



## The Effect of Endurance Training on Plasma Levels of ICAM, VCAM, and OPG in Rats with Experimental Myocardial Infarction: A Gender-Based Study

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### Abstract

**Background:** The purpose of this study was to investigate the effect of four weeks of endurance training (EXE) on inflammatory markers predicting atherosclerosis by gender.

**Materials and Methods:** Forty male and female Wistar rats were divided into 4 groups including male myocardial infarction (MI), male MI + EXE, female MI, and female MI+EXE. After the induction of MI with two intraperitoneal injections of isoproterenol (150 mg/kg), the training groups performed an (EXE) program for 4 weeks on a treadmill (speed 18 m/min, 30 minutes, 5 sessions per week). The animals were sacrificed 24 hours after the last training session. Finally, data were analyzed using a two-way analysis of variance and Fishers' least significant difference post hoc test.

**Results:** Despite the clinical difference in the training groups, the intercellular adhesion molecule (ICAM,  $3.74 \pm 0.61$  ng/mL) was more significant in the female MI + EXE group ( $P=0.009$ ).

**Conclusion:** In general, despite observing clinical changes, there were no significant vascular cell adhesion molecules and osteoprotegerin (OPG) after EXE in cardiovascular inflammatory factors in male and female rats following MI. Nevertheless, gender had a significant independent effect on the ICAM index. The results showed that ICAM values were higher in female rats in comparison with male rats.

**Keywords:** Myocardial infarction, Sports rehabilitation, Inflammatory biomarkers

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### Introduction

Ischemic heart disease causes the most death, disability, and financial burden in the developed world compared to other diseases. Among these diseases, myocardial infarction (MI) has attracted cardiologists' most attention and concern (1). MI can be defined as irreversible damage to myocardial muscle fibers due to persistent and long-term ischemia (2). There are several risk factors for MI, the most important of which is atherosclerosis, which is a slow and progressive inflammatory process leading to partial or complete blood flow blockage by increasing the expression of adhesive molecules, cell migration, LDL-C invocation, and fibrous tissue proliferation (3). Intercellular adhesion molecule (ICAM-1) is an immunoglobulin-like adhesive molecule in which leukocytes and endothelial cells increase plasma levels during cardiovascular disease, autonomic disorders, and various types of cancer. Vascular cell adhesion molecule (VCAM-1) as a vascular adhesion molecule also plays a pivotal role in the initiation and progression of the

atherosclerosis process, and an increase in its levels in patients with MI has adverse consequences (4). Several pathways and factors have been identified concerning the mechanism of MI, one of which is osteoprotegerin (OPG). Elevated OPG is a possible cause of vascular deformity and atherosclerosis. Several concomitant clinical studies have shown that serum OPG levels are associated with cardiovascular disease including coronary artery disease, mortality, and poor prognosis following acute MI, and vascular calcification (5). Previous research has reported an increase in serum OPG levels in patients with MI (6). OPG is related to coronary calcification and has been suggested to predict plaque growth in the general female population. Population that indicates different functions of OPG depending on gender (7). Although the mechanism of change of adhesion molecules based on gender has not been appropriately explained, gender has been suggested as a risk factor for MI (the mean age of onset is 64.5 and 70.3 years for men and women, respectively). Investigations on animal samples revealed

that the hearts of female rats are inherently more resistant to ischemia-reperfusion damage compared to male rats. Accordingly, gender can be the cause of observed differences in the symptoms of MI after clinical interventions (8). Nowadays, much attention has been paid to the management of cardiovascular disorders, especially MI, regulation of anti-inflammatory mechanisms, and an increase in inflammatory suppressants (9). Regular exercise is associated with a reduction in inflammatory factors while simultaneously increasing the levels of anti-inflammatory agents, indicating the anti-inflammatory effects of exercise (10). Endurance training (EXE) seems to accelerate the inflammatory process after MI by modulating the expression of tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and *interleukin* (IL-10) genes. Animal studies have also demonstrated that exercise before MI can increase the prevention and tolerance of this complication, reduce left ventricular deformity, and accelerate the healing process (11). Accordingly, the study of changes in the levels of inflammatory factors such as ICAM-1 and VCAM-1 following exercise as effective inflammatory mechanisms in the process of MI is of considerable importance. On the other hand, a limited body of research exists on the effect of gender following endurance and subsurface training. In addition, some studies found no significant difference between men and women by examining the association between plasma levels of the ICAM-1 adhesion index and high-risk factors for cardiovascular disease (12). However, in some cases, researchers examined the endothelial function of healthy adolescents and reported that boys had higher plasma levels of adhesive molecules in comparison with girls (13). It is debatable to what extent the positive effects of EXE on the inflammatory markers of MI are gender-dependent. Statistics and evidence show that the incidence of MI is higher among men than women.

### Objectives

Therefore, this study aimed to evaluate the effects of EXE on the inflammatory indices of male and female rats following experimental MI.

### Materials and Methods

#### *Samples and Research Environment*

The present study was designed as a semi-experimental research plan (post-test with the control group) using a clinical and applied research method.

The statistical population of the study consisted of male and female Wistar rats aged 12-14 weeks with a mean weight of 250-300 g, from which 40 animals (20 male and 20 female rats) were selected as the statistical sample. The sample size was determined based on the literature, and the animals were divided equally and randomly relying on a simple randomization method using a random table of numbers. Then, the animals were randomly assigned to 4

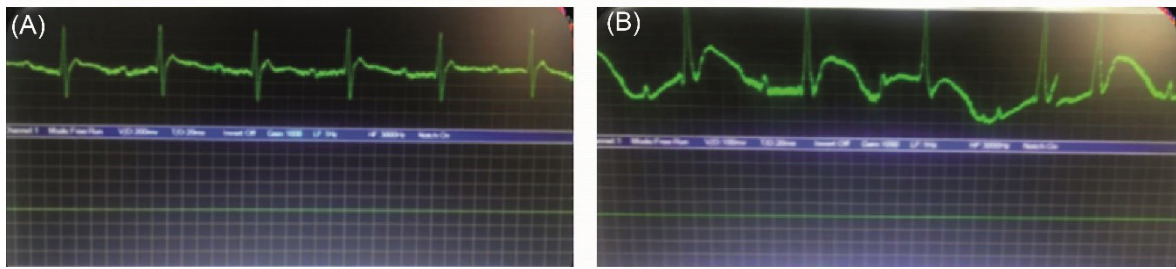
groups (male MI, male MI + EXE, female MI, and female MI + EXE). Before the experiments, the animals were kept in polycarbonate cages for two weeks under standard 12/12-hour light-dark cycle, temperature ( $22 \pm 3^\circ\text{C}$ ), and humidity ( $50 \pm 5\%$ ). The status of air pollutants was set at the desired level of the pollutant standard index via two silent air conditioners (14). The rats freely accessed water and food (Pars Food Company, Tehran, Iran).

#### *MI Induction Protocol*

All study groups were affected by the infarct protocol, and the subcutaneous injection of isoproterenol (ISO, Sigma-Aldrich, USA, 150 mg/kg) was used for induction MI (15). For ISO measurement, a digital Sartorius laboratory scale was applied with an accuracy of one-tenth of a gram of the element. This substance was employed to dilute a standard saline solution (0.05 cc) for two consecutive days for 24 hours. The injection dose was selected based on a pilot study. This substance in animal models, especially rats, is one of the standard methods for inducing MI. ISO-induced MI is a standard model for studying the effects of certain drugs on MI because of its similarity to human MI. This method of isoprenaline produces adrenoceptor- $\beta$  free radicals and affects cell metabolism to such an extent that it causes myocardial necrosis by generating cytotoxic free radicals (16). Forty-eight hours after the last injection, 2 rats from each group were randomly selected and subjected to experimental conditions to induce infarction. MI was demonstrated based on changes in clinical signs and electrocardiography (GE Healthcare, USA) with increased cardiac enzymes such as the cardiac troponin I (cTnI) marker, which was 294/168 pg/mL in infarcted rats while not detected in healthy rats. Serum troponin I concentrations are extremely low or undetectable in patients without heart diseases (16). Further, the ST segment of the electrocardiogram of the healthy rat group (Figure 1A) indicates the development of a heart attack compared to the rat with MI (Figure 1B).

#### *Endurance Training Protocol*

After transferring the rats to the research environment, they were kept under new conditions for two weeks. From the second week, before the start of the training course, the program was introduced on how to work on the treadmill for a week and every day for 10 minutes at a speed of 8 meters per minute and with a zero slope on the treadmill (Bionic-Mobin Company, model DSI-580) according to previous research (14). According to previous evidence, this amount of exercise is not enough to lead to a significant change in aerobic capacity (16). To simulate running in the familiarization phase, exercises were done on a treadmill by sound conditioning and stimulation. The animal was trained to avoid approaching, resting, and dealing with the electric shock section at the end of the device (16). After one week of familiarity with



**Figure 1.** (A) Electrocardiogram of a healthy rat. (B) Electrocardiogram of rat infarction.

the treadmill, male and female training groups entered the four-week EXE protocol. The main program of these groups included 4 weeks of running on a treadmill at a speed of 18 meters per minute for 30 minutes and 5 times a week. This program was a zero-slope exercise program performed by warming and cooling for 3 minutes at a speed of 8 m/minute. The control groups did not exercise during the experiment and were kept in cages.

#### **Blood Collection and Biochemical Assays**

In this study, 24 hours after the last training session, the samples were anesthetized and sacrificed with a mixture of ketamine and xylazine (75 and 10 mg/kg, respectively). After direct anesthesia, blood sampling was performed from the right atrium of the rat heart with 10 cc tubular syringes. The collected blood was poured into a clot activator serum tube and subjected to ambient temperature for 10 minutes. The serum was separated by centrifugation (Hermel model Z200A, Germany) for 5 minutes at 5000 rpm. Then, the plasma levels of ICAM, VCAM, and OPG components were taken by the ELISA method according to the instructions of the manufacturer of animal model kits (East Biopharm Company, inter- and intra-assay change coefficients of less than 10, 1.4, and 8%, and the sensitivity of the measurement methods was 0.05 and 0.2 ng/mL, and 7.8 pg/mL, respectively). While observing ethical issues, it was attempted to avoid any physical harassment and unnecessary methods at various stages.

#### **Statistical Analysis**

Descriptive statistics operations were used to determine the mean and standard deviation of the variables of each group. The Kolmogorov-Smirnov test was applied to

determine the normality of the data distribution. Levene's test was also performed to check the homogeneity of variance. Two-way ANOVA was employed to investigate the independent and interactive effects of gender and exercise variables on dependent variables. The effect size ( $\mu$ ) was reported in addition to the significant level. Furthermore, Fishers' least significant difference post hoc test was used if significant differences were observed between groups. The Pearson correlation test was also utilized to describe the relationships between intergroup indices. Data were analyzed using IBM SPSS (version 26), and statistical significance was considered at  $P < 0.05$ .

#### **Results**

The obtained data had natural distribution and homogeneity of variance ( $P > 0.05$ ). The results of inferential statistics showed no significant difference between the mean weight of the control and experimental groups. The mean and standard deviation of study variables in separate groups are presented in Table 1.

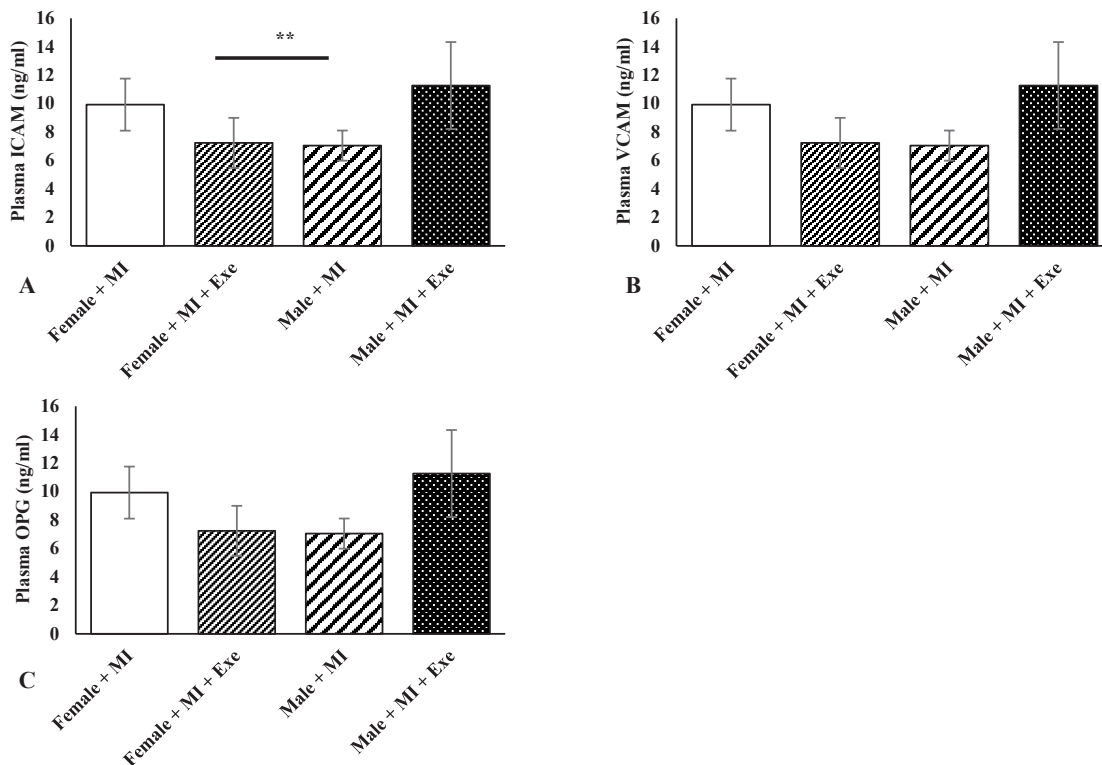
The results demonstrated that acute injury due to infarct induction caused the injury axis to be tilted toward the epicardium and ST-segment, elevated in the electrocardiographic strip of infarcted rats compared to healthy specimens. Moreover, the amount of cardiac enzyme marker troponin I in MI rats was 252.106 pg/mL, which was not detectable in healthy rats (Figure 1).

Based on the results of ANOVA test, gender had a significant independent effect on the ICAM index [training effect ( $F = 1.55$ ,  $\mu = 0.061$ ,  $P = 0.225$ ), gender effect ( $F = 7.659$ ,  $\mu = 0.242$ ,  $P = 0.011$ ), and interactive effect ( $F = 0.002$ ,  $\mu = 0.001$ ,  $P = 0.962$ )]. The results of *post hoc* test (Figure 2A) regarding the significance of the gender effect revealed higher ICAM values in the female

**Table 1.** Mean and Standard Deviation of Study Variables

Variable/Group	Female + MI	Female + MI + EXE	Male + MI	Male + MI + EXE
Weight (g)	249.87±16.02	260.1±14.79	313.87±15.8	300.62±12.52
ICAM (ng/mL)	3.44±0.63	3.74±0.61	2.73±0.56	3.06±0.79
VCAM (ng/mL)	4.11±1.23	3.42±1.05	4.03±0.39	3.19±1.26
OPG (ng/mL)	3.06±0.77	2.84±0.67	3.08±0.54	2.48±0.67

Note. MI: Myocardial infarction; ICAM: Intercellular adhesion molecule; VCAM: Vascular cell adhesion molecule; OPG: Osteoprotegerin; EXE: Endurance training.



**Figure -2.** Changes in Inflammatory Factors Including ICAM (Section A), VCAM (Section B), and OPG (Section C) in Response to Rehabilitation Exercises Considering the Effect of Gender in Male and Female Wistar Rats. Note. ICAM: Intercellular adhesion molecule; VCAM: Vascular cell adhesion molecule; OPG: Osteoprotegerin; \*\* $P < 0.01$ .

rats of the MI + training group compared to the male rats of the MI group ( $P = 0.009$ ) while no significant difference was observed between the other groups.

The findings (Figure 2B) indicated that the effects of gender, EXE, and their interactive impact on the plasma VCAM levels of male and female experimental groups were not significant [EXE ( $F = 3.752, \mu = 0.135, P = 0.065$ ), gender ( $F = 0.161, \mu = 0.007, P = 0.692$ ) and interactive effect ( $F = 0.038, \mu = 0.002, P = 0.846$ ).

Regarding the results on OPG changes (Figure 2C), although its values were lower in the experimental groups compared with the control groups, there was no significant difference between the mean groups [EXE ( $F = 2.615, \mu = 0.098, P = 0.119$ ), gender ( $F = 0.432, \mu = 0.018, P = 0.517$ ), and interactive effect ( $F = 0.549, \mu = 0.022, P = 0.466$ )].

The correlation coefficient between ICAM in female + MI with OPG in female + MI and ICAM in male + MI were reported as ( $r = 0.910, P = 0.004$ ) and ( $r = 0.779, P = 0.039$ ), respectively. In addition, a correlation was found between VCAM in male + MI and female + MI ( $r = 0.832, P = 0.02$ ). A positive relation was reported for VCAM in female + MI + EXE with VCAM in male + MI + EXE ( $r = 0.864, P = 0.012$ ) and OPG in male + MI + EXE ( $r = 0.783, P = 0.038$ ). Additionally, OPG in male + MI with ICAM in male + MI + EXE ( $r = 0.876, P = 0.01$ ) showed a direct correlation coefficient. OPG in female + MI with OPG in female + MI + EXE ( $P = 0.008, r = -0.888$ )

represented an inverse correlation (Table 2).

**Discussion**

This study aimed to determine the effect of 4 weeks of EXE on the plasma levels of inflammatory markers in male and female rats with experimental MI. The results of dependent variables showed that no significant change was observed after EXE in the ICAM inflammatory index of the experimental groups. However, the concentration of this index in the trained groups was significantly higher compared to the untrained groups. In line with the results of the present study, Nielsen and Lyberg and Khademi et al reported that the levels of ICAM-1 adhesion molecules in rats after maximal exercise, marathon running, and

**Table 2.** The Results of the Pearson Correlation Coefficient Test

Variables and Groups	Correlation Level	Variables and Groups
ICAM in female+MI	$r = 0.910, P = 0.004$	OPG in female+MI group
ICAM in female+MI	$r = 0.779, P = 0.039$	
VCAM in female+MI+EXE	$r = 0.864, P = 0.012$	VCAM in male+MI+EXE
VCAM in male+MI	$r = 0.832, P = 0.02$	VCAM in female+MI
VCAM in female+MI+EXE	$r = 0.783, P = 0.038$	OPG in male+MI+EXE
OPG in male+MI	$r = 0.876, P = 0.01$	ICAM in male +MI+EXE
OPG in female+MI	$P = 0.008, r = -0.888$	OPG in female+MI+EXE

Note. ICAM: Intercellular adhesion molecule; VCAM: Vascular cell adhesion molecule; OPG: Osteoprotegerin; MI: Myocardial infarction; EXE: Endurance training.



after 10 weeks of intense intermittent training demonstrated an increase (17, 18). In this regard, no significant difference was observed in human research by examining the effect of 14 weeks of regular aerobic exercise on the serum levels of ICAM-1 in female subjects (19). Ranković et al also reported no change in the serum levels of this index during a review of 3 weeks of aerobic training at the rehabilitation center and home (20). Additionally, 8 weeks of selected aerobic exercise, preliminary swimming, and intermittent and continuous aerobic exercise with 45%-80% intensities significantly affected ICAM-1 concentrations in middle-aged patients with type 2 diabetes, women with hypertension, and patients with heart failure (21). The lack of adhesion molecules in these studies contrasts with the reports of decreased blood adhesion and its effect on reducing the concentration of inflammatory factors as a result of exercise. Mogharnasi et al and Saetre et al found that serum ICAM-1 levels in male rats and patients with arterial disorders could be significantly reduced by exercise and EXE (22, 23). Based on the results of studies by Aksoy et al and Jalaly et al examining the effect of 10 and 12 weeks of moderate-intensity aerobic exercise program, and there was a significant reduction in the concentration of ICAM-1 molecules in patients with heart failure (24, 25). On the other hand, Farsi et al found that moderate and high-intensity EXE had the same effects on reducing ICAM-1 and VCAM in diabetic rats (26). Regardless of the effective mechanisms of EXE on reducing the concentration of adhesive molecules, it is difficult to explain the significant increase or non-change in ICAM-1 concentrations under moderate-intensity EXE. Apparently, in our study, the intensity of exercise or some disruptive factors caused muscle damage and intracellular damage, and consequently, the plasma concentration of ICAM-1 indicated an increase. Another finding of the study after 4 weeks of EXE was a non-significant decrease in VCAM-1 levels in the male and female experimental groups. Soori et al and Hosseini and Akbarighara reported a non-significant decrease in this index after 8 weeks of aerobic exercise in obese menopausal women and rats (27, 28), which is in line with the results of the present study. However, after reviewing the effect of aerobic exercise on inflammatory factors in cardiac patients, Pearson et al found a significant decrease in the VCAM-1 factor. Nonetheless, researchers have called for more research in this area due to the complexity and multiple pathways in the immunity process and the improvement of inflammatory factors (29). In addition, when evaluating the effect of exercise on endothelial inflammation factors, they observed no significant decrease in VCAM-1 levels (23). Contrary to these results, Nelson et al stated that cell adhesion molecules significantly increased after the end of the race in both groups of marathon and half marathon runners (17).

Asad et al and Bartzeliotou et al also reported that serum VCAM-1 levels increase due to inflammation after prolonged exercise (30, 31). The reduction of adhesion molecules due to endurance activities is related to other factors and the mechanism of reduction of TNF- $\alpha$  and IL-6 cytokines. In pathological conditions accompanied by an increase in the level of adhesive molecules, regular exercise improves the development and improvement of endothelial function by reducing the inflammation caused by the adhesion of leukocytes and platelets to the endothelium. Physical activity improves endothelial function by inducing changes in the transcription levels of cell adhesion molecules by increasing shear stress and nitric oxide expression (32). Further, lower levels of inflammation due to adaptation to exercise may be associated with the antioxidant effects of endurance exercise. By increasing the antioxidant capacity of the body, these exercises greatly reduce oxidative stress and sympathetic stimulation and reduce the concentration of VCAM-1 by anti-inflammatory cytokines. On the other hand, the mechanism of increased VCAM-1 levels is related to stimulating growth factors. Accordingly, the invasion of circulating cells into the tissue depends on the proteases that destroy the extracellular matrix, and the levels and activity of the metalloproteinase matrix increase following the physical activity. Therefore, physical activity as a stimulus can change the use of circulating cells (33). However, none of the mentioned cases in this study have been measured, and their relationship and effect cannot be expressed in the absence of significant differences in cell adhesion molecules. Regarding the effect of gender on physiological responses induced by exercise, the study findings showed no significant difference in the serum ICAM-1 concentration of the control groups. Furthermore, 4 weeks of endurance activity increased the rate of this index in two experimental groups of males and females although this increase was not significantly different in both genders. Significant differences between the two experimental groups of females and the control group of males can also be attributed to the high base rate of the index in females and the additive effects of EXE on this index. As regards the serum index of VCAM-1, the findings revealed that the serum level was not significantly different in the control and experimental groups. The values of this index in both genders were similarly affected by the duration of EXE. According to the literature review, there are limited studies on the effect of gender on the inflammatory processes caused by exercise. For this reason, the possible effective mechanisms in both genders are not well known. Demerath et al reported no significant difference between men and women regarding the plasma level of ICAM-1 and VCAM-1 indices with high-risk factors for cardiovascular diseases (34). Chen et al investigated the relationship between adhesion factors and endothelial function in healthy adolescents and

concluded that boys have higher plasma levels of adhesion molecules in comparison with girls (35). Conversely, Valipour et al found no significant difference between the ICAM-1 inflammatory index of the two genders when studying the effect of gender on endothelial function and lipid profile (12). In the study of Fan et al, the plasma levels of ICAM-1 and VCAM-1 were higher in adults compared to young people although no significant difference was observed between women and men (36). The dependent variables showed that after EXE, no significant change was observed in the OPG index of male and female experimental groups. However, the concentration of this index significantly decreased in the trained groups compared to the control groups. OPG is a soluble glycoprotein from the TNF- $\alpha$  receptor family and is involved in many physiological and pathological processes such as atherosclerosis. Moreover, it has been reported to increase in subjects with reduced ST segment. However, it is unclear whether this is a factor in itself or a consequence (37). On the other hand, physical activity on circulating serum OPG levels is still unknown and controversial. Researchers indicated that OPG levels are lower in sedentary girls compared with athletic girls. Significant increases in OPG concentrations have also been reported in postmenopausal women after a course of aerobic exercise twice a week, each session lasting 30 minutes of brisk walking (38). Consistent with the results of the present study, Sponder et al examined the effect of 8 months of endurance activity and observed no significant change in serum OPG levels (39). Accordingly, the non-significant decrease in the OPG index in the present study is probably due to the incomplete regeneration process and response to inflammation caused by infarction after four weeks of EXE. Previous studies demonstrated that changes in OPG may be more pronounced in women due to the greater inflammation of TNF- $\alpha$  receptors, and as a result, factors associated with cardiovascular complications such as OPG are expected to increase during menopause (40). However, no difference in OPG levels was found between male and female groups in the present study. Thus, no definite opinion can be given in this regard due to the lack of information about the similar effect of physical activity on inflammatory indicators in both genders.

### **Limitations of the Study**

One of the limitations of this study was the use of a short period of interventions. It was intended to reduce the pain of animals due to the methodology of the study. Further, it was meant to reduce the number of sacrifices, therefore, a small sample size was selected, which can affect the study findings. Otherwise, measuring other parameters could provide more clear findings in this regard. In addition, it has to be remembered that due to the precise control of the experimental procedure, it is difficult to generalize

and compare findings with other studies, especially studies on human models.

### **Conclusion**

Overall, the findings of the present study did not show significant changes after 4 weeks of moderate-intensity EXE in cardiovascular inflammatory factors in male and female rats following MI. However, gender exerted a significant independent effect on the ICAM index. Based on the results, ICAM levels were higher in female exercise rats compared to male rats while other plasma levels represented no differences between the two genders. In most previous research studies, different results were obtained regarding changes in adhesion molecule levels and inflammatory markers following exercise.

It seems that many interfering variables must be controlled during the studies in order to achieve clear and valid results in this field. The most important possible factors in the differences are the type of the subjects, gender, and baseline levels of the inflammatory indicators of the subjects. Depending on the principle of response to exercise, decreasing or increasing serum levels of adhesive molecules may rely on the intensity, duration, and repetition of exercise sessions. It may also be more effective to use exercise before MI than after having a complication.

### **Conflict of Interest Disclosures**

The authors declare that they have no conflict of interests.

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### **Ethical Statement**

The Ethics Committee of Islamic Azad University, Science and Research Branch (No. IR.IAU.SRB.REC.1398.062) approved the experimental protocol of this study. It was performed under the National Institutes of Health guide for the care and use of laboratory animals (No. 80-23), emphasizing that minimal animals should be sacrificed and minimal pain should be imposed during the study. This article is taken from the Ph.D. dissertation with the code 20021423981005.

### **Authors' Contributions**

MA and BA: Conceptualization, methodology, investigation, resources, data curation, visualization, supervision, project administration, and funding acquisition. HF: Software, validation, formal analysis, original draft preparation, and finally, reviewing and editing.

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### **Informed Consent**

In the present study, animal models were used and ethical principles were observed at all stages.

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