Research Paper:
Effects of Aerobic Exercises on Patients With Coronary Artery Disease

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ABSTRACT

Introduction: Prescribing the Adrenergic beta-Antagonists is very common in treating cardiovascular diseases. The aim of this study was to compare the effects of aerobic training in patients with coronary artery disease, prescribed two different types of beta-blockers (selective and non- selective) on the patient's lipid profile (Lipoproteins) and FBS (Blood Glucose).

Materials and Methods: Sixty patients with coronary artery disease, aged 45-65 years, were compared in two groups of selective (n=36) and non-selective (n=24) users of beta-blockers. The training program consisted of 8 weeks of aerobic exercise on the treadmill (3 sessions per week, about 50 minutes per session, with an intensity of 40% to 60% of the heart rate reserve). Each study patient's lipid profile and FBS level were obtained before the onset of the study and after the end of the intervention. The collected data were analyzed using repeated-measures Analysis of Variance (ANOVA).

Results: In the selective group, lipid profile and FBS did not significantly change. In the non-selective group, FBS and triglyceride levels were significantly reduced after the intervention; however, HDL, LDL, and total cholesterol levels were not significantly changed ($P>0.05$).

Conclusion: The results of this study showed that aerobic training in patients with CAD who used non-selective beta-blockers has more positive effects.

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Introduction

Cardiovascular disease is the leading cause of death, globally. In 2019, approximately 55.4 million individuals died worldwide; of which, 15 million (about 27% percent) were induced by cardiovascular disease; nearly 8.9 million of them were concerned with ischemic heart disease alone [1].

Coronary Artery Disease (CAD) refers to conditions in which, the narrowing of the coronary arteries leads to decreased blood flow to the heart muscle [2]. The main cause of the cardiovascular disease is atherosclerosis. Some risk determinants were identified that may increase the risk of developing atherosclerosis. Mainly, they include high serum Total Cholesterol (TC), Low-Density Lipoprotein Cholesterol (LDL), and High-Density Lipoprotein Cholesterol (HDL), as well as hypertension, smoking, diabetes, obesity, and a sedentary lifestyle [3].

Aerobic exercise, a component of cardiac rehabilitation, is an essential treatment modality for reducing cardiovascular mortality in patients with CAD [4]. Aerobic exercise was demonstrated to improve the prognosis of Cardiovascular Disease (CVD). Compared to pharmacotherapy, aerobic exercise is easier to perform and has fewer adverse effects [5].

Multiple studies focused on the relationship between aerobic exercise and HDL. Accordingly, they found that HDL levels are more sensitive to aerobic exercise than LDL and Triglyceride (TG) levels [6-9]. Increased LDL concentrations were repeatedly identified to be associated with an increased risk of myocardial infarction and vascular death [10]. High-Density Lipoprotein (HDL) is a strong, consistent, and independent predictor of cardiovascular events, i.e., confirmed by numerous prospective studies on different racial and ethnic groups worldwide [11, 12] Decreasing serum cholesterol can help reduce the risk of CAD [13]. In addition, TG can enter the arterial wall and then accumulate there; thus, causing the possibility of atherosclerosis [14]. It is reported that exercise can induce lower plasma TG concentrations [6, 7].

Unlike HDL, the effect of exercise on LDL is inconsistent in individuals. There are even completely contrary results [6, 7]. Some studies reported that aerobic exercise alone did not change the fasting blood LDL levels [9]. In some patients with mild to moderate dyslipidemia, the researchers found that after a few months of aerobic exercise, LDL did not change significantly [15].

Exercise can help improve lipids profile. Pedersen and Saltin concluded that exercise can positively impact symptoms and physical health by investigating multiple meta-analyses about exercise and lipid profiles [16].

Numerous factors lead to different results on the effects of aerobic exercise on lipoprotein levels, such as various training times or training intensities. Some researchers believe that to keep this effect longer, aerobic exercise time also needs to be longer; also, exercise intensity, time, and exercise volume influence exercise-induced changes in blood lipids. To further reduce LDL and TG levels, it is necessary to increase the aerobic exercise intensity. However, this is difficult to achieve in individuals with CAD who are of limited exercise capacity or other risk factors [6, 9].

Exercise plays an essential role in reducing mortality and morbidity associated with cardiac rehabilitation programs due to its physiological effects on the body [17, 18]. According to recent guidelines, beta-blockers are recommended as the first line of heart attack prevention regimens. Beta-Blockers reduce mortality and disease complications in individuals with hypertension, CAD, acute myocardial infarction, and heart failure [19].

Beta-Blockers are generally divided into two subgroups, as follows: cardio-selective beta blockers that possess a higher affinity for cardiac β1-receptors than for β2-receptors; and non-cardio-selective beta-blockers [20]. The effect of beta-blockers on the human body is inconsistent with the physiological effects of exercise. Beta-Blockers, reduce heart rate, heart contractile strength, and blood pressure; thus, they decline the myocardium's need for oxygen and improve chest pain. However, aerobic exercise, by increasing the need for oxygen and blood supply to active muscles, increases heart rate and blood pressure, during exercise [19]. A long-term administration of beta-blockers in some patients with the features of metabolic syndrome, could increase triglyceride levels and decrease high-density lipoprotein levels [21]. The antagonism of peripheral beta-adrenergic receptors is much less with the cardio-selective beta-blockers. Besides, lower doses of these agents present negligible effects on lipoprotein parameters. Thus, for patients who require a beta-blocker, a cardio-selective agent may be preferred [22, 23].

Cardiac rehabilitation is mainly based on exercise prescribing. Besides, it is important to recognize how certain medications, like beta-blockers, affect patients' ability to perform an effective and safe exercise; then design exercise programs that meet the specific needs of patients [24]. The effect of different types of beta-blockers on the patient's exercise program during cardiac rehabilitation is neglected in choosing the prescribed beta-blocker. Therefore, due to the widespread prescription of these medications in CAD, we intended to study the interaction effects of beta-blockers and aerobic training on FBS and lipid profile. We also separately compared them in selective versus non-selective beta-blockers between patients with CAD.

Materials and Methods

This was a quasi-experimental clinical trial. The population of the study included patients with CAD who were referred to the cardiac rehabilitation center of Shahid Madani Hospital in Tabriz City, Iran. Sampling was performed among the available and field samples of CAD patients who were treated with one of the drugs of two different types of beta-blockers (selective or non-selective) due to CAD. The study samples were entered into the research after fulfilling the basic conditions and obtaining informed consent.

The number of eligible patients who participated in the study included 62; of which, 25 subjects were taking non-selective beta-blockers (propranolol or carvedilol) and 37 were taking selective beta-blockers (atenolol or metoprolol). The gender distribution in the groups was to some extent similar. In the non-selective group, 79.2% and 20.8% of the subjects were male and female, in sequence. In the selective group, 69.4% were male and 30.6% were female. In the non-selective group, 50% of patients received propranolol and 50% carvedilol; in the selected group, 83.3% of patients used metoprolol, and 16.7% used atenolol. One of the patients in the non-selective group was excluded from the study due to the addition of digoxin to his treatment plan and the interaction of this drug with beta-blockers. Furthermore, one of the patients in the selective beta-blockers group could not continue to participate in the study due to lower limb problems. Therefore, in this study, 60 patients with CAD in two groups of selective (n=36) versus non-selective (n=24) beta-blocking agents were evaluated.

Sampling was performed among the available cases, which included almost all eligible cases. Patients entered the study after the inclusion criteria were met. Being in the low or moderate risk stratification, awareness of the research process by obtaining informed consent, and the ability to perform exercise was some of the inclusion criteria of the research. Moreover, the inability to exercise and using synergistic drugs or other medications that reduce the effect of beta-blockers were also some of the exclusion criteria of the study. Patients were gradually referred to the cardiac rehabilitation center; thus, the sampling and research process lasted approximately a year.

Contrary to the usual where old methods are used and not much attention is paid to new guidelines, the exercise protocol in this study was adjusted to ACSM's guidelines for exercise prescription and some other newer principles, including the following components [7, 25]:

According to the objectives of the study, the type of exercise for patients was continuous aerobic training, i.e., performed using a treadmill.

Three sessions of aerobic training were performed every other day per week, for 8 weeks.

Exercise intensity was determined by the Karvonen formula in the range of 40% to 60% of the reserved heart rate. When beta-blockers suppress heart rate, it is problematic to use the target heart rate (Karvonen equation) to measure the intensity of exercise. Therefore, we considered this point in calculating the maximum heart rate before calculating the target heart rate, by the following equations [17].

Maximum Heart Rate in CAD patients taking beta-blockers equation:

$$HR\ max=164-(0.7\times Age)$$

Heart Rate Reserve equation:

$$HRR\ (Heart\ Rate\ Reserve)=HR\ max-HR\ rest$$

Target heart rate (Karvonen equation):

$$Target\ HR=(HRR\times\%\ Intensity)+HR\ rest$$

Each session lasted 20-45 minutes for the main stage of training (conditioning phase), excluding the time required for warming up, cooling down, and stretching, and lasted an average of 50 minutes.

Exercise progress was separately defined per patient based on their conditions. It depended on some factors, such as age, functional capacity, and health conditions. In patients with favorable appearance and general conditions, the main phase of their training was increased to 5 to 10 minutes for one to two weeks. The intensity of the exercise started from 40% of the reserve heart rate, and after the patient could complete the main phase of the training for 20 minutes without any problems, the intensity of the workload gradually increased to a maximum of 60% of the reserve heart rate.

Laboratory tests included Lipid Profile (HDL, LDL, total cholesterol, & triglyceride) and FBS, i.e., performed once 48 hours before the start of the study and once after the end of the cardiac rehabilitation period; the results of the study were then statistically evaluated. The tests were performed taking by following the below considerations:

• The type of diet can affect the results of blood lipid tests; thus, the study subjects were requested to fast 12 hours before the test.

• During fasting, the study subjects avoided eating food and any snacks. Concurrently, they could drink the usual amount of water but avoid smoking, chewing gum, and exercising.

• The research subjects were requested to avoid eating high-fat foods for a week before taking blood samples.

• Blood samples were obtained from all examined patients at around 8 AM.

First, the Kolmogorov-Smirnov test was used to test the normality of the data. Since the distribution of research was normal, repeated-measures Analysis of Variance (ANOVA), Dependent Samples t-test, Independent Samples t-test, and Pearson correlation were used. The analyses were also performed in two sections; descriptive statistics and inferential statistics. In the part of the descriptive statistics, a general description of the research variables was presented and in the inferential statistics part, the distribution of the scores of variables was evaluated. Then, the study variables were compared in the selective and non-selective groups before and after the intervention. The significance level for the study was set at 5%; therefore, the researchers attempted to be 95% sure of the study result, willing to accept the wrong result, 5% of the time.

Results

For all variables studied before and after the intervention and their changes, the mean and standard deviation values were calculated and reported in Table 1.

The Dependent Samples t-test was used to compare the mean values before and after the intervention in the non-selective group. The Dependent Samples t-test data are listed in Table 2. In the non-selective group, the mean FBS and TG levels significantly decreased after the intervention. The mean HDL, LDL, and TC levels did not change significantly.

Dependent Samples t-test was also used to compare the mean values of the variables before and after the intervention in the selective group. The Dependent Samples t-test results are provided in Table 3. Based on Table 3, in the selective group, none of the variables significantly changed after the intervention.

To compare the mean FBS levels before and after the intervention in the selective and non-selective groups, repeated-measures ANOVA was used. The ANOVA results indicated that the interactive effect of time and group on the FBS of the subjects at the 95% probability level was significant (P=0.016, Eta-squared=0.10, F=6.18). In other words, the rate of FBS change of the subjects was significantly different before the intervention and after the intervention in the selective and non-selective groups. FBS loss was observed in the non-selective group, while an increase was observed in the selective group (Tables 4 and 5).

The relevant results suggested that the interactive effect of time and group was not significant on the HDL of the subjects at the 95% probability level (P=0.58, Eta-squared=0.005, F=0.31). In other words, the rate of change in the HDL of the subjects was not significantly different before the intervention and after the intervention in the selective and non-selective groups (Tables 6 and 7).

The obtained results revealed that the interactive effect of time and matched normal group was not significant on the LDL of the explored subjects at the 95% probability level (P=0.80, Eta-squared=0.001, F=0.06). In other words, the rate of change in the subjects' LDL did not significantly differ before the intervention and after the intervention in the selective and non-selective groups (Tables 8 and 9).

The collected results indicated that the interactive effect of time and matched normal group was not significant on the TG level of the subjects at the 95% probability level (P=0.62, Eta-squared=0.004, F=0.24). In other words, the rate of change in the TG of the subjects was not significantly different before the intervention and after the intervention in the selective and non-selective groups (Tables 10 and 11).

Table 1. Descriptive indices of the examined variables

Variables	Mean±SD					
	Non-selective ß-blocker group		Selective ß-blocker group		Total	
	Pretest	Posttest	Pretest	Posttest	Pretest	Posttest
Age	5.42±6.36	-	56.44±7.67	-	56.03±7.14	-
Height	169.83±6.98	-	167.85±8.31	-	168.64±7.81	-
Weight	83.62±9.38	82.10±8.88	79.51±7.84	79.56±7.87	81.15±8.66	80.57±8.31
BMI	29.11±3.83	28.60±3.88	28.30±3.21	28.30±3.17	28.62±3.46	28.42±3.44
Waist circumstance	98/02±4.77	96.52±4.60	97.89±6.30	96.56±5.95	97.94±5.69	96.54±5.41
Exercise capacity (MET)	7.40±2.37	10.27±2.28	8.88±2.33	10.03±2.69	8.29±2.44	10.13±2.52
Weight difference	-	-1.53±2.80	-	0.05±0.79	-	-0.58±2.01
BMI difference	-	-0.50±0.92	-	0.00±0.27	-	-0.20±.066
Waist circumstance difference	-	-1.50±1.02	-	-1.33±1.04	-	-1.40±1.02
Exercise capacity difference	-	2.86±2.23	-	1.16±2.75	-	1.84±2.67

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The achieved results demonstrated that the interactive effect of time and matched normal group on the TC of the subjects was not significant at the 95% probability level (P=0.59, Eta-squared=0.005, F=0.29). In other words, the rate of change in the TC of the subjects before and after the intervention was not significantly different in the selective and non-selective groups (Tables 12 and 13).

Discussion

In this study, the effects of 8 weeks of aerobic exercise were compared on lipid profile and FBS levels in CAD patients who used one of the two groups of selective versus non-selective beta-blockers. The effects of aerobic exercise interventions have been extensively studied on various diseases. A systematic review and meta-analysis of RCTs, including 48 trials with a total of 8940 patients revealed that exercise-based cardiac rehabilitation was associated with a significant reduction in total cholesterol and triglyceride levels. There was no significant dif-

Table 2. Dependent samples t-test results to compare the Mean±SD of the study variables before and after the intervention in the non-selective group

Variables	Time	Mean±SD	t	Degrees of freedom	Sig.
Weight	Before intervention	83.62±9.38	2.67	23	0.014
	After intervention	82.10±8.88			
BMI	Before intervention	29.11±3.83	2.68	23	0.013
	After intervention	28.60±3.88			
Waist circumstance	Before intervention	98.02±4.77	7.19	23	0.001
	After intervention	96.52±4.60			
Exercise capacity	Before intervention	7.40±2.37	-6.30	23	0.001
	After intervention	10.27±2.28			

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Table 3. Dependent Samples t-test results to compare the Mean±SD of the variables before and after the intervention in the selective group

Variables	Time	Mean±SD	t	Degrees of freedom	Sig.
Weight	Before intervention	79.51±7.84	-0.35	35	0.732
	After intervention	79.56±7.87			
BMI	Before intervention	28.30±3.21	-0.04	35	0.966
	After intervention	28.30±3.17			
Waist circumstance	Before intervention	97.89±6.30	7.73	35	0.001
	After intervention	96.56±5.95			
Exercise capacity	Before intervention	8.88±2.33	-2.53	35	0.016

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Table 4. Box and Levin test results to examine the homogeneity of covariance matrix and FBS variance error

Variales	M Box	F	Degrees of freedom 1	Degrees of freedom 2	Sig.
	6.211	**3.229**	**3**	**126888.236**	**0.055**
Before intervention	-	1.365	1	58	0.247
After intervention	-	1. 487	1	58	0.233

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Figure 1. FBS levels before and after intervention in the selective and non-selective groups

Table 5. Results of repeated mixed ANOVA test to examine the effect of group and time on patient's FBS

Source of change	Sum of squares	Degrees of freedom	Mean of squares	F	Sig.	Eta squared
Time effect (before & after)	193.235	1	193.235	0.746	0.391	0.013
Group effect	766.735	1	766.735	0.560	0.457	0.010
Interactive effect if time & group	15099.068	1	1599.068	6.176	0.016	0.096
Time error	15016.632	58	258.907	-	-	-
Group error	79343.132	58	1367.985	-	-	-

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Table 6. Box and Levin test results to investigate the homogeneity of covariance matrix and HDL variance error

Variable	M box	F	Degrees of freedom 1	Degrees of freedom 2	Sig.
	1.138	**0.364**	**3**	**126888.236**	**0.779**
Before intervention	-	0.424	1	58	0.517
After intervention	-	0.221	1	58	0.64

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ference in the levels of low-density and high-density lipoprotein cholesterol, compared to conventional care [27].

A large body of literature examined the effects of aerobic exercise on TC and triglyceride in some patients. Depending on the sample, time, intensity, frequency, a form of exercise, duration of randomized controlled trials, and different types of nutrition, the specific effects of aerobic exercise on patients' blood lipid levels may vary. Additionally, medications, like beta-blockers can affect glucose and lipid metabolism; they also differ in their mechanism of action and their effect on glucose and lipid metabolism based on differences in the type of beta-blockers [14]. The present study data indicated that in the non-selective group, the mean of the two variables FBS and triglyceride levels, significantly decreased after the intervention. The mean values of HDL, LDL, and TC levels did not significantly change. However, in the selective group, none of the studied variables significantly changed. The findings of this study can be summarized as follows in Table 4:

The statistical comparison of research results between selective and non-selective groups reflected that the rate of changes was not significant in patients' TG and TC, before and after the intervention. Aerobic exercise in these two variables, especially in the non-selective group significantly decreased TG levels and was beneficial for both groups of patients; however, no significant difference was observed in the effects of aerobic exercise between the study groups. The rate of changes in HDL and LDL in individuals before and after the intervention was not sig-

Table 7. Results of repeated mixed ANOVA test to examine the effect of group and time on patient's HDL

Source of change	Sum of squares	Degrees of freedom	Mean of squares	F	Sig.	Eta squared
Time effect (before & after)	104 196	1	104 196	3.668	0.060	0.059
Group effect	14.535	1	14.535	0.111	0.740	0.002
Interactive effect of time & group	8.778	1	8.778	0.309	0.580	0.005
Time error	1647.795	58	28.410	-	-	-
Group error	7578.183	58	130.658			

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Figure 2. HDL levels before and after intervention in the selective and non-selective groups Journal of Exercise Science and Medicine

nificantly different in any of the selective and non-selective groups. In other words, the effect of aerobic exercise on LDL and HDL levels was not significant in the patients; the mean of these two variables was not significantly different in individuals after the intervention.

The present study findings indicated that the rate of FBS changes in individuals before and after the intervention was significantly different in the selective and non-selective groups. A decrease in FBS was observed in the group taking non-selective medications; however, in the group that took selective beta-blockers, it manifested no significant effect. Even a slight increase was observed in FBS. Therefore, the effect of aerobic exercise on FBS changes was more beneficial in CAD patients using non-selective beta-blockers, which reduced this cardiovascular risk factor. Therefore, using beta-blockers of both selective and non-selective types may neutralize some

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Figure 3. LDL levels before and after intervention in the selective and non-selective group Journal of Exercise Science and Medicine

of the positive effects of aerobic exercise observed in previous studies. Non-Selective beta-blockers, especially carvedilol, are lipophilic; however, selective beta-blockers, especially atenolol, are hydrophilic. Accordingly, non-selective beta-blockers with higher fat solubility have a higher volume of distribution and hepatic first-pass effect and may have more central effects due to their greater entry into the central nervous system [19, 20, 28].

Furthermore, drug binding to plasma proteins in non-selective beta-blockers is much greater than that in selective beta-blockers [5]. As a result, exercise-active muscles have greater access to non-selective beta-blockers, especially carvedilol, which also present vasodilatory effects. This is probably why the positive effects of aerobic exercise were greater in patients using non-selective beta-blockers. Selective beta-blockers, such as atenolol and metoprolol are non-vasodilating and decrease blood pressure, as they reduce cardiac output and may increase or have no significant effect on peripheral vascular resistance. Consequently, these beta-blockers are associated with exacerbating glycemic and lipid control [14].

Very few cardiac patients were referred to cardiac rehabilitation centers; therefore, the size of the study population was small. Consequently, the researchers selected almost the entire population as a sample. Subsequently, the study sample size was restricted. Another limitation of this study was the lack of complete control of patients' nutrition despite providing the same nutritional recommendations to all of them, because differences in the type of nutrition may affect laboratory results [3].

The widespread introduction of various pharmacotherapies, as part of the routine management of cardiac patient therapies, may offset the magnitude of benefit associated with exercise-based rehabilitation. An argument put forward against the primary use of beta-blockers has been concerned about adverse metabolic effects, like unfavorable effects on lipids or insulin sensitivity [29]. Moreover, selective beta-blockers are indicated for patients with asthma, or diabetes, in whom ß2-receptor antagonism might associate with an increased risk of adverse effects [28]. Furthermore, based on the results of a review article conducted in 2013 by Ladage et al. [30], as well as a clinical trial conducted in 1990 by Ades PA et al. [31], it was suggested that selective beta-blockers might be preferred to non-selective beta-blockers in cardiac patients involved in the exercise.

Conclusion

The present findings of this study did not support these recommendations. Based on the research data, we concluded that the positive effects of aerobic exercise in reducing FBS and TG levels in patients with CAD who used non-selective beta-blockers were greater than the selective beta-blocker group. Aerobic exercise did not significantly improve lipid profile and FBS levels in patients taking selective beta-blockers; however, it had a more positive effect on those taking non-selective beta-blockers. Therefore, it is generally recommended that using non-selective beta-blockers may be preferred in patients with CAD who participate in aerobic exercise-based cardiac rehabilitation programs to benefit more from the positive effects of aerobic exercise.

Ethical Considerations

Compliance with ethical guidelines

All procedures of the project were carried out per ethical principles and the national norms and standards for conducting medical research in Iran and approved by the ethical committee for medical research. This study is under the support of Guilan University's Medical Research Ethics Committee (Code: IR.GUMS.REC.1398.061).

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Authors' contributions

Supervising review & editing: Farhad Rahmani-Nia; Methodology, writing – original draft preparation: Arash Layegh; Data collection and Data analysis: Naser Aslanabadi.

Conflict of interest

The authors declared no conflicts of interest.

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