The effects of an eight-week aerobic exercise on serum levels of CRP, IL-6, and fibrinogen in middle-aged women

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Abstract: Inflammatory markers increase the risk of cardiovascular disease. Predicting the risk of coronary artery disease, serves an important role in treating and preventing the progression of the disease. Aerobic exercise decreases the risk of coronary artery disease by reducing inflammation. The current study investigated the effect of a period of selective aerobic exercise on the serum levels of CRP, fibrinogen, and IL-6 among the middle-aged women. Twenty-four middle-aged women were equally split into two groups, control and experimental. The experimental group underwent 30-min exercise sessions with the increasing intensity of 50-75% maximum heart rate, three times a week for 8 weeks. Blood samples were taken from both groups twice (24 hours before and 24 hours after the training) in order for the measurement of the intended factors. A paired sample t-test was used to compare the pre-test and post-test data. In order to test the difference between the two groups, independent t-test was used at a significant level (P<05/0). Normality of the data was checked by using the Kolmogorov Smirnov test. The results of the study revealed that 8 weeks of aerobic exercise induced a significant difference in the levels of CRP (p = 0.001), fibrinogen (p = 0.004), and IL-6 (p = 0.022) between the two groups. According to current research results, performing a period of regular aerobic exercise, while applying the overload principle and intensity, can cause the reduction of inflammatory markers of cardiovascular disease, which along with aging can be a determining factor in the atherosclerosis, especially in sedentary people.

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1. Introduction

Scientists have long been interested in the human health and disease. Cardiovascular disease is one of the most important diseases which each year countless people succumb to it (1). Considering that atherosclerosis is a progressive disease, and that it also is considered the leading cause of death (1), predicting the risk of coronary artery disease plays an important role in treating and preventing the progression of it (2).

Chronic inflammation and thrombosis is very effective in the prevalence and progression of atherosclerosis and the conversion of a stable atherosclerotic plaque to a fixed obstructive lesion (3). Several studies have revealed the link between inflammatory markers and the risk of coronary artery disease (4). The relationship between inflammatory markers, such as adhesion molecules, fibrinogen, Interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and coronary artery disease is suitable for the prediction of the disease (5). Previous investigations have also shown that in most cases, coronary artery disease correlates well with the number and severity of cardiovascular risk factors (6).

Fibrinogen can be considered an important inflammatory marker which induces tissue damage and infection and the development of atherosclerosis (7). Fibrinogen is a glycoprotein synthesized in the liver. Induced by IL-6, fibrinogen serves a vital role in platelet aggregation, endothelium impairment, coagulation process, blood viscosity, and the concentration of red blood cells (8). According to research presented at American Heart Association, a decrease in fibrinogen level by 10 milligrams per deciliter, reduce incidence of coronary heart disease by 15% (9). Fibrinogen levels along with plasma IL-6 are elevated with inflammation (10). Secreted by leukocytes, IL-6 is a multifunctional pro-inflammatory cytokine as well as a mediator of inflammatory processes which its serum level is low in normal people (11). An increased IL-6 serum level is associated with increased incidence of coronary artery disease, and anti-inflammatory treatments reduce acute coronary syndromes by reducing interleukin-6 levels (12). On the other hand, rupture of an atherosclerotic plaque triggers the release of IL-6, regional accumulation of macrophages and the process of coronary artery occlusion (13). C-reactive protein is also a subclinical inflammatory marker which its five-fold increase heightens the risk of coronary artery disease (14). CRP is correlated inversely with insulin sensitivity and directly with the risk of type 2 diabetes (15). It is also high in the people with high body fat (16).

With regard to the importance of cardiovascular disease with advancing age, especially in sedentary people and with considering the results of previous studies, exercise trainings can decrease the inflammatory markers, and consequently reduce the risk of coronary heart disease. Few researchers have investigated the effect of regular exercise or aerobic exercise on predictive inflammatory markers of cardiovascular disease. Even though there is evidence that exercise training can reduce inflammation, more research is needed to find out the mechanism of this reduction, intensity, and the time of physical activity which greatly reduce the inflammation. For this reason, the current study investigates the effect of eight-week aerobic exercise training on the inflammation markers fibrinogen, IL-6, and CRP in the sedentary middle-aged women.

2. Material and Methods

In this quasi-experimental and functional research inactive middle-aged women as well as some cardiovascular inflammatory markers (fibrinogen, IL-6, and CRP) have been studied. After the announcement for participation in the study, 120 middle-aged women expressed their willingness to take part in the research. After the explanation of method and under the supervision of a physician and health questionnaire, twenty-four healthy women with a mean age of 42.5 years who had the physical ability to participate in the aerobic exercise training period were randomly selected. They had no history of certain diseases, such as diabetes, fat, high blood pressure, cardiovascular disease and cancer. They also lacked a regular physical activity for at least 6 months before the start of exercise trainings. The participants were equally divided into two distinct groups: exercise group (mean BMI 28.92) and control group (mean BMI 27.89). Height, weight, body mass index, resting heart rate, and anthropometric data of the subjects were measured and recorded in individual forms just before the start of physical training.

The Subjects in the exercise group embarked on an 8-week physical training in a gym in accordance with exercise protocol every other day or three times a week, with the purpose of increasing intensity from 50% of their maximum heart rate in the first week to 75% in the last week. To estimate the maximum heart rate (MHR) of the subjects, 220-age formula was used.

The length of time for each aerobic exercise session was 60 minutes. The exercise sessions consisted of 10-minutes stretching exercises for pre-exercise warm-up, followed by 40 minutes of the major exercise at 50-75% of their maximum heart rate (first two weeks 50-60%, fourth to fifth weeks 60-70%, sixth to eight weeks 75%). The main part of the sessions consisted of jogging on a treadmill (DKCity SX6-20ML Treadmill) for 15 minutes at progressively increasing speed and 25 minutes of regular and coordinated physical activities ended with 10 minutes of seated exercises and cool-down. In the early weeks, the duration of main exercise was added and the cooling-down decreased according to the overload principle and protocol.

Subjects' heart rates were measured several times during the exercise via the carotid pulse and a heart rate monitor (Polar F1mt, Finland) in order to monitor exercise intensity. Blood samples were collected 24 hours before the first training session and 24 hours after the last session. Finally, the blood samples were centrifuged to remove plasma. Then the plasma was transferred and stored frozen in a standard freezer at a certain degrees Celsius. The chemical analysis and measurement of the levels of ICAM-1, VCAM-1, and E-selectin were carried out using standard ELISA Kit (Bender Med, Austria) and an ELISA reader, made in USA.

Research data was processed with the help of SPSS software, version 18 (SPSS Inc. Chicago Illinois, United States). The central trend indices and dispersion indices were shown through descriptive statistics. The Kolmogorov-Smrirnov test was used to review the data distribution types. For survey the effect of exercise training on selected factors on each group dependent t test was used and to compare pretest and post-test data means in each group, the statistical independent t test was used. All the statistical tests were performed at the 95 percent confidence level ($p < 0.05$).

3. Results

The data were classified according to average and standard deviation in either groups of control and exercise. The Kolmogorov-Smirnov test showed normal distribution of data in all stages of post-test and pre-test. Descriptive statistics results of the difference of inflammatory cardiovascular risk markers in either groups between the pre-test and post-test are given in table 1. The mean difference between the pre-test and post-test in the inflammatory marker CRP in exercise group was -0.60 while it was 0.14 in the control group, fibrinogen levels were -22.83 and 21.74 in exercise group and control group, respectively, and the levels of IL-6 in exercise group were -0.61 and 0.26 in the control group.

Table 1. Descriptive data for inflammatory factors difference between pre test and post test

	Control Group	**Aerobic Training Group**
CRP(mg/l)	0.14±0.38	-0.60±0.58
Fibrinogen(mg/dl)	21.74±42.94	-22.83±21.79
IL-6(pg/ml)		0.26±0.71

Data are means ±sd

Table 2. Ddependent t test results on control and exercise group

	Group	**Pretest**	**Post test**	**t**	**P-Value**
CRP(mg/l)	Control	3.20±0.86	3.34±0.80	-1.267	0.231
	Training	3.60±0.41	2.99±0.55	3.581	0.004
Fibrinogen(mg/dl)	Control	292.19±59.36	315.61±69.64	-1.966	0.075
	Training	297.36±55.11	274.53±55.39	3.629	0.004
IL-6(pg/ml)	Control	2.92±1.53	3.19±0.99	-1.309	0.217
	Training	2.69±1.13	2.07±0.69	2.105	0.059

Significance was set at P<0.05.

Table 3. Independent t test results on control and exercise group

	Levene's Test for Equality of Variances		**t- test for Equality of Means**		
	F	**Sig**	**Means Difference**	**t**	**P-Value**
CRP (mg/l)	0.535	0.472	-0.75	-3.688	0.001
Fibrinogen (mg/dl)	10.43	0.004	-44.57	-3.20	0.004
IL-6 (pg/ml)	1.318	0.263	-0.88	-2.474	0.022

Significance was set at P<0.05

According to the data in table 2, all three factors (CRP, fibrinogen, and IL-6) were significantly lowered in the aerobic exercise group in comparison with the control group. As table 3 and the results of independent t-test indicate, a significant difference was observed in the levels of CRP (p = 0.001), fibrinogen (p = 0.004), and interleukin-6 (p = 0.22) in the mean difference of pre-test and post-test of control and exercise group after 8 weeks of aerobic exercise training.

4. Discussions

This study investigated the (effect of) 8 weeks of aerobic exercise on some of the cardiovascular inflammatory markers. Research have shown that inflammatory markers are involved in early stages of atherogenesis, i.e. atheroma plaque formation, including causing arterial endothelial dysfunction (17), formation of fatty pads and platelets (18), and the blood clots (thrombus) that cause heart attack and stroke. The adhesion of leukocytes, neutrophils, and monocytes to vascular endothelial cells and migration of leukocytes into the subendothelial spaces are among the main developmental processes of atherosclerosis (19).

C-reactive protein (CRP) exerts its physiological influence through two major mechanisms: connection with the monocyte activities (20) and increase in the adhesion molecules synthesis which recruits Leukocytes to bind on the surface of vascular endothelial, and therefore strengthen and expands inflammatory process in the vascular endothelium. In addition, inflammatory markers interacting with other risk factors, increase atherosclerotic-related diseases. For example, (elevated) levels of CRP and IL-6 predict the development of diabetes (21). Different researches have been carried out on the effect of exercise training on these markers. Most of the researches have shown that aerobic exercise is associated with decreased cardiovascular outcomes in healthy people (22) as well as people with heart disease (23) and diabetic patients by significantly reducing peripheral inflammatory markers, such as IL-6, CRO, and TNF-α. Previous studies have shown that undergoing a period of aerobic trainings, such as continuous running and aerobic exercises had a significant impact on reducing these markers (24).

Past studies have indicated a significant association between regular exercise training and inflammatory markers (25, 26). These researches suggest that people who are physically active have lower levels of inflammatory markers. For example, long-term aerobic exercise reduces CRP (27). The relationship between lower levels of inflammation and physical activity causes one of the mechanisms of heart protection. The common concept of pathophysiological mechanism is the atherosclerosis-related inflammation, production of inflammatory cytokines in response to oxidized LDL stimulation, and macrophages along with the sclerotic plaque (28). It has been stated that regular exercise training decreases levels of oxidized LDL (29), IL-6, and TNF-α (28). Therefore, the effect of regular trainings may be responsible for the reduction of CRP levels in the experiment group.

Potential mechanisms related to exercise and circulating CRP levels could be explained by finding that repeated exercise training may lower basal plasma interleukin concentration (30). One of the most important interleukins responsible for the decrease in CRP levels in the individuals following exercise training is IL-6, a pro-inflammatory cytokine, and has been shown to stimulate CRP synthesis in the liver and is secreted from adipocytes.

Some mechanisms have been presented by which aerobic exercise alters the regulation of inflammation. Exercise training can reduce the causes of endothelial dysfunction which improves endothelial function by increasing the nitric oxide secretion, and thus decrease inflammation (31). Aerobic exercise training may also reduce the gene expression and serum levels of leukocyte adhesion molecules. Thus, the response of monocytes inhibits endothelial cells, and finally the production of cytokines. Aerobic exercise reduces oxidative stress. Exercise training also increase body's antioxidant defense system (32). Elevated fibrinogen levels ramp up the risk of thrombosis. High levels of fibrinogen and/or plasminogen activator inhibitor is one of the risk factors of atherosclerosis which is related to the blood coagulation system and cause inhibition of fibrinolysis. Investigations have revealed that exercise can reduce fibrinogen by the process of its decomposition (33).

Aerobic exercise may reduce fibrinogen levels by increasing plasma volume. Therefore, regular aerobic exercise lowers fibrinogen levels by reducing catecholamine stimulation and increasing the muscle blood flow and the total blood volume (34). Reducing body fat percentage could decrease IL-6 produced in adipose tissue, and since IL-6 stimulates fibrinogen synthesis, its reduction leads to the reduction of fibrinogen (35). In a study on middle-aged men and women, Rothenbacher & et al. (2003) found out that acute-phase protein, such as CRP, ICAM-1, IL-6, and lipid profile are decreased by increasing time spent for exercise training from one hour to more hours per week (36).

After 6 months of aerobic exercise on women and men in different age groups, Huffman (2006) said that 6 months of aerobic exercise training do not bring about significant changes in CRP levels in the absence of major changes in diet (37). Thus, one import reason in the lack of statistical association of physical activity with reduced inflammatory markers could be the absence of other lifestyle modulators, such as diet and weight loss with exercise interventions. After 20 weeks of standard exercise training on 625 healthy men and women who lived a sedentary lifestyle, Lakka & et al. (2005) reported that exercise training was effective in people with high CRP levels (38). Accordingly, one reason for the effectiveness of exercise in reducing CRP levels can be the high CRP basal levels of the subjects. El-sayed & et al. (1995) examined the effects of a 12-week exercise training (30 minutes per session, 3 times/week) on fibrinogen levels of a group of 25 participants (aged 26-38 years). The results have shown that despite the increased maximal aerobic power and a 6% decrease in fibrinogen level in the exercise group, the decline was not statistically significant (39). The above mentioned reports on the impact of exercise training on plasma fibrinogen levels are somehow inconsistent with the current study. This inconsistency may stem from differences in the study groups, assessment methods, basic inflammatory markers, and study plan. Hamedi nia & et al (2007) studied the impacts of 13 weeks of aerobic exercise, three sessions per week, at the intensity of 75-85% maximum heart rate. The results of this research indicated a significant decrease in the CRP and WBC levels (40). It is, of course, worth mentioning that the subjects of this study were middle-aged obese men. For this reason, the ground serum levels of CRP and WBS were significantly higher than lean men. In 2006, Ergün studied middle-age healthy men in order to evaluate the long term effects of regular exercise (three times per week). He provided the participants (n = 32) in experimental group with 80 minutes of regular exercise training (a combination of several sports). Despite significant difference in the levels of uric acid, glucose, and LDL between the two groups, no significant difference was observed in the levels of CRP and fibrinogen (41). The contradictory results may be due to the basic levels of inflammatory markers, and the effect of exercise type and intensity on the endothelial function.

Boghrabai & et al. (2012) also investigated the impacts of moderate-intensity exercise on the serum levels of pro-inflammatory cytokines. The subjects, divided into an obese and a lean group, performed three 30-minutes aerobic exercise sessions per weeks for three months on a treadmill at 65-75% of their maximum heart rate. They suggested that the decrease in the levels of IL-6 was observed only in the lean participants with a significant reduction in the IL-6 level as compared to TNF levels and decrease in adipose tissue (42). Friednereich & et al (2007) also examined the inflammatory marker changes and the effect of a yearlong aerobic exercise intervention among women. After 12 months of physical activity, he observed a significant statistical difference in the levels of CRP in the exercise group in comparison with the control group. Although the IL-6 and TNF-α levels decreased, no significant difference was observed between the two groups. They concluded that the decreased CRP level was due to the body fat loss as a result of physical activity (43). Some differences between the present study and the previous researches are generally due to the differences in statistical population, age groups, intensity and duration of exercise, type of exercise, diet, basic inflammatory markers, and the lifestyle of individuals.

In view of the findings of previous researches along with the current study, regular aerobic exercise is likely to decrease the cytokine production in adipose tissues, muscle, and mononuclear cells. It probably increases antioxidant capacity, causes weight loss, improves the endothelial function, and induces a significant decrease in cardiovascular inflammatory markers. Therefore, it is possible to reduce inflammatory markers related to cardiovascular disease and decrease the risk of atherosclerosis in middle-aged sedentary women by doing a period of regular aerobic exercise training while applying the overload principle and intensity. More researches on the impacts of aerobic exercise training with different intensity, duration, and frequency than the present study and also with exerting control on the diet of the predictive markers in cardiovascular diseases are necessary.

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