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The Effect of Aquatic and Dryland Resistance Training on Peroxisome Proliferator Activated Receptor- α Gene Expression in Middle-aged Women's Peripheral Blood Mononuclear Cell after Coronary Artery Bypass Grafting

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ABSTRACT

Background. Cardiac rehabilitation program is aimed at reducing secondary risk factors and improving function in patients undergoing coronary artery bypass grafting run which ultimately may delay or reduce mortality in patients. A major component of cardiac rehabilitation program is exercise. **Objective(s).** This study is aimed at evaluating the effect of aquatic and dryland training on Peroxisome Proliferator Activated Receptor- α (PPAR- α) gene expression in middle-aged women's peripheral blood mononuclear cells (PBMNCs) after coronary artery bypass grafting. **Methods.** Thirty middle-aged women with cardiovascular disease were categorized into three groups comprising control (CON), aquatic resistance training (ART) and dryland resistance training (DRT). The dryland training program lasted for eight weeks of resistance training (3 sessions per week/ 60 minutes per session) and included two to three sets of 12-15 repetitions with 60% of 1RM. The aquatic resistance training lasted for eight weeks (3 sessions per week/ 60 minutes per session), with 60 to 80% of 1RM for each exercise primarily. Fasting blood samples were taken from all participants 48 hours both before the beginning of the training program and after the last training session. PPAR α relative gene expression was identified by Real-Time PCR method. **Results.** It is showed a significant increase in the relative PPAR α gene expression in both aquatic and dryland resistance training groups ($F= 15.573$, $P= 0.001$). It is found a significant difference in aquatic and dryland resistance training groups as regards PPAR α gene expression ($P= 0.001$, $t= -6.954$; $P= 0.001$, $t= -5.871$; respectively). **Conclusion.** The results revealed that both of them on land and water training, increase PPAR α gene expression in middle-aged women after coronary artery bypass and a possible reverse cholesterol transport process can be improved, so it is recommended that this type of training program, cardiac rehabilitation should be employed.

KEY WORDS: PPAR- α , Exercise Training, Coronary Artery Bypass Grafting, Peripheral Blood Mononuclear Cells.

INTRODUCTION

Cardiovascular diseases are the primary cause of death and disability in the world (1, 2).

Coronary artery disease refers to the complete or partial narrowing or blockage of the coronary

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artery due to atherosclerosis, spasm or thrombosis, in which it is impossible to provide myocardial muscle with oxygen, thereby resulting in angina and heart attack (3). Coronary artery bypass grafting (CABG) is a type of treatment in which the coronary blood flow increases through a bypass created by linking the areas before and after the blockage in the coronary arteries (4). In fact, only coronary artery bypass grafting can guarantee the survival of ischemic patients when medical treatment proves ineffective (5). Related studies indicated that approximately 35,000 to 50,000 heart surgeries are performed in Iran annually (6).

One of the causes of cardiovascular disease is changes in fatty acid balance (Homeostasis). It was shown that the effect of fatty acids is exerted through binding to soluble nuclear receptors and regulating of genes expression (7). Peroxisome proliferator activated receptors (PPARs) are among the most important nuclear receptors playing a vital role in obesity-related metabolic diseases such as hyperlipidemia, insulin resistance, and coronary artery diseases, and controlling fat homeostasis by regulating the expression of the genetic networks involved in metabolism, transport, storage and disposal of fat (8, 9). Regarding the effect of PPAR gene expression in atherosclerotic lesions and the down-regulation of multiple atherogenic genes, it has been suggested that the stimulation of PPAR expression or activity may have a beneficial effect on atherosclerotic disease process (9) and mainly control cellular metabolism (carbohydrate, fat and protein) and cellular differentiation (10). There are three isotopes of PPAR, called PPAR α , PPAR β/δ and PPAR γ , whose distributions vary in different tissues (8). PPAR α , which is expressed in the liver, heart, muscle, and kidney (9), regulates the transcription of some genes involved in the oxidation of cardiac fatty acids (11). The effect of PPAR agonists on the up-regulation of ATP binding cassette type A (ABCA1) has been scientifically confirmed (12). As a member of the large ATP binding cassette (ABC) family, (13) ABCA1 is essential for transmitting lipids through plasma membrane and maintaining the desirable HDL-C levels (14). These mechanisms can partly protect biological cells against cholesterol build-up. However, the modern

lifestyle, automation resulting in lack of physical activity, high-fat diets, changes in body composition, muscle strength and functional capacity have increased the risk of coronary artery diseases (CAD) requiring coronary artery bypass grafting (15). Cardiac rehabilitation is one of the most important measures for increasing the effectiveness and decreasing the complications of heart surgeries (16). Cardiac rehabilitation programs aim at limiting physical-psychological effects of cardiovascular disease, reducing the risk of sudden death or recurrent stroke, controlling cardiac symptoms, stabilizing and reversing the atherosclerotic process and improving psychosocial status (17). The impacts of exercise on cardiac rehabilitation have been highlighted during the recent decades (18). The low cost and attractiveness of these exercises can motivate patients to partake in cardiac rehabilitation programs (19). Traditionally, exercises performed in cardiac rehabilitation programs are mainly aerobic in nature, and include walking, jogging or biking. Researchers have recently discovered that resistance training can also be beneficial in rehabilitation programs. Furthermore, America Heart Association has recommended that resistance training should be included in cardiac rehabilitation programs twice a week (20). Based on previous studies on aquatic exercises, patients suffering from cardiovascular diseases claim to avoid swimming owing to adverse cardiorespiratory changes during swimming. It has also been reported that even light swimming can cause maximum oxygen consumption and heart rate overreactions particularly in patients with poor swimming skills. However, based on recent studies, the activities during which the head is kept above water- including walking in water or modified water games at appropriate temperatures- can be suitably low risk exercises for patients with coronary artery diseases. These activities motivate the patients further to carry out these exercises and optimize the anticipated cardiovascular adaptations resulting from exercising. Water sports- apart from swimming- which are done in upright positions and follow the principles are harmless activities, positively producing hemodynamic responses (20). Aquatic training is a comprehensive treatment approach designed to aid rehabilitation in different states

and to increase patients' self-confidence (21). Invasive procedures employed for treating cardiovascular diseases can undermine patients' physical, emotional and mental strength. Therefore, an approach with recreational and refreshing properties as well as treatment would be welcomed by patients (22). Although the use of hydrotherapy has increased dramatically during the past two decades owing to its impressive benefits (23), inadequate attention has been paid to the effects of aquatic training on cardiovascular diseases, thus leading to a notable absence of research in the field of aquatic resistance training (20). Some researchers have recently focused on the effects of PPARs activities on fat metabolism (24, 25) and studied the relationship between physical activities and PPARs gene expression. However, most of these studies were carried out on healthy subjects (26, 27) or animal models (28, 29), and mainly examined aerobic exercises and reported different results (26, 28, 29). In one study, Chen *et al.* (2014) reported a significant increase in PPAR- δ gene expression in skeletal muscles (vastus lateralis) after ten weeks of progressive resistance training in young men and women (30). In another study, Chen *et al.* (2016) found increased levels of PPAR- δ in skeletal muscles after single-session resistance training in young men and women (31). Regarding the relationship between reverse cholesterol transport (RCT) and cardiovascular diseases, the positive effect of physical activities on key factors affecting this process (14, 28, 32, 33) and the role of cardiac rehabilitation in limiting mental and physical effects of the disease, it appears that studying the factors involved in this process- especially the expression of genes and their regulatory mechanisms- can contribute to the prevention or more effective treatments of cardiovascular diseases. In addition, studies on the effects of rehabilitation on cardiac patients can evidently provide us with new information as well as new

ways of decreasing mortality in cardiac patients after coronary bypass grafting. There has only been limited research on the effect of aquatic resistance training on reverse cholesterol transport (20) with a noticeable gap in studies which focus on the effects of such trainings on the expression of genes in patients who have undergone CABG. As a pioneering research in the field of cardiac rehabilitation, the current study is aimed at examining PPAR α gene expression in peripheral blood mononuclear cells (PBMNCs) in middle-aged women having had CABG, after 8 weeks of aquatic and dryland resistance training programs.

MATERIALS AND METHODS

Participants. The statistical population of the present study comprised middle-aged female patients who had undergone coronary artery bypass previously and were referred to Shafa Hospital in Kerman. Thirty volunteers (aged 43-56 years) who met the inclusion criteria were selected for this study from the entire population.

Patients were excluded from this study if they had unstable angina, decompensated heart failure, and myocardial infarction within the last month, problematic ventricular arrhythmias (15) or any other limitations examined by the doctor. After initial clinical assessment and evaluation of the severity and extent of the heart disease by a physician, patients were included in the study if they had already had coronary bypass, had a homogeneous level of the disease, were relatively fit to carry out the exercises and had undergone coronary artery bypass between 3 months to 3 years before the study. Following a random screening, the participants were divided into control group (CON) (n=10), the aquatic resistance training group (ART) (n=10) and dryland resistance training group (DRT) (n=10). The basic anthropometric characteristics of the subjects are described in Table 1.

Table 1. Sample size and basic characteristics of subjects in each group (mean \pm standard deviation)

Variables Groups	Weight (kg)	Age (yrs.)	Height (m)
Dryland resistance training	81.1 \pm 9.50	49.9 \pm 4.14	155.7 \pm 2.26
Aquatic resistance training	79 \pm 10.48	50.2 \pm 3.61	159 \pm 6.09
Control group	72 \pm 10.26	49.6 \pm 4.06	158.8 \pm 4.82

Dryland training program. Dryland training program included eight weeks of resistance training (3 days a week /60 minutes per session) and consisted of warm-up (10 minutes), main activity (30 to 40 minutes) and cooling down (10 minutes). One-repetition maximum for subjects was determined using the formula (one-repetition maximum=amount of weight / [1.0278 – (0.0278 × the number of repetitions)] (34). Afterwards, the 8-session main activity was performed. It included machine bench press, seated cable row, inner thigh movements, Lat pulldown, pec deck, outer thigh movements, curl-ups, and hyper-extension with 2-3 sets of 12-15 repetitions with 60 % of one-repetition maximum. There were 30-second rests between exercises, and 5-minute rests between sets. One-repetition maximum test was repeated at the end of the fourth week in order to adjust the training protocol to the changes. According to the results obtained through this test, the training protocol continued until the end of the eighth week (20).

Aquatic resistance training. Aquatic training took place in a shallow pool (120 cm deep) at a temperature between 28-30°C. Aquatic training exercises (with 60 to 80% of one-repetition maximum for each exercise) lasted for 8 weeks (3 sessions per week/ 60 minutes per session) and included a warm-up (10 minutes), main activity (30-40 minutes) and cooling down (10 minutes). The main activity comprised 3 sets of upper-body dumbbell exercises including: shoulder shrugs, shoulder horizontal extension, shoulder extension with external rotation, and shoulder press with rotation, and lower body exercises with ankle weights including standing leg curls, supported squats, inner and outer thigh abduction, and sliding backward and forward with partial to full ranges of motion, with 8 repetitions during the first four weeks, and 10 repetitions during the 5th to 8th weeks. The training program of each session is different from other sessions, and was based on the principles of kinesiology, exercise science (20).

RNA, cDNA Synthesis. 10 ml of fasting blood samples were taken from brachial veins of subjects in all three groups 48 hours both prior to the beginning of the training program and after the last training session. The samples were collected in a test tube with EDTA anticoagulant

and transferred to the laboratory. After the isolation of mRNA of PBMN cells (14), the synthesis of cDNA was done using 200 ng of mRNA, primers oligo (dT) and Kit (Fermentas GmbH, which was made in Germany). Real-Time-PCR method was employed to investigate the expression of PPAR α . Table 2 illustrates the sequence of PPAR α primers (27) and Beta-actin (14).

Table 2. Oligo nucleotide sequences of primers

Gene	Type	Primers sequence
PPAR α	forward	tgaacgatcaagtga cat tgc
	Reverse	tgggaa gag aaa gat atc g
B-Actin	forward	cctatgttctcagcagcttc
	reverse	gaatttctggctgt ccc tg

Real-Time PCR. Polymerase chain reaction was performed by BIO RAD (C1000 TM Thermal Cycler) in microplates with 96 wells Real Time PCR which was run to measure the level of gene expression and the parameters for a two-step PCR were 95 °C, for 5 min, 1 cycle, then 95 °C, for 10 seconds and then 60 °C, for 30 seconds, 45 cycles and parameters for melting curve program were 55 to 95 (incremented 0.5 for f seconds) (35).

Statistical Analysis. The number of copies of the target and reference genes was measured by using cycle threshold (36). The data were then analyzed using descriptive and inferential statistics. Owing to the normal distribution of data in Shapiro-Wilk test, analysis of covariance was used to determine the differences between groups, whereas paired-samples t-test was used to find the differences within groups (SPSS version 16), with the significance level set at $p < 0.05$.

RESULTS

The results revealed a significant increase in PPAR α relative gene expression in PBMN cells in the aquatic and dryland resistance training groups compared to the control group ($F=15.573$, and $p=0.001$). In addition, the results of the aquatic training group indicated a larger number of insignificant changes on PPAR α gene expression in BPMN cells

compared to the dryland training group ($p=0.38$). Paired-samples t-test showed a significant difference in aquatic and dryland resistance training groups regarding PPAR α

gene expression in PBMN cells ($t=-6.954$ and $p=0.001$; $t=-5.571$, and $p=0.001$; respectively) (Figure 1).

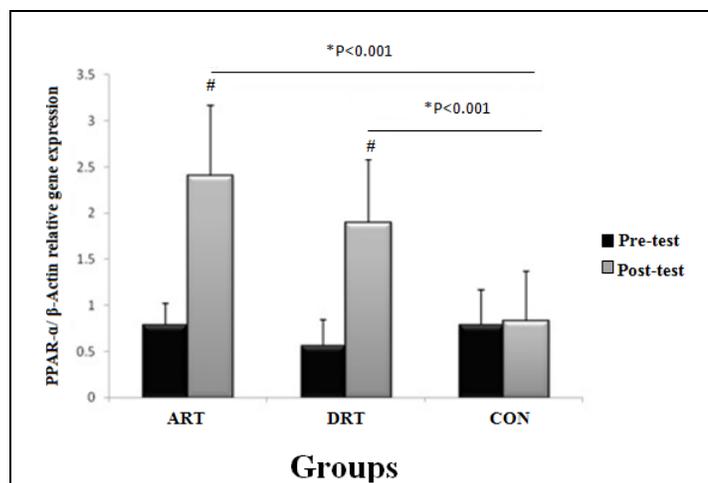


Figure 1. Peroxisome proliferator activated receptors (PPAR- α) gene expression in peripheral blood mononuclear cells (PBMNCs) of each group after 8 weeks of training. The results are expressed as mean \pm SD. Each column is for five subjects per group. **ART:** Aquatic resistance training. **DRT:** Dryland resistance training. **CON:** Control group. *: significant difference between groups. #: significant difference within groups.

DISCUSSION

The results of the current study indicated an up-regulation of PPAR α gene expression among CABG patients as a result of aquatic and dryland trainings. These positive changes were significantly different from the control group. However, there were no significant differences between the two training groups. Furthermore, the results of the aquatic training group showed a larger number of insignificant changes on PPAR α gene expression in BPMN cells compared to the dryland training group. This could be attributed to the entertaining nature of water games or higher motivation of subjects to follow the aquatic training program.

Cardiac rehabilitation programs aim at limiting physical-psychological effects of cardiovascular disease, reducing the risk of sudden death or recurrent stroke, controlling cardiac symptoms, and stabilizing and reversing the atherosclerotic process. Although studies have reported 18% of cardiovascular problems among patients participating in a comprehensive

cardiac rehabilitation program 10 years after coronary artery bypass grafting, this percentage increases to 35% among patients who refuse to participate in any rehabilitation programs (16). Studies investigating CABG patients have mostly focused on the role of physical activity in improving the quality of life through the evaluation of physical performance and muscle strength, social functioning, mental health, as well as body composition and lipid profile in these patients (15, 16, 37). Moghadam *et al.* (2009) studied the effect of aerobic and resistance training on functional capacity factors, serum lipid profile, blood pressure and muscle strength during cardiac rehabilitation. The control group in this study did only aerobic exercises while the other three performed a combination of aerobic and resistance training. Due to the combined therapeutic training in that study, there was an improvement in muscle strength in addition to the statistically significant changes in the blood serum HDL levels (38).

Afzalaghaiee *et al.* (2010) investigated the effect of cardiac rehabilitation on changes in blood lipid profile of Iranian men and women with coronary artery disease. Their rehabilitation program comprised 24 sessions of aerobic exercises including jogging on treadmill, pedaling on a stationary bike and arm ergometer workout, which resulted in significant changes in cholesterol factors, LDL, LDL/HDL ratio, and cholesterol/ HDL ratio (39). There has only been limited research on the effect of aquatic resistance training on reverse cholesterol transport (20) with a noticeable gap in studies which focus on the effects of such trainings on the expression of genes in patients who have undergone CABG. As a pioneering research in the field of cardiac rehabilitation, the present study is aimed at investigating PPAR α gene expression in PBMN cells in middle-aged women having had CABG, after 8 weeks of aquatic and dryland resistance training programs. As reported, the APT-dependent transporters in BPMN function as independent risk factors used for predicting atherosclerosis (14). BPMN cells were selected as the target tissue owing to the role of PPARs in the activation of ABCs (12) and the relative availability of these cells compared to other tissues. The results of the current study showed an up-regulation of PPAR α gene expression among CABG patients as a result of aquatic and dryland trainings. These positive changes were significantly different from the control group. However, there were no significant differences between the two training groups. In addition, the results of the aquatic training group showed a larger number of insignificant changes on PPAR α gene expression in BPMN cells compared to the dryland training group. This could be attributed to the entertaining nature of water games or higher motivation of subjects to follow the aquatic training program.

Previous studies have reported different responses of PPAR α gene expression to different exercises (26-29, 40). The study of Boucher *et al.* (2008) indicated an increased gene expression of PPAR γ after 8 weeks of light training (26). Spangenburg *et al.* (2009) examined the changes in PPAR gene expression in skeletal muscles after heavy training and only observed insignificant changes in PPARs after

each exercise (40). Iemitsu *et al.* (2002) found that exercising improves the induction of a decrease in PPAR α levels in the cardiac tissue of elderly mice (41). Petridou *et al.* (2007) investigated the effect of an 8-week optional wheel-running on the expression of various isoforms of PPAR, but did not observe any significant differences in the content of PPAR in the liver, muscle and fat tissues in the training and control groups (29). Tunstall *et al.* (2002) also investigated ergometer training programs (63% of maximal oxygen uptake, lasting for 60 minutes/9 days) done by healthy men and women. However, their result is different from those of the present study since they did not find any significant changes in PPAR α gene expression in skeletal muscle (42). This difference could be attributed to the type, intensity or duration of the training, which failed to induce the up-regulation of Peroxisome proliferator-activated receptors. As suggested in a study, increasing protein and mRNA levels of PPAR α gene requires training programs of at least 6 weeks with 60% to 80% maximal oxygen uptake (27). Russel *et al.* (2003) reported a significant increase in PPAR α gene expression in skeletal muscles in men who performed 8 weeks of resistance training (27). According to Fatone *et al.*, a combination of two-session aerobic training (55% to 70% maximal oxygen uptake) and circuit training (60% to 80% one-repetition maximum) results in a significant increase in PPAR α gene expression after 6 to 12 months, whereas PPAR γ increased after only 6 months (43). The findings of both researches are consistent with the results of the current study.

As reported in numerous researches, PPARs regulate an extensive network of genes involved in glucose and fat metabolism. In other words, PPAR α regulates fatty acid transport, mitochondrial fatty acid oxidation and ketogenesis (44). Also, physical activities stimulate lipolysis and increase the levels of free fatty acids which subsequently influence the direct effect of exercising on transcription factors of metabolism (27). PPAR α activators decrease the availability of fatty acids to produce triglyceride rich in very low-density lipoprotein (VLDL) in the liver. Hence, the physiological role of PPAR α receptor is to receive the total fatty acids in the food in key tissues. PPAR α

activity affects the expression of some encrypted genes for proteins involved in HDL-C metabolism. It also increases reverse cholesterol transport by accelerating the release of cholesterol from peripheral cells and cholesterol efflux in the liver which is achieved through vascular expression of HDL-C receptors, ABC-I transporters and scavenger receptor class B type I (SR-BI). In general, PPAR α affects lipid profile by increasing the production of HDL-C, accelerating the cholesterol efflux and hepatic uptake, and provides significant health benefits by increasing the protective effects of HDL-C. Furthermore, heightened activity of PPAR α increases the expression of lipoprotein lipase and apolipoprotein A-V (apo A-I) while it decreases the expression of apo C-III in the liver. As a result, VLDL particles are reduced, resulting in lower plasma triglyceride levels (45). In other words, PPAR α is known as one of the deterrents of atherosclerosis. To prevent atherogenesis, PPAR α agonists regulate ABCA1 in order to promote cholesterol efflux from macrophage and prevent early atherosclerosis (12). Several studies have shown that stimulating (PPAR α and PPAR γ) increases the expression of liver X receptor (LXR). As endogenous PPAR α agonists, fatty acids may also be effective in increasing LXR α expression (46). In other words, PPAR α agonists stimulate the ABCA1 gene expression through the LXR pathway (47). Given that PPAR γ activators can regulate LXR gene expression, they can also affect the levels of mRNA in ABCA1 indirectly. On the other hand, PPAR δ ligands regulate ABCA1 gene expression directly and through an unknown mechanism (48). LXR ligands stimulate the expression of ABCA1, ABCG1 and ABCG4 - which increase cholesterol efflux to HDL- through reverse cholesterol transport in macrophages. LXRs also increase the transcription of apolipoproteins (apo E, apo-C in macrophages and apo-D in fatty tissue) which are cholesterol receptors. Furthermore, LXRs positively regulate lipoprotein lipase, cholesterol ester transfer protein (CETP), and phospholipid transfer protein (PLTP), which are all involved in the reconstruction of lipoprotein (49). LXR also stimulates the synthesis of bile acids through its target gene, i.e cytochrome P450, family 7, subfamily A, member 1 (CYP7A1),

which is the main enzyme involved in the conversion of cholesterol into bile acids (50). Therefore, as regards the increase in the expression of PPAR and LXR due to exercising, some researchers have suggested that PPAR activation will lead to the primary activation of LXR. As a result, LXR causes the up regulation and increased expression of ABCA1 and ABCG1 transporters, resulting in further reverse cholesterol transport eventually (26).

Moreover, this research was limited to the effects of regular exercises on blood cells which might be showing similar effects on fat cells, hepatic cells and other types involved in fat metabolism. In other words, the difficulty of collecting human biopsy samples and the high costs of measuring multiple parameters involved in the process of reverse cholesterol transport were among the limitations of the current study, and affected the objective of this research which was to carry out a precise and comprehensive investigation of various cellular and molecular mechanisms.

CONCLUSION

The present study showed the desirable effects of aquatic and dryland resistance training on PPARs in women who have undergone CABG previously. Both training programs proved to be beneficial if included in cardiac rehabilitation of CABG patients. Given that many people currently suffer from atherosclerosis or require CABG, these training programs require further studies to investigate the effects of exercising on CABG patients.

APPLICABLE REMARKS

- Both types of resistance training on land and water can improve fat metabolism and some factors involved in the process of reverse cholesterol transport, the process of beneficial effects on patient recovery after coronary artery bypass surgery and therefore, this type of training is recommended on the part of the rehabilitation of the patient.

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