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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/cm^2) 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 important 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-1β 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/cm^2) 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°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% VO_{2max}, and the high-intensity group ran on the treadmill as fast as 34 m per minute, which is equal to 80% - 85% VO_{2max} (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 (EASTBIOPHARM, 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 ± 17.88	187.71 ± 11.40[b]	186.46 ± 8.33[b]
IL-6, ng/mL	202.24 ± 16.74	189.04 ± 8.11	181.07 ± 9.89
FBS, mg/dL	138.50 ± 13.40	124.04 ± 14.59	123.36 ± 16.25
Insulin, IU/mL	11.07 ± 0.57	10.42 ± 0.86	10.26 ± 0.96
HOMA	68.07 ± 6.54	57.11 ± 4.91[b]	56.45 ± 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]

[a]Values are expressed as mean ± SD.
[b]Analysis 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

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

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Ethical Approval: The present study was approved by the Ethics Committee of Ferdowsi University of Mashhad with the code of IR.MUMS.REC.2016.131 at Ferdowsi University of Mashhad.

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References

1. Havel PJ. Control of energy homeostasis and insulin action by adipocyte hormones: leptin, acylation stimulating protein, and adiponectin. *Curr Opin Lipidol*. 2002;**13**(1):51–9. doi: 10.1097/00041433-200202000-00008. [PubMed: 11790963].
2. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur Cytokine Netw*. 2006;**17**(1):4–12. [PubMed: 16613757].
3. Kirk EA, Sagawa ZK, McDonald TO, O'Brien KD, Heinecke JW. Monocyte chemoattractant protein deficiency fails to restrain macrophage infiltration into adipose tissue [corrected]. *Diabetes*. 2008;**57**(5):1254–61. doi: 10.2337/db07-1061. [PubMed: 18268047].
4. Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. *Nature*. 1997;**389**(6651):610–4. doi: 10.1038/39335. [PubMed: 9335502].
5. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. *J Clin Endocrinol Metab*. 1998;**83**(3):847–50. doi: 10.1210/jcem.83.3.4660. [PubMed: 9506738].
6. Olson TP, Dengel DR, Leon AS, Schmitz KH. Changes in inflammatory biomarkers following one-year of moderate resistance training in overweight women. *Int J Obes (Lond)*. 2007;**31**(6):996–1003. doi: 10.1038/sj.ijo.0803534. [PubMed: 17299382].
7. Kim JH, Bachmann RA, Chen J. Interleukin-6 and insulin resistance. *Vitam Horm*. 2009;**80**:613–33. doi: 10.1016/S0083-6729(08)00621-3. [PubMed: 19251052].
8. Kahn BB, Flier JS. Obesity and insulin resistance. *J Clin Invest*. 2000;**106**(4):473–81. doi: 10.1172/JCI10842. [PubMed: 10953022]. [PubMed Central: PMC380258].
9. Morino K, Petersen KF, Dufour S, Befroy D, Frattini J, Shatzkes N, et al. Reduced mitochondrial density and increased IRS-1 serine phosphorylation in muscle of insulin-resistant offspring of type 2 diabetic parents. *J Clin Invest*. 2005;**115**(12):3587–93. doi: 10.1172/JCI25151. [PubMed: 16284649]. [PubMed Central: PMC1280967].
10. Weiss ST. Obesity: insight into the origins of asthma. *Nat Immunol*. 2005;**6**(6):537–9. doi: 10.1038/ni0605-537. [PubMed: 15908930].
11. Suzuki K, Nakaji S, Yamada M, Totsuka M, Sato K, Sugawara K. Systemic inflammatory response to exhaustive exercise. Cytokine kinetics. *Exerc Immunol Rev*. 2002;**8**:6–48. [PubMed: 12690937].
12. Markovitch D, Tyrrell RM, Thompson D. Acute moderate-intensity exercise in middle-aged men has neither an anti- nor proinflammatory effect. *J Appl Physiol (1985)*. 2008;**105**(1):260–5. doi: 10.1152/japplphysiol.00096.2008. [PubMed: 18467550]. [PubMed Central: PMC2494829].
13. Frydelund-Larsen L, Akerstrom T, Nielsen S, Keller P, Keller C, Pedersen BK. Visfatin mRNA expression in human subcutaneous adipose tissue is regulated by exercise. *Am J Physiol Endocrinol Metab*. 2007;**292**(1):E24–31. doi: 10.1152/ajpendo.00113.2006. [PubMed: 16868228].
14. Rees A, Thomas N, Brophy S, Knox G, Williams R. Cross sectional study of childhood obesity and prevalence of risk factors for cardiovascular disease and diabetes in children aged 11-13. *BMC Public Health*. 2009;**9**:86. doi: 10.1186/1471-2458-9-86. [PubMed: 19317914]. [PubMed Central: PMC2667418].
15. Irwin ML, Whitt MC, LaMonte MJ, Drowatzky KL, Ainsworth BE. Relationship between Physical Activity and Body Fat in Women. *Med Sci Sports Exercise*. 2001;**33**(5). doi: 10.1097/00005768-200105001-01282.
16. Eckardt K, Taube A, Eckel J. Obesity-associated insulin resistance in skeletal muscle: role of lipid accumulation and physical inactivity. *Rev Endocr Metab Disord*. 2011;**12**(3):163–72. doi: 10.1007/s11154-011-9168-2. [PubMed: 21336841].
17. Gerosa-Neto J, Antunes BM, Campos EZ, Rodrigues J, Ferrari GD, Rosa Neto JC, et al. Impact of long-term high-intensity interval and moderate-intensity continuous training on subclinical inflammation in overweight/obese adults. *J Exerc Rehabil*. 2016;**12**(6):575–80. doi: 10.12965/jer.1632770.385. [PubMed: 28119880]. [PubMed Central: PMC5227320].
18. Many G, Hurtado ME, Tanner C, Houmard J, Gordish-Dressman H, Park JJ, et al. Moderate-intensity aerobic training program improves insulin sensitivity and inflammatory markers in a pilot study of morbidly obese minority teens. *Pediatr Exerc Sci*. 2013;**25**(1):12–26. doi: 10.1123/pes.25.1.12. [PubMed: 23406700].
19. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol*. 2011;**11**(9):607–15. doi: 10.1038/nri3041. [PubMed: 21818123].
20. Steckling FM, Lima FD, Boufleur J, Farinha DLDS, Alexandre F, Soares A. Obesity, Inflammation and Aerobic Physical Exercise. *Ann Sports Med Res*. 2015;**2**(2):1017.
21. Smith-Ryan AE, Melvin MN, Wingfield HL. High-intensity interval training: Modulating interval duration in overweight/obese men. *Phys Sportsmed*. 2015;**43**(2):107–13. doi: 10.1080/00913847.2015.1037231. [PubMed: 25913937]. [PubMed Central: PMC4427241].
22. Baum M, Muller-Steinhardt M, Liesen H, Kirchner H. Moderate and exhaustive endurance exercise influences the interferon-gamma levels in whole-blood culture supernatants. *Eur J Appl Physiol Occup Physiol*. 1997;**76**(2):165–9. doi: 10.1007/s004210050229. [PubMed: 9272775].
23. Garekani ET, Mohebbi H, Kraemer RR, Fathi R. Exercise training intensity/volume affects plasma and tissue adiponectin concentrations in the male rat. *Peptides*. 2011;**32**(5):1008–12. doi: 10.1016/j.peptides.2011.01.027. [PubMed: 21291933].
24. Lee S, Farrar RP. Resistance training induces muscle-specific changes in muscle mass and function in rat. *J Exercise Physiol Online*. 2003;**6**(2).
25. Sampelean D, Hanescu B, Han A, Adam M, Casoinic F. The prognosis of glycoregulation disturbances and insulin secretion in alcoholic and C virus liver cirrhosis. *Rom J Intern Med*. 2009;**47**(4):387–92. [PubMed: 21179921].
26. Jin CH, Rhyu HS, Kim JY. The effects of combined aerobic and resistance training on inflammatory markers in obese men. *J Exerc Rehabil*. 2018;**14**(4):660–5. doi: 10.12965/jer.1836294.147. [PubMed: 30276190]. [PubMed Central: PMC6165976].
27. Pasavand P, Hosseini SA, Farsi S. Effects of moderate and high intensity endurance trainings on INFγ and TNFα of Streptozotocin induced diabetic rats. *Int J Appl Exercise Physiol*. 2018;**7**(3):55–67.

28. Fashi M, Agha-Alinejad H, Mahabadi HA, Rezaei B, Pakrad BB, Rezaei S. The effects of aerobic exercise on NF-κB and TNF-α in lung tissue of male rat. *Novel Biomed*. 2015;**3**(3):131–4.
29. Arslan M, Ipekci SH, Kebapcilar L, Dogan Dede N, Kurban S, Erbay E, et al. Effect of Aerobic Exercise Training on MDA and TNF- alpha Levels in Patients with Type 2 Diabetes Mellitus. *Int Sch Res Notices*. 2014;**2014**:820387. doi: 10.1155/2014/820387. [PubMed: 27437465]. [PubMed Central: PMC4897068].
30. Mantzoros CS, Moschos S, Avramopoulos I, Kaklamani V, Liolios A, Doulgerakis DE, et al. Leptin concentrations in relation to body mass index and the tumor necrosis factor-alpha system in humans. *J Clin Endocrinol Metab*. 1997;**82**(10):3408–13. doi: 10.1210/jcem.82.10.4323. [PubMed: 9329377].
31. Staal-van den Brekel AJ, Dentener MA, Schols AM, Buurman WA, Wouters EF. Increased resting energy expenditure and weight loss are related to a systemic inflammatory response in lung cancer patients. *J Clin Oncol*. 1995;**13**(10):2600–5. doi: 10.1200/JCO.1995.13.10.2600. [PubMed: 7595713].
32. Suzuki K, Totsuka M, Nakaji S, Yamada M, Kudoh S, Liu Q, et al. Endurance exercise causes interaction among stress hormones, cytokines, neutrophil dynamics, and muscle damage. *J Appl Physiol (1985)*. 1999;**87**(4):1360–7. doi: 10.1152/jappl.1999.87.4.1360. [PubMed: 10517764].
33. You T, Berman DM, Ryan AS, Nicklas BJ. Effects of hypocaloric diet and exercise training on inflammation and adipocyte lipolysis in obese postmenopausal women. *J Clin Endocrinol Metab*. 2004;**89**(4):1739–46. doi: 10.1210/jc.2003-031310. [PubMed: 15070939].
34. Powers SK, Ji LL, Leeuwenburgh C. Exercise training-induced alterations in skeletal muscle antioxidant capacity: a brief review. *Med Sci Sports Exerc*. 1999;**31**(7):987–97. doi: 10.1097/00005768-199907000-00011. [PubMed: 10416560].
35. Dehghan A, Farzanegi P, Abbaszadeh H. Effects of Exercises on IL-6 and GLUT4 Expression in Diabetic Rats. *Res Mol Med*. 2019. doi: 10.18502/rmm.v6i2.4539.
36. Balducci S, Zanuso S, Nicolucci A, Fernando F, Cavallo S, Cardelli P, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. *Nutr Metab Cardiovasc Dis*. 2010;**20**(8):608–17. doi: 10.1016/j.numecd.2009.04.015. [PubMed: 19695853].
37. Tang H, Xie MH, Lei Y, Zhou L, Xu YP, Cai JG. The roles of aerobic exercise training and suppression IL-6 gene expression by RNA interference in the development of insulin resistance. *Cytokine*. 2013;**61**(2):394–405. doi: 10.1016/j.cyto.2012.11.027. [PubMed: 23294974].
38. Christiansen T, Paulsen SK, Bruun JM, Pedersen SB, Richelsen B. Exercise training versus diet-induced weight-loss on metabolic risk factors and inflammatory markers in obese subjects: a 12-week randomized intervention study. *Am J Physiol Endocrinol Metab*. 2010;**298**(4):E824–31. doi: 10.1152/ajpendo.00574.2009. [PubMed: 20086201].
39. Kohut ML, McCann DA, Russell DW, Konopka DN, Cunnick JE, Franke WD, et al. Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. *Brain Behav Immun*. 2006;**20**(3):201–9. doi: 10.1016/j.bbi.2005.12.002. [PubMed: 16504463].
40. Libby P, Bonow R, Mann D, Zipes D. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicin*. 8th ed. Saunders; 2007.
41. Hashemian M, Vakili A, Akaberi A. Effect of glucose–insulin–potassium on Plasma concentrations of C-reactive protein in acute ST-Elevation Myocardial Infarction; A Randomized Clinical Trial. *Pak J Med Sci*. 2011;**27**(3):4.
42. Kakhk H. The Effect of Resistance Training, Aerobic Training and Detraining on the Lipid Profile and CRP in Obese Girls. *J Sabzevar Univ Med Sci*. 2011;**18**(3):188–97.
43. Abedi B. The effects of 12-wk combined aerobic/resistance training on C-reactive protein (CRP) serum and interleukin-6 (IL-6) plasma in sedentary men. *Yafteh*. 2012;**14**(4):95–106.
44. Namazi A, Agha Alinejad H, Piry M, Rahbarizadeh F. Effect of short long circles resistance training on serum levels of homocysteine and CRP in active and inactive women. *J Endocrinol Metab*. 2010;**12**(2):169–76.
45. Gleeson M. Immune function in sport and exercise. *J Appl Physiol (1985)*. 2007;**103**(2):693–9. doi: 10.1152/japplphysiol.00008.2007. [PubMed: 17303714].
46. de Graaf-Roelfsema E, Keizer HA, van Breda E, Wijnberg ID, van der Kolk JH. Hormonal responses to acute exercise, training and overtraining. A review with emphasis on the horse. *Vet Q*. 2007;**29**(3):82–101. doi: 10.1080/01652176.2007.9695232. [PubMed: 17970286].
47. Youngren JF, Keen S, Kulp JL, Tanner CJ, Houmard JA, Goldfine ID. Enhanced muscle insulin receptor autophosphorylation with short-term aerobic exercise training. *Am J Physiol Endocrinol Metab*. 2001;**280**(3):E528–33. doi: 10.1152/ajpendo.2001.280.3.E528. [PubMed: 11171609].