The Effects of 8-Week Aerobic Exercises on Serum Levels of Cell Adhesion Molecules among Middle-Aged Women

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Abstract

Introduction: Cell adhesion molecules and inflammation mediators ramp up the activities of vascular endothelial, and researchers consider them as new predictive markers in cardiovascular diseases. With decreasing inflammation, physical
activity can reduce coronary heart disease (CHD) risk. The study was aimed to investigate the effect of one period of selective aerobic training on serum levels of ICAM-1, VCAM-1, and E-selectin in middle-aged women. **Methods:** Twenty-four healthy middle-aged women participated in this quasi-experimental research. They were equally divided into two groups, control group and experimental group. Subjects in experimental group performed exercise training at increasing intensity of 50 to 75% of their maximum heart rate for eight weeks and three sessions per week for 40 minutes. Blood samples were drawn from both groups twice (24 hours before and 24 hours after the training) in order to measure the intended factors. 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<0.05). Normality of the data was checked by using the Kolmogorov Smirnov test. **Results:** Significant difference in the pre-test and post-test mean score of control and experimental groups was observed in serum levels of ICAM-1 and E-selectin (p = 0.005 and p = 0.045 respectively), whereas no change was observed in VCAM-1 level (p = 0.093). **Conclusion:** The results of the current study indicated that a regular aerobic exercise training while applying overload principle and intensity decreases inflammatory markers related to the incidence, prevention, and control of the cardiovascular diseases, and also reduces the risk for atherosclerosis. **Keywords:** Aerobic exercise, Cell adhesion molecules, Middle-aged women

1. Introduction

Accurate prediction of the risk for cardiovascular disease (CAD) plays an important role in preventing its progression(Turk & Laughlin, 2004). Epidemiological studies indicate that the prevalence of atherosclerosis is increasing all over the world because of the adoption of Western life-style and it will reach the epidemic levels in the coming decades(Bonow, Smaha, Smith, Mensah, & Lenfant, 2002). According to a report by American Heart Association, the underlying cause of cardiovascular diseases is inflammation, and the systemic inflammation plays a central role in the progression and development of atherosclerosis (Abramson & Vaccarino, 2002). Atherosclerosis is associated with inflammation, so that the attachment of circulating leukocytes to endothelium in response to the chemotactic cytokines released by blood vessel cells is one of the first steps in the development of atherosclerosis. Endothelial adhesion molecules appear on the surface of activated endothelial cells and cause the entry of inflammatory cells into the arterial wall (Eschen, Christensen, Toft, & Schmidt, 2005). The studies on the evaluation of suitable inflammatory markers associated with atherogenesis have been increasing in recent years. Since the adhesion of monocytes to endothelium via vascular cell adhesion molecule (VCAM-1),
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intercellular adhesion molecule (ICAM-1), and E-selectin is the first marker in atherogenesis, special attention has been paid to them and many studies have reported a relation between adhesion molecules and acute or chronic atherosclerosis vascular disease (Peter et al., 1997). Many researchers believe that the increased level of soluble adhesion molecules is associated with the increased risk of infraction in normal subjects and patients with coronary artery disease (CAD) (Malik et al., 2001).

Selectins cause the initial rotation of leukocytes across the endothelial. ICAM-1 serves an important role in the leukocyte movement and adhesion along the endothelial, and an inflammatory condition increases the molecules (Gearing & Newman, 1993). The adhesion of circulating leukocytes to vascular endothelial cells and their migration into the subendothelial spaces are among the main developmental processes of atherosclerosis (Albelda, Smith, & Ward, 1994). It is also confirmed that chronic endothelial activation often shows its dysfunction, which plays an integral role in the incidence of atherosclerosis and cardiovascular diseases (Ross, 1999).

To date, many studies have been carried out investigating the effect of exercise training on the inflammatory cardiovascular risk markers and the adhesion to vascular endothelial cells. Signorelli & et al. (2003) investigated the changes in blood cytokine and ICAM-1 levels in patients with peripheral artery disease after treadmill exercise testing. The results indicated lower levels of IL-1β, TNF-α, ICAM-1, VCAM-1, P&E-selectin in patients as compared to the control group, and after the exercise testing the above-mentioned variables showed a significant increase. These results confirmed that the increased activity of white blood cells is an indication of systematic atherosclerosis, because the inflammatory markers are elevated in the condition of mechanical blood pressure (Signorelli et al., 2003). Adamopoulos & et al. (2001) studied the effect of 12 weeks of exercise trainings on peripheral inflammatory markers in patients with chronic heart failure and said that the performance of exercise at 70 to 80% maximum heart rate on a bicycle ergometer for 30 minutes a day, five days a week significantly reduces the inflammatory markers (TNF-α, ICAM-1, and VCAM-1) (Adamopoulos et al., 2001).

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. Hence, the accurate prediction of cardiovascular disease risk can play an important role in the prevention of such diseases. So far, researchers have not been able to get a certain result about the changes of these inflammatory markers caused by exercise training and replacing with traditional markers predictive of cardiovascular disease. Although it has been proven that the exercise training can decrease the inflammation, more studies have to be done to find out the mechanism of this reduction, intensity, and the time of physical activity which causes the most reduction in the inflammation. For this reason the current study investigates the effects of eight-week aerobic exercise trainings with certain intensity on the
changes of adhesion molecules (E-selectin, VCAM-1, and ICAM-1) in the middle-aged women.

2. Materials and methods

Inactive middle-aged women as well as some cardiovascular inflammatory markers (E-selectin, VCAM-1, and ICAM-1) have been studied in this quasi-experimental and functional research. After the announcement for participation in the study, 120 middle-aged women expressed willingness to take part in the research. Following 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 exercises. These twenty participants were equally divided into two distinct groups: exercise group (mean BMI: 28.92) and control group (mean BMI: 27.89). Before launching the physical activity, height, weight, body mass index, resting heart rate, and anthropometric data were measured and recorded in individual forms. The measurements were taken in order to homogenize the subjects.

The Subjects in exercise group began physical activities in a gym in accordance with exercise protocol three times a week (every other day) for a period of 8 weeks, with the aim 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 warm-up, followed by 40 minutes of main 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 F1nt, 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 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-Smirnov 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.

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

<table>
<thead>
<tr>
<th>Control Group</th>
<th>Aerobic Training Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICAM-1(ng/ml)</td>
<td>5.28±23.40</td>
</tr>
<tr>
<td>VCAM-1(ng/ml)</td>
<td>6.97±28.09</td>
</tr>
<tr>
<td>E-selectin (ng/ml)</td>
<td>0.55±3.83</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Pretest</th>
<th>Post test</th>
<th>t</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICAM-1(ng/ml)</td>
<td>Control</td>
<td>230.85±84.14</td>
<td>236.13±83.89</td>
<td>-0.782</td>
</tr>
<tr>
<td></td>
<td>Training</td>
<td>253.19±106.47</td>
<td>218.46±78.76</td>
<td>3.140</td>
</tr>
<tr>
<td>VCAM-1(ng/ml)</td>
<td>Control</td>
<td>508.62±117.29</td>
<td>515.60±125.80</td>
<td>-0.860</td>
</tr>
<tr>
<td></td>
<td>Training</td>
<td>543.17±120.48</td>
<td>528.47±121.27</td>
<td>1.581</td>
</tr>
<tr>
<td>E-selectin</td>
<td>Control</td>
<td>26.41±7.53</td>
<td>26.96±7.103</td>
<td>-0.497</td>
</tr>
<tr>
<td>(ng/ml)</td>
<td>Training</td>
<td>27.31±8.31</td>
<td>24.05±8.07</td>
<td>2.334</td>
</tr>
</tbody>
</table>

Significance was set at P<0.05.

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 and Table 2 presents the Dependent t test results on control and exercise group. The mean difference between the pre-test and post-test in the inflammatory marker ICAM-1 levels in exercise group was -34.73 while it was 5.28 in the control group, VCAM-1 levels were -14.69 and 6.97 in exercise and control group, respectively, and the levels of E-selectin in exercise group were -3.23 and 0.55 in the control group.

As table 3 and the results of independent t-test show, after 8 weeks of aerobic exercising, a significant increase was observed in the mean difference of pre-test and post-test of control and exercise group in the levels of ICAM-1 (p = 0.005) and E-selectin (p = 0.045), but no significant difference was observed in the VCAM-1 levels (p = 0.093).
Table 3. Independent t test results on control and exercise group

<table>
<thead>
<tr>
<th></th>
<th>Levene's Test</th>
<th>T- test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>Sig</td>
</tr>
<tr>
<td>ICAM-1(ng/ml)</td>
<td>1.454</td>
<td>0.241</td>
</tr>
<tr>
<td>VCAM-1(ng/ml)</td>
<td>0.281</td>
<td>0.601</td>
</tr>
<tr>
<td>E-selectin (ng/ml)</td>
<td>0.455</td>
<td>0.507</td>
</tr>
</tbody>
</table>

Significance was set at P<0.05.

4. Discussions

The results indicate that 8 weeks of aerobic exercise cause significant changes in the serum levels of E-selectin and ICAM-1 in the participants in the exercise group as compared to the control group, though there were no observable difference in the serum VCAM-1 levels between the two groups. The results of the study confirm findings from previous studies that a regular physical activity and cardiorespiratory fitness are associated with lower cardiovascular inflammatory markers (Adamopoulos et al., 2001).

Inflammation serves a central role in different stages of atherosclerosis, such as early formation and progression of atheroma, plaque instability and rupture, and artery stenosis followed by angioplasty (Michishita, Shono, Inoue, Tsuruta, & Node, 2008). The process of inflammation includes the adhesion of leukocytes, neutrophils and monocytes to endothelial cells followed by the transmigration of leukocytes through the endothelium in the arterial wall (Libby & Simon, 2001). Previous reports have described that inflammatory markers are involved in early stages of atherogenesis, i.e. atheroma plaque formation, including causing arterial endothelial dysfunction (Heinrich, Castell, & Andus, 1990), formation of fatty pads and platelets (Michishita et al., 2008), and the blood clots (thrombus) that cause heart attack and stroke (Libby & Simon, 2001). ICAM-1 and VCAM-1, members of the immunoglobulin superfamily, are key factors of gradual leukocytes infiltration in inflammatory damages and the amount of endothelial activity (Ito et al., 2002).

Davis & et al. (1993) investigated the expression of adhesion molecules ICAM-1, VCAM-1, PECAM, and E-selectin in samples of human coronary arteries (normal artery (n = 12), predominantly fibrous plaques (n = 23), and plaques containing extracellular lipid (n = 26)). They observed that ICAM-1 and E-selectin are located in focal segments of the endothelium and normal arteries showed no VCAM-1 staining. Findings of this study indicated that ICAM-1 was strongly and constantly expressed by all types of plaques and macrophages along the endothelium. E-selectin expression was confined to endothelial cells and occurred on the surface in 35 percent of fibrous and 20 percent of lipid-containing plaques. Adventitial vessels adjacent to plaques showed endothelial expression of
ICAM-1 and E-selectin. Altogether, the expression of cell adhesion molecules is an important element in the inflammatory components of atherosclerosis and contributes to monocyte and lymphocyte activity (Davies et al., 1993).

Immobility with subsequent weight gain put individuals at risk for metabolic syndromes, such as type 2 diabetes, high blood pressure, and abnormal fat distribution, and it also creates lipid profiles and defective inflammatory which can be effective in the developmental process of atherosclerosis as well (Sharman & Volek, 2004). Long-term regular exercise produces known cardiovascular benefits which reduce the prevalence of cardiovascular disease in healthy people and patients, in case that an intense exercise increases the pro-inflammatory cytokines and these pro-inflammatory cytokines lead to the increased gene expression and serum levels of leukocyte adhesion molecules which increase the response of monocytes in endothelial cells (Simpson, Florida-James, Whyte, & Guy, 2006). Regular physical activity probably has a protective effect against cardiovascular disease. Exercise training directly affects cardiovascular disease by augmenting plasma and blood levels, reducing blood viscosity, and increasing stroke volume and VO2 max (Geffken et al., 2001). However, lower levels of inflammation may be associated with antioxidative effects of exercise training due to their compatibility with each other. Scientific evidence suggests that aerobic and endurance training significantly decreases the oxidative stress by increasing the antioxidative capacity (Somani & Husain, 1996). Regular exercise trainings, also, inhibits the adipose tissue release of cytokines by reducing sympathetic stimulation, and consequently cell adhesion molecule concentrations decrease (Ding et al., 2005).

Hiruki & et al. reported the relationship of ICAM-1 and E-selectin with obesity, particularly central obesity (Ito et al., 2002). Regarding the mechanisms underlying the post-exercise decreased adhesion molecules, it seems that the reduction is due to the loss of body fat in subjects. Adipose tissue plays an important role since it is responsible for pro-inflammatory cytokine secretion (Tracy, 2001) and both IL-6 and TNFα are expressed by adipose tissue (Kern et al., 1995). They also affect the endothelial function (Bhagat & Vallance, 1997) and stimulate the production or gene expression of chemokines and adhesion molecules (Jang, Lincoff, Plow, & Topol, 1994). Reduction of body fat appears to result in reduced TNF-α and IL-6 and reduction of these cytokines lowers the production and secretion of adhesion molecules. The decline of ICAM-1 and E-selectin as a result of physical activity might be related to the reduction of C-reactive protein, because the synthesis of CRP in the liver is largely under the control of IL-6 (Heinrich et al., 1990). Besides, the study of Pasceri & et al. (2000) indicated that CRP increases the expression of ICAM-1 and E-selectin in endothelial cells (Pasceri, Willerson, & Yeh, 2000). Another probable mechanism underlying the decline of adhesion molecules as a result of exercise trainings can be related to the free oxygen radicals. Investigations have revealed that free oxygen radicals cause adhesion molecules expression (Adamopoulos, Parissis, & Kremastinos, 2003). It has also been proposed that exercise training enhance the antioxidant defense system (Rush, Turk, & Laughlin, 2003). Therefore, the
improvement of antioxidant defense system reduces the free oxygen radicals and subsequently the adhesion molecules. Although a handful of studies have examined the association between regular physical activity and inflammatory markers, their findings on the effects of aerobic exercise training on plasma levels of adhesion molecules, a reliable indicator for evaluating general inflammation, are contradictory. To investigate these markers, Wand & at al. (2005) performed 30 minutes of daily aerobic exercise (jogging on a treadmill), and they observed significant decrease in ICAM-1 level and pro-inflammatory cytokines. They concluded that reduction of inflammatory markers inhibits the inflammatory brain damage in young rats (Wang, Yang, & Yu, 2001). Hamedi nia & et al. (2007) also carried out a research on relatively heal thy obese men assessing the effects of endurance and resistance exercise on circulating soluble adhesion molecules. The study observed that aerobic exercise significantly decreased percentages of ICAM-1 levels (17.69%) and E-selectin (27.6%) and resistance training significantly reduced them (26.75% and 30.2% respectively). Findings of his studies can be considered consistent with those of the current study (Hamedinia MR, 2007).

In a study aimed to investigate the effects of aerobic exercise on the systematic inflammatory response in patients with coronary artery disease for cardiac rehabilitation, Illic & et al. (2007) studied 29 male patients and 23 female patients with stable coronary heart disease. The subjects underwent two stages of regular aerobic exercise. The results of the study showed that six weeks of aerobic training did not affect the number of leukocytes, and no significant difference was observed in the ICAM-1 level of patients who underwent the two-stage regular aerobic exercise and those who didn’t. Though, significant difference in the VCAM-1 and CRP levels was observed (Illic et al., 2007). The difference between results of the present study and those of Illice could be due to different subjects and types of intervention.

5. Conclusion

Considering the results of previous researches and the current one, regular aerobic exercise is probably associated with decreased cytokine production by adipose tissue, muscle and mononuclear cells, increased antioxidant capacity, weight reduction and improvement of endothelial function and significant decline in cardiovascular inflammatory markers. Hence, it is possible to reduce the inflammatory markers in the incidence of cardiovascular diseases, and reduce the risk of atherosclerosis among sedentary middle-aged women by regular aerobic exercise training and with applying overload principle and intensity. Further researches on the effects 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.
References


[26] Signorelli, S. S., Mazzarino, M. C., Di Pino, L., Malaponte, G., Porto, C., Pennisi, G., et al. (2003). High circulating levels of cytokines (IL-6 and TNFalpha), adhesion molecules (VCAM-1 and ICAM-1) and selectins in patients with peripheral arterial disease at rest and after a treadmill test. Vasc Med, 8(1), 15-19.


Received: February 18, 2013