The effects of 8 weeks aerobic exercise on levels of homocysteine, HS-CRP serum and plasma fibrinogen in type II diabetic women

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Abstract: The risk of cardiovascular disease (CVD) is many times higher among people with diabetes. Presence of diabetes increases the risks of heart attacks and strokes in people up to 2 to 6 times. There are a lot of inflammatory markers predicting cardiovascular heart diseases, including homocysteine, high-sensitivity C-reactive protein (hs-CRP) and fibrinogen. The purpose of this study was to investigate the effect of 8 weeks of aerobic exercise on blood levels of inflammatory markers in diabetic women. Methods: Subjects consisted of thirty sedentary middle-aged women with diabetes who were randomly assigned to two groups of experimental (n = 15) and control (n = 15) groups. The program included eight weeks of aerobic exercise training (3 sessions per week, 60 minutes per session) with the intensity of 50 to 75 percent of maximal oxygen consumption. Homocysteine levels and hs-CRP and fibrinogen of blood were measured before and after exercise. Findings: Independent samples t-test analysis indicated a significant decrease in levels of homocysteine, hs-CRP and plasma fibrinogen in experimental group (P <0/05), but no significant change has been observed in control group. Conclusion: Thus, in general, regular aerobic training reduces the risk of stroke and improves health of diabetic middle-aged women by lowering homocysteine, fibrinogen and hs-CRP.

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1. Introduction

Type II diabetes and chronic inflammatory markers are strongly associated with increase of cardiovascular risk (1). Nowadays most preventions from the risk of CVD in people with diabetes, focus on the treatment of high blood pressure, reduction of cardiovascular risk factors, including LDL, hs-CRP and fibrinogen, as well as increase of HDL, tobacco cessation, nutrition therapy, and encouragement to do physical activities (2).

People with diabetes are at risk of myocardial infarction occurrence twice as much as common people. Also chances of survival of these individuals following cardiac events have been reported to be one time less than common people (2). Overall, diabetic women suffering from CVD, regardless of menopausal status, are between 4 to 6 times more at risk of developing CVD. While diabetic men are exposed to CVD 2 to 3 times more than those healthy men and women (3). Homocysteine is a small sulfur-containing amino acid which is synthesized in amino acid methionine and needs certain vitamins such as B12, B6 and folate for metabolism (4). Homocysteine is an amino acid in the body which is used to build proteins (structure and strength) of tissues. However, excessive amounts of it in blood may increase the risk of stroke and certain types of heart disease and blood vessel disease in arms, and legs (peripheral vascular disease). Homocysteine can also be useful in estimating the risk of peripheral artery diseases (4). High level of Homocysteine can cause numerous effects, including atherosclerosis, and cardiovascular problems and venous thrombosis (5). Clinical studies suggest that the increase in homocysteine to 5 mmol per liter is the same as increase of total cholesterol amount to 20 mg per deciliter. Several studies indicate that the relationship between homocysteine levels and atherosclerosis is stronger than the relationship between cholesterol and atherosclerosis (6,7). The most critical inflammatory indicator and a strong independent predictor of the risk of cardiovascular incidents has been introduced to be hs-CRP, the increase of which is associated with 2 to 5 times increased risk of cardiac events. CRP increases in people with excessive body fat. It is inversely associated with insulin sensitivity and directly related to the risk of Type II diabetes (8). Fibrinogen is a plasma glycoprotein that is produced in liver and is comprised of three polypeptide chains Aα, Bβ, and r. Similar to CRP, This molecule is

synthesized by liver cells under influence of the induction of Interleukin 6 (IL 6). Half-life of it is three to five days, and it plays a major role in platelet aggregation, endothelial damages, coagulation processes, blood cell aggregation and blood viscosity. When IL 6 levels of plasma increase during inflammation, fibrinogen levels rise, too (9). Nikbakht reported that physical activity does not have any impact on the concentration of fibrinogen and homocysteine levels in blood serum of active and inactive men, and there is no significant correlation between them (10).

Taghian declared that after a 12-week program of moderate-intensity aerobic exercise, homocysteine and CRP levels reduced in young women (11). Kadoglo investigated the effect of 6 months of aerobic exercise on blood sugar levels, hs-CRP, TNFα, IL-18, IL-10, BMI and adiponectin in diabetic patients and reported the optimal impacts of this training program. They showed that 8 weeks of regular aerobic exercise can reduce hs-CRP levels (12). Zoppini studied the effect of 6 months aerobic exercise of moderate intensity on hs-CRP and TNFα diabetic patients. The results suggested that the physical activity of moderate intensity did not create any changes in hs-CRP and TNFα (13). Baldochy showed that 12 months of aerobic - resistance exercise significantly reduces hs-CRP levels in diabetic patients (14). In recent decades researches conducted on the relationship between aerobic exercise , homocysteine, hs-CRP and fibrinogen levels have presented conflicting results. Some research have reported a direct relationship (11, 15, 16, 17) and some have indicated that there is no association (10, 18, 19). Because aerobic exercise has a very important role on cardiovascular disease prevention, it has always been sought for as a cure for many diseases, especially diabetes and cardiovascular disease. Therefore research in this case can lead to some interesting results. It is worth noting that no research have been found in the country (Iran) in relation to aerobic exercise and levels of homocysteine, hs-CRP and fibrinogen in women with type II diabetes. Due to the high number of people with diabetes and those at risk of heart disease in Iran, the aim of the present study is to study the effect of 8 weeks of aerobic exercise on homocysteine, hs-CRP levels and plasma fibrinogen of type II diabetic women.

2. Method

This study used a quasi-experimental and applied design for research. The research included 30 subjects who were aged and inactive women. They were selected according to the research recall from diabetic population of Shahid Qodsi shahr Clinic in Mashhad. After examining them by a cardiologist, obtaining their consent for participation in the research and taking blood samples, we randomly divided them into two groups, control group (n = 15) and experimental group (15 people). Exercise program consisted of 8 weeks (3 sessions per week) aerobic exercise with intensity of 60% to 75% of maximum heart rate of the subjects. Heart rate was calculated for each subject using the formula 220 minus age. It was controlled by using Polar heart rate meter (model 1000 Pvks made in Germany). Each session consisted of 15 minutes of warm-up with stretching and exercise, the main body of exercise (including 35 minutes of running at a distance of 1/5 mile at a constant speed and intensity of 50% to 75% of maximum heart rate) and a 10 minute cool-down with stretching and running softly. Before and after the workout, fat levels, homocysteine, hs-CRP and fibrinogen of subjects were determined to evaluate the effect of exercises. In order to control the diet to prevent interference on measured values (homocysteine, fibrinogen, and hs-CRP), 3 days prior to the exercise protocol, subjects provided researchers with their diets.

Then by review and assessment of calorie of meal by a researcher and a nutritionist, the diet to be followed before the blood sample was provided. Also prior to bloodletting at the beginning of training, the subjects were advised to avoid eating and doing vigorous physical activity for 14 hours. (Drinking water was permitted). Blood samples were collected from subjects' left brachial vein in sitting position. They were gathered in tubes containing sodium citrate for plasma separation and tubes containing anticoagulant for serum separation. Then they were sent to medical diagnosis laboratory for analysis. To measure homocysteine levels With ELISA Method, Homocysteine test kit made by Pars Co. from Iran was used. Hs-CRP level was measured by using a special kit made by Pars Co. (Tehran - Iran).

This kit has been designed to measure CRP in the range of 0/1 to 20 mg per liter and the minimum hs-CRP level which can be measured is at least 0/1 mg per liter. Plasma fibrinogen was measured using specific ELISA kit. Actions taken on the data included descriptive statistics (mean and standard deviation) and inferential statistics. Kolmogorov-Smirnov test was used to check the normality of data distribution. After determining the normal distribution of all data, paired samples t-test was implemented to compare the intra group results and to check the intergroup results independent samples t-test was applied. The data obtained were analyzed using SPSS version 17. The level of significance (05/0> P) was considered.

3. Findings

Two groups of subjects were matched in terms of age, height, weight, BMI and body fat percentage. (Table 1) Paired samples t-test results showed that in experimental group, weight, BMI and body fat percentage has dropped significantly.

Also, homocysteine levels, hs-CRP and fibrinogen have declined significantly.

None of these variables had a significant change in control group (05/0P <) (Table 2). Independent samples t-test revealed that the amount of weight loss, BMI and body fat percentage in subjects of experimental group was significantly higher than those (subjects) in the control group. Also reduction rate in the amount of homocysteine levels, hs-CRP and fibrinogen in subjects of the experimental groups was significantly higher than in the subjects of the control groups (P<0/05) (Table 2)

Table 1: description of subjects' characteristics and the differences between the two groups before the start of the study.

Variable	Experimental group	control group	difference amount
Age	41.46± 3.1	41.06± 4.0	0.763
Height	1/64± 0/05	1/64± 0/05	0/93
Weight	70.64±7.48	72.6± 7.59	0.483
BMI	25.59± 1.95	26.60±1.95	0.168
Fat	2.35 ± 30.13	29.77± 2.5	0.688

Table 2: The rate of changes in dependent variables as a result of aerobic exercise

P	Control group				Experimental group		variable
	P2	Post-test	Pre-test	P1	Post-test	Pre-test	
0.000	0.055	72/9±7/62	72/6±7/59	0.000	68/72±7/16	70/64±7/48	Weight
0.002	0.638	29/68±2/33	29/77±2/5	0.001	28/95±2/11	30/13±2/35	Fat
0.000	0.055	26/71±1/95	26/60±1/95	0.000	24/90±1/84	25/59±1/95	BMI
0.000	0.395	2/19±0/38	2/18±0/38	0.000	2/20±0/32	2/45±0/38	Hs
0.002	0.707	7/57±0/37	7/56±0/37	0.002	7/26±0/32	7/43±0/37	Hm
0.000	0.265	326/73±27/15	325/13±26/31	0.000	/66±26/22	330/6±26/31	Fib

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4. Discussion

Since no research has been conducted on the effects of 8 weeks of aerobic exercise training on serum homocysteine, hs-CRP and fibrinogen levels in diabetic women so far, this is the first study in which the effects of 8 weeks of aerobic exercise on homocysteine levels, hs-CRP and fibrinogen levels in type II diabetic women has been investigated. The results of this study indicated that after 12 weeks of aerobic exercise homocysteine levels decreased significantly. Najari showed that 8 weeks of aerobic exercise does not affect homocysteine levels of young men (20). Dehghan declared that 8 weeks of aerobic exercise is effective on reduction of homocysteine levels in elderly non-athlete women (21). Increase in homocysteine or Hyper homocysteinemy in the body by mechanisms such as endothelial dysfunction, increased flat muscle cell growth of vascular wall, increased platelet adhesion and increased LDL oxidation and deposition in the arterial wall can cause atherosclerosis. In diabetic patients, hyperglycemia and hyperinsulinemia associated with insulin resistance affect metabolism of homocysteine by influencing glomerular filtration and affecting key enzymes such as methylene tetrahydrofolat reductase. Inactivation of protein in diabetics interacts with elevated homocysteine levels and causes further blood vessels damage. Plasma homocysteine accelerates the effect of Direct cytotoxic of glucose on in endothelial cells patients with diabetes (22). Results of this study showed plasma fibrinogen levels decreased significantly after aerobic exercise of experimental group. Furukawa studied the impact of a 12-week walking program on fibrinogen levels of 32 to 57 year old women of and reported that this factor did not change significantly after exercise (23). In a cross-sectional study Mynt reported an inverse relationship between a regular physical activity and fibrinogen levels (24). Schneider studied the impact of 6 weeks aerobic exercise on plasma fibrinogen levels in diabetic patients and after 6 weeks there was no change in plasma fibrinogen levels (25). According to previous studies, age, sex and disease of subjects in addition to duration, intensity and type of exercise are important factors that affect the response of fibrinogen to regular exercise. Several mechanisms could explain the decrease in fibrinogen in this study. Normal fibrinogen level is between 400-200 mg per liter. Despite diet control of subjects before sampling, these changes can be attributed to exercise. In the present study, BMI of subjects in the experimental group decreased significantly in comparison with the control group. Lower BMI and subsequent weight loss leads to reduction of inflammatory factors. Therefore it is believed that weight loss is important in the treatment of type II diabetes (26). Regular aerobic exercise can decrease fibrinogen

concentration in blood by reducing catecholamine stimulations and increasing blood flow to muscles and also increasing overall blood volume (23). Reduction of fat percentage which was observed in the subjects of this research can reduce IL-6 which is built in adipose tissue and since IL-6 is a stimulator in synthesis of fibrinogen, its reduction results in decreased fibrinogen (23, 27). Type II diabetes is accompanied with obesity and increased fat, in general, too much fat can cause inflammation in the body that is stimulating to increase in blood fibrinogen. As a result, Reduction of body fat which occurred in subjects of the present research can reduce inflammatory processes and lower fibrinogen concentration in the blood (23). Reduction of Fractional Synthesis Rate (FSR) as a result of long-term sports training is another mechanism for decrease of fibrinogen levels (28). Sheikholeslami and colleagues studied the effects of moderate and high-intensity resistance training on hs-CRP and fibrinogen in healthy men. In his research two experimental groups began practicing in two modes and after 6 weeks of exercise, decrease in hs-CRP and fibrinogen has been observed in the experimental group (29). Stewart and colleagues examined the effects of 12 weeks of physical activity in young and older women and demonstrated that serum CRP decreased during the 12-week physical activity (30). These findings are consistent with the findings of this study. Palmer evaluated whether physical activity has an effect on inflammatory markers in patients with intermittent claudication? Therefore, 19 patients with intermittent claudication were tested on a treadmill. The results showed that exercise increases plasma IL_6 concentrations. However, no change was observed in hs-CRP and TNF-alpha (31). Normal levels of hs-CRP in diabetic and obese patients are higher than normal people and it may indicate mild inflammation. Part of IL-6 which stimulates Fibrinogen and hs-CRP production is accumulated in adipose tissue. Decrease in hs-CRP levels of serum improves endothelial structure and insulin sensitivity and reduces mononuclear cells of the blood. As a sensitive marker of inflammation, hsCRP is used for diagnosis of patients at risk of increase of heart disease. This protein is made in liver by muscle cells in coronary arteries as part of the immune system response to infection or injury. High levels of Hs-CRP in the blood may be associated with an increased risk of heart attack, stroke and sudden cardiac death (32, 33, 34). Given the existing evidence, exercises of aerobic and resistance type can be effective on the amount of hs-CRP serum in diabetic patients. Vigorous physical activities enhance inflammatory cytokines in the immune system by exacerbation of inflammatory responses such as hemolysis. Thus, mode, duration and intensity of exercise may have a significant impact on intensity of inflammatory responses. Inflammatory processes play a special role in the pathogenesis (pathogenic), atherosclerosis and Type II diabetes. Increase in serum levels inflammatory biomarkers is considered as one of the emerging risk factors for many chronic diseases. In people with type II diabetes level of inflammatory markers and markers related to endothelial performance increases significantly. Adipose tissue is also an important source in stimulating the production of pro inflammatory cytokines. And evaluating the levels of released cytokines from this tissue determines the status of inflammatory processes in the body. Imperfect function of pancreas causes disturbance in absorption of insulin by the tissues targeted by insulin in body. Continued increase in insulin and glucose levels in blood waste systems in the body. Imperfect function of insulin prevents burning of sugar and saves it as fat (adipose tissue) which results in elevation of blood concentrations and systolic and diastolic blood pressure in diabetic patients. As a result of increase in blood viscosity in diabetic patients, blood clotting factors such as fibrinogen and inflammatory factors such as homocysteine, CRP and other cytokines rise. Insulin resistance and Hyperinsulinemy are associated with atherogenesis of (accumulation of fat containing plaques on the inner layer of vessel wall) plasma lipid. Increase in concentration of plasma insulin can increase synthesis of low-density lipoprotein (LDL) and it is consequently followed by hypertriglyceridemia. Gradual elimination of fats and apolipoproteins from LDL particles is possible by following a regular aerobic exercise. Insulin stimulates the synthesis of flat cells of arterial lining and increases collagen synthesis in endothelial cells which is associated with a reduction in return of lipid plaques. There is a relationship between elevated homocysteine and lipids. Synthesis of homocysteine leads to reduction of HDL and increase of plasma cholesterol. Lipids can prevent absorption of B vitamins which are one of the most important factors in lowering plasma homocysteine. Liver is the major organ for the metabolism of homocysteine and lipids. Impaired metabolism of methionine in liver can result in increased homocysteine. Mechanism of increase in CRP and fibrinogen may predispose patients to arterial thrombosis and it is then followed by damage to endothelial cells, inhibition of fibrinolysis, coagulation activation and impaired nitric oxide production. This is while reduction of these factors can be considered the impact of the reduced process of atherogenesis which is itself caused by aerobic exercise. Several remedies have been proposed for

treatment of type II diabetes and the following risks of this disease. Performing exercise and using a variety of diets have so far shown different results. The results of majority of these studies highlighted benefits of aerobic exercise on reducing inflammatory factors in these patients (12). Exercise has some beneficial effects on atherosclerosis risk factors caused by diabetes, such as obesity, hyperglycemia, high levels of LDL-c, CRP, IL-6, IL-8, TNFα, homocysteine , fibrinogen , decrease in HDL-c and increase in the level of triglyceride. By controlling blood sugar levels and insulin sensitivity in diabetic patients, regular aerobic activity can reduce related diseases such as common cardiovascular diseases in these individuals and is consistently considered as an anti-inflammatory agent. These exercises are accompanied with beneficial changes in development of muscle mass, effective storage of glucose and increased glucose uptake from bloodstream, and improved insulin resistance. These factors highlight the beneficial effects of exercise on compatibility. In summary, from results of the present investigation it can be concluded that moderate-intensity aerobic exercise has positive effects on the levels of inflammatory markers in diabetic women. This investigation has shown distinct benefits. Since it has been attempted to have a statistical sample which is aligned and equal in terms of gender, and not having chronic diabetes complications or regular exercise program, it seems that the data obtained in this investigation is caused by the independent variable rather than interfering or intervening variables. Thus it can be inferred that regular moderate intensity aerobic exercise reduces homocysteine hs-CRP and fibrinogen in women with Type II diabetes and it can play a role in prevention, improvement and treatment of complications of diabetes.

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