Adiponectin is not altered with exercise training despite enhanced insulin action

MATTHEW W. HULVER,1 DONGHAI ZHENG,1 CHARLES J. TANNER,2 JOSEPH A. HOUMARD,2 WILLIAM E. KRAUS,4 CRIS A. SLENTZ,4 MADHUR K. SINHA,5 WALTER J. PORIES,3 KENNETH G. MACDONALD,3 AND G. LYNIS DOHM1

Departments of 1Physiology, 2Exercise and Sport Science Human Performance Laboratory, and 3Surgery, East Carolina University, Greenville 27858; 4Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710; and 5Linco Research Inc., St. Charles, Missouri 63304

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Adipose tissue was once thought to simply be a storage depot for energy surplus; however, it is now known that adipocytes also secrete multiple proteins that modulate various biological functions. These proteins are collectively known as adipokines and include leptin, tumor necrosis factor (TNF)-α, plasminogen-activator inhibitor type I, adiponectin, and resistin. Recently, an adipokine referred to as adiponectin (also known as Acrp 30, AdipoQ, apM-1, and GBP28) has been independently identified and characterized (14, 16, 18, 22). Unlike other adipokines, mRNA expression (14) and adiponectin plasma levels (1) are reduced with obesity and diabetes. Adiponectin may also be a marker for coronary artery disease (CAD), as low plasma adiponectin levels are associated with the presence of CAD (12).

Hu et al. (14) originally demonstrated that adiponectin was reduced in murine models of insulin resistance and obesity, which was subsequently confirmed in humans (12, 25). Recently, Hotta et al. (13) reported parallel decreases in insulin action and plasma levels of adiponectin with the progression of obesity in rhesus monkeys. Yamauchi et al. (27), through the administration of recombinant adiponectin, alleviated hyperglycemia and hyperinsulinemia and successfully reversed insulin resistance in obese mice. Also, Fruebis et al. (8), using a proteolytic cleavage product of adiponectin, induced an increase in fatty acid oxidation and weight loss in mice. These findings suggest that adiponectin may not be merely a passive factor regulated by insulin resistance and obesity. Additional support for the role of adiponectin in the pathogenesis of insulin resistance comes from two independent genetic studies (4, 24). Vionnet et al. (24) mapped a diabetes susceptibility locus in a native French cohort to human chromosome 3q27, which encodes adiponectin. In addition, Comuzzie et al. (4) demonstrated a quantitative-
trait locus on 3q27 strongly linked to the metabolic syndrome in European individuals.

Weight loss (9, 10) and exercise (23, 29) are common clinical interventions for the treatment of insulin resistance. Two recent publications have reported significant increases in plasma adiponectin with weight loss (12, 28). Yang et al. (28) also reported that with weight loss, an increase in adiponectin was associated with enhanced insulin action. However, to date, there are no reports on the effects of exercise training on plasma adiponectin levels. Given that exercise training improves insulin sensitivity, we sought to determine the effects of exercise training on plasma adiponectin. For the purpose of comparison, we also examined adiponectin responses to weight loss where insulin action is also improved.

**EXPERIMENTAL PROCEDURES**

**Study groups.** An exercise group and a weight loss group were examined. The exercise group consisted of 11 previously sedentary, healthy subjects [3 females, 8 males; age, 51.1 ± 6.8 yr; body mass index (BMI), 29.1 ± 0.9 kg/m²] who participated in a 6-mo endurance training program. The weight loss group consisted of 14 morbidly obese subjects (3 males, 11 females; age, 42.5 ± 10.1 yr; BMI, 46.8 ± 1.2 kg/m²) who underwent gastric bypass surgery. Of the weight loss subjects, four were classified as having non-insulin-dependent diabetes mellitus (NIDDM), and ten were classified as non-diabetic, according to the criteria established by the National Diabetes Data Group. None of the weight loss subjects had any disease other than diabetes and/or obesity, and subjects from both the exercise training and weight loss groups were weight stable for ≥2 mo before entry into the study. The experimental protocol was explained to each subject, and informed consent was obtained. The project was approved by the East Carolina University Policy and Review Committee on Human Research.

Insulin action and fasting circulating levels of glucose, insulin, and adiponectin were assessed before and after 6 mo of exercise training and 1 mo before and again after gastric bypass surgery when a stable body mass was achieved (∼12 mo) in the weight loss subjects.

**Exercise intervention.** The exercise training subjects were selected from a larger, randomized, controlled clinical trial designed to study the effects of exercise training regimens differing in dose (kcal/wk) and/or intensity [relative to peak VO₂ peak)] on established cardiovascular risk factors (15). Exercise training was supervised and included treadmill walking/running, stair climbing, and cycling. After a 6-wk ramping period, all participants exercised 4 days/wk for ∼45 min at 65–80% VO₂ peak for 6 mo. Average time and distance per week were 175 min and 17 miles, respectively. All physiological measures were assessed 24 h after the last training session. A goal of the exercise training program was to minimize weight loss in an attempt to focus on the effect of exercise alone.

**Weight loss intervention.** Gastric bypass surgery was performed, as previously described (10), in the weight loss subjects. After surgery, all patients were followed at 6- to 8-wk intervals for weighing and dietary counseling, and a plateau in weight was declared when three consecutive weights varied by ≤1 kg.

**Body composition.** Body composition was assessed via hydrostatic weighing in the exercise training group but not in the weight loss group. The hydrostatic weighing procedure was offered to all weight loss subjects before gastric bypass surgery, but no patients elected the procedure due to difficulties involved in submersion and fear of water. Thus, for the weight loss subjects, we present BMI, which is obtained consistently.

Residual volume was determined by the O₂ dilution method, as described by Wilmore (26). Body density was determined by hydrostatic weighing, with percent body fat calculated using residual volume and body density with the equations of Brozek et al. (3), as described previously (13).

**Insulin action.** Insulin action was determined with a 3-h intravenous glucose tolerance test (minimal model) (2). Glucose and insulin dosages were calculated on the basis of body mass for the exercise training subjects and body surface area in the weight loss subjects. Dosages were different between groups due to the high body mass of morbidly obese subjects (R. N. Bergman, personal communication). After fasting samples were obtained, glucose (50%) was injected into a catheter placed in an antecubital vein at a dose of 1.7 mmol/kg (exercise training subjects) or 12 g/m² of body surface area (weight loss subjects). Insulin, at a dose of 150 pmol/kg (exercise training subjects) or 1.5 U/m² body surface area (weight loss subjects), was injected at minute 20. Blood samples were obtained at minutes 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 and centrifuged, and plasma was frozen at −80°C for the subsequent determination of insulin and glucose. Insulin was determined with immunoassay (Access Immunoassay System; Beckman Coulter, Fullerton, CA) and glucose with an oxidation reaction (YSI model 2300 Stat Plus, Yellow Springs Instrument, Yellow Springs, OH). An insulin sensitivity index (SI) was calculated on the basis of the minimal model as described by Bergman et al. (2). SI is an index of the ability of insulin to promote the disposal of glucose, with a higher SI indicating enhanced insulin sensitivity.

**Plasma adiponectin.** Plasma adiponectin was assessed using a commercially available radioimmunoassay kit (cat. no. HADP-61HK, Linco Research, St. Charles, MO).

**Statistical analysis.** Differences in all measured variables before and after the exercise and weight loss interventions were compared by paired t-test. Pearson correlational analyses were performed for all clinical characteristics and plasma adiponectin levels before and after the exercise and weight loss interventions. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS, v. 10.0, SPSS, Chicago, IL). Data were presented as means ± SE, and statistical significance was accepted as P ≤ 0.05.

**RESULTS**

**Effects of exercise training and weight loss.** PRE and POST values for all measured variables are displayed in Table 1. Six months of exercise training resulted in significant decreases in fasting insulin (−18%) and significant increases in SI (−98%), with no changes in body mass, fat mass, BMI, fasting glucose, or adiponectin. Plasma adiponectin levels were not significantly related (P > 0.05) to BMI (PRE, r = −0.46; POST, r = −0.38), fat mass (PRE, r = −0.06; POST, r = 0.19), plasma glucose (PRE, r = −0.48; POST, r = −0.51), or SI (PRE, r = 0.51; POST, r = 0.40) before or after exercise training. However, plasma levels of adiponectin and insulin (PRE, r = −0.63, P = 0.04; POST, r = −0.60, P = 0.05) were significantly related pre- and postexercise training (Fig. 1).
Approximately 12 mo after gastric bypass surgery, the weight loss subjects demonstrated significant decreases in body mass (−40%), BMI (−40%), fasting insulin (−78%), and glucose (−25%) and significant increases in SI (432%) and adiponectin levels (281%). Plasma adiponectin levels were not significantly related (P > 0.05) to BMI (PRE, r = −0.165; POST, r = −0.44) or plasma glucose (PRE, r = −0.07; POST, r = −0.10) before or after weight loss. SI was significantly related to plasma adiponectin prior to (r = 0.72, P = 0.004) but not following (r = 0.38) weight loss. Plasma levels of adiponectin and insulin were not significantly related before (r = −0.45) weight loss but were significantly related afterward (r = −0.62, P = 0.02; Fig. 1).

Diabetic and nondiabetic surgery patients differed only in fasting glucose levels before weight loss (diabetic, 10.0 ± 2.7 mmol/l vs. nondiabetic, 5.3 ± 0.2 mmol/l), and the presence of diabetes had no influence on the change in any measured variables with weight reduction (data not shown).

### Table 1. Measured variables before and after exercise training and weight reduction

<table>
<thead>
<tr>
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<th>Exercise (n = 11)</th>
<th>Weight Loss (n = 14)</th>
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<tbody>
<tr>
<td></td>
<td>PRE</td>
<td>POST</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>91.9 ± 3.8</td>
<td>91.6 ± 3.9</td>
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<tr>
<td>Fat mass, kg</td>
<td>26.5 ± 1.8</td>
<td>26.7 ± 2.2</td>
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<tr>
<td>BMI, kg/m²</td>
<td>29.1 ± 0.9</td>
<td>29.3 ± 0.9</td>
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<tr>
<td>Fasting insulin, pmol/l</td>
<td>81.8 ± 15.1</td>
<td>69.6 ± 13.8*</td>
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<tr>
<td>Fasting glucose, mmol/l</td>
<td>5.3 ± 0.2</td>
<td>5.1 ± 0.1</td>
</tr>
<tr>
<td>SI, pmol·l⁻¹·min⁻¹</td>
<td>2.9 ± 0.6</td>
<td>5.1 ± 1.0</td>
</tr>
<tr>
<td>Plasma adiponectin, μg/ml</td>
<td>6.3 ± 1.5</td>
<td>6.6 ± 1.8</td>
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</table>

Values are means ± SE. BMI, body mass index; SI, insulin sensitivity index. *Significantly different from PRE.

**DISCUSSION**

Peripheral insulin resistance is a primary disorder in both obesity and NIDDM (19). In animals and humans, plasma adiponectin concentrations are lower in states of insulin resistance compared with healthy controls (12, 14, 25). Weight loss (10) and exercise training (23, 29) are successful and common treatments for insulin resistance. Previous reports (12, 28) demonstrate increased adiponectin concentrations with weight reduction. The effects of exercise training on this novel adipocytokine are unknown. Our data suggest that both weight loss and exercise training significantly improve insulin ac-
tion, but only the former significantly increases plasma adiponectin.

The weight loss- and exercise-related improvements in insulin sensitivity reported in the present study are in agreement with results from our laboratory (10, 23, 29) and others (9, 28). In addition, our findings of increased plasma adiponectin concentrations with weight reduction support the data of Hotta et al. (12) and Yang et al. (28). However, in contrast to weight loss, exercise training had no effect on circulating adiponectin levels despite significant improvements in insulin action. This novel finding suggests that adiponectin is not a contributory factor to the exercise-related improvements in insulin sensitivity.

There is currently no available literature mechanistically linking adiponectin to improved insulin sensitivity. TNF-α-induced defects in insulin signaling have been implicated in the pathogenesis of insulin resistance (7, 11, 17). Thus a feasible hypothesis, which has been proposed previously (10), is that adiponectin may improve insulin sensitivity by inhibiting the detrimental effects of TNF-α on insulin action. It has been suggested that adiponectin serves as a protective mechanism against the development of coronary artery disease, as TNF-α-induced expression of endothelial molecules is inhibited by adiponectin (20, 21). The negative correlations between plasma levels of adiponectin and insulin observed in the present study are in agreement with previous findings (12). Hotta et al. (12) suggested that plasma insulin levels do not acutely affect plasma adiponectin, as the daily profile of plasma adiponectin was not altered by food intake. Thus the negative relationship between plasma levels of adiponectin and insulin may be a result of decreased insulin sensitivity due to TNF-α-induced defects in insulin signaling. Investigations examining the effect of adiponectin on TNF-α signaling and insulin sensitivity are warranted.

On the basis of the results of the present study, it is also plausible that exercise and weight loss improve insulin sensitivity either partially or completely via different mechanisms, with adiponectin functioning as a contributing factor to weight loss-associated enhanced insulin action but not exercise-related improvements in insulin action. This notion is supported by previous randomized, controlled trials comparing the effects of weight loss and aerobic exercise on glucose tolerance (5, 6). Dengel and colleagues (5, 6) observed an additive effect of aerobic exercise training and weight loss on glucose tolerance in two separate studies. In older men (5), insulin area during a glucose tolerance test was reduced by 32, 29, and 50% in response to weight loss alone, aerobic exercise training alone, and aerobic exercise training plus weight loss, respectively. In middle aged sedentary men (6), similar results were observed, with 21, 18, and 42% reductions in insulin area during a glucose tolerance test after weight loss alone, aerobic exercise training alone, and aerobic exercise training plus weight loss, respectively. The fact that exercise combined with weight loss results in significantly improved insulin action compared with weight loss alone and exercise alone provides evidence that the effects of exercise and weight loss on insulin sensitivity function via different mechanisms.

In conclusion, there was no change in plasma adiponectin concentration with exercise training that did not alter body mass, despite an improvement in insulin action. In contrast, plasma adiponectin increased in conjunction with insulin action after weight loss. These findings suggest that adiponectin may contribute to improved insulin action with weight loss but not with exercise training.

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REFERENCES


