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Effects of 8 Weeks of Aerobic Exercise on Matrix Metalloproteinase-9 and Tissue Inhibitor Levels in Type II Diabetic Women

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Abstract

***Background*:** Increased vascular stiffness is a marker of atherosclerosis, which is diagnosed in the early stages of diabetes II. Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) are a family of proteolytic enzymes necessary for structure and function of great vessels. This study examined the effects of 8 weeks of aerobic exercise on MMP_9 and TIMP-1 levels in type II diabetic women.

***Materials and Methods*:** This is a quasi-experimental study which included 20 in type II diabetic women with mean age of 53.2±2.5 years, body mass index (BMI) of 28.73±2.27 and fat percentage of 30.6±2.05, who were randomly divided into two groups: aerobic exercise group (8 weeks, 3 sessions per week for 50 minutes) and control group. To examine changes in MMP_9 and TIMP-1, 5 ml of blood was taken from the brachial vein of patients before and 48 hours after completion of exercise period and after 12 hours of fasting at rest. Data analysis was performed using SPSS-16 software with the independent and paired *t*-tests.

***Results*:** A significant decrease was observed in body mass index and body fat percentage in the experimental group ($p<0.05$). Compared with the control group, the aerobic exercise group showed a significant decrease in MMP_9 ($p=0.01$) and a significant increase in TIMP-1 levels ($p=0.02$) after 8 weeks of aerobic exercise.

***Conclusion*:** The results showed that aerobic exercise as a stimulus can change the levels of matrix metalloproteinases and their tissue inhibitors in order to prevent cardiovascular diseases in diabetics.

Introduction

Cardiovascular disease is a leading cause of mortality in diabetics. American Heart Association defined diabetes as equivalent to coronary arteries disease, so that it includes more than 65-70% of all deaths in diabetics [1]. Matrix metalloproteinases are a family of proteolytic enzymes which reduce extracellular matrix proteins such as collagen and elastin [2]. Matrix metalloproteinases (MMPs) family has at least 18 members in humans who are divided into five sub-groups based on structural similarities and substrate-specific features: collagenases, gelatinases, stromelysins, membrane metalloproteinases and others (e.g. matrilysin, metalloelastase, etc.). Among these five sub-groups, MMP_2 (Matrix Metalloproteinase-2) and MMP_9 (Matrix Metalloproteinase-9) are the most active members among the MMPs family. MMP_9 are produced by neutrophils, macrophages, osteoclasts, T lymphocytes and cancer cells, which can affect basement cell membrane collagens, gelatins, fibronectin, elastin, glycosoaminoglycans, proteoglycans, laminin, and so on [3, 4]. Due to high sugar, MMPs have higher levels in diabetics, compared with normal people [5]. MMPs are inhibited irreversibility in blood circulation by TIMPs (Tissue inhibitor of metalloproteinase), which are a protease inhibitor in a broad range [6, 7]. Previous studies show that degradation of extracellular matrix components is important for biological processes. In other words, these activities takes place naturally under physiological conditions such as embryonic development, angiogenesis, wound healing, etc., but pathological processes such as diseases and stressful conditions like heavy sports activities stimulate inflammatory processes and gene expression related to MMPs and increase their production and activity, disturbing the balance between MMPs and their endogenous inhibitors (e.g. TIMPs) [6, 7].

That is, increased activity of MMPs occurs without adequate endogenous inhibitors, which leads to tissue inflammation, heart defects, etc [3, 6, 8]. Papazafiropoulou compared plasmatic levels of MMP_9 in two diabetic and non-diabetic groups. The results showed that MMP_9 levels did not differ between the two groups, but TIMP-1 levels in the diabetic group were lower than the other group [9]. In a study on type II diabetics, Kadoglou et al. showed that 16 weeks of aerobic exercise can reduce MMP_9 levels [10]. The discussion of protease types is completely new, particularly matrix metalloproteinases

(MMPs) as the front line and the final ring in the long chain of reaction of the immune system cells and inflammatory mediators and their response to sports activities, and very few studies have been done in this area.

Materials and Methods

This is a quasi-experimental research with two experimental and control groups. To examine the effects of aerobic exercise and metalloproteinase-9 and its inhibitor, 20 eligible patients were randomly selected among patients referred to Shahid Qodsi Diabetes Center in Mashhad in 2012. During a session, objectives and stages of the study were explained in detail to subjects. Then, each subject signed a written consent form and a questionnaire. Next, subjects were randomly divided into two groups: aerobic exercise group (8 weeks, 3 sessions per week for 50 minutes from 35 minutes in the first session to 50 minutes in the last session) and control group (no exercise during the study). After examinations by a specialty physician, none of the subjects had chronic kidney diseases, thyroid disorder, hypertension and coronary arteries disease. Arterial blood pressure was defined as when systolic pressure is greater than 140 mmHg or diastolic pressure is greater than 90 mmHg or when patients are treated for hypertension. Coronary arteries disease was defined as the presence of angina pectoris, history of myocardial infarction, positive stress test and 50-percent blockage of coronary arteries. All participants were asked not to change anything in their lifestyle (diet, activity level, etc.). Their diet and medication were matched and controlled based on the proposed diet of a dietitian at the Diabetes Center. Anthropometric indices including height, weight and body mass index (BMI), and body fat percentage were measured at the beginning and end of the study. BMI was calculated by the formula (weight/height^2) (Kg/m^2). Moreover, to calculate body fat percentage, first the subcutaneous fat thickness was calculated for three points of triceps, hip-bone suprailiac and abdomen-skinfold for subjects using caliper (slim-guide model made in Japan) and the Jackson and Pollock formula [11]. Fat percentage of each point was measured three times rotationally. A total of 5 cc of blood was taken from brachial vein of patients before and 48 hours after completion of exercise and after 12 hours of fasting at rest. MMP_9 and TIMP-1 were measured using ELISA kit (R&D Systems, Minneapolis, MN, USA). Each session included the following: warm up by stretching movements and jogging for 5-10 minutes, then the main exercise at 60% of maximum heart rate (heart rate was controlled by Polar heartbeat detectors, Model T31 (made in England) and then cool down for 5-10 minutes. The obtained data was analyzed using SPSS-16 software. In this study, quantitative data was represented as mean±SD. The paired sample *t*-test was used to compare changes within groups and the independent sample *t*-test was used to compare changes between groups. $p<0.05$ was considered statistically significant.

Results

The participants were 20 type II diabetic women with a mean age of 53.2±2.5. Table 1 shows descriptive information related to age, height, weight, BMI and body fat percentage of subjects in different groups.

According to table 2, the results show a significant decrease in MMP_9 levels ($p=0.006$) and a significant increase in TIMP-1 levels ($p=0.016$). No significant changes were observed in the control group after 8 weeks ($p>0.05$). Compared with the control group, the aerobic exercise group showed a significant decrease in MMP_9 levels ($p=0.01$) and a significant increase in TIMP-1 levels ($p=0.02$) after 8 weeks of aerobic exercise.

Table 1. Average of descriptive information of subjects in both aerobic exercise and control groups

Variables	Aerobic exercise	Control
Age (years)	53±1.6	53.4±3.4
Height (cm)	160±2.2	154±2.1
Weight (kg)	71.6±2.4	70.4±3.8
BMI (kg/m^2)	27.69±2.23	29.78±2.31
Body fat (%)	31.66±2.3	29.54±1.81

*: Data are represented as mean±SD

Table 2. Mean serum concentrations of MMP_9 and TIMP-1 in the aerobic exercise and control groups

Variables	Groups	Pretest	Posttest	*p*-Value*	Average difference	*p*-Value**
MMP_9 (ng/ml)	Aerobic exercise	340.65±55.75	291.68±32.7	±	0.006*	0.01**
	Control	322.35±12.29	323.56±90.63	±	0.91	
TIMP-1 (ng/ml)	Aerobic exercise	191.28±18.92	201.17±14.7	±	0.016*	0.02**
	Control	193.89±21.58	193.65±19.23	±	0.94	

*: Statistically significant at $p<0.05$ according to the independent samples *t*-test results for comparison between groups; **: Statistically significant at $p<0.05$ according to the paired sample t-test results for comparison within groups

Discussion

In recent years, much attention has been paid to enzymes degrading extracellular matrix or matrix metalloproteinases (MMPs). The results of this study show that at the end of 8 weeks compared with the beginning of the study, MMP_9 levels decreased significantly in the aerobic exercise group compared with the control group. This decrease could be due to adaptation to aerobic exercise in the exercise group.

The relationship between coronary arteries and high MMP_9 levels has been well documented, while lower MMP_9 levels are associated with reducing and preventing cardiovascular diseases [12, 13]. Lower MMP_9 levels are also associated with decreased fat oxidation, which shows self-regulation of MMP_9 expression in directing monocytes and macrophages [14]. Niessner et al. reported a significant reduction in MMP_9 levels after 12 weeks of endurance exercise in patients with coronary arteries, which is consistent with the results reported in diabetic patients [15]. In two studies conducted by Robert et al., a significant inhibition of MMP_9 levels was observed after dietary intervention and a sports activity period in children and men with metabolic syndrome [14-16].

Although it is difficult to determine whether only exercise intervention was effective in the two studies or not, both studies make emphasis on changing lifestyle can include the effect of sports activities on MMP_9 levels. The results of the present study are consistent with those of Niessner, Robert and Kadoglou [10, 14, 15]. As tissue MMPs secrete, their inhibitors act; and the ratio of MMPs and their inhibitors are very important. In normal conditions, a functional balance maintains between them and for this reason, analysis and synthesis of extracellular matrix is balanced. Any disease or physical/mechanical pressures, such as sports activities, cause reaction of defense cells, inflammation, secretion of pre-inflammatory cytokines, and finally, activation of MMPs. Then, the reaction of their inhibitors, such as tissue inhibitors or TIMPs immediately begins. Since the inflammation caused by severe physical pressures in such a case increases, the balance between MMPs and their inhibitors disturbs, i.e. increased activity of MMPs without adequate endogenous inhibitor (which is the inhibitor TIMP-1 in this study) leads to the incidence of a variety of injuries and deceases [2-4]. In this study, the activity of tissue inhibitor (TIMP-1) also showed a significant increase in the aerobic exercise group compared to the control group. In fact, the results showed that there is an inverse relation between the serum levels of MMP9 and TIMP-1 in both groups. However, it was significant in the aerobic exercise group and insignificant in the control group. It may represent higher activity of MMP_9 proteinase due to activeness and dynamic pressures induced by exercise in the aerobic exercise group and its consequences, such as renovation and repairing muscular and joint damages or angiogenesis or sedentariness in the control group due to tissue and muscle atrophy in one hand, and it can reflect the reinforcement of strong inhibitor of TIMP-1 in the exercise group due to the consistency caused by physical activity to deal with activities over the allowed limit of MMPs inflammatory markers, on the other hand [2, 4, 10].

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Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

Conflict of Interest

The authors declare no conflict of interest.

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