

The Effect of Regular Aerobic Training on Tumor Necrosis Factor-Alpha (TNF- α) in Males With Type II Diabetes

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Background: A growing body of literature suggests that systemic inflammation is associated with obesity, type II diabetes and metabolic syndrome.

Objectives: The aim of this study was to evaluate the effect of three months of aerobic training on serum Tumor Necrosis Factor-alpha (TNF- α), as an inflammatory cytokine, in males with type II diabetes.

Patients and Methods: Twenty-four adult obese males aged 38 to 48 years and Body Mass Index (BMI) of 30 to 36 kg/m² with type II diabetes were randomly divided to exercise (n=12) and control (n=12) groups. The exercise group completed an aerobic training program (for three months, three times/week) and the control group did not participate in the exercise program. Fasting serum TNF- α and all anthropometrical markers were measured before and after the training program. Data was analyzed by independent-paired sample T test.

Results: Exercise training resulted in a significant increase in body weight (P<0.001), body fat percentage (P<0.001), BMI (P<0.001) and abdominal circumference (P<0.001). There was no significant difference in serum TNF- α before-compared to after-training program (P=0.83).

Conclusions: Based on these data, we conclude that the aerobic training program does not have an anti-inflammatory property with emphasis on serum TNF- α in type II diabetic patients.

Keywords: Type II diabetes; Inflammation; Aerobic Training; Obesity

1. Background

Cardiovascular Diseases (CVD) are currently among the main causes of death around the globe (1). Lipid abnormalities in the metabolic syndrome and diabetes are the background of this disease. Inflammation caused by increase in inflammatory cytokines in blood circulation is among predictive factors of cardiovascular disease, type 2 diabetes and metabolic syndrome (2). On the other hand, even in younger subjects, obesity and being overweight is associated with an increase in dyslipidemias, hypertension and insulin resistance (3). The increase in adipose tissue leads to physiological and morphological changes such as increase in secretion of pro-inflammatory cytokines (4). Although the physiological mechanisms of insulin resistance and impaired insulin secretion, that are the main determinants of type 2 diabetes (5-7), are completely unknown, clinical studies have alluded to the pivotal role of increasing markers or inflammatory cytokines, such as Tumor Necrosis Factor-alpha (TNF- α) (8, 9). Increase in adiponectin expression in terms of increase in TNF- α has also been reported (10). Increase in TNF- α systemic level is known as an inflammatory

marker in fat individuals, and weight loss has been introduced as a key intervention to reduce its plasma concentration (10, 11). Scientific findings on TNF- α response to exercise are inconsistent. However, in another study, TNF- α was decreased significantly in skeletal muscle of elderly subjects following exercise (12). In some studies, interventions such as exercise, weight loss, and dietary or antioxidants consumption, to reduce inflammatory cytokines, in patients with diabetes have been studied (10). In support of these findings, 12-week endurance training led to a reduction in inflammatory cytokine expression (13). However, in a recent study, after 12 weeks of exercise, while TNF- α level remained unchanged a significant decrease in C-Reactive Protein (CRP) levels was observed in obese individuals (14). Some other studies also showed no change in TNF- α by exercise training when compared to the baseline (15, 16).

2. Objectives

Regarding the inconsistent findings in this field, the current study aimed to determine the long-term effects

of aerobic exercise (three months) on serum levels of this proinflammatory cytokine in males with type II diabetes.

3. Patients and Methods

3.1. Human Subjects

The participants were twenty-four adult obese subjects aged 43 ± 4 years (Body Mass Index (BMI) of 31.4 ± 1.6 kg/m²) with type II diabetes, who were selected by accessible sampling, and were divided randomly to exercise ($n = 12$) and control ($n = 12$) groups. This experimental study was approved by the Ethics Committee of Islamic Azad University, South Tehran Branch, Iran. All subjects completed the consent process and provided written informed consents prior to randomization.

3.2. Inclusion and Exclusion Criteria

Subjects of both groups were inactive, non-smokers and non-alcoholics. Inclusion criteria for the study group were as follows; existing type 2 diabetes for at least three years, being between the age of 30 and 50 years, and having a BMI of 30 or above. A detailed history and physical examination of each subject was obtained. None of the participants had been involved in exercise training or a controlled diet within the previous six months. Those with self-reported physician-diagnosed metabolic disorders such as cardiovascular or cardiorespiratory diseases, hypertension, cancer or fatty liver were excluded. Subjects who were unable to avoid taking drugs for 12 hours before blood sampling were excluded.

3.3. Anthropometry

Anthropometrical measurements were performed before and after the exercise program. Body weight, height, waist circumference and percentage of body fat measurements were obtained by standard methods. Body weight was measured following overnight fasting. Height of the barefoot subject was measured twice to ± 0.2 cm. Body Mass Index was calculated as weight (kg) divided by squared height (m). Abdominal and hip circumferences were measured with a non-elastic tape and the ratio between them (AHO) was calculated. Body fat percentage was estimated by the bioelectrical impedance method (Omron Body Fat Analyzer, Finland).

3.4. Blood sampling and Exercise Protocol

Venous blood was collected from subjects after an overnight fast between 8:00 am and 9:00 am. Blood samples were used to assay glucose, insulin and serum TNF- α for all participants. The subjects were advised to avoid any physical activity or exercise 48 hours before blood sampling. Homeostasis Model Assessment (HOMA) index was calculated using the insulin resis-

tance formula as the product of fasting plasma glucose (mM) and insulin (μ U/mL) divided by the constant 22.5. All blood samples were separated by centrifugation and aliquots were frozen at -80°C until assayed. The Enzyme Linked Immunosorbent Assay (ELISA) reader method (SCO GmbH Reader MPR 1, SCO, Germany) was used to determine serum TNF- α (Human TNF- α Kit, Biovendor, Austria). The Intra-assay coefficient of variation and sensitivity of the method were 5.0% and 6 pg/mL, respectively. All measurements were repeated 48 hours after the last exercise session. The exercise program lasted three months (three times/week) with the exercise intensity between 60% and 80% of the age-predicted maximum heart rate. Each session lasted 45 to 60 minutes and included 15 minutes of warm up and flexible exercises and continued with 30 to 40 minutes of aerobic exercise (running on a treadmill and stationary cycling) and 5 to 10 minutes of cool down at the end. In each session, the intensity was controlled and monitored using the Polar heart rate tester. During this 12-week period, participants in the control group did not participate in any exercise training.

3.5. Data Analysis

The Statistical Package for Social Sciences (SPSS) for Windows was used for statistical analysis. The normality of the variables was determined by the Kolmogorov-Smirnov test. To compare anthropometrical markers and serum TNF- α between the two groups at baseline, the independent sample T-test was used. Difference in each variable pre and post training was compared using the Student's paired t-test. A P value of < 0.05 was accepted as significant in two-tailed tests.

4. Results

As mentioned previously, in this study, we investigated the effect of three months of an aerobic exercise program on serum TNF- α in non-trained adult men with type II diabetes. At baseline, the patients had fasting glucose (218 ± 42 mg/dL), serum insulin (8.34 ± 1.15 μ U/mL) and insulin resistance (4.43 ± 0.78). Baseline and post training anthropometrical indexes and clinical characteristics of the two groups are shown in Table 1. All data are presented by means and standard deviations. Based on the independent t-test analysis, no significant differences were found in serum TNF- α and all anthropometrical markers between exercise and control groups at baseline. Exercise training resulted in a significant decrease in body weight ($P < 0.001$), BMI ($P < 0.001$), body fat percentage ($P < 0.001$), abdominal circumference ($P < 0.001$) and other anthropometrical markers. There was no significant difference in serum TNF- α pre and post-training ($P = 0.83$). On the other hand, the aerobic exercise program was not associated with significant changes in serum TNF- α in the studied patients.

Table 1. Means and Standard Deviations of Anthropometrical Markers and Serum TNF- α Before and After the Intervention ^{a, b}

Variables	Control Group		Exercise Group	
	Pre-Training	Post-Training	Pre-Training	Post-Training
Weight, kg	94.7 \pm 4.79	94.5 \pm 4.23	93.7 \pm 6.6	88.6 \pm 6.4
Waist circumference, cm	106 \pm 5	106 \pm 5	106 \pm 6.4	102 \pm 6.4
Hip circumference, cm	103 \pm 4.20	103 \pm 4.15	104 \pm 4.8	98 \pm 3.6
Abdomen to hip ratio	1.02 \pm 0.01	1.03 \pm 0.01	1.02 \pm 0.02	1.02 \pm 0.03
BMI, kg/m ²	31.57 \pm 1.35	31.52 \pm 1.30	31.17 \pm 1.93	29.48 \pm 1.88
Body fat, %	31.1 \pm 1.08	31.1 \pm 0.99	31.13 \pm 1.33	25.62 \pm 1.87
TNF- α , pg/mL	36.4 \pm 6.45	37 \pm 6.14	36.1 \pm 3.97	37.1 \pm 14.9

^a Abbreviations: BMI, Body mass index; TNF- α , Tumor Necrosis Factor-alpha.
^b Data are presented as mean \pm SD.

5. Discussion

The findings of the present study showed that three months of aerobic exercise does not affect serum TNF- α as the pro-inflammatory cytokine in males with type II diabetes. Scientific studies support the pathophysiological role of TNF- α in atherosclerosis and cardiovascular disease. Some researchers have noted that insulin resistance is one of the main factors that increases inflammatory cytokine secretion in obese subjects (17). Insulin resistance is also inversely correlated with serum adiponectin, as anti-inflammatory cytokines, in type II diabetic patients (18). The prevalence of obesity in patients with type 2 diabetes mellitus has been reported in both developed and developing country (19). The change in TNF- α expression in adipose tissue is directly related to the rate of obesity and hyperinsulinemia levels (20, 21). Increased levels of other inflammatory adipokines such as leptin in obese patients with type II diabetes compared to non-obese patients with type II diabetes was reported by another previous study (22). Obesity is associated with higher levels of TNF- α (23). Studies on both obese humans and animals have pointed out that an increase in the secretion of TNF- α by adipose tissue is associated with a decrease in insulin sensitivity (20, 24). On the other hand, weight loss in healthy or sick obese individuals is associated with reduction of TNF- α secretion and insulin resistance (25). However, in this study, a three-month aerobic exercise program did not significantly change serum levels of TNF- α in patients with diabetes. Although some previous studies have alluded to a significant reduction in TNF- α and other inflammatory cytokines in response to long-term training programs (26-28), yet in line with the present study, some recent studies have reported no change in this inflammatory cytokine following long-term training program in healthy or sick obese individuals (29, 30). For example, in one study, a 12-month exercise program did not lead to changes in TNF- α , adiponectin and triglyceride levels in obese subjects (31). Furthermore, findings of a recent study showed 16 weeks of rapid walking led to an in-

crease in serum levels of TNF- α in the absence of change in IL-6 and adiponectin in obese and overweight individuals (32). Regarding the effect of long-term training on the level of cytokines in obese populations (healthy or sick), some previous studies have noted that inflammatory or anti-inflammatory cytokines improvement is possible only if the training program is associated with a significant reduction in body weight (weight loss) (33). In addition to anti-inflammatory properties, the results of a recent study showed that aerobic exercise, as a stimulus, can change the levels of matrix metalloproteinases and their tissue inhibitors in order to prevent cardiovascular diseases in patients with diabetes (34). However, in this study, although the three-month aerobic exercise program caused significant reduction in body weight, and other anthropometric markers and body composition indicators, such as percentage of body fat in studied subjects, yet it did not lead to a significant change in serum levels of TNF- α . In this context, although the findings of this study is somewhat surprising and controversial, but some previous studies also reported no change in TNF- α or other inflammatory cytokines following a long-term training program, even in the presence of weight loss (35, 36). On the other hand, some other studies have reported that at least a 10% reduction in body weight is necessary for improvement of inflammatory or anti-inflammatory cytokines (37). However, there is no general consensus on determining the effect of different training programs on inflammatory cytokines in patients with type II diabetes or other obese individuals, healthy or sick. Regarding to the inconsistency in findings of studies in this area, the researchers found that the differences in study results are related to variations in the type of training program or measurement tools, weight changes, sampling time, initial fitness level, changes in plasma volume and type of population studied (38, 39). However, it should also be noted that exercise could lead to local anti-inflammatory effects in skeletal muscles but not in circulating levels (40). It is also possible that despite no change in

systemic levels of inflammatory cytokines, exercise training is associated with decreased expression of this cytokine. Although some previous studies support the anti-inflammatory effect of long-term aerobic training on healthy or sick obese individuals, yet the finding of our study showed that serum TNF- α , as a pro-inflammatory cytokine, remained without change after three months of aerobic training in adult males with type II diabetes. It seems that inconsistency in findings of this study with other previous studies is due to differences in the types of protocols, duration, intensity and frequency of exercise sessions or initial fitness level of studied subjects. Further studies are necessary to elucidate the significance of exercise training, as an anti-inflammatory intervention, in patients with diabetes or other obesity-related disease.

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Authors' Contributions

Study concept and design: Hassan Ghasemalipour. Drafting of the manuscript: Mojtaba Eizadi. Statistical analysis: Masoud Hajirasouli. Administrative, technical, and material support: Mojtaba Eizadi.

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