



## Original Article

## The Effect of Eight-Week Aerobic Exercises on Vascular Cellular Adhesion Molecule-1, Intracellular Adhesion Molecule and Body Composition of Addicts Treated with Methadone

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## ABSTRACT

**Background:** Drug consumption and addiction lead to serious cardiovascular diseases as well as inflammation. Cellular adhesion molecules are glycoproteins that mediate a leukocyte reaction to inflammation. This study aims to determine the effect of aerobic exercises on some cardiovascular factors in addicts treated with methadone.

**Methods:** This is a semi-experimental research. To conduct this research, 30 male addicted patients treated with methadone with a mean age of  $33.53 \pm 15.42$  years,  $70.06 \pm 15.42$  kg weight and  $174.8 \pm 5.69$  cm were selected after medical screening and randomly divided into experimental ( $n=16$ ) and control ( $n=16$ ) groups. First, the height, weight and body mass index (BMI) of participants in both groups were measured. Blood samples were taken from the subjects in order to measure the intercellular adhesion molecules 1 (sICAM) and cellular vascular adhesion 1 (sVCAM) in serum. The experimental group had an aerobic exercise program including use of a treadmill with a 40 to 50% maximum heart rate in the beginning and then, a 70 to 80% maximum heart rate. The control group had only a follow-up. After 8 weeks, all variables were measured in both groups. Correlated t-test and independent t-test were used for intragroup and intergroup comparisons ( $P < 0.05$ ).

**Results:** Results showed that after 8 weeks aerobic exercises, there was no significant difference in ICAM-1 ( $P=0.397$ ), VCAM-1 ( $P=0.521$ ), and BMI ( $P=0.223$ ).

**Conclusion:** Although 8-weeks aerobic exercise was not effective and sufficient for BMI, ICAM-1 and VCAM-1 indicators of the addicts treated with methadone, but it reduced ICAM-1 and VCAM-1 in the exercise group.

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## Introduction

Addiction is a phenomenon that has been around for a very long time in human communities; recently, people's awareness has undeniably increased as have scientific advancements in different fields. The prevalence of addiction is increasing among different classes of people

in the society and the age of addiction is lower due to fast and more dangerous ways of drug consumption [1].

Drug dependence is one of the major dilemmas of people in the recent decade; unfortunately, the number of victims are increasing day by day and it leads to physical, mental, family and social problems [2]. The rate of drug addiction has increased in recent years although different ups and downs have been seen. The highest number of addicts come from the age range of 20-35 year olds 60-70% of addicts are illiterate or of a low-level of literacy and the prevalence of addiction in men has been reported

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as 10 times that of women. [3].

Regarding the destructive side-effects of drugs on cardiovascular disease, most people believe that opioids are effective in preventing and reducing the risk of cardiovascular disease [4] but the results of the research show the opposite i.e. the most common cause of mortality in addicts is coronary artery disease and atherosclerosis [5].

Cardiovascular atherosclerosis disease is the major cause of more than 19 million annual deaths around the world [6]. The Heart Association of US declared that the development of cardiovascular disease has an inflammatory cause and general inflammation plays a key role in the progress of atherosclerosis [7]. Increasing evidence shows that pro-inflammatory cytokines and cellular adhesion molecules (CAMs) that increase vascular endothelial and are introduced as new inflammatory indicators, have high sensitivity and accuracy in the diagnosis and prognosis of cardiovascular disease; they also play an important role in atherosclerosis pathogenesis [8, 9]. Regarding the increase in intracellular adhesion molecule (ICAM-1) and vascular cellular adhesion molecule-1 (VCAM-1) concentration in serum following inflammation, they can be used as indicators of predicting the risk of heart stroke, diagnosis and evaluation of coronary artery disease and atherosclerosis [10]. Basically, inflammation is the cause of most cardiovascular disease. The stimulation and damage of vessels as a result of some drugs, directly, and increasing the shear pressure, indirectly, increase the sensitivity of vascular endothelial adhesion cells like sICAM-1 and sVCAM-1 [11]. Adhesion molecules are glycoprotein receptors that appear in different surfaces of cells and inflammation sites and as the adhesion receptor of white cells, they mediate the transfer of these cells to the tissues. Some of these molecules are soluble in plasma and their presence shows vessel endothelial disorder [12].

In addition to inflammatory factors, the increase in blood lipid and cholesterol has been introduced as an important factor in the prevalence of cardiovascular disease. There is a direct relationship between the risk of cardiovascular disease and cholesterol level [13]. The findings of studies showed that the ratio of waist to cervix and waist to height ratio are the best predictors of cardiovascular risk factors in men, and the ratio of waist to cervix and waist circumference are the best predictors in women [14]. Various treatments and drugs have been proposed to prevent and reduce the destructive and permanent effects of opioids up till now. Among them, recent research has determined exercise and physical activity as the most useful and suitable method in this regard and positive effect can be enhanced by regular planning [15]. Some research has shown that physical activity without diet can make the weight and BMI increase slower; these are some of the cardiovascular risk factors in addicts [13]. Regular and long-term exercise along with improvement in the function, regulation of body weight, lipid mass, improvement of lipid profile and a reduction in belly fat, reduce the prevalence of cardiovascular disease and

increase the longevity of people [16].

Various studies have shown that suitable exercises, long-term have more useful effects than diets on a person's health. Using determinates of endothelial function is useful in determining the effects of exercises on different statistical samples. A few researchers have studied the relationship between all types of regular endurance exercises and inflammatory indicators. The findings of the researchers concerning the effect of endurance exercises on the plasma concentration of adhesion molecules as a reliable indicator of general inflammation are contradictory. Some studies emphasized the reduction of sICAM-1 and sVCAM-1 of serum after exercise. Kargarfard et al (2016) compared the effect of HIT and endurance exercises on sICAM-1 and sVCAM-1 in fat and thin adolescents. Their results showed that sICAM-1 was significantly reduced in both groups but VCAM-1 decreased only after HIT exercises [17]. Riahi et al (2019) studied the effect of eating garlic and swimming on adhesion molecules. Their findings showed that eight weeks training and eating garlic caused a significant reduction in sICAM-1 but it had no effect on sVCAM-1 changes in male rats [18]. J. Zhopini et al (2006) emphasized the significant reduction of ICAM-1 plasma level after 6 months aerobic exercises on old, overweight, immobile and diabetic subjects but studies also showed no change after exercise. K. Izava (2009) showed that by adjusting and correcting [19] some types of training and diet in a 24 week lifestyle modification plan for 89 diabetic patients, despite the change in waist circumference, blood pressure and fasting glucose, VCAM-1 and ICAM-1 in plasma did not change [20]. The findings of the J. Sabatier et al (2008) study indicated the lack of change in sICAM-1 after 14-weeks of aerobic exercise in healthy and non-active women [21].

Regarding the importance of addiction and the increasing prevalence of using drugs and the inclination of youths to use drugs, the importance of cardiovascular disease and the harmful effects of drugs on the new risk factors of these diseases among people, this research tries to study the problem by considering the role of exercise in the prevention and treatment of this problem. This research aims to study the effect of 8-weeks of aerobic exercise on treadmills on the adhesion cells and body composition of addicted treated with methadone.

## Methods

This is a semi-experimental pre-test post-test research with a control group. When selecting the subjects and coordination, first, the researcher referred to Royesh Addiction Clinic in Isfahan. Based on the negotiation of the authorities of this clinic, the number of men who consumed opioids and heroin was 70. Then, a session was held with the presence of all the people in the clinic and some information was provided to them. Participants registered to enroll in the study. After that, qualified people were selected based on the inclusion criteria. Some inclusion criteria were: age range of 20 to 45 years old, 5-10 years of drug consumption with mean of 2gr

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consumption per day, treatment with methadone, lack of cardiovascular, musculoskeletal, and metabolic diseases that limit exercise, lack of regular exercise history in recent 6 months. Subjects were examined by the clinic physician to confirm their health so as to be able to participate in training finally, among the volunteers who possessed the above qualities, 42 subjects were selected to participate in the study. Subjects were randomly placed in control (21) and experiment (21) groups. 9 subjects of the experiment group and 5 subjects in the control group did not refer to the clinic due to drug abuse and were excluded from the study after 4 weeks. To compensate their loss, especially in the experiment group, another request for participants was done in the clinic among patients and 4 subjects were added to the experiment group; the number of subjects in the experiment group reached 16. During one session, participants get familiarized with the type of study, objectives, its advantages and risks and their informed consent was obtained. This study was approved by the Ethics Committee of Biomedical School of Islamic Azad University, Isfahan Branch (Khorasgan). Anthropometric indicators including height, weight, and BMI were measured with minimum clothing and without shoes. The weight of subjects were measured with a Germany made scale with 0.1 kg precision and their height with a tape meter with 0.5 cm precision. BMI was obtained by dividing the weight on square of height.

Before starting training sessions, subjects participated in three sessions to get familiar with the training, training principles, and using a treadmill. All training was carried out in the presence of a physician and sports expert. The experiment group, in addition to consuming methadone for 8-weeks and taking part in 3 sessions per week of aerobic training, participated in treadmill training under the supervision of a sports expert and physician. First, the subjects' heart rate was controlled by Polar heart rate monitor accurately by the researcher to observe overload and determine intensity. The training plan was set as sub-maximum i.e. with 40-50% of maximum heart rate of an individual and increased to 70-80% of maximum heart rate after improving physical readiness and aerobic capacity. Overload rule was used in this training by increasing the time of training. The training was as follows. Before a rest, 10 minutes warm-up was done. In the first two weeks of exercise, training was done with a maximum heart rate of 40-50% and 15 minutes walking on a treadmill; in the second 2-weeks, training was done with maximum heart rate of 50-60% and 15 minutes walking on treadmill; in the third 2-weeks, training was done with maximum heart rate of 60-70% and 15 minutes walking on treadmill; finally, in the fourth 2-weeks,

training was done with maximum heart rate of 70-80% and 15 minutes walking on treadmill and 10 minutes to cool down [22]. Patients were recommended to stop the training when they felt extreme fatigue in order to prevent any accidents. Control group had normal daily activities in the 8-weeks.

In order to measure biochemical variables, blood samples were taken after 21 hours while fasting and in two steps, i.e. 24 hours before starting the program and after 8 weeks with the cooperation of an addiction clinic physician. The subjects were asked to not do intense activity for two days before giving blood samples. 5cc of blood was taken in a seated position from the arm veins of subjects. The blood samples were centrifuged after collection and the isolated serum was kept in -80°C in freezers until measurement. Biochemical analysis and plasma measurement of ICAM-1 and VCAM-1 was done with Elisa kit for ICAM-1 and VCAM-1, made by Buster Biological Company, EKO 537 model Human VCAM-1, ICAM-1 ELISA Kit ( Range : 156 pg/ml - 10,000 pg/ml). It is worthy to mention that there was no intervention for the control group and before the intervention, the subjects were ensured that their relevant information would be studied confidentially and anonymously and finally, it would be reported in the general form.

After collection, the data were analyzed with SPSS software version 21. Shapiro-Wilk test was used to ensure the normal distribution of data. Correlated t-test was used for intragroup comparison and independent t-test for intergroup comparison (comparing the differences and post-tests). Error was considered at  $P < 0.05$  level.

## Results

This study was conducted on 30 addicted men treated with methadone. Table 1 shows the demographic information and central measures of subjects in the pretest including weight and BMI.

Table 2 shows the intergroup changes of research variables in experiment and control groups. The results of BMI variables showed that there was no significant difference between the control and experiment groups in intergroup comparison ( $P = 0.0223$ ). Table 3 did not show a significant difference between the two groups after 8 weeks aerobic exercises regarding ICAM. There was no significant difference between the two groups in terms of VCAM ( $P = 0.521$ ).

## Discussion

Despite the useful effects of morphine in the acute

**Table 1:** Descriptive characteristics of subjects before intervention

Variables	Experiment	Control
Age (year)	33.53±6.83	33.53±6.83
Height (cm)	174.80±5.69	174.80±5.69
Amount of used opioids (gr)	2.03±1.36	2.5±1.35
Amount of used methadone (cc)	19.35±10.41	21.00±7.76
Duration of addiction (year)	9.57±5.09	9.62±4.31

Table 3: Comparing mean weight and BMI of two study groups

Variables	Experiment		Control	
	Pretest	Posttest	Pretest	Posttest
Weight (kg)	71.71±18.56	70.00±17.16	68.62±12.52	68.06±12.75
BMI (kg/m <sup>2</sup> )	23.35±5.55	22.81±5.01	22.41±3.54	22.23±3.74

Table 2: Intergroup comparison of variables before and after training in experiment and control groups' subjects (mean±SD)

Variable	Group	Pretest	Posttest	P	Independent
BMI (kg/m <sup>2</sup> )	Experiment	23.35±5.55	22.81±5.01	1.247	0.223
	Control	22.41±3.54	22.23±3.74		
ICAM-(pg/ml)	Experiment	5579.3±1451.4	3906.3±1138.7	0.86	0.397
	Control	6199.5±1479.6	4889.4±1346.9		
VCAM-(1pg/m)	Experiment	13998.9±1636.9	10505.5±1214.4	0.651	0.521
	Control	13408.7±2037.5	10487.5±1699.6		

phase of cardiovascular problems, it seems that the long-term use of opium may be harmful to the cardiovascular systems. Various studies have shown the adverse effects of drug misuse and some risk factors of CAD [4]. The results of the research showed that 8-weeks aerobic exercises reduced the ICAM-1 and VCAM-1 in both experiment and control groups but there was no significant change in ICAM-1 and VCAM-1 of subjects, compared to each other. Since the researchers believe that endurance training is an important factor in cardiovascular health and reduction of risk-factors, it was expected that a significant change would occur in adhesion molecules between the two groups. The lack of a significant change in serum level of ICAM-1 and VCAM-1 between the experiment and control group after aerobic exercise in our research is consistent with the findings of Mastero et.al [23], Smith et.al [24], Akimoto et.al [25], Nemet et.al [26], and Hosseini [27]. findings. Regarding this, Haghiri et.al (2016) studied the changes of ICAM-1 and VCAM-1 and CRP serum level in middle-aged men who had previously suffered heart failure after the 8-weeks aerobic exercise. The aerobic exercise, by reducing inflammatory indicators of VCAM-1 and CRP, played an important role in the prevention and control of cardiovascular disease in middle-aged men who had suffered heart failure [28]. The results of this research are inconsistent with our results. The reason for this inconsistency is the health level of participants. Being healthy or ill is an essential factor in observing the effect of physical activity. Changes in serum ICAM-1 may be influenced by changes in the concentration of blood's lipids and antioxidant effects of exercise [29]. In another research, Kargafard et.al (2016) studied the effect of endurance exercise on ICAM-1 and VCAM-1 and blood pressure of overweight and normal adolescents. In this research, after 8 weeks endurance training for 30 overweight and 30 healthy adolescents, there was a significant difference between the two groups and training significantly reduced the ICAM-1 and VCAM-1 levels [30]. Another reason of inconsistency of the results of their research with the present research was the different BMI in both groups. Since obesity has a direct relationship with inflammation, it can somewhat explain the difference. Being overweight and obesity is the abnormal accumulation of fat which may damage

health. Obesity is a mild inflammatory condition in which the production of pro-inflammatory cytokines increases with white fat tissue. Fatty acids and cytokines coincide to activate the downstream inflammatory pathways in such a way that activating these pathways produces transcription factors related to the expression of inflammation cytokine genes and induces the production of cytokines; therefore, spreading the inflammation [17].

In this regard, Rector et.al's study (2006) indicated a 25% reduction in serum ICAM-1 level in obese or overweight subjects after a 6-week weight loss program (including aerobic exercise and diet) [31]. Another reason for the inconsistent results of Rector's study and our study is the high BMI of subjects in their research. Inflammatory and cellular adhesion molecules are higher in number in obese people. Aerobic exercise is effective in changing biomarkers of inflammation and cell adhesion [8]. The studies showed that exercise and physical activity, by reducing fat tissue (especially belly fat), adjusts the inflammatory factors like IL-6, TNF- $\alpha$ , and CRP, on the one hand, and improves lipid profile of blood and increases HDL-C in plasma and stimulates the prostacyclin release of vessels or smooth muscles and suppresses platelets on the other hand. The results of Vog et.al's (2004) study showed a significant reduction of ICAM-1 and CRP in plasma after participation in 2 weight control programs including diet and daily aerobic activity in women after menopause [32]. which are inconsistent with our results.

A possible cause can be controlling diet. The above results indicate that the effect of training is observable when it accompanies a diet. Some researchers emphasized the simultaneous adjustment of daily physical activity and diet as one part of correcting lifestyle in order to improve lipid and inflammatory profile and showed that due to the positive relationship between the level of plasma inflammatory indicators with blood lipids and some anthropometric factors like BMI, fat percentage and waist to hip, a low-fat and high-fiber diet and exercise are necessary in this regard [33]. Physical activity may adjust the effective mechanisms in regulating adhesion molecules like renin angiotensin system and reducing the release of chemical mediators and inflammatory factors like NFK-B in adjusting the vascular inflammation.

NFK-B exists in cytoplasm in inactive form and

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mediates the beginning of endothelial activity of mediators and translation of ICAM-1. In addition, Angiotensin 2 stimulates NADPH oxidase and increases the emergence of ICAM-1. Each of these mechanisms can somehow explain the changes in the concentration of adhesion molecules in the two exercise groups [34].

According to Adamopolus et.al (2001) the implementation of 12-weeks exercise (30 minutes biking with 70-80% maximum heart rate 5 days per week) in cardiac patients was accompanied with the significant reduction of inflammatory factors like ICAM-1 which are not consistent with our results. A reason for this is the illnesses of the people participating in this research. Another possible cause is the duration of the research. In the present research, the length of exercise was 8 weeks that may not be sufficient for changing adhesion molecules. Physical activity can improve the endothelial antioxidant defense, blood and suppression of nitric oxide and active oxygen and by increasing the production of nitric oxide by endothelial cells, and consequently, regulating the tone of vessels, suppression of platelets accumulation and controlling the adhesion of mediators to the vessels, adjust the endothelial activity and general inflammation [35]. We can say that exercise and physical activity are effective in preventing the severity of disease in these subjects due to improvement of endothelium restoration capacity by increasing the number or function of stem cells. Stem cells, after transferring from bone marrow and migrating to the damaged endothelium, differentiate to adult adhesion endothelial cells and help the growth, repair of vessels and improvement of endothelium function [36]. Another limitation of this research is the lack of accurate control of subjects' diet and initial level of physical and cardiac readiness before exercise. It is suggested that these factors be taken into account in a future research.

### Conclusion

In this study, the lack of a significant difference in the body composition may be due to the training duration, intensity and duration of activity. On the other hand, the reduction was observed in adhesion molecules in the control group but it was not statistically significant. The reason for the reduction of adhesion molecules in the control group was using methadone as the medicine to replace drugs. Methadone is a synthetic pain killer with 48-72 hours half-life which has good pain killing effects and had been used for a long time on addicts by physicians, but we cannot say that physical exercise was ineffective. This study, by manipulating food, intensity and duration of exercise, will provide a better understanding of effective mechanism on changing ICAM-1 and VCAM-1.

**Conflict of interest:** None declared.

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