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Effect of Aerobic Exercise Program on Inflammatory Parameters and Framingham Risk Score in High Cardiac Risk Patients

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ABSTRACT

Objectives: The aim of this study was to determine the effects of an 8-week aerobic exercise program on the inflammatory parameters and the Framingham risk score in patients with high cardiac risk.

Methods: The patients with high cardiac risk according to National Cholesterol Education Program Adult Treatment Panel-3 criteria were studied. Totally, 50 patients were included in the study, and 25 (50.0%) patients were applied to an aerobic exercise program for 30 min/day for 3 days a week. There were 25 (50.0%) patients in the control group.

Results: The study included 50 patients and the mean age of the patients was 61.0±5.0 years. At the end of the study, hs-CRP levels decreased in the exercise group [1.1 (0.1–4.2) mg/dL vs 0.9 (0.1–3.8) mg/dL] and in the control group [1.2 (0.2–4.3) mg/dL vs 1.0 (0.1–4.0) mg/dL] (<0.001 and p=0.008, respectively). Homocysteine levels [13.4 (4.8–27.3) µmol/L vs 11.8 (4.0–21.6) µmol/L] decreased in the exercise group, but they did not change in the control group [13.2 (5.1–28.2) µmol/L vs 13.4 (4.4–27.1) µmol/L] (p<0.001, and p=0.776, respectively). Fibrinogen levels decreased in the exercise group [4.1 (1.6–5.9 g/L vs 3.4 (1.2–5.0) g/L], but they did not change in the control group [4.0 (1.4–6.1) g/L vs 3.9 (1.4–5.7) g/L] (p<0.001 and p=0.348, respectively). The Framingham risk score decreased in the exercise [24.1±2.9 vs 20.3±3.3] and control groups [22.8±2.7 vs 19.5±2.7] (p<0.001 and p<0.001, respectively).

Conclusion: Regular aerobic exercise is effective and safe to prevent probable cardiovascular events in high cardiac risk patients in addition to medical therapy.

Keywords: Exercise, C-reactive protein, fibrinogen, homocysteine

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INTRODUCTION

Coronary artery disease (CAD) is the most common cause of death among men over 45 years old and women over 65 years of age in developing countries.[1] CAD is the most common type of cardiovascular disease in adults.[2] While CAD prevalence tends to decrease in developed countries, it is increasing in developing countries in Eastern Europe and Asia.[3,4] Defined as classic risk factors for CAD, age (men ≥ 45 years, women ≥ 55 years or early menopause), family history of CAD, active smoking, hypertension (blood pressure > 140/90 mmHg or receiving antihypertensive therapy), hypercholesterolemia (total cholesterol > 200 mg/dL, LDL cholesterol > 130 mg/dL), and low HDL cholesterol value (<40 mg/dL). Despite the development of new pharmacological agents for basic risk factors for atherosclerosis, the desired reduction in deaths due to cardiovascular diseases has not been achieved. Currently, there is a need

for new applications that support the treatments used and increase their effectiveness. In addition to the classical risk factors, the new factors defined also affect the risk status of the person. These include obesity, physical inactivity, atherogenic diet, subclinical atherosclerosis, lipoprotein (a) and homocysteine elevation, and prothrombotic and proinflammatory factors. Directing patients to exercise and explaining the harms of physical inactivity is a simple and effective method that can be applied especially in primary healthcare institutions. In this way, the clinical benefit will be obtained at every stage.

In this study, it was aimed to evaluate the effect of exercise on the inflammatory parameters and the cardiac risk score in patients with high cardiac risk.

METHOD

This study is a prospective clinical study programmed to evaluate the changes in the cardiac risk levels and inflammatory parameters after an 8-week aerobic exercise program in cardiac high-risk patient groups compared with the pretreatment and to investigate the differences between the group receiving only medical therapy and not exercising. Patients who were admitted to the cardiology outpatient clinic of Kocaeli University Research and Practice Hospital with a high risk for cardiovascular disease were included in this prospective study. Exclusion criteria from the study are age ≥75 years, patients with ischemia/chest pain during the exercise test, history of stroke, recent acute inflammatory event, another systemic disease that requires treatment, uncontrolled hypertension, and physical restrictions that will prevent aerobic exercise work on the walking belt.

Detailed anamnesis of the patients was taken, and physical examinations were performed. The patients were asked about age, gender, height, weight, pharmacological treatments used, chronic disease status, systemic diseases, and exercise habits. Ten-year cardiac risks were calculated according to the Framingham risk score.[5] The study was described to patients who were found to be at high risk according to the third report of the National Cholesterol Education Program, Adult Treatment Panel (NCEP-ATP III) criteria (equivalent to CAD – diabetes mellitus, peripheral artery disease, abdominal aortic aneurysm, carotid artery disease, or 10-year cardiac risk of ≥20%).[5]

All patients gave blood samples from the left antecubital vein at least 12 h after fasting at the beginning and end of the study. Samples were sent to determine the high sensitivity C-reactive protein (hs-CRP), fibrinogen, and homocysteine levels in the biochemistry laboratory of our hospital. Before the study, a stress test was applied to the patients with Quinton 710 model device according to Bruce protocol. In the ECG recorded during exercise, the test was considered positive in the case of developing horizontal or down-sloping depression of ≥1 mm after 60–80 ms after the J segment of the ST segment or chest pain during exercise.

AHA-NCEP-ATP III step 2 diet was organized by recommending lifestyle changes (not smoking and drinking alcohol, exercising regularly) for the modification of cardiac risk factors. Antilipidemic treatment was initiated for all patients according to blood lipid profile levels and guidelines. The data available after the program were compared with baseline values and patients in the medical treatment group.

NCEP-ATP III guide uses the Framingham risk score to determine the risk of CAD.[5] According to this scoring, the risk factors to be used in determining the treatment target are gender, age, total cholesterol, HDL cholesterol, systolic blood pressure, and smoking of the person. Subjects are scored individually according to these variables. According to the total score, the risk of having a 10-year cardiac event lower than 10% was classified as low, those between 10% and 20% are classified as medium, and those above 20% are classified as high risk.

Routine biochemical examinations were carried out in the Aeroset (Abbott) device of the central laboratory of our hospital by spectrophotometric method. Fibrinogen was studied using the coagulometric method in STA compact device. Homocysteine was detected in the immulite 2000 (DPC Diagnostics, LA, USA) device, and hs-CRP level was determined using the nephelometric method on Beckman Array 360 Nephelometer device (Beckman Coulter, Miami, USA).

To obtain the most appropriate physiological and health beneficial effects from the exercise program, it should be tailored to the individual.[6] This application includes the type, duration, and progression of the exercise. Each program should consist of three phases as warm-up, exercise, and cool-down processes. The exercise program starts with low-intensity aerobic exercise for 5–15 min and continues with joint range of motion and stretching exercises. It should consist of exercises that are 20 beats/min lower than the number of heartbeats desired to be achieved in normal exercises.

For an effective and reliable exercise program, exercise sessions should be created with appropriate intensity, duration, and frequency.[5] The intensity must be above a certain threshold. Heart rate and VO2 maximum (VO2max) methods can be used to determine exercise intensity. In the heart rate method, the maximal heart rate is calculated according to age (220 - age). VO2max is the maximum amount

of oxygen used by a person during the maximal dynamic exercise. This indicates the amount (mL/min/kg) of oxygen used per person during exercise, in liters or milliliters per kilogram. During exercise, respiratory gases are measured with a spirometer. Oxygen consumption when exercise is terminated is considered to be the VO2max value.

The exercise is finished with a low-intensity exercise that takes 5–10 min.[5] A gradual return of heart rate and blood pressure to pre-exercise levels is tried to be achieved. In this phase, the pump activity of the muscle is maintained after intense exercise, thus blocking blood accumulation.

Patients to be taken to exercise were allowed to rest for at least 10 min before the program. The exercise program was performed on the Star Trac 3900 model walking belt for 8 weeks, 3 days a week for 30 min (5 min of warm-up, 20 min of maximum effort, and 5 min of cooling). The severity of aerobic exercise was calculated using the maximum heart rate method. The high-intensity aerobic exercise program was arranged to be 70%–89% of the target heart rate. Eligible patients started the program at a speed of 2 km/h and a 0-degree slope. The speed was increased by 0.5 km/h every minute. When the targeted heart rate was reached, the speed and slope were kept constant, and the exercise was continued. The slope was increased to 5 degrees when patients tolerated 5 km/h speed. During the exercise program, blood pressure was measured manually at an interval of 5 min.

All data were analyzed in SPSS for Windows 17 statistical software program. Descriptive data were presented as frequency and percentage for categorical variables and mean, standard deviation, median, minimum, and maximum values for continuous variables. Continuous variables between dependent groups were compared using the paired t-test and the Wilcoxon t-test, according to their distribution. Student's t-test and the Mann–Whitney U test were used to compare continuous variables with and without normal distribution, respectively. Categorical variables were compared using the Chi-squared test. A p-value less than 0.05 was accepted statistically significant.

RESULTS

A total of 50 participants were enrolled in the study of which 25 (50.0%) patients were determined to be in the exercise group and 25 (50.0%) patients in the control group.

There was no significant difference between the exercise and control groups in terms of age and gender (p=0.974 and p=0.098). Demographic characteristics, anthropometric measurements, and medical treatments in the exercise and control groups are summarized in Table 1.

At the beginning of the study, there was no significant difference between the exercise and control groups in terms of blood inflammation parameters, exercise time, and the Framingham risk score (p>0.05). Blood inflammation parameters, the Framingham risk score, and exercise time in the exercise and control groups at the beginning of the study are summarized in Table 2.

Table 1. Demographic characteristics, anthropometric measurements, and medical treatments in the exercise and control groups

	Exercise group (n=25)	Control group (n=25)	p
Age (years)	61.0±5.0	62.0±5.0	0.974*
Gender			
Male	3 (12.0)	7 (28.0)	0.098†
Female	22 (88.0)	18 (72.0)	
BMI (kg/m^2)	34.5±7.3	33.2±7.9	0.965*
Body weight (kg)	88.7±18.6	85.0±20.7	0.823*
Waist circumference (cm)	101.1±12.5	103.6±12.7	0.981*
Hip circumference (cm)	116.6±12.8	108.5±10.4	0.015*
Waist to hip ratio	0.8 (0.7–1.2)	0.9 (0.7–1.3)	0.850†
Diabetes mellitus	19 (76.0)	21 (84.0)	0.875‡
Hypertension	15 (60.0)	17 (68.0)	0.689‡
Smoking	23 (92.0)	15 (60.0)	0.008‡
Statin use	21 (84.0)	24 (96.0)	0.384‡
Fibric acid use	5 (20.0)	9 (36.0)	0.146‡

BMI: Body mass index.

Data are presented as mean±standard deviation, n (%) and median (minimum–maximum).

*Student's t-test, †Mann–Whitney U test, ‡Chi-squared test.

Table 2. Blood inflammation parameters, the Framingham risk score, and exercise time in the exercise and control groups at the beginning of the study

	Exercise group (n=25)	Control group (n=25)	p
hs-CRP (mg/dL)	1.1 (0.1–4.2)	1.2 (0.2–4.3)	0.481*
Fibrinogen(g/L)	4.1 (1.6–5.9)	4.0 (1.4–6.1)	0.796*
Homocysteine (μmol/L)	13.4 (4.8–27.3)	13.2 (5.1–28.2)	0.557*
Framingham score	24.1±2.9	22.8±2.7	0.450†
Exercise time (s)	410.3±133.1	412.1±80.4	0.731†

CRP: C-reactive protein.

Data are presented as median (minimum–maximum) and mean±standard deviation.

*Mann Whitney U test, †Student's t-test.

At the end of the study, a decrease was found in hs-CRP and Framingham score in the both groups, while a significant decrease were observed in homocysteine and fibrinogen levels only in the exercise group. The changes in inflammation parameters, Framingham risk score, and exercise time in the exercise and control groups are summarized in Table 3.

DISCUSSION

A sedentary lifestyle causes serious health problems. High blood pressure, obesity, diabetes, and CAD risk factors increase especially in middle age and above.[7] Aerobic exercise has protective properties for atherosclerosis by inhibiting vascular smooth muscle cell proliferation, platelet aggregation, and monocyte adhesion by increasing nitric oxide. It also regulates the endothelial function and aerobic metabolism of skeletal muscle. Exercise has been shown to increase capillary density and heart volume, and reduce heart rate.

Despite the beneficial effects of exercise and physical activity on inflammation, the same effect was not found in all types of exercises.[7,8] Different exercise types have different effects on inflammatory markers and coronary events that may develop. Although it was found that running, walking, and lifting weights decreased the risk of cardiovascular disease in a study in which 44452 men were taken, swimming and cycling seemed to be not effective.[8] In addition, another study conducted with 4072 people showed that aerobic dancing and jogging reduce inflammation more than other types of exercises.[7]

Hyperhomocysteinemia is commonly seen in the general population. The vast majority of these are in the form of a moderate increase in total homocysteine levels (5–30 µmol/L) and about 1% increase in severity (>30 µmol/L). Serious elevations indicate hereditary impairment in homocysteine degradation, while moderate elevations are observed in the C677T gene variation of the inadequate vitamin intake and methylenetetrahydrofolate-reductase enzyme.[9] The development of cardiovascular disease has been shown to increase in severe hyper-homocysteinemia and has led to the idea of counting the height of homocysteine as one of the cardiovascular risk factors. Homocysteine has been shown to induce endothelial cell damage, stimulate vascular smooth muscle cell growth, directly activate the coagulation cascade, increase LDL cholesterol oxidation, and lead to artery wall storage.[10] The potential of moderate increases to lead to increased risk remains uncertain.[11] It has been found that homocysteine levels increase with physical inactivity, smoking, body mass index increase, alcohol, and caffeine use.[12,13] However, the effect of exercise on homocysteine levels is still controversial. In some studies, it was determined that the level of homocysteine increased as a result of increased protein turnover and catabolism in the liver after acute exercise.[13] Therefore, vitamin B and folate supplements are recommended especially for those who do heavy aerobic exercise. In addition, there are studies showing that homocysteine levels may decrease or do not change with exercise.[13] In another study, it was suggested that there was a 12% decrease in homocysteine levels with a 12-week aerobic exercise program, thus the cardiac risk could be reduced by 20%.[14]

Plasma fibrinogen is an acute phase reactant synthesized in the liver, and its synthesis can increase 20 times with strong inflammatory stimulation. It is a major coagulator protein that plays an important role in platelet aggregation and blood viscosity. The Framingham study has shown that high fibrinogen levels increase the risk of cardiovascular disease in men and women aged between 47 and 59 years.[15] In the studies conducted, it was seen that the incidence of cardiovascular disease is two to three times higher in patients with high fibrinogen levels. It has been shown that there may be a significant decrease in fibrinogen levels

Table 3. Changes in inflammation parameters, the Framingham risk score, and exercise time in the exercise and control groups

	Exercise group (n=25)			Control group (n=25)		
	Basal	8 weeks	p	Basal	8 weeks	p
hs-CRP (mg/dL)	1.1 (0.1–4.2)	0.9 (0.1–3.8)	<0.001*	1.2 (0.2–4.3)	1.0 (0.1–4.0)	0.008*
Fibrinogen (g/L)	4.1 (1.6–5.9)	3.4 (1.2–5.0)	<0.001*	4.0 (1.4–6.1)	3.9 (1.4–5.7)	0.348*
Homocysteine (µmol/L)	13.4 (4.8–27.3)	11.8 (4.0–21.6)	<0.001*	13.2 (5.1–28.2)	13.4 (4.4–27.1)	0.776*
Framingham score	24.1±2.9	20.3±3.3	<0.001†	22.8±2.7	19.5±2.7	<0.010†
Exercise time (s)	410.3±133.1	480.0±124.1	<0.001†	412.1±80.4	408.2±87.8	0.634†

CRP: C-reactive protein.

Data are presented as median (minimum–maximum) and mean ± standard deviation.

*Wilcoxon t-test, †Paired t-test.

with lifestyle changes involving exercise programs.[16] Its level has been observed to tend to decrease in physically active individuals.[17]

There are several different mechanisms of decreasing fibrinogen levels through exercise.[17] It contributes to the decrease of serum fibrinogen level by increasing the circulating plasma volume of the exercise. In addition, exercise decreases the amount of inflammatory fatty tissue and decreases the release of cytokines, which are acute phase reactants, and fibrinogen levels.

In a meta-analysis evaluating 25 studies, it was found that CRP, fibrinogen, and von Willebrand factor levels were found to be significantly lower in the exercise group.[18] Endurance exercise in healthy elderly individuals for 6 months has been found to result in a 13% decrease in fibrinogen levels, a 39% increase in tissue plasminogen actor levels, and a 58% decrease in plasminogen activator inhibitor-1 levels.[19] Additionally, such aerobic exercise programs, which provide a decrease in the fibrinogen level, can positively affect cardiovascular mortality.

In a study conducted, it was found that after the aerobic exercise program in middle-aged women, 10-year cardiac risk levels of patients decreased significantly according to the Framingham risk score.[20] It was seen that the aerobic exercise program reduces cardiac risk in line with previous studies, but similar changes were observed in the lifestyle change and medical treatment group. When we look at the results, although the exercise program is beneficial in risk modification, it suggests that it should be given with dietary and necessary medical treatment support.

CRP, which is a classic acute phase reactant, is a member of the pentaxin protein family in the immune response.[21] In the meta-analysis of 14 studies, individuals with the highest basal CRP level were found twice as risky for vascular events even after improvement for other risk factors.[22] A significantly increased vascular risk was found in patients with increased CRP levels even in the absence of hyperlipidemia.[23] It was observed that serum CRP levels decreased significantly with the aerobic exercise program, and serum CRP value decreased as exercise capacity increased.[24] In the acute period of exercise, IL-6 is secreted from contracted muscle cells and joints, and the CRP level may increase. When regular exercise is continued, this response is modified and serum CRP levels decrease.[25] In some studies, it was observed that CRP levels were not affected by the exercise program.[26] However, the general view is that exercise programs reduce CRP. It has been found that CRP level is directly related to subcutaneous and total body fat amount, frequency, and level of physical activity.[24,27] Greater CRP reduction in the exercise program group suggests that the inflammatory reaction regressed more with the aerobic exercise program and benefited more to reduce cardiovascular risk.

Significant benefits were obtained in blood values and in reducing the risk level in the patients participating in the study. The absence of exercise-related complications in patients shows that the exercise program performed under appropriate conditions is safe. Primary health care professionals should remind to all patients about the importance of exercise.

The limitations of our study include the low number of patients and relatively short follow-up. Besides, VO2max was also not used in our study. In addition, the high number of female patients in the aerobic exercise group prevented gender comparisons. Although the study was planned with 30 patients and 12 weeks in both groups. Due to the decrease in patient compliance in the following weeks, it was completed at the end of the 8th week and 25 patients each. It became difficult to obtain appropriate data because a few patients did not participate in the program regularly. The 8-week program was considered adequate as previous literature samples were available (3, 4, 6, 8, and 12 weeks).[28–30]

CONCLUSION

In patients who are considered to have a high risk of cardiac events, it seems effective and safe to implement regular aerobic exercise programs and to reduce cardiac risk in addition to medical treatment. This situation shows us that exercise practices should become widespread, and it is necessary to encourage people to exercise as a public health improvement program. Primary healthcare professionals should be more courageous in encouraging patients to exercise.

Disclosures

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