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Research Article

# Adiponectin/TNF-α Ratio Following a Selected Aerobic Training in Sedentary Adult Obese Men

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## Abstract

**Background:** Based on clinical studies, low adiponectin and high tumor necrosis factor alpha (TNF-α) are associated with obesity and related diseases such as type 2 diabetes and insulin resistance.
**Objectives:** In this study, we aimed to investigate the effect of an aerobic training program on adiponectin, TNF-α, and adiponectin/TNF-α ratio in adult obese men.
**Patients and Methods:** For this purpose, 24 sedentary adult obese men matched for age (38 ± 3.23 years) and body mass index (31.94 ± 3.26 kg/m$^2$) were selected and divided into exercise (aerobic training) and control groups. Exercise subjects participated in an aerobic exercise training intervention for 12 weeks (3 times/week) and the control group did not participate in aerobic intervention. Anthropometric and biochemical data including fasting serum adiponectin, TNF-α, and adiponectin/TNF-α ratio were measured before and after aerobic training for each participant in each group. Data were analyzed by both independent and paired sample *t* test.
**Results:** Compared to pre-training, fasting serum adiponectin decreased significantly ($P = .019$), but serum TNF-α was not changed by aerobic training ($P = .057$). A significant increase was observed in adiponectin/TNF-α ratio in exercise subjects after aerobic training ($P = .008$).
**Conclusions:** Based on these data, we conclude that aerobic training intervention is associated with improved inflammatory profile in obese subjects.
**Keywords:** Obesity, Inflammatory profile, Aerobic exercise

## Background

Nowadays, obesity is frequently mentioned as an important cardiovascular risk factor and cause of death (1,2). Accordingly, the severity of dyslipidemia, hypertension, insulin resistance, and glucose intolerance (3) increases in response to obesity (4). Adipose tissue is an active endocrine and metabolic organ that releases adipokines, which are key regulators of glucose metabolism, fatty acid consumption and inflammation (4,5). Adiponectin is one of the adipokines secreted by adipose tissue, which plays an important role in the metabolism of carbohydrates and lipids as well as systemic inflammation due to anti-inflammatory properties through promoting insulin sensitivity and fat oxidation in skeletal muscles. Adiponectin serum levels decrease in the case of obesity, insulin resistance, and cardiovascular disease (6). Tumor necrosis factor-alpha (TNF-α) is also one of the inflammatory cytokines secreted by adipose tissue. TNF-α levels increase in obese individuals or with obesity-related diseases that are closely correlated with insulin resistance in insulin-sensitive tissues by affecting insulin-induced glucose uptake (7). According to the above-mentioned materials, a combination of adipokines, inflammatory or anti-inflammatory cytokines, and an imbalance between these compounds in blood circulation or other active tissues probably increase the risk or severity of many chronic metabolic diseases, especially in obese or overweight patients.

It seems that weight loss or reduced body fat percentage by external interventions such as manipulation of diet or regular training program may significantly regulate levels of this peptide mediator or the balance between these peptides. Scientific studies have revealed confounding and heterogeneous findings in this context. Some studies have reported improvement (8,9) or no change (10,11) in levels of inflammatory and anti-inflammatory cytokines after long-term periods of training programs in either presence or absence of weight loss. For example, in study by Eizadi (2014), a short- time exercise test increases serum adiponectin in the absence of change in the insulin

sensitivity in type 2 diabetic patients (12). In another study, 2-month weight-loss program based on exercise training and diet significantly reduced TNF-α levels and increased serum adiponectin levels in obese patients with asthma (13). In another study, no significant changes were observed in adiponectin and TNF-α serum levels after a period of 12-month training program (14). A review of literature revealed confounding findings and suggested an imbalance in cytokine response or insulin resistance and lipid profile to long-term training programs. Therefore, further studies should be performed in this area.

Cytokine level in obese individuals or patients or their response to training programs was not only the parameter studied in several recent studies, but also the ratio of inflammatory to anti-inflammatory cytokines was introduced as a potential predictor of inflammatory diseases, particularly in obese individuals.[15] For example, a close association was reported between adiponectin-to-TNF-α ratio (adiponectin/TNF-α) and cardiovascular risk factors such as triglyceride/high-density lipoprotein (TG/HDL), Low-density lipoprotein (LDL)/HDL, HDL and TG in a recent study (15).

## Objective

Apart from measuring response of these cytokines to exercise interventions or other external interferences, the ratio of inflammatory to anti-inflammatory cytokines such as adiponectin/TNF-α ratio should be determined to improve inflammatory profile using different training programs among obese individuals or patients. Therefore, the present study primarily aimed to determine the effects of 12-week aerobic training on adiponectin/TNF-α ratio in inactive obese adult men.

## Patients and Methods

### Study Subjects and Study Inclusion

A total of 24 sedentary adult obese males aged 38 ± 3.23 years, with the weight of 99 ± 6.35 kg and body mass index (BMI) of 31.94 ± 3.26 kg/m$^2$ volunteered to take part in this study. The subjects were randomly divided into exercise (aerobic training intervention, n = 12) and control (no training, n = 12) groups. This study was approved by the Ethics Committee of Islamic Azad University (South Tehran Branch). The nature and purpose of the study were carefully explained to the participants before a written consent was obtained.

Inclusion criteria for study group were determined as obesity (30 ≤ BMI ≤ 36). Subjects in both groups were inactive, non-smoker, and non-alcoholic. Participants were included if they had not been involved in regular physical activity in the previous 6 months. None of the subjects used drugs or therapies for obesity, and no injury that would prevent daily exercise. The exclusion criteria were as follows: patients with known history of type 2 diabetic, cardiovascular or cardiorespiratory diseases, hypertension, cancer or fatty liver, neuromuscular disease, cardiopulmonary disease and those who had undergone chest surgery or other major operations.

### Anthropometric Measures

All anthropometric measurements were made by the same trained general physician before and after training protocol for 2 groups. Body weight and height were measured on the same day to the nearest 0.1 kg and the nearest 0.1 cm, respectively. Obesity was measured by BMI. BMI was measured for each individual by division of body weight (kg) by height (m$^2$). The waist girth was measured at the level of the umbilicus horizontally without clothing, while the hip girth was measured at the level of the greatest protrusion of the gluteal muscles with underwear. Body fat percentage was determined using body composition monitor (OMRON, Finland).

### Laboratory Parameters and Training Protocol

Blood samples were collected before and 48 hours after aerobic intervention of 2 groups to measure serum adiponectin and TNF-α levels. Participants were instructed not to do heavy physical activity for at least 48 hours before blood collection. Venous blood was collected from participants in the seated position between 8:00 AM and 9:00 AM after 12-hour water-only fast. Serums were immediately separated and stored at -80°C until the assays were performed. ELISA assay was used to determine serum adiponectin and TNF-α. The intra-assay coefficient of variation and sensitivity of the method were 5.9% and 1-50 μg/mL, respectively for adiponectin and 6.0% and 5.0 pg/mL for TNF-α.

The exercise protocol included aerobic exercise training, lasting for 12 weeks (3 times/week) consisting of a warm-up, then a 30- to 40-minute treadmill exercise at a work intensity of 30%-80% of peak heart rate, followed by a cooling-down period. Target heart rate was monitored by polar telemetry. Exercise intensity and exercise volume at initial training sessions were in the minimum mentioned range. Control subjects were instructed to continue their habitual activities.

### Statistical Analysis

Data were analyzed by computer using the SPSS for Windows, version 15.0. Normal distribution of data was analyzed by the Kolmogorov-Smirnov normality test. Independent *t* test was used to compare each parameter between 2 groups, before and after training. Student's independent *t* test was applied to compare the pre- and post-training values of each group. *P* value less than .05 was considered as significant in a 2-tailed test.

## Results

Anthropometrical parameters in response to aerobic intervention in studied subjects were one of the aims in

the present study. Independent *t* test was used to compare each parameter between 2 groups before and after training. Baseline and post-training anthropometrical indices of 2 groups are shown in Table 1.

No differences were observed in the age, body weight, and other anthropometrical indices between 2 groups at baseline (see Table 1). However, significant differences were found in all anthropometrical markers between 2 groups at post-training. Student's independent *t* test was applied to compare the pre- and post-training values of each group. Based on data analysis of paired *t* test, aerobic training resulted in significant decrease in weight ($P = 0.012$), BMI ($P = .009$), body fat percentage ($P = .003$), and abdominal circumference ($P = .014$), but these variables remained without change in control subjects ($P > .05$) (see Table 1).

We measured serum adiponectin and TNF-α levels before and after exercise intervention and compared them between 2 groups by above-mentioned statistical methods. Table 2 shows the descriptive biochemical features of the study groups.

At baseline, no significant difference was found in serum adiponectin and TNF-α levels between 2 groups, but a significant difference was observed in serum adiponectin level between 2 groups after aerobic intervention ($P = .038$).

Compared to pre-training (based on paired sample *t* test), fasting serum adiponectin increased significantly ($P = .019$) after exercise program, but this clinical variable did not change in control subjects.

In contrast, serum TNF-α level was not significantly different between 2 groups after aerobic intervention. In addition, serum TNF-α level did not change with aerobic intervention in exercise group ($P = .057$).

The main aim of present study was to determine the effect of 12 weeks aerobic training on adiponectin/TNF-α ratio in obese males. A significant difference was found in adiponectin/TNF-α ratio between 2 groups after aerobic training ($P = .006$). Aerobic training resulted in significant increase in adiponectin/TNF-α ratio ($P = .008$).

## Discussion

Main finding of the study was significant increase in adiponectin/TNF-α ratio in response to aerobic training. In other words, a 12-week aerobic training, 2 times a week, significantly increased adiponectin/TNF-α ratio in adult obese males who previously had an inactive lifestyle. It is necessary to mention that training program was associated with significant weight loss, reduction in body fat percentage and abdominal obesity in the studied population, while no significant change was observed in any of these variables in the control group.

Although adiponectin had anti-diabetic and anti-inflammatory effects on fat mass and insulin resistance (6), these compounds had no biological effects on fat mass and insulin resistance (16). Weight loss-induced increase in adiponectin levels improved insulin sensitivity in normal obese individuals and obese patients (17,18). In the present study, aerobic intervention significantly increased serum adiponectin levels. Evidence suggested that adiponectin levels were improved in response to aerobic exercise-induced weight loss. However, Wenning et al showed that although 3-month resistance training significantly reduced resistin levels, no changes were observed in adiponectin levels in overweight patients with type 2 diabetes (19). Oh et al showed that 6-month modified lifestyle using diet and exercise leads to significant changes in adiponectin, leptin, TNF-α, interleukin 6 (IL-6) and IL-1β levels in elderly women with metabolic syndrome (20). However, consistent with findings of the present study, Tang et al showed that

**Table 1.** Mean and Standard Deviation of Anthropometrical Markers Before and After Intervention in Studied Groups

| Groups | Pre-training | | | Post-training | | |
|---|---|---|---|---|---|---|
| | Control | Exercise | *P* | Control | Exercise | *P* |
| Weight (kg) | 100.4 ± 3.51 | 98 ± 9.28 | .236 | 101.9 ± 3.96 | 92.4 ± 8.86 | .001 |
| AC (cm) | 107.1 ± 4.09 | 107.27 ± 9.11 | .368 | 107.44 ± 4.27 | 10 ± 7.87 | .001 |
| BMI (kg/m²) | 32.57 ± 1.90 | 31.54 ± 2.54 | .267 | 33.06 ± 1.59 | 29.63 ± 2.11 | .001 |
| BF (%) | 33.12 ± 1.55 | 31.88 ± 3.33 | .411 | 32.97 ± 1.12 | 28.04 ± 2.75 | .001 |

Abbreviations: AC, abdominal circumference; BMI, body mass index; BF, body fat percentage.

**Table 2.** Mean and Standard Deviation of Biochemical Markers Before and After Intervention in Studied Groups

| Groups | Pre-training | | | Post-training | | |
|---|---|---|---|---|---|---|
| | Control | Exercise | *P* | Control | Exercise | *P* |
| Adiponectin (kg) | 5.60 ± 1.31 | 5.95 ± 1.42 | .237 | 5.53 ± 1.46 | 6.97 ± 1.83 | .038 |
| TNF-α (cm) | 34.8 ± 2.73 | 35.2 ± 6.79 | .323 | 34.7 ± 3.42 | 27.3 ± 10.47 | .178 |
| Adiponectin/TNF-α ratio | 0.16 ± 0.03 | 0.17 ± 0.05 | .351 | 0.15 ± 0.04 | 0.29 ± 0.14 | .006 |

Abbreviations: TNF, Tumor necrosis factor.

8-week swimming training significantly increased serum levels and expression of adiponectin and GLUT4 in obese rats with type 2 diabetes (21). Sheu et al showed that 12-week aerobic exercise combined with diet led to 4 kg reduction in body weight, increase in adiponectin levels by 34% and decrease in insulin levels and fasting glucose in obese women (22). Varady et al pointed out that if training program decreases body weight by 5%, adipokines' profiles would be improved (23).

Considerable data support adiponectin as an important adipose-derived insulin sensitizer that enhances fatty acid oxidation and alters hepatic gluconeogenesis (24). Globular adiponectin increases glucose uptake in skeletal muscle cells via GLUT4 translocation and subsequently reduces the rate of glycogen synthesis and shifts glucose metabolism toward lactate production (25). These effects are consistent with the increased phosphorylation of AMP kinase and acetyl-CoA carboxylase and oxidation of fatty acids induced by globular adiponectin (25).

Despite significant increase in adipokines in response to weight loss and decrease in body fat percentage due to aerobic exercise in the present study, no significant changes were observed in TNF-α serum levels. In other words, although 3-month aerobic exercise decreased TNF-α serum levels in obese middle-aged men, this reduction was not statistically significant. Consistent with findings of the present study, Lebon et al showed that 6-month aerobic exercise causes no changes in levels of TNF-α and other inflammatory markers such as C-reactive protein (CRP) and IL-6 in postmenopausal obese women (26). Brunelli et al showed that although a significant reduction was observed in resistin and CRP after 24-week combined training in middle-aged obese women, no significant changes were observed in serum levels of TNF-α and IL-6 (27). Lopes et al found out that 12-week combined training (aerobic-resistance) significantly decreased body weight, body fat percentage, and insulin resistance and increased maximum oxygen consumption. Although CRP, leptin and insulin resistance were significantly decreased, no significant changes were observed in other effective markers in inflammatory profile such as adiponectin, resistin, IL-6, IL-10, and TNF-α (28). However, Donges et al showed that 12-week aerobic and resistance training significantly decreased TNF-α and IL-6 levels in middle-aged obese men (29). Talebi-Garakani and Safarzade showed that 4-week resistance training significantly decreased TNF-α levels and other inflammatory markers in diabetic mice (30). Ho et al highlighted that 12-week aerobic training decreased TNF-α levels in obese and overweight individuals by 20% (31). In the present study, although 22% decrease in TNF-α levels in response to aerobic training was statistically insignificant, this reduction in TNF-α levels is clinically important. On the other hand, insignificant reduction in TNF-α levels in this study may be attributed to small sample size or dispersed scores.

Increase in adiponectin/TNF-α ratio was the main finding of the present study. In other words, aerobic training significantly increased adiponectin/TNF-α ratio in middle-aged obese men, although changes in TNF-α levels in response to aerobic intervention was insignificant. According to these findings, it can be concluded that 12-week aerobic training improved inflammatory profile in obese middle-aged men. The relationship of inflammatory-to-anti-inflammatory cytokines ratio with some components of obesity such as insulin resistance was significant. For example, Hashem et al reported a significant relationship between insulin resistance and IL-10-to-TNF-α ratio in type 2 diabetes (32). Similar to adiponectin, IL-10 is another effective anti-inflammatory cytokine in lipid profile and insulin resistance in healthy obese individuals and obese patients.[32] In this context, a significant relationship was reported between adiponectin/TNF-α ratio and cardiovascular risk factors in cardiovascular patients (33).

IL-6 and TNF-α are potent inhibitors of adiponectin gene expression and secretion in adipose tissue (34,35). It has been speculated that adiponectin has strong anti-inflammatory properties, because it inhibits macrophage activation and TNF-α action (36,37). There is considerable evidence that adiponectin directly acts to increase nitric oxide production (38,39) and adenosine monophosphate activated kinase (40) indirectly decreases levels of CRP and IL-6 through the dose-dependent, reciprocal inhibition of TNF-α (41). An in vitro study showed that plasma adiponectin levels of 5–25 μg/mL had significant inhibitory effects on TNF-α–induced monocyte adhesion and adhesion molecule expression, suggesting an increased risk of adverse health effects at serum concentrations below this level (41).

## Conclusion

Findings of this study showed that although 12-week aerobic training insignificantly decreased TNF-α serum levels in obese middle-aged men, adiponectin levels significantly increased. However, 22% decrease in TNF-α in response to aerobic intervention is clinically important in the studied population. Despite this evidence, it seems that aerobic intervention improved inflammatory profile in obese men. This is because aerobic intervention significantly increased adiponectin/TNF-α ratio in these people. Findings of this study and other previous evidence showed that improvement in inflammatory profile can be attributed to weight loss-induced aerobic training. However, a definite conclusion requires further studies in the field of Molecular Cell Biology.

## Authors' Contribution

BA and ME participated in study concept and design, as well as drafting the manuscript. SS conducted the

statistical analyses. HP and MS performed administrative, technical, and material support.

## Conflict of Interest Disclosures

All authors declare that there is no conflict of interests.

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