The Effects of Concurrent Training during Cardiac Rehabilitation on Plasma MMP-9 and TIMP-1 Levels in Myocardial Ischemic Patients

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Abbreviations: MMPs: Matrix Metalloproteinase Enzymes; TIMP-1: Tissue Inhibitor of Metalloproteinase-1; 1RM: One Repetition Maximum; EG: Experimental Group; CG: Control Group; MHR: Maximum Heart Rate; RPE: Borg Rating of Perceived Exertion; ELISA: Enzyme-Linked Immunosorbent Assay; MCP-1: Monocyte Chemoattractant Protein-1; Ox-LDL: Oxidized Low-Density Lipoprotein

ABSTRACT

Background: Matrix metalloproteinase enzymes (MMPs) play a destructive role in atherosclerosis resulting in occurrence of cardiac ischemia. The aim of this study was to investigate the effect of concurrent training during cardiac rehabilitation on plasma levels of MMP-9 and tissue inhibitor of metalloproteinase-1 (TIMP-1) in patients with myocardial ischemia.

Methods: Sixteen cardiac ischemic patients who were in the process of clinical cardiac rehabilitation were randomly assigned to experimental (n = 8) or control (n = 8) groups. The patients in experimental group performed concurrent exercise for eight weeks (one hour / three session per week) with the intensity of 40-60% of one repetition maximum and 60-80% maximum heart rate. Pre- and post-intervention blood samples were taken to assess plasma MMP-9 and TIMP-1 concentrations using ELISA method.

Findings: Independent T-test showed the patients in experimental group had a significant decrease (t = 2.431; p = 0.029) in MMP-9 plasma concentration and a significant increase (t = 3.202; p = 0.006) in plasma levels of TIMP-1 compared to the control group. A significant within-group reduction in MMP-9 levels (t = 0.695; P = 0.008) and a significant within-group increase in TIMP-1 levels (t = 3.964; P = 0.005) were observed in the experimental group, while the pre- to post-value changes in MMP-9 and TIMP-1 levels in the control group were not statistically significant.

Conclusion: It seems that the favorable changes in MMP-9 and TIMP-1 following eight weeks of physical exercise prevent the progression of atherosclerosis and recurrence of cardiac ischemia during the process of cardiac rehabilitation.

Keywords: Matrix Metallopeptidases, Tissue Inhibitor of Metalloproteinase, Exercise Training, Cardiac Rehabilitation, Cardiac Ischemia

Introduction

Cardiac ischemia is considered as one of the deadliest heart diseases. According to the reports from American Heart Association, one third of cardiac patients suffer from ischemic heart ailment [1]. Several genomic and environmental factors including but not limited to family history, gender, age, smoking, hypertension, diabetes, hyperlipidemia, and lack of physical activity can potentially contribute to atherosclerosis and subsequently ischemic heart disease [2,3]. Atherosclerosis, a chronic inflammatory disease, is characterized as the accumulation of fat and other substances on the inner surface of artery walls [4]. In the atherosclerotic situation, due to the deficiency of blood flow in the coronary arteries, an acute blockage occurs which is defined as a heart attack [5]. With the progression of atherosclerosis, the smooth muscle cells move toward the intima in response to growth factors released by active macrophages and endothelial cells. Active macrophages weaken the extracellular matrix and support the platelet fibrosis by producing matrix metalloproteinases (MMPs) suggesting a prominent role in the process of atherosclerosis and rupturing the artery walls [6]. Matrix metalloproteinases (MMPs), which are a large group of protease enzymes, are responsible for the breaking down of extracellular matrix.

To date, 26 members of MMP family have been identified, and among them, gelatinase-B (or MMP-9) has a higher activity than other members [7] with a well-documented potential in developing cardiovascular disease in human populations [8]. Based on the evidence, myocardium expression of MMP-9 is increased in the patients with coronary artery disease [9,10]. However, due to the damaging role of MMPs, their activity is strongly regulating by four tissue inhibitors (TIMPs) namely TIMP-1, TIMP-2, TIMP-3, and TIMP-4 which can control the detrimental activities of MPPs in vertebrates [11]. Among the TIMP family, it has been reported that TIMP-1 is a potent inhibitor of many MMPs including MMP-9 [12] and play a key role in the structure and function of myocardium ae well as the control of extracellular matrix proteolysis in cardiovascular system [12]. Recurrence of cardiac ischemia and its unfavorable consequences are a major concern among cardiac ischemic patients as well as cardiovascular specialists [8]. Nowadays, with developing clinical centers, medical strategies, and patients' knowledge in diagnosing early signs of heart disease the rate of mortality has been clearly decreased; however, some of these patients with the acute symptoms have been hospitalized for the second and third time and some of them still may have died [13].

In addition to pharmacological treatments and implementing medical interventions on coronary arteries, cardiac rehabilitation program has been well-documented in controlling the risk factors, improving life quality, and reducing the mortality rate [14]. The cardiac rehabilitation program is designed to limit the physiological and psychological consequences of cardiovascular disease, reduce the risk of sudden death or stroke, control cardiac symptoms, and decline the atherosclerosis [15]. Physical exercise is frequently used as a non-pharmacological and supplemental method in the process of medical treatment for a variety of reasons [16]. As an incentive method, physical exercise can be used during cardiac rehabilitation programs due to its low cost and attractiveness [17]. The type of physical exercise used in cardiac rehabilitation programs is generally aerobic in forms of walking, running, or cycling [18]. However, it has been recently reported that a well-designed resistance training program accompanied by aerobic exercise can be considered as a helpful strategy in rehabilitation programs. In this regard, the American Heart Association has also recommended that resistance training be performed twice a week in cardiac rehabilitation programs [18].

According to the recent scientific reports, the implementation of physical exercise in rehabilitation programs can lead to effective outcomes on some clinical indicators involved in the occurrence of atherosclerosis [19]. In a study examining the effect of cardiac rehabilitation on the atherosclerosis biomarkers in patients with cardiac ischemia, the authors reported that performing physical exercise during cardiac rehabilitation programs will prevent re-occurrence of cardiac ischemia [20]. However, due to the increasing prevalence of ischemic heart disease [1] and considering the importance role of MMPs particularly MMP-9 in the formation and stabilization of atherosclerotic plaque, few studies have yet examined the effects of a well-planed physical exercise during cardiac rehabilitation on the levels of metalloproteinases and their tissue inhibitors in patients with cardiac ischemia [21,22]. Therefore, the need for a comprehensive investigation in this promising area is clearly evident and the present study is designed to examine this imperative issue.

Materials and Methods

The present study is an experimental controlled clinical trial. Sixteen cardiovascular patients with atherosclerotic symptoms who were referred to a cardiac hospital in Mashhad, Iran were selected and randomly assigned to an experimental (n = 8) or control (n = 8) group. Scheme of the study design is shown in Figure 1. Before the commencement of the study, patients in both groups were monitored by a cardiologist and were reported to have symptoms of coronary heart disease. For each patient, a file including demographic information, history, clinical cardiac reports, and anthropometric data was provided. At the beginning of the rehabilitation program, an initial assessment of cardiac function was conducted using echocardiographic devices. During the study, participants in both groups followed the prescribed medications and diets (with a particular amount of calorie and macronutrients per kilogram of body weight for all participants) which were provided by a dietitian

and a cardiologist. The patients in experimental group completed an eight-week moderate concurrent exercise program with 40-60% of their one maximum repetition.

According to the American Heart Association guidelines, the patient's exercise intensity was monitored to be between 60 and 80% of their maximum heart rate [23] using the individualized electrocardiograms connecting to each participant during exercise sessions. Moreover, Borg Rating of Perceived Exertion (RPE) scale was also used to a further control of the exercise intensity, and the patients in experimental group were asked to keep their activity intensity between level 11 (relatively light) and level 13 (somewhat difficult) [24]. The concurrent training protocol is shown in Table 1. Before the commencement of training sessions, participants in experimental group were informed and introduced to devices and exercises in one session and then practiced three sessions per week for eight weeks. Each training session lasted about one hour performing mixed aerobic and anaerobic exercises using treadmills, bikes, ergometers, physio balls, and light weights. At the starting of each raining sessions 5 minutes of warm-up, 5 minutes of walking on treadmill, 5 minutes of bike pedaling, and 5 minutes of upper-body ergometer pedaling were done with three minutes of inactive rest between each aerobic exercise.

Table 1: Concurrent training protocol.

Week	Training Sessions	Resistance Training				Endurance Training	
		Sets	Rest Interval (min)	Repetition	Intensity (%1RM)	Volume (min)	Intensity (%MHR)
1	3	3	2	10	40	15	60 - 65
2	3	3	2	10 - 11	40	15	60 - 65
3	3	3	2	11 - 12	40	15	65 - 70
4	3	3	2	11 - 13	50	15	65 - 70
5	3	3	2	12 - 13	50	15	70 - 75
6	3	3	2	13 - 14	50	15	70 - 75
7	3	3	2	14 - 15	60	15	75 - 80
8	3	3	2	15	60	15	75 - 80

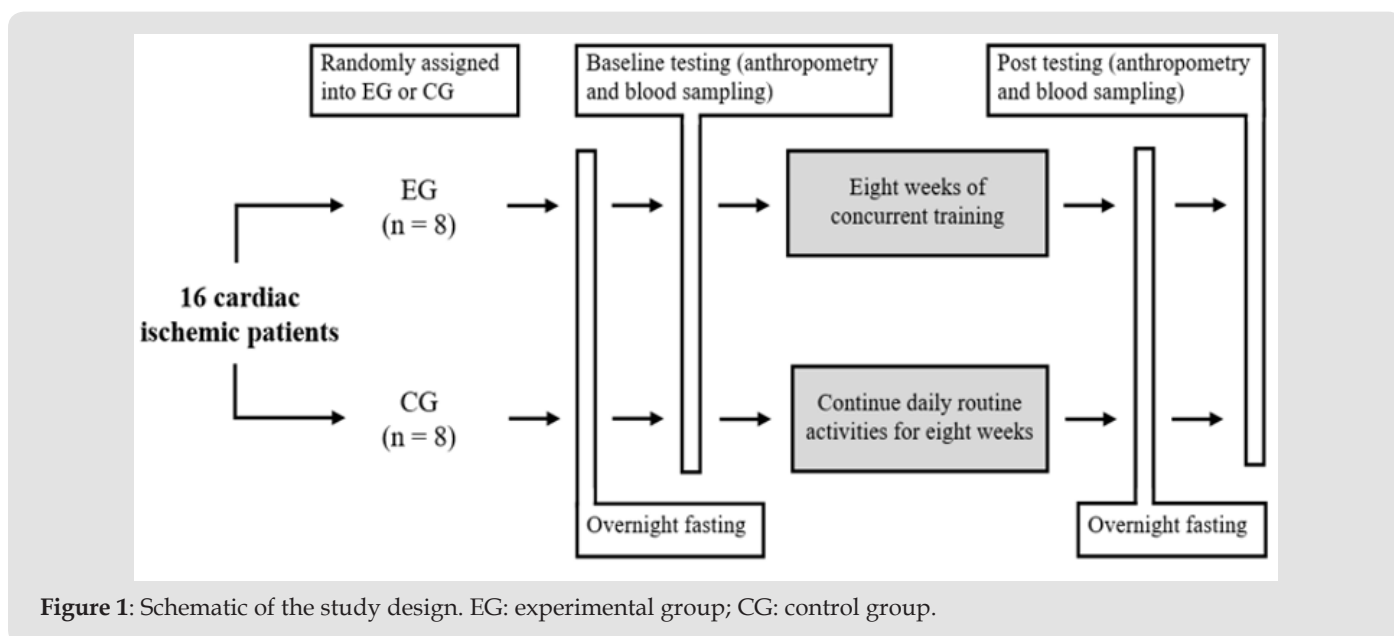**Note:** 1RM: One Repetition Maximum; MHR: Maximum Heart Rate.

Figure 1: Schematic of the study design. EG: experimental group; CG: control group.

After 5 minutes of rest, the individuals gradually performed the following workouts with 10 repetitions in three sets in the initial training sessions and to 15 repetitions in the advanced sessions. The workouts consisted of squat with a physio ball, shoulder flexion, shoulder abduction, elbow flexion, hip flexion, hip abduction, ankle plantar flexion, and ankle dorsi flexion. The workouts were initially performed using the patient's own body weight or limb weight, and gradually improved using therabands and light weights [25]. A careful supervision was applied during the training sessions, and the patients were constantly questioned about the amount of pressure based on the Borg scale. If the value of Borg scale was reported below 11 or above 13, the participant was asked to increase or decrease the effort, respectively.

Laboratory Methods: Fasting 10^{cc} blood samples were obtained 48 hours before the first training session and 48 hours after the last training session from the participants' antecubital vein in both groups. Blood samples were collected in lavender-top tubes containing anti-coagulant EDTA, and then were carried to laboratory for plasma separation by 3000^{rpm} centrifuging for 10 minutes. Subsequently, plasma samples were frozen and stored at -80°C for further analysis. Plasma MMP-9 and TIMP-1 concentrations were assessed by Enzyme-Linked Immunosorbent Assay (ELISA) method using Awareness Stat Fax 2100 device according to the instructions of the ELISA kits (R&D Systems, Minneapolis, MN, USA).

Results

Data distribution was normal according to the results from Shapiro Wilk test. The baseline characteristics of the participants are shown in Table 2. The independent T-test showed a significant decrease in plasma MMP-9 concentration (t = 2.431; p = 0.029) and a significant increase in TIMP-1 plasma levels (t = 3.202; p = 0.006) following the exercise intervention in the exercise group compared to the control group. According to the correlated T-test, a significant within-group decrease in MMP-9 levels (t = 0.695; p = 0.008) and a significant increase in plasma TIMP-1 concentrations (t = 3.964; p = 0.005) were observed in the experimental group, while within-group changes in MMP-9 and TIMP-1 levels were not significant in the control group. (t = 0.21; p = 0.838 and t = 0.46; p = 0.66, respectively) (Figure 2).

Table 2: Baseline characteristics of the participants in experimental (n = 8) and control (n = 8) groups (mean ± SD).

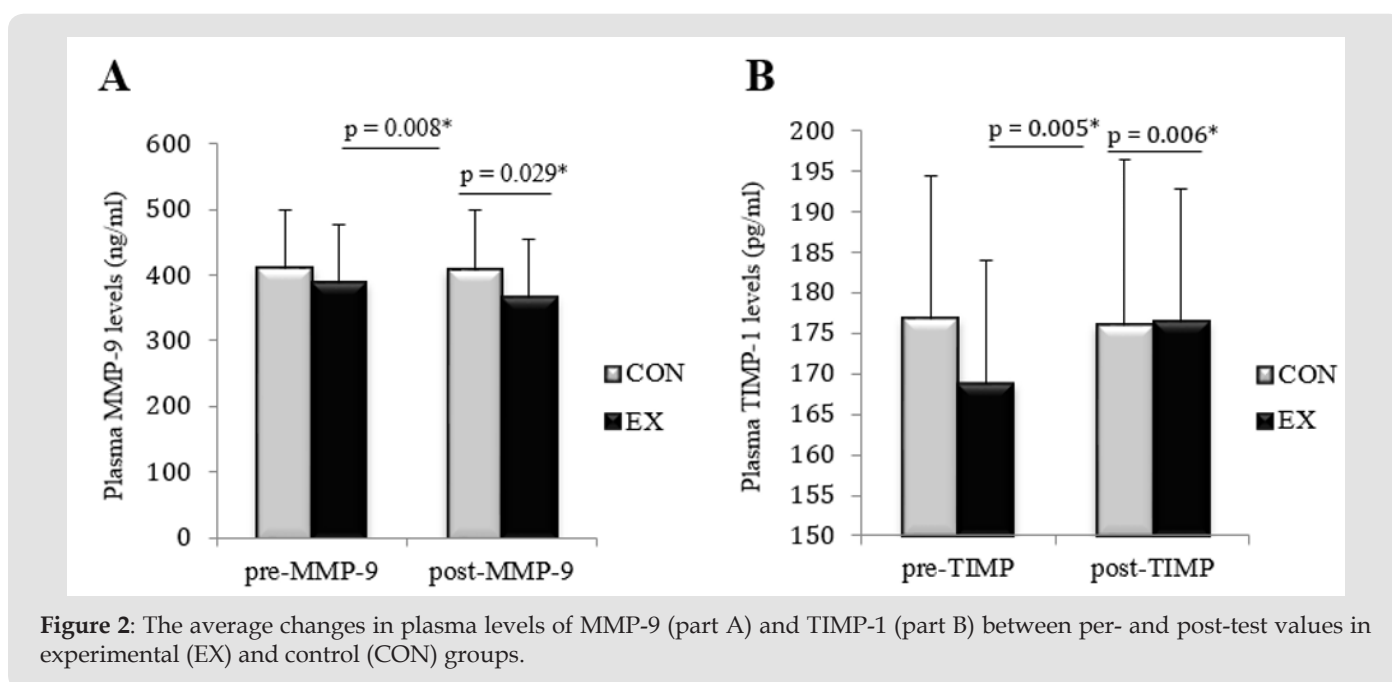| Age (y)	Experimental Group	Control Group
	56.25 ± 6.21	54.09 ± 6.33
Height (m)	1.72 ± 3.1	1.74 ± 4.7
Weight (kg)	72.2 ± 8.73	76.7 ± 7.45
Body Mass Index (kg/m^2)	24.7 ± 2.94	25.11 ± 2.24

Figure 2: The average changes in plasma levels of MMP-9 (part A) and TIMP-1 (part B) between per- and post-test values in experimental (EX) and control (CON) groups.

Discussion

Present study showed that after eight weeks of moderate physical exercise during the cardiac rehabilitation period, MMP-9 levels decreased and TIMP-1 levels increased, and significant within-group changes in MMP-9 and TIMP-1 levels were observed in the experimental group. To date, the investigations assessing the effects of exercise on MMPs and TIMPs levels have often been conducted in healthy, obese, or diabetic populations as well as animal models. Seydanlou and Farzanegi in 2014 reported a significant 20% decrease in MMP-2 levels and a significant 26%

increase in TIMP-1 levels of overweight individuals following eight weeks of Pilates training [26]. Consistent with our results, Kadoglou, et al. in 2013 found a significant increase in TIMP-1 concentrations following six weeks of treadmill running in animal models [27], similar to the results of Koskkinen's study but in humans [28]. Although the effectiveness of physical exercise on MMP-9 and TIMP-1 levels are well documented in the literature, limited studies have reported no change in the aforementioned variables following different exercise interventions. Previously, Mackey, et al. reported that a 10-kilometer road and water running has no effect on MMP-2 and MMP-9 levels in young men [29].

Moreover, according to the results of a study by Hoier, et al., eight weeks of cycling training with the intensity of 60% maximum oxygen consumption did not affect the TIMP-1 levels in healthy men [30]. However, these inconsistent findings might be justified by different training methods, varied participants' characteristics, and different sampling methods (muscle biopsy vs blood sample) used in the aforesaid investigations. Metalloproteinase matrix enzymes are believed to alter the formation of the cardiovascular matrix during natural biological processes [31]. However, in pathophysiological processes of various diseases, the expression and activity of these type of proteolytic enzymes are increased due to the increased secretion of proinflammatory cytokines leading to breakdown of several collagens and gelatinases, as well as detrimental effects on microanatomical tissue structures. As a result, exacerbation of inflammatory state and emerging of various heart and vascular diseases might occur with advancing time [32,33]. In a study examining the role of matrix metalloproteinase 1, 2, 3, and 9 in acute myocardial infarction, the authors reported that the plasma concentrations of various MMPs in patients with myocardial infarction were significantly increased [8].

They concluded MMP-9 may play a prominent physiological and pathological role during the stage of myocardial infarction to heart failure, more especially considering the fact that improper vascular redisposition of MMP-9 may promote atherosclerosis *via* weakening of atherosclerotic plaques [34]. It seems the potential mechanisms for reducing exercise-induced MMP-9 levels during cardiac rehabilitation is the changes in the levels of monocyte chemoattractant protein-1 (MCP-1) [35]. MCP-1 attracts monocytes to inflammatory sites located in the vascular subendothelial space. These monocytes are able to differentiate into macrophages and be converted to foam cells *via* absorbing oxidized low-density lipoproteins (Ox-LDL), suggesting an important role for MCP-1 in the pathogenesis of atherosclerosis [36]. The inhibition of MCP-1 by relevant inhibitors prevents plaque inflammation and stops the rupture of disposed plaques [37]. On a better note, MCP-1 in myocytes and smooth vascular cells stimulates the expression of MMP enzymes and consequently induces inflammatory cytokines and MMP enzymes in cardiac myocytes [38].

Although MCP-1 levels were not measured in the present study, several studies have reported a reduction in MCP-1 following exercise suggesting a beneficial effect of physical exercise on heart patients. Thus, MCP-1 reduction is likely links to decreased plasma MMP-9 levels following regular exercise [39]. The activity of MMP inhibitors and the ratio of MMPs to TIMPs are as important as the secretion of tissue MMPs. Under normal conditions, a physiological balance between MMPs and TIMPs is stablished, and the extracellular matrix breakdown and synthesis is well-adjusted. Any disease or mechanical stress that results in decreased immune cells, increased inflammation, secretion of proinflammatory cytokines, and the activity of MMPs, consequently triggers the immediate inhibitory response particularly activation of TIMPs [40]. Hence, the inhibition of MMP proteolytic activity has been suggested as a therapeutic approach in various heart diseases [41-43].

Conclusion

In the present study, an inverse relationship between the bioactivity of MMP-9 and TIMP-1 was observed following eight weeks of exercise intervention in ischemic cardiac patients. Considering the favorable effects of physical exercise on cardiac rehabilitation, it can be suggested that patients with cardiac ischemia can accelerate their recovery process and reduce the risk of stroke reoccurrence by doing moderate intensity of physical exercise at least three time per week.

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Conflict of Interest

No conflicts of interest are declared by the authors.

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