement therapy for at least 3 years before enrollment, which did not change for the duration of the study. Thirty-seven of the women studied at baseline completed 6 months of dietary- or exercise-induced weight loss (30 Caucasians and 7 African Americans, 12 of which were on hormone replacement therapy).

Weight loss treatments

For 6 months, all women attended weekly weight loss classes led by a registered dietitian for instruction in the principles of a hypocaloric diet that followed the American Heart Association Step I (24) guidelines with restriction of caloric intake by 250–350 kcal/day, as previously described (13). Compliance to the weight-loss classes was ~80%. Twenty-five women also exercised three times a week on nonconsecutive days using treadmills and cycle ergometers at >60% VO_{2max} for 45 min (n = 16) or using eight exercises on pneumatic variable-resistance machines (Keiser K-300; Keiser Sports Health, Fresno, CA) and dumbbells (n = 9) (13,25).

Table 2—Univariate correlations between inflammatory markers and aerobic fitness, adiposity, glucose utilization (M) and insulin sensitivity (M/I) at baseline (n = 58)

Pearson's correlation coefficients	VO _{2max} (ml · kg ⁻¹ · min ⁻¹)	BMI (kg/m ²)	Fat (%)	VAT (cm ²)	M (μmol · kg _{FFM} ⁻¹ · min ⁻¹)	M/I (μmol · kg _{FFM} ⁻¹ · min ⁻¹ /pmol/l)
Log CRP (μg/ml)	-0.30*	0.33*	0.25	0.05	-0.45†‡	-0.46†‡
Log TNF-α (pg/ml)	-0.11	0.16	0.05	0.04	-0.03	-0.07
STNFR-1 (pg/ml)	-0.22	0.43†	0.20	0.29*	-0.09	-0.12
STNFR-2 (pg/ml)	-0.14	0.19	0.12	0.29*	-0.06	-0.13
Log IL-6 (pg/ml)	-0.48‡	0.55‡	0.34*	0.05	-0.17	-0.24§
IL-6sR (μg/ml)	-0.12	0.15	-0.04	0.13	0.20	0.17

*P < 0.05; †P < 0.01; ‡P < 0.001; §P = 0.08.

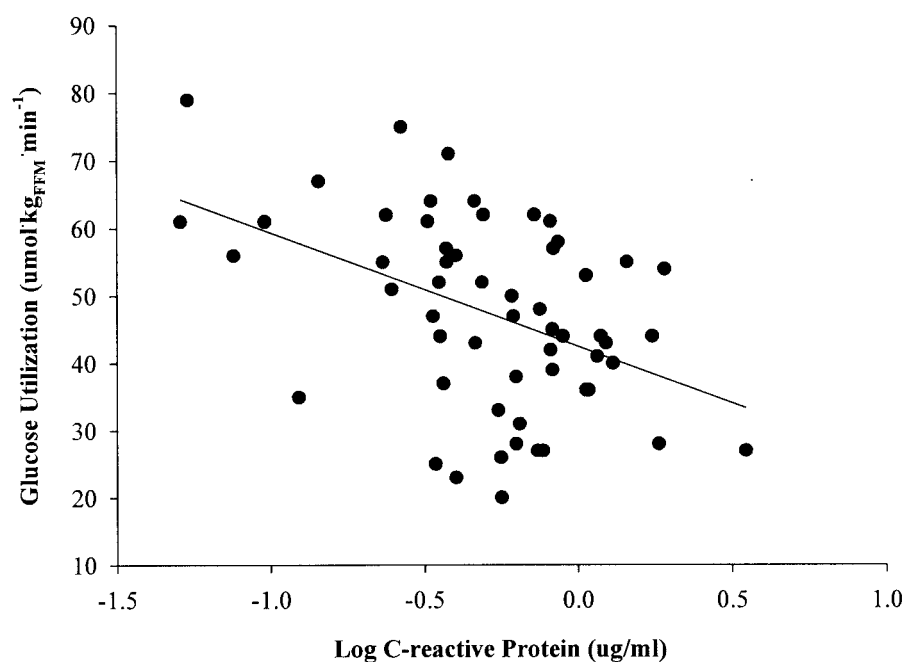


Figure 1—Relationship between glucose utilization and CRP in obese postmenopausal women ($r = -0.45$, $P < 0.01$).

VO_{2max} and body composition

VO_{2max} was measured using a continuous treadmill test protocol that has been previously described (25). Height and weight were measured to calculate BMI as weight (kg)/height (m²). Fat mass, lean tissue mass, and bone mineral content (BMC) were determined by dual-energy X-ray absorptiometry (Model DPX-L; Lunar Radiation, Madison, WI) using the 1.3z DPX-L extended analysis program. Fat-free mass (FFM) is reported as lean tissue plus BMC. A single 5-mm computed tomography scan was taken at the L₄-L₅ region using a General Electric Hi-Light Scanner to determine relative proportions of visceral adipose tissue (VAT) area and subcutaneous adipose tissue (SAT) area (12).

Hyperinsulinemic-euglycemic clamps

All subjects were weight stabilized (<1 kg) for at least 2 weeks before metabolic testing before and after the interventions and were provided with a eucaloric diet for 2 days before the clamp by a registered dietitian to control nutrient intake, as previously described (26). All testing was performed in the morning after a 12-h overnight fast. Glucose clamps were performed 36–48 h after any exercise. Peripheral tissue sensitivity to exogenous insulin was measured using the hyperinsulinemic-euglycemic clamp technique (27). Arterialized blood was obtained from a dorsal heated hand vein (28). Basal

glucose, insulin, and cytokine levels were measured in the fasted state. A 10 min, priming and continuous infusion of insulin (240 pmol · m⁻² · min⁻¹, Humulin; Eli Lilly, Indianapolis, IN) and a 20% glucose solution infusion was performed for 180

min. During the clamp, blood samples were obtained every 5 and 10 min for the determination of plasma glucose and insulin levels.

The plasma glucose and insulin levels during all clamps averaged 5.19 ± 0.05

Table 3—Metabolic characteristics of postmenopausal women before and after weight loss ($n = 37$)

	Before	After
Age (years)	57 ± 1	—
Weight (kg)	86.4 ± 2.3	80.3 ± 2.2*
Body fat (%)	46.8 ± 0.8	43.5 ± 0.8*
Fat mass (kg)	40.2 ± 1.6	34.9 ± 1.5*
FFM (kg)	45.0 ± 1.1	44.2 ± 0.9†
VAT (cm ²)	147.8 ± 8.4	121.6 ± 7.2*
SAT (cm ²)	470.0 ± 19.4	399.9 ± 17.8*
VO _{2max} (l/min)	1.73 ± 0.06	1.74 ± 0.06
Plasma glucose (mmol/l)	5.2 ± 0.1	4.9 ± 0.1*
Plasma insulin (pmol/l)	54 ± 3	48 ± 2*
Glucose utilization		
μmol · kg ⁻¹ · min ⁻¹	26.3 ± 1.3	31.0 ± 1.4*
μmol · kg _{FFM} ⁻¹ · min ⁻¹	52.4 ± 2.4	56.0 ± 2.4†
Insulin sensitivity		
μmol · kg ⁻¹ · min ⁻¹ /pmol/l	0.058 ± 0.003	0.069 ± 0.003‡
μmol · kg _{FFM} ⁻¹ · min ⁻¹ /pmol/l	0.112 ± 0.006	0.124 ± 0.006†
CRP (μg/ml)	5.7 ± 0.6	5.3 ± 1.0‡
TNF-α (pg/ml)	2.25 ± 0.50	2.44 ± 0.55
sTNFR-1 (pg/ml)	776 ± 33	728 ± 30†
sTNFR-2 (pg/ml)	1,842 ± 72	1,801 ± 68
IL-6 (pg/ml)	1.89 ± 0.12	1.59 ± 0.13‡
IL-6sR (pg/ml)	23,225 ± 997	22,857 ± 867

Data are means ± SEM. Significantly different before vs. after weight loss: * $P < 0.001$; † $P < 0.05$; ‡ $P < 0.01$.

Table 4—Univariate correlations between changes in inflammatory markers and changes in glucose utilization (M) and insulin sensitivity (M/I) (n = 37)

Pearson's correlation coefficients	ΔM		$\Delta M/I$	
	$\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$	$\mu\text{mol} \cdot \text{kg}_{\text{FFM}}^{-1} \cdot \text{min}^{-1}$	$\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}/\text{pmol/l}$	$\mu\text{mol} \cdot \text{kg}_{\text{FFM}}^{-1} \cdot \text{min}^{-1}/\text{pmol/l}$
$\Delta\text{Log CRP}$ ($\mu\text{g/ml}$)	-0.33*	-0.28†	-0.29‡	-0.23
$\Delta\text{Log TNF-}\alpha$ (pg/ml)	-0.13	-0.14	-0.07	-0.08
$\Delta\text{Log sTNFR-1}$ (pg/ml)	-0.45§	-0.43	-0.36*	-0.28‡
$\Delta\text{Log sTNFR-2}$ (pg/ml)	-0.25	-0.29	-0.24	-0.27
$\Delta\text{Log IL-6}$ (pg/ml)	-0.48§	-0.38*	-0.51§	-0.41*
$\Delta\text{IL-6sR}$ ($\mu\text{g/ml}$)	-0.17	-0.12	-0.14	-0.08

* $P < 0.05$; † $P = 0.09$; ‡ $P = 0.08$; § $P < 0.0005$; || $P < 0.01$.

mmol/l and 478 ± 7 pmol/l ($n = 96$, i.e., 58 pre- and 37 postintervention). This was $97.6 \pm 0.1\%$ of the desired goal with a coefficient of variation (CV) of $4.9 \pm 0.2\%$ in all clamps ($n = 96$).

Analysis of blood samples. Blood samples were collected in heparinized syringes and placed in prechilled test tubes containing 1.5 mg EDTA/ml blood. The blood samples were centrifuged at 4°C , and plasma was stored at -70°C until analysis. Plasma glucose was measured with the glucose oxidase method (Beckman Instruments, Fullerton, CA). Insulin was determined by radioimmunoassay (Linco, St. Louis, MO). All cytokines were measured by Quantikine enzyme-linked immunosorbent assay kits (high sensitivity for IL-6 and TNF- α) (R&D Systems, Minneapolis, MN). The inter- and intra-assay CVs were $<6\%$ for IL-6 and the soluble receptor assays and $<12\%$ for TNF- α . C-reactive protein was measured using an automated immunoanalyzer (Immulite; Diagnostics Products, Los Angeles, CA) with inter- and intra-assay CVs of 7.5 and 4.4%, respectively. Samples for glucose, insulin, and cytokines were measured in duplicate, and the average of the two values were used in the statistical analyses. The duplicate samples for the cytokines required a CV $<15\%$, or the sample was reanalyzed.

Statistical analyses

For the hyperinsulinemic-euglycemic clamps, the mean concentration of glucose and insulin was calculated for each sample time point. The trapezoidal rule was used to calculate the integrated response over 30-min intervals from 30 to 180 min for each subject. The integrated response was divided by its time interval to compute mean concentrations. Glu-

cose utilization (M) for 30-min intervals was calculated from the amount of glucose infused after correction for glucose equivalent space (glucose space correction). Insulin sensitivity was expressed as M/I, which represents the amount of glucose metabolized per unit of plasma insulin (I), and was calculated by dividing the glucose utilized by the insulin concentration during the last 60 min of the clamp for each subject.

The CRP, IL-6, and TNF data were not normally distributed, therefore the logarithm was used for parametric statistical analyses. Associations at baseline were tested using linear regression analyses. Differences between pre- and postintervention measures of all variables were determined using a paired *t* test. Univariate regression analysis was used to determine predictors of glucose utilization and insulin sensitivity. Stepwise regression analysis was used to determine whether changes in markers of inflammation were significant predictors of changes in glucose utilization. Statistical significance was set at $P < 0.05$ for all tests. All data were analyzed by SPSS statistical software (SPSS, Chicago, IL). All values are expressed as means \pm SEM.

RESULTS

Baseline characteristics

The baseline characteristics of the women in this study are shown in Table 1. Although all women were overweight or obese, sedentary, and of a similar age, there was wide variation in glucose utilization, insulin sensitivity, and inflammatory markers.

Pearson correlation coefficients between all of the inflammatory markers and $\text{VO}_{2\text{max}}$, BMI, fat percentage, VAT, M,

and M/I at baseline are shown in Table 2. CRP and IL-6 concentrations correlated negatively with $\text{VO}_{2\text{max}}$, and CRP, sTNFR-1, and IL-6 concentrations correlated positively with BMI. Only IL-6 concentrations were directly related to percentage of fat, whereas both sTNFR-1 and sTNFR-2 concentrations correlated positively with VAT. Glucose utilization and insulin sensitivity were lower in women with higher CRP concentrations (Fig. 1) and tended to be lower in women with higher IL-6 levels.

We next determined whether M and M/I were independently related to CRP at baseline in these women. Since univariate analyses showed that race (M: $r = -0.41$ and M/I: $r = -0.43$; $P < 0.01$), BMI (M: $r = -0.31$ and M/I: $r = -0.32$; $P < 0.05$) and $\text{VO}_{2\text{max}}$ (M: $r = 0.26$ and M/I: $r = 0.29$; $P < 0.05$) were the only other variables associated with M and M/I, we used linear regression analyses to co-vary the relationship between M and M/I and CRP for these variables. The results showed that CRP concentrations remained significantly associated with M (partial $r = -0.30$; $P = 0.03$) and M/I (partial $r = -0.32$; $P = 0.02$), indicating that CRP is a predictor of both glucose utilization and insulin sensitivity independent of total and regional adiposity, race, and aerobic fitness.

Effects of weight loss treatments

Body weight, percentage body fat, fat mass, FFM, VAT, and SAT decreased ($P < 0.05$) (Table 3), whereas $\text{VO}_{2\text{max}}$ (in liters per minute) did not change after weight loss. Fasting plasma glucose and insulin levels decreased by 6 and 10%, respectively ($P < 0.001$). Glucose utilization increased by 10% (in $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and 16% (in $\mu\text{mol} \cdot \text{kg}_{\text{FFM}}^{-1} \cdot \text{min}^{-1}$) ($P <$

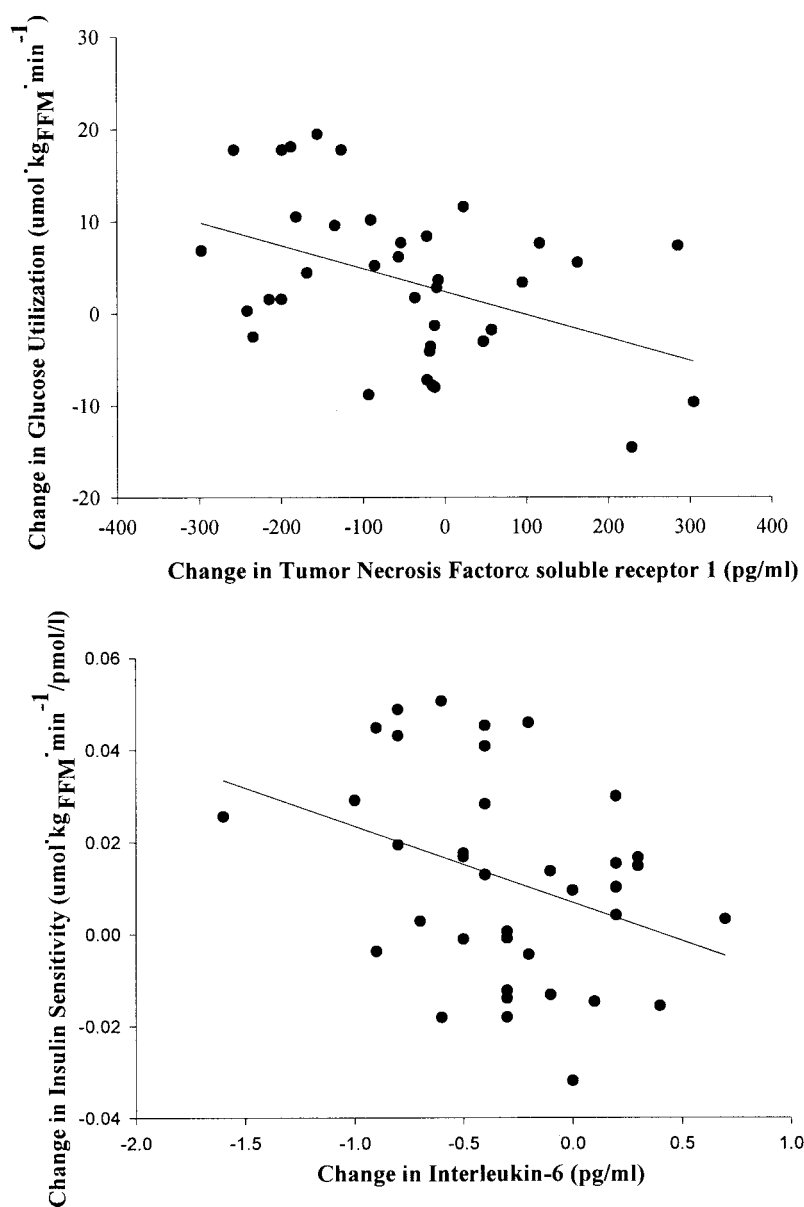


Figure 2—A: Relationship between weight loss–induced changes in glucose utilization and changes in sTNFR-1 in obese postmenopausal women ($r = -0.43$, $P < 0.01$). B: Relationship between weight loss–induced changes in insulin sensitivity and changes in IL-6 concentrations in obese postmenopausal women ($r = -0.40$, $P < 0.05$)

0.05), and insulin sensitivity increased 23% (in $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and 16% (in $\mu\text{mol} \cdot \text{kg}_{\text{FFM}}^{-1} \cdot \text{min}^{-1}$, $P < 0.05$). CRP, IL-6, and sTNFR-1 concentrations decreased ($P < 0.05$, Table 3), but concentrations of TNF- α , sTNFR-2, and IL-6sR did not change. Changes in M and M/I were inversely related to changes in fat mass ($r = -0.38$ and $r = -0.41$, $P < 0.05$) and VAT ($r = -0.49$ and $r = -0.57$, $P < 0.01$), whereas only the change in M/I was inversely related to the loss of SAT ($r = -0.48$, $P < 0.01$).

We next examined whether the improvements in glucose metabolism were related to declines in inflammatory markers. Changes in M and M/I were inversely related to changes in CRP, sTNFR-1 and IL-6 (Table 4 and Fig. 2A and B). Changes in M and M/I were not related to changes in IL6sR, TNF- α , or sTNFR-2. The changes in total fat mass, VAT, CRP, IL-6, and sTNFR-1 were put in a stepwise regression model to determine the strongest independent predictor of changes in M and M/I with weight loss. Changes in VAT

entered the model first ($r = -0.49$, $P < 0.01$), followed by changes in sTNFR-1 (cumulative $r = -0.64$, $P < 0.01$) to predict changes in M . Changes in VAT and IL-6 were both independent predictors of changes in M/I ($r = -0.57$ and cumulative $r = -0.68$, $P < 0.01$).

CONCLUSIONS— Inflammation likely plays a key role in the development of type 2 diabetes. Thus, interventions that reduce inflammation and improve insulin resistance would have important clinical implications. Our results show that in postmenopausal women, increases in glucose utilization and insulin sensitivity with weight loss are related to reductions in circulating cytokines, specifically sTNFR-1 and IL-6, and this relationship is independent of decreases in total body and visceral fat. Moreover, this occurs with a relatively modest amount of weight loss.

Concentrations of CRP, TNF- α , and IL-6, considered sensitive markers of subclinical systemic inflammation, are elevated in obesity and type 2 diabetes (1,7). Our study in postmenopausal women focuses on the relationship between markers of inflammation and insulin resistance. At baseline, CRP is the only inflammatory marker associated with insulin-stimulated glucose uptake and insulin sensitivity. This is consistent with previous reports in postmenopausal women (9) and in Pima Indians (10), as well as findings in the Insulin Resistance Atherosclerosis Study (IRAS), where CRP was associated with insulin sensitivity determined by the frequently sampled intravenous glucose tolerance test (29). Thus, it is clear that insulin resistance is linked to CRP in diverse populations.

In animal models, TNF- α induces insulin resistance by decreasing insulin receptor and IR substrate phosphorylation, while producing other modifications in the insulin-signaling cascade (31). In humans, insulin resistance is associated with increased expression of skeletal muscle TNF- α (30). Yet we and others (9) did not find a relationship between plasma TNF- α and glucose utilization, suggesting that local rather than systemic TNF- α may be more important to insulin resistance.

Neither glucose utilization nor insulin sensitivity was related to circulating concentrations of sTNFR-1 or -2 in these women before intervention. This is in

contrast to a report (8) in younger obese women where glucose utilization was associated with sTNFR-2 levels. In addition, sTNFR2 decreased with a 12-week exercise training regimen, and this decline was related to an increase in insulin sensitivity (8). However, in our study, the decrease in sTNFR-1, and not sTNFR-2, concentration was an independent predictor of the improvement in glucose utilization with weight loss. Although the biological functions of the TNF receptors are not completely understood, TNFR-1 is involved in proinflammatory and cytotoxic responses, whereas TNFR-2 may merely vary the response produced by TNFR-1 (32). In addition to TNF- α , other cytokines can bind to these receptors, which are elevated in inflammatory states, even in the absence of change in TNF- α concentrations (33). Accordingly, our finding that changes in inflammation are associated with improvements in insulin-stimulated glucose uptake raises the possibility that weight loss induced by diet and exercise training may provide the pathway to concurrently reduce inflammation and insulin resistance.

IL-6 is another cytokine produced in adipose tissue and released into the systemic circulation. Although Vozarova et al. (10) found that glucose utilization was negatively related to plasma IL-6 concentrations in Pima Indians, we did not see a significant relationship between these parameters in obese postmenopausal women before treatment. This is similar to other reports in postmenopausal women (9) and obese subjects with and without diabetes (34) when glucose utilization is determined at low physiologic insulin concentrations. However, when IL-6 is measured in adipose tissue and glucose utilization is determined at maximal insulin concentrations, IL-6 concentrations are inversely correlated with maximal insulin responsiveness in vivo and in vitro (34). This suggests that measurement of local IL-6 concentrations may be more sensitive than that measured in the systemic circulation. Yet, we did find that change in IL-6 concentration is an independent predictor of the change in insulin sensitivity with weight loss, suggesting that systemic IL-6 may be an important mechanistic mediator of improvements in glucose homeostasis.

We conclude that improvements in glucose metabolism with modest weight loss in overweight and obese postmeno-

pausal women are associated with decreases in cytokine concentrations, suggesting that a reduction in inflammation is a potential mechanism that mediates changes in insulin resistance. Future studies should be directed at the examination of either skeletal muscle or adipose tissue cytokine production and whether modulation of local inflammatory markers with weight loss impacts changes in systemic insulin resistance.

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