





Original Article

Effect of Eight Weeks of Aerobic and Aerobic-Resistance Trainings after Coronary Artery Bypass Grafting on Expression of CCL2 and CCL5 in Middle-Aged Men

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Received: 2020/05/18

Revised: 2020/05/18

Accepted: 2020/07/30



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ABSTRACT

Background and objectives: Chemokines are a group of proteins involved in both innate and adaptive immunity with a significant role on homeostasis and immune system development. The present study aimed to evaluate effects of eight weeks of cardiopulmonary rehabilitation exercise after coronary artery bypass surgery on expression of chemokines CCL2 and CCL5 in peripheral blood mononuclear cells of middle-aged men.

Methods: The study was performed on 45 middle-aged men that had undergone coronary artery bypass surgery. The subjects were randomly divided into three groups of control (n=15), aerobic exercise (n=15) and combined aerobic-resistance exercise (n=15). The trainings were performed three times a week for eight weeks at 60-75% of target heart rate. Fasting blood samples were collected 24 hours before the first training session and 48 hours after the last training session. Lymphocytes were separated by centrifugation. Change in gene expression was investigated by real time-PCR. Data were analyzed in SPSS (version 16) using one-way analysis of variance and Tukey's post hoc test.

Results: The eight week exercise training significantly decreased expression of CCL2 compared to the control group.

Conclusion: Rehabilitation exercise can be an effective way to prevent, control or reduce atherosclerosis by lowering expression of CCL2 and CCL5.

Keywords: Cardiac Rehabilitation, Gene Expression, MCP-1, RANTES.

DOI: 10.29252/mlj.15.1. 19

INTRODUCTION

Cells, proteins and inflammatory responses play a fundamental role in the development and advancement of atherosclerosis (1). This chronic inflammatory condition occurs in the artery walls and involves both the innate and acquired immune systems (2). According to Ross, atherosclerotic lesions mainly consist of macrophages and T-lymphocytes and involve particularly specialized cellular and molecular responses to be explained merely by atherosclerosis being an inflammatory condition (3). Atherosclerosis develops as soon as arterial inflammation starts, the endothelium gets activated, and pre-inflammatory proteins such as chemokines are synthesized, leading to a significant increase in the expression and the emergence of cellular adhesion molecules (4). Chemokines are a large family of secreted proteins with a small molecular weight that play a pivotal role in various physiological and pathological processes, such as hematopoiesis, angiogenesis, inflammation, atherosclerosis, infection and immune system diseases (5, 6). In terms of function, chemokines are divided into two groups: inflammatory chemokines and constitutively expressed chemokines. The former plays a significant role in the migration of leukocytes to the inflammation site and are involved in the innate immune responses by migrating neutrophils, monocytes/macrophages, dendrites and natural killer cells (7). Studies show that CCL2 and CCL5 are actually the main indices of inflammation development. Monocyte chemo-attractive protein 1 (MCP-1), also known as CCL2, is a chemokine that attracts monocytes to the inflammation site in the sub-endothelial space of the arteries. These monocytes are capable of differentiation into macrophages and foam cells by removing OX-LDL, hence playing an important part in the pathogenesis of atherosclerosis (8). Studies show that there is a direct relationship between MCP-1 plasma level and common atherosclerosis risk factors such as hs-C-reactive protein (hs-CRP), plasma fibrinogen and intima media thickness of the carotid artery (9).

CCL5 (RANTES) is a CC chemokine, which is mainly released from T-cells and plaques and stimulates the migration of monocytes, macrophages and T-cells (10). These

chemokines are trivially found in the healthy heart, but the expression rises in heart failure-associated hypertrophy. Therefore, this chemokine has been recently introduced as an indicator of heart failure, cancer, inflammation and tissue damage (10).

Physical exercise is known as a major preventer of cardiovascular diseases; however, the relationship between physical exercise and changes in CCL2 and CCL5 expression has not been determined yet. A few studies have dealt with the effect of physical exercise on the expression of these inflammation indicators in patients with heart disease. For example, Billebeau et al. reported that 40 sessions of endurance exercise reduce plasma biomarkers in patients with chronic heart failure (11). A large number of studies have also been carried out on different physical exercises and their outcome within a rehabilitation program. While exercise programs for coronary artery bypass graft (CABG) surgery patients have been mainly focused on endurance exercises, such as aerobic training (12), increasing evidence show that resistance exercise can be more effective in patients if accompanied by aerobic exercises. Such trainings can be applied as a complementary treatment or even as a treatment replacement for patients who are unable to perform aerobic exercises (13). There have also been reports of a decline in CABG patients' muscle mass, which is responsible for decrease in the muscle power, functional capacity, change in body composition and reduced quality of life (14). In this regard, Moosavi et al. investigated the effect of combined training on *ABCG1* gene expression in mononuclear cells after CABG in middle-aged men. They concluded that combined training, as a part of the cardiac rehabilitation process, seems to augment the process of reverse cholesterol transfer by affecting the expression of the *ABCG1* gene (15). Our knowledge of chemokines and changes in their expression as a predictor of heart failure is limited and unattended to. In addition, the effect of physical exercise on patients with cardiovascular disease is not determined yet. Therefore, the present study aimed to evaluate effects of eight weeks of cardiac rehabilitation training on expression of CCL2 and CCL5 in peripheral blood mononuclear cells (PBMC) of middle-aged

men who had undergone CABG.

MATERIALS AND METHODS

Forty-five participants were selected from the Javad-Al-Aeme hospital and randomly divided into three groups: aerobic exercise (n=15), combined exercise (n=15) and control (n=15). Inclusion criteria were age range of 40-60 years, willingness to participate in the study, cognitive health, normal vision and hearing, blood pressure of <160/100 mmHg, no history of acute or advanced diseases that could limit exercise ability and inability to use auxiliary devices for walking such as cane and walker. Exclusion criteria included use of medications, occurrence of ventricular arrhythmias, ST elevation or fall during training sessions, respiratory disturbance during rehab and unstable angina. The study was approved by the ethics committee of Islamic Azad University of Neyshabour, Iran (code:IR.IAU.NEYSHABUR.1396,13). The subjects in the aerobic and combined exercise groups participated in an eight-week training program based on the recommendations of the American College of Sport Medicine (16). Table 1 presents biometrics and some characteristics of the subjects. One week before the first exercise session, the subjects attended an introductory session to become familiarized with the trainings. The rehabilitation program was carried out three sessions per week for eight weeks. Aerobic training included walking on a treadmill for 20-30 minutes, cycling on a fixed bike (10-12 minutes) using the bicycle's ergometer (10 minutes). The subjects warmed-up at the beginning and cooled down at the end of each session with stretching exercises. The trainings began at moderate intensity (60% of maximum heart rate) (17), but the duration and intensity of the trainings increased gradually according to the subjects capacity, so that in the final maximum heart rate. The exercise intensity was assessed using the Borg scale (18, 19). The resistance training program included three sets of physioball squat, shoulder flexion, hip flexion, shoulder abduction, hip abduction, elbow flexion, plantar flexion and ankle dorsiflexion with 8-15 repetitions. The activities were initially performed with eight repetitions using a weak theraband (yellow). Then, two repetitions were added to each activity every session until reaching 15 repetitions. The gradual increase of repetitions

continued after increasing the strength of the theraband (pink) (20).

Blood samples (10 ml) were taken after 10-12 hours of fasting, one day before the first training session and 48 hours after the last training session. RNA was extracted using a commercial kit (Qiagen, Germany). Complementary DNA (cDNA) was synthesized using a cDNA synthesis kit (QuantiTect Reverse Transcription Kit cDNA synthesis, Qiagen, Germany) according to the manufacturer's instructions. Real-time quantitative PCR was performed using the Quanti Fast SYBR Green PCR Kit (Qiagen, GmbH, Germany). PCR reaction solution (10 µl) contained 1 µl of single-strand cDNA, 5 µl of master mix, 1µl of each primer and 2µl of RNase- free water. Expected fragment size and oligonucleotide primer sequences for *CCL2*, *CCL5* (21) and β -actin genes (22) are listed in table 2.

PCR was carried out in a Bio-Rad thermal cycler (USA). PCR products were subjected to session, the intensity was increased to 80% of electrophoresis on 1.5% agarose gel. Melting curve analysis and a threshold cycle comparison method was applied to measure the number of target and reference genes (23). Data were analyzed with SPSS 16.0 using one-way ANOVA and the Tukey's post hoc test.

RESULTS

One-way ANOVA showed a significant difference in the relative expression of *CCL2* gene in PBMN cells between the control group, the aerobic exercise group and the combined exercise group ($P=0.011$, $F=5.37$). Moreover, there was a significant difference between the control group and the aerobic exercise group ($P=0.041$) and between the control group and the combined exercise group ($P=0.012$) in terms of *CCL2* gene expression (Table 3). Based on the results of one-way ANOVA, there was no significant difference in the expression of *CCL5* between the study groups ($P=0.903$, $F=0.102$).

Table 1. Biometrics and some characteristics of the subjects

Group	Age (year)	Height (m)	Weight (kg)	Post-intervention weight (kg)	Duration of disease (months)	Body mass index (kg/m ²)
Control	47.4±2.75	170.9±3.9	80.01±8.8	79.2±9.21	149±69.12	28/22±2/46
Aerobic training	46.9±3.23	171.1±3.6	80.14±9.12	80.1±9.3	150±68.19	22/18±2/01
Combined training	47.4±3.23	170.2±3.5	80.16±8.99	79.03±8.95	150±69.01	26/60±2/09

Table 2. Oligonucleotide sequence of primers

Primer sequence	Type	Gene
5-GTCTCCCACCACCATCTT-3	Forward	CCL2, CCL5
5-TCTGTCTCTGAGTGTAGCCTTAGC-3	Backward	
TCCCTGGAGAAGAGCTACG	Forward	β-Actin
GTAGTTTCGTGGATGCCACA	Backward	

Table 3. One-way ANOVA and Tukey test results for each group

Variable	Group	Pre-test	Post-test	Kolmogorov-Smirnov test		ANOVA		Tukey's test
				Z	Sig.	F.	Sig.	F
CCL2 (pg/ml)	Control	1.000 ± 0.000	**1.0 ± 19.33	0/842	0.477	5/370	°°0.011	**0.041 **0.012
	Aerobic	1.000 ± 0.000	**0.0 ± 67.44	0.669	0.761			
	Combined	1.000 ± 0.000	**0.0 ± 61.47	0.660	0.777			
CCL5 (pg/ml)	Control	1.000 ± 0.000	0.82 ± 80/15	0.830	0.496	0.102	0.903	0.904 0.936
	Aerobic	1.000 ± 0.000	0.70 ± 87.80	0.346	1.000			
	Combined	1.000 ± 0.000	0/34 ± 86.87	0.552	0.921			

** Significant difference between control group and the exercise groups.

°° Significant difference between the aerobic and the combined exercise groups.

DISCUSSION

We observed a significant decrease in the expression of CCL2 in CABG patients after eight weeks of aerobic and combined exercise rehabilitation. However, we found no significant difference between aerobic and combined exercises in this regard. It is pointed out here that cardiac rehabilitation is so far the first therapeutic intervention that results in a decrease in expression of genes involved in the development of atherosclerosis. These findings are in accordance with results of most previous studies (24-27) but inconsistent with results of Shi et al. (28) and Van Wijk (29). In the study of Wilmore, endurance exercise reduced MCP-1 and IL-8 in the circulatory system of patients who were susceptible to coronary events. In the study of Trøseid et al., eight weeks of combined endurance and resistance exercise significantly decreased plasma level of MCP-1 and IL-8 in patients with metabolic syndrome. In a review study on the relationship between MCP-1 polymorphism and coronary artery disease based on ethnicity, Pan et al. found that MCP-1A2518G (genotype AG+GG) is a risk factor for coronary artery disease. In another study, high-intensity interval training reduced plasma level of MCP-1 in the visceral and subcutaneous adipose tissue. Inconsistent with these results, Van Wijk et al. reported no relationship between CCL2 gene promoter polymorphism and coronary artery disease. In a similar study by Shi et al., there was no significant relationship observed between A-2518G polymorphism of MCP-1 gene and acute coronary syndrome in a Chinese population. There is a significant direct relationship between the plasma level of MCP-1 and common risk factors of atherosclerosis such as plasma fibrinogen and hs-CRP and intima media thickness of carotid artery (29). Findings of the present study showed that eight weeks of rehabilitation slightly decreased CCL5 expression in CABG patients. These findings are in accordance with those of Baturcam et al. (30) and Versteylet al. (31) but inconsistent with findings of Liu et al. (32). Baturcam et al. studied the effects of physical exercise on expression of CCL5 and its receptor in the adipose tissue of obese people. They found a direct association between CCL5 and CCR5 expression in the adipose tissue and the level of IL-6 and TNF- α .

Therefore, exercise may be beneficial for reducing the deteriorative effects of obesity through CCL5 signaling in the adipose tissue (30). In the study of Versteylet al., serum level of CCL18 was related to coronary artery disease and CCL5 was separately related to coronary artery obstruction and initiating heart disease (31). Kraaijeveld et al. concluded that high circulating levels of CCL5 might be a marker for unstable angina (33). In contrast, lower serum CCL5 level was found to be associated with coronary heart disease (34). A rise in inflammatory indices may indicate development of atherosclerosis, suggesting that even after CABG, patients may be still susceptible to cardiovascular disease (35).

A few studies have investigated the effects of cardiovascular rehabilitation on the inflammatory indices after open heart surgery. In a study by El Missiri and Taher on 80 patients with acute myocardial infarction or acute coronary syndrome, a rehabilitation program significantly reduced hs-CRP in patients with ischemic heart disease, lessened the number of chain smokers and decreased body mass index (36). Silva et al. studied the effects of inflammatory biomarkers on the effectiveness of physical exercise in patients with heart failure, and found that pre-inflammation and pre-fibrosis biomarkers have a differential effect on functional capacity during physical activity (37).

Eight weeks of aerobic resistance training significantly improved the biomechanical function of cardiac muscles in myocardial infarction and CABG patients (38). Physical activity directly influences the cardiovascular system by increasing blood and plasma volume, decreasing blood viscosity, increasing stroke volume and VO_{2max} . It is recommended to conduct future studies on the effect of different training protocols on both traditional and novel indices of atherosclerosis in people of different age and physical conditions.

CONCLUSION

Based on the results, the eight-week cardiac rehabilitation training can significantly decrease expression of CCL2 in post-CABG patients. Therefore, this type of exercise could be recommended for prevention of coronary artery occlusion after CABG.

ACKNOWLEDGEMENTS

We would like to express our gratitude to Dr. Alavi for guiding us throughout this research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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How to Cite:

Alavizadeh NS, Rashidlamir A M, Hejazi S. [Effect of Eight Weeks of Aerobic and Aerobic-Resistance Trainings after Coronary Artery Bypass Grafting on Expression of CCL2 and CCL5 in Middle-Aged Men]. *mljgoums*. 2021;15(1):19-25. DOI: 10.29252/mlj.15.1.19