



Inflammatory Markers in Response to Different Intensity of Aerobic Exercise in Obese Male Wistar Rats

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Abstract

Background: The lack of physical activity and obesity causes mild chronic inflammation that is associated with increased plasma levels of inflammatory markers. Evidence suggests that physical activity can reduce inflammatory markers.

Objectives: The purpose of this study was to determine the effects of eight weeks of aerobic training with two intensities on levels of tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and insulin resistance in obese Wistar rats.

Methods: Twenty-four Wistar male rats (fourteen weeks old and weighing 250 - 300 g, body mass index > 30 g/cm²) were used. After two weeks of familiarity with the laboratory environment, the animals were randomly divided into three groups: (1) high-intensity aerobic exercise (n = 8); (2) moderate-intensity aerobic exercise (n = 8), and control (n = 8). The rats in moderate and high-intensity aerobic exercise groups were performed an increasing training for eight weeks and five days a week and one session per day for 60 minutes running at different speeds on a rodent motor-driven treadmill. Data were analyzed by paired sample t-test and repeated measures (ANOVA) for the inter-group and intra-group comparison of the variance changes.

Results: Significant differences were found in serum TNF- α levels (P = 0.027 and F = 3.42), IL-6 levels (P = 0.043 and F = 2.99), and insulin resistance index (P = 0.008 and F = 4.69) between the moderate, high-intensity aerobic exercises, and control groups. The levels of TNF- α concentration was significantly different between moderate-intensity and control group (P = 0.01) and between the high-intensity and control groups (P = 0.01). The insulin resistance index in MI (P = 0.01) and HI (P = 0.01) groups significantly decreased compared to the control group.

Conclusions: The results of the present study show that both types of moderate-intensity and high-intensity aerobic exercise lead to the reduction of TNF- α , interleukin-6, and insulin resistance index compared to the control group. Further studies are needed to shed light on the effects of different types of exercise on such indices, especially the use of long-term training sessions.

Keywords: Aerobic Training, Inflammatory Markers, Obesity Insulin Resistance

1. Background

Obesity is defined as abnormal or excessive fat accumulation, with adipose tissue. On the other hand, lipid storage has an important role in actively regulating energy homeostasis, insulin sensitivity, and carbohydrate and lipid metabolism (1). In obese individuals, chronic inflammation is the most important factor associated with increased adipose tissue mass and insulin resistance because tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6) levels, which are chemical agents secreted from adipose tissue, act as important inducers of insulin resistance development in obese people (2). However, uptake of macrophages from adipose tissue is the most impor-

tant cause of inflammatory processes and the major source of inflammatory factors such as TNF- α and IL-6 in obese individuals (3). During obesity, the expression of genes is increased due to various factors of the adipose tissue (4). Studies have shown that the levels of IL-6 and obesity positively correlated with each other (5). Interleukin-6 is a pro-inflammatory cytokine that predicts cardiovascular diseases. Research results suggest that IL-6 regulates acute phase proteins, anti-inflammatory, and immune inhibitors and may negatively regulate acute response (6). Some researchers have also declared that IL-6 induction has a significant effect on insulin secretion from pancreatic β -cells (7). In the state of insulin resistance most commonly attributed to obesity, pancreatic β -cells become

normal at maintaining blood sugar levels (8). Adipokine secretion is enhanced from adipose tissue, which can disrupt the insulin signaling pathway and glucose-mediated insulin secretion such as glucose homeostasis and lipid metabolism (9). Among these proteins, TNF- α has been related to obesity and insulin resistance, which can mediate insulin resistance in obese animals (9). Moreover, TNF- α is one of the most important cytokines secreted from adipose tissue and increases pro-inflammatory cytokines such as IL-6 and IL-1 (10). Interleukin-6 levels can increase up to 100-fold in response to exercise and decrease after physical activity (11). Studies show that physical activity has different effects on these two cytokines. According to the results of studies, the anti-inflammatory effect of exercise activity has been confirmed (12) on pro-inflammatory and anti-inflammatory cytokines (13). There is an inverse relationship between fitness and markers of inflammation, such as serum IL-6 and leukocyte count (12).

Evidence suggests that several factors, such as various factors, contribute to obesity, including sedentary behavior and reduced fitness (14). One of the easiest ways to achieve good health and maintain a normal weight has been reported to participate in physical activity, leading to the consumption of one-third of the energy in active individuals (15). Currently, regular aerobic exercise can be a strong non-pharmacological therapeutic tool to reduce obesity and prevent overweight, which is also effective in modulating insulin resistance and reducing the progression of chronic infections and inflammation (16). Paying attention to the intensity and type of exercise is very important in the effectiveness of exercise in preventing inflammatory factors. Model exercise with moderate intensity can reduce risk factors such as IL-6 and TNF- α while increasing insulin sensitivity (17, 18). The low body fat prevents fat cell damage and hypoxia experience, thereby decreasing pro-inflammatory cytokines of IL-6 and TNF- α by increasing the secretion of adiponectin and anti-inflammatory cytokines (19). However, modeling exercises with high-intensity aerobic exercise is also effective in improving insulin sensitivity and increasing the release of anti-inflammatory molecules (20, 21). In this regard, Baum et al. (22), Reported that moderate to severe exercise intensity on inflammatory markers resulted in a decrease in TNF- α in the moderate-intensity group, whereas IL-1 β remained unchanged after intense exercise. Given the discrepancies of research findings in this area, it seems that there is still no consensus on the effect of aerobic exercise in general and the effect of intensity of this type of exercise, especially on important inflammatory markers.

2. Objectives

The purpose of this study was to determine the effects of eight weeks of aerobic training with two intensities on some inflammatory indicators in obese Wistar rats.

3. Methods

The present research is an experimental study using an animal model. Twenty-four healthy male Wistar rats (aged 14 weeks with a weight of 250 - 300 g and a mass index of over 30 g/cm²) were evaluated. These animals were bought from Razi Serum Institute of Iran. The rats were provided with a standard diet (devised by Behparvar Company) to get used to the laboratory conditions. A high-calorie-diet was imposed on the rats at the end of the sixth week to induce obesity in them. The approximate weight of rats reached 250 - 300 g by the end of the 14th week. The rats were kept in polycarbonate cages under controlled environmental conditions with an average $23 \pm 1^\circ\text{C}$ temperature, $50 \pm 3\%$ humidity, 12-hour light and 12-hour dark cycles, and free access to laboratory rodent food and water for 2 weeks. Then, the rats were divided into three randomly-picked groups. Animals were randomly divided into three groups: (1) moderate-intensity aerobic exercise (n = 8); (2) high-intensity aerobic exercise (n = 8), and control (n = 8) groups.

High-intensity and medium-intensity aerobic training programs were conducted five sessions per week and 60 minutes per session on rodent treadmills (made by Mobin Bionic Research Production Company in Iran whose treadmills have an adjustable elevation ranging between -15 to 15 degrees, and can be programmed for several consecutive trainings with various speeds, shocks, elevations, and accelerations) for eight weeks. After the animals adjusted to the program (and were familiarized with the aerobic training protocol), they walked the treadmill with a zero-degree elevation and with a speed of 10 m per minute for the first week. The duration and speed of the training were gradually recorded during the second and third weeks so that the medium-intensity group ran on the treadmill as fast as 28 m per minute, which is equal to 70% - 75% $\text{VO}_{2\text{max}}$, and the high-intensity group ran on the treadmill as fast as 34 m per minute, which is equal to 80% - 85% $\text{VO}_{2\text{max}}$ (23). When the training program finished, the speed was reduced to zero inversely so that the animal could cool down (Table 1).

The rats were anesthetized using a xylazine (3 - 5 mg per kg body weight) and ketamine (30 - 50 mg per kg body weight) combination 48 hours after the last training session and a 12-hour fast. After anesthesia was confirmed by examining leg retraction, a 5 - 6 cm incision

Table 1. The Aerobic Exercise Protocol During Eight Weeks

| Groups/Weeks | First | Second | Third | Fourth | Fifth | Sixth | Seventh | Eighth |
|--|-------|--------|-------|--------|-------|-------|---------|--------|
| High-intensity aerobic exercise | | | | | | | | |
| Speed | 10 | 15 | 20 | 22 | 24 | 27 | 31 | 34 |
| Duration | 15 | 27 | 35 | 45 | 54 | 59 | 60 | 60 |
| Moderate-intensity aerobic exercise | | | | | | | | |
| Speed | 10 | 15 | 20 | 21 | 23 | 24 | 26 | 28 |
| Duration | 15 | 27 | 34 | 40 | 46 | 52 | 58 | 60 |

was cut through the rats' abdominal area, a 5 - 6 cm incision was made in the abdominal area of the rat, and 5 mL of blood was collected from the right ventricle of each mouse (24). Serum levels of TNF- α , IL-6, and insulin were measured with a mouse-specific ELISA kit (EASTBIO PHARM, China, licensed in the USA). Insulin resistance index was also calculated using HOMA-IR equation (25): Insulin resistance = serum insulin (microunit/dl) \times serum glucose (mmol/L)/22.5.

Collected data were analyzed using SPSS software V.16 at a $P \leq 0.05$ significance level. After the normal distribution of data and variances' homogeneity were confirmed using the Shapiro-Wilk statistical test and Levene's test, respectively. In addition, a paired sample *t*-test and one-way ANOVA test were conducted to examine the inter-group and intra-group differences, respectively. Post hoc Tukey test was also conducted to perform a couple of comparisons between the groups.

4. Results

Significant differences were found in serum TNF- α levels ($P = 0.027$ and $F = 3.42$), IL-6 levels ($P = 0.043$ and $F = 2.99$), and insulin resistance index ($P = 0.008$ and $F = 4.69$) concentration between the moderate- and high-intensity aerobic exercise and control groups. The results of the Tukey test showed that there were significant differences in levels of TNF- α concentrations ($P = 0.01$) between the moderate-intensity aerobic exercise and control groups as well as between high-intensity aerobic exercises and control groups ($P = 0.01$). No significant differences were found between the moderate-intensity aerobic exercise and control group in terms of serum IL-6 ($P = 0.61$). Moreover, no significant difference was observed between high-intensity training and control groups in terms of the levels of IL-6 ($P = 0.20$). The insulin resistance index showed significant differences ($P = 0.01$) between the moderate-intensity and control groups (57.11 ± 4.91 vs. 68.07 ± 6.54) ($P = 0.01$) as well as the high intensity and the control groups (56.45

± 10.59 vs. 68.07 ± 6.54). At the end of the period of the eight weeks of aerobic training, the bodyweight of rats in the control group increased ($P = 0.001$). Moreover, there was a significant decrease ($P = 0.001$) in moderate and high-intensity aerobic exercise groups compared to the control group (Table 2 and 3).

Table 2. The Variation of TNF- α , IL-6, and Insulin Resistance Index in Experimental and Control Groups After Eight Weeks of Aerobic Exercise^a

| Variable | C | MI | HI |
|-----------------------|--------------------|---------------------------------|--------------------------------|
| TNF- α , ng/mL | 204.51 \pm 17.88 | 187.71 \pm 11.40 ^b | 186.46 \pm 8.33 ^b |
| IL-6, ng/mL | 202.24 \pm 16.74 | 189.04 \pm 8.11 | 181.07 \pm 9.89 |
| FBS, mg/dL | 138.50 \pm 13.40 | 124.04 \pm 14.59 | 123.36 \pm 16.25 |
| Insulin, IU/mL | 11.07 \pm 0.57 | 10.42 \pm 0.86 | 10.26 \pm 0.96 |
| HOMA | 68.07 \pm 6.54 | 57.11 \pm 4.91 ^b | 56.45 \pm 10.59 ^b |

^a Values are expressed as mean \pm SD.

^b Analysis of variance between the three sessions data the significant at 0.05.

5. Discussion

According to the present result, the levels of TNF- α concentration were significantly reduced in moderate- and high-intensity aerobic exercise groups compared to the control group. These findings are consistent with the findings of Jin et al. (26), Pasavand et al. (27), and Fashi et al. (28). However, it is inconsistent with the findings of Arslan et al. (29). TNF- α is one of the most important pro-inflammatory cytokines, which has a strong association with leptin levels and energy metabolism in the body (30). In this regard, there is a complex relationship between energy metabolism and TNF- α ; thus, increased levels of TNF- α in the blood may increase resting metabolism and energy expenditure, and weight loss (31). Participation in regular physical activity results in decreased concentrations of interleukins (32). Obesity can be strongly linked to the level of inflammation. Therefore, the reduction of body fat and increased lipolysis following the prolonged aerobic

Table 3. The Variation of Weight in Experimental and Control Groups^a

| Variable | Stages | C | MI | HI |
|-----------|-----------|----------------------------|----------------------------|----------------------------|
| Weight, g | Pre-test | 295.75 ± 1.81 | 295.16 ± 1.40 | 295.41 ± 2.15 |
| | Post-test | 302.58 ± 1.16 ^b | 287.41 ± 4.25 ^b | 287.08 ± 4.23 ^b |

^aValues are expressed as mean ± SD.

^bAnalysis of variance between the three sessions data the significant at 0.05.

exercise with stimulating hormone-sensitive lipase activity (33) can be a mechanism by which inflammation is reduced. In the present study, the weight of rats in the training group significantly decreased at the end of the training period, which was due to the decrease in the levels of IL-6 and TNF- α . Also, physical exercise has antioxidant effects. Although one exercise session increases the rate of oxidative metabolism followed by oxidative stress, there is evidence that long-term aerobic exercise can increase capacity. The body's antioxidant defense significantly reduces oxidative stress (34).

According to the findings, the levels of IL-6 levels have been reduced in the moderate and high-intensity aerobic exercises compared with the control group, but these changes were not statistically significant. The results of this study are consistent with some studies (35-37). However, the results of this study do not agree with Christiansen et al. (38). One of the major mechanisms for the reduction of IL-6 in obese individuals is the change in body weight variables. Exercise significantly reduces weight also appears to decrease serum levels of IL-6 (39). It seems that differences in results are due to differences in age, race, training programs, diet, and type of subjects. Because IL-6 is one of the proinflammatory cytokines secreted from adipose tissue and its circulating levels are directly related to the amount of fat (40). The effect of exercise and physical activity on IL-6 production is strongly dependent on the muscle mass of the body and duration of training (41). Intracellular muscle glycogen concentration is an important driver for IL-6 production. In other words, IL-6 also acts as a cytokine sensitive to glycogen stores (42). Interleukin-6 produced by the contracting muscle is often increased in vigorous and short-term exercise (43). This increase is due to the effects of exercise on adipose tissue, lipolysis, and lipid oxidation (44) on glycogen homeostasis and its anti-inflammatory effect. The increase of IL-6 in these conditions by inhibiting interleukin-10 and decreasing TNF- α can have an inhibitory effect on T-cell activity (45). Research has shown that IL-6 levels also increase during intense exercise activities associated with inflammation and tissue damage. Also, since the concentration of IL-6 is associated with muscle fuel stores, especially glycogen,

long-term activity can deplete these stores and decrease IL-6 (42).

Based on the results of this study, moderate- and high-intensity aerobic training led to a significant decrease in insulin resistance in obese Wistar rats. Increased blood glucose uptake might decrease insulin resistance due to the activation of adenosine monophosphate kinase (AMP) and increased insulin receptors, increased GLUT4 carrier, and muscle glycogen synthetase activity (46). Regular physical activity has been reported to affect muscle uptake in addition to increasing the number of GLUT4 receptors and carriers. In the present study, the insulin resistance index was significantly decreased in two groups of aerobic exercise. Another reason for the decrease in insulin resistance appears to be an improvement in the function of insulin receptors due to increased aerobic capacity, antioxidant capacity, and oxidative enzymes related to aerobic metabolism that affect insulin action, such as cytochrome C oxidase (47).

5.1. Conclusions

The results of the present study show that both types of moderate-intensity and high-intensity aerobic exercise lead to the reduction of TNF- α , IL-6, and insulin resistance index rather than the control group. Further studies are needed to shed light on the effects of different types of exercise on such indices, especially the use of long-term training sessions.

Supplementary Material

Supplementary material(s) is available [here](#) [To read supplementary materials, please refer to the journal website and open PDF/HTML].

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Footnotes

Authors' Contribution: Contribution of the authors is in accordance with the research regulations.

Clinical Trial Registration Code: The clinical trial registration code was IR.MUMS.REC.2016.131.

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