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ORIGINAL RESEARCH

# The effect of special training exercise on FGF21 expression and FGFR-1 among CABG patients

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**Abstract**

**Background:** The aim of this study is to evalute special training exercise on the FGF21 and FGFR-1 among coronary artery bypass surgery (CABG) patients.
**Materials and Methods:** The study method was semi-experimental and the statistical population was patients who had heart disease, after coronary artery bypass surgery.
**Results:** The study results showed 8 weeks of special exercises among the experimental group had a significant increase in the expression levels of FGF21 and FGFR1 among CABG patients, compared to the control group. Physical activity may increase FGF21 levels, which is an important factor in oxidative stress and inflammation.
**Conclusion:** The study results showed 8 weeks of special exercises among the experimental group had a significant increase in the expression levels of FGF21 and FGFR1 among CABG patients, compared to the control group. Physical activity may increase FGF21 levels, which is an important factor in oxidative stress and inflammation.

**Keywords:** Special training exercise, FGF21, FGFR-1, CABG patients

## Introduction

Cardiovascular disease, according to the WHO report, will be the main factor of death all over the world by 2020. Cardiovascular disease is a global health issue despite widespread advances in recent decades[1]. Coronary artery disease (CAD) is a main cause of death in developed countries. It is happened by blockage of the arteries (atherosclerosis), which supplies blood to the heart muscle; the atherosclerotic process causes a significant narrowing of one or more coronary arteries. CAD treatment is designed to relieve the symptoms of myocardial ischemia and prevent myocardial infarction or sudden death. In many cases, the only useful treatment is re-vascularization by coronary artery bypass graft (CABG) surgery[2]. It can be, with certainty, said that no action in the field of treatment of cardiovascular diseases has affected the patients' life quality as much as heart surgery. Checking biomarkers of subclinical atherosclerosis and the pharmacological reduction of cardiovascular risk factors is still common[1]. Fibroblast growth factors (FGFs) secrete signalling proteins. Most FGFs, as paracrine or endocrine signals, play an important role in the growth, health and major organs disease, including the liver, kidneys, brain and bone. FGFs, as paracrine or endocrine signals, are also effective in heart growth and health and disease. Findings provide new insights about the FGF role in the heart performance and potential treatment strategies for heart disorders[3]. The metabolic properties of endocrine FGF21 have extensively studied over the last decade. Previous studies showed the fat-reducing, anti-inflammatory and antioxidant properties of FGF21. It is secreted in response to a wide range of physiological and pathological stimuli, mainly in liver and lipid tissue. It improves lipid profiles among animal and laboratory studies, also, inhibits key processes in the pathogenesis of atherosclerosis. It exerts its effects on the cardiovascular system through dependent mechanisms and Adiponectin. However, the signaling pathways through which FGF21 exerts its effects on endothelial cells remain unknown; it need further investigation[4]. High circulating FGF21 levels in cardiovascular disease have also raised a question about whether FGF21 can be used as a marker to predict subclinical atherosclerosis and cardiovascular disorders. The anti-atherosclerotic effects of FGF21 have investigated through two recent clinical trials; the FGF21 analogue significantly improved cardiac disorders among obese patients with type 2 diabetes[4]. This study evaluates recent developments and suggests FGF21 may play an important role in atherosclerosis. Seven important proteins are created by alternative compounds, which have different FGF binding properties that interact independently with FGF and FGFR; they are essential for stabilizing the relationship between FGFs and FGFRs. The FGF-FGFR-heparansulfate complex leads to FGFR dimerization and direct activation of intracellular tyrosine kinase domains, followed by key intracellular signaling pathways, including Jak-STAT activator[5]. The level of angiogenic growth factors can change during cardiovascular surgery, for example, coronary artery bypass graft. Possible changes in the concentration of these factors can be measured in plasma before, during and after surgery[6]. Plasma levels of FGF-21 were determined in patients during and after CABG surgery. Concentrations of FGF-21 increased during surgery and returned to preoperative levels six hours after surgery, indicating that the heart could be a potential source of FGF-21. They also agree with other researchers that the administration of exogenous FGF-21 may be useful in patients undergoing coronary artery bypass graft surgery[7]. Exercise is a key element in patients with CAD. Cardiac rehabilitation (CR) usually begins during hospitalization (first stage), followed by a supervised outpatient 3-6 months program (second stage), and continues in the maintenance phase with minimal or no supervision (third stage). According to the American College of Sports Medicine, those with CABG should do aerobic exercise 3 to 5 times a week for 20 to 60 minutes per session with an intensity of 40 to 80% Vo2Peak. Resistance training is recommended 2 to 3 times a week with an intensity of 40 to 50% of voluntary contraction with a maximum of 10 to 15 repetitions[8]. For coronary heart disease patients, moderate-intensity exercise improved their performance and functional ability; it may provide more safety during unsupervised exercise. Low-intensity exercise also increases the acceptance of exercise programs,

especially for unhealthy and elderly patients. Cardiac rehabilitation exercise, without significant side effects or other side effects, increases activity capacity. For CABG patients, previous studies reported an increase in vO2peak, and the increase in absolute value depends on different exercise protocols and fitness primitive levels. Previous studies showed resistance training (RT) can only improve muscle strength. Sumide et al. reported a 6-month aerobic exercise and resistance training program are beneficial for CABG patients[9]. Short-term exercise for CABG patients can improve cardiorespiratory function, muscle strength, cardiac function, ventilation efficiency, hemodynamic function and life's quality. According to the above mentioned, the aim of this study was the evaluation of special training exercise on the FGF21 and FGFR-1 among CABG patients.

**Materials and Methods**

Sixteen patients were selected after coronary artery bypass grafting. They were selected after initial clinical evaluations including taking history, previous history of cardiovascular disease, clinical examinations and diagnostic procedures such as electrocardiogram, echocardiography and exercise test. Exclusion criteria included the physician's diagnosis, patients' absence from the exercise program and also lack of interest to participate.

*Data collection tools*

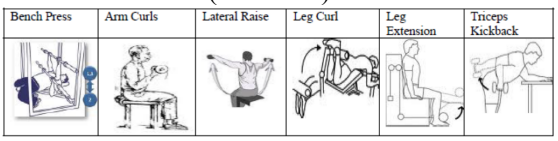
The process of study was fully explained to them, which included how to collect information, measuring height, weight, age, time and place of the class, etc. After the initial explanation, pre-tests were performed. Then, the subjects were randomly divided into two groups of control and experiment. Experiment group were exercised for 8 weeks; 3 sessions per week. At the end of 8 weeks, pre-test were repeated for them and recorded as post-test.

*Aerobic exercise program*

This program was designed and implemented similar to the Wisloff et al. program and the American College of Sports Medicine standards[8]. According to the patient's initial condition and the recorded exercise results, the heart rate range and the level / intensity or speed rate on treadmill for each patient were recorded on their file sheets. Patients were rested, between rotations for 5 to 10 minutes, depending on individual circumstances.

*Resistance training protocol*

Resistance training was performed for the experimental group, three times a week for 8 weeks (24 sessions). Resistance training recommendations of the American College of Sports Medicine (ACSM) was used in this study for those undergoing coronary artery bypass grafting (CABG)[8]. They performed a resistance training program based on the primitive level RM-1. They performed RM-1 test for six exercises at first day. Weight training started from 50% RM -1 and the intensity of training gradually increased to 75% RM-1. Six exercises focused on arm, shoulder and leg strength. Resistance training included bench press, arm curls, lateral raise, leg curl, leg extension and triceps kickback. Patients began resistance training with one set of 10 repetitions and gradually increased to two and three sets with a two-minute break between each set (as below).




*Data Implementation*

Following 12 hours of fasting and 48 hours of inactivity, the blood sampling process was performed from 7 to 8 morning by three laboratory experts, under the researcher supervision, from the right vein of the arm and in a sitting position. In order to separate the plasma from the blood, the test tubes were placed into the centrifuge at 3000 rpm for 10 minutes. The obtained plasma was then frozen at -80 ° C to measure the amount of desired variables. FGF21 and FGFR-1 levels were measured by ELISA kit.

*Statistical Analysis*

Shapiro-Wilk test was used to determine the normality of data distribution. Levene test was used to check the homogeneity of variances. In order to examine the changes within the group, the Paired sample t test is used for the dependent groups. Also, to test the statistical hypotheses, the parametric test of analysis of covariance (ANCOVA) was used; then, Bonferroni test was used. Significance level was considered $p < 0.05$ for all calculations.

## Results

The descriptive characteristics are shown in Table 1.

**Table 1. Mean and standard deviation of individual characteristics**

| Group | Variables | Experiment | Control |
|---|---|---|---|
| Pre test | Age | 14.6 ± 60.50 | 07.5 ±60.51 |
| Pre test | Height | 88.2 ± 40.177 | 69.10 ± 40.166 |
| Pre test | Weight | 73.8 ± 72.71 | 63.8 ± 12.91 |
| Post test | | 73.8 ± 72.71 | 63.8 ± 12.91 |
| Pre test | Heart rate at rest (number per minute) | 65.6 ± 60.77 | 07.5 ± 60.82 |
| Post test | | 51.7 ± 72 | 89.4 ± 80 |
| Pre test | Systolic blood pressure (millimeters of mercury) | 66.4 ± 40.127 | 36.7 ± 40.132 |
| Post test | | 5 ± 123 | 55.6 ± 129 |
| Pre test | Diastolic blood pressure (millimeters of mercury) | 41.6 ± 2.79 | 95.7 ± 2.80 |
| Post test | | 23.9 ± 8.73 | 54.5 ± 4.79 |
| Pre test | Total fat percentage | 76.4 ± 42.24 | 12.4 ± 12.29 |
| Post test | | 92.3 ± 90.20 | 8.3 ± 14.31 |
| Pre test | Total body strength (kg) | 15.28 ± 8.160 | 06.55 ± 4.135 |
| Post test | | 34.25 ± 166 | 4.13 ± 4.131 |

Data statistical comparison by Paired sample t test showed a selected training program on FGF21 level among the CABG patients in the pre-test stage compared to the post-test stage among the Experiment group had a significant increase ($p = 0.04$). Data statistical comparison by Paired t test showed a selected training program had no significant effect on FGFR1 level among CABG patients in the pre-test stage compared to the post-test stage for Experiment group ($p = 0.171$). Data analysis by covariance analysis test showed there was a significant difference in the FGF21 rate changes between the Control and Experiment groups ($p = 0.014$). The results of covariance analysis test for FGFR1 showed there was a significant difference between two groups ($p = 0.039$).

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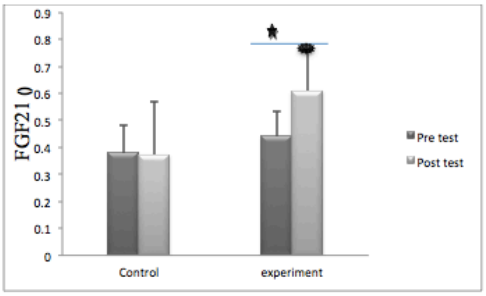
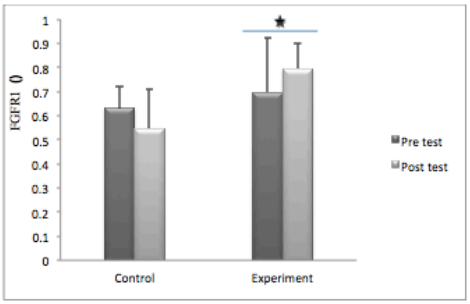
**Figure 4-1. FGF21 changes in control and experiment groups**




★ Significant differences with the control group

● Significant differences with Pre test

**Figure 4-2. FGFR1 changes in control and experiment groups**




★ Significant differences with the control group

● Significant differences with Pre test

## Discussion

The effect of a special training program on FGF21 and FGFR1 levels among CABG patients was investigated in this study. Data analysis showed this program on FGF21 level of CABG patients, in the pre-test stage compared to the post-test stage, had a significant increase for experiment group. Changes in FGF21 level of the control group, in the post-test stage compared to the pre-test stage, were not significantly different. Data analysis showed FGF21 changes of the experiment group, compared to the control group, had a significant increase. Also, FGFR1 levels changes of the control and experiment groups in the post-test phase were not significantly different from the pre-test. Data analysis also showed FGFR1 changes in the experiment group compared to the control group had a significant increase. Fibroblast growth factors (FGFs) as well as signaling proteins were secreted. Most FGFs, as paracrine or endocrine signals, play an important role in growth, health, and disease in major organs, including the liver, kidneys, brain and bone. FGFs also play an important role as paracrine or endocrine signals for heart growth, health and disease. These findings

provide new insights into the role of FGF in the heart and potential treatment strategies for heart disorders[10] . Kokkinos et al. 2017, investigated the role of FGF in atherosclerosis[11]. The metabolic properties of FGF21 have extensively studied over the past decade. Previous studies have shown the fat-reducing, anti-inflammatory and antioxidant properties of FGF21. FGF21 is secreted mainly in liver and adipose tissue in response to a range of physiological and pathological stimuli. Animal and laboratory studies of FGF21 have been shown to improve fat profiles and inhibit key processes in the pathogenesis of atherosclerosis. It exerts its effects on the cardiovascular system through dependent mechanisms and Adiponectin. However, the signaling pathways through which FGF21 exerts its effects on endothelial cells remain unknown and need further investigation. Recent findings from population studies should be confirmed before using FGF21 as a commercial marker in clinical settings in independent groups. The anti-atherosclerotic effects of FGF21 were investigated in two recent clinical trials, where treatment with the FGF21 analogue significantly improved cardiac profile in obese patients with type 2 diabetes. This study evaluated recent developments that suggest that FGF21 may play a role in atherosclerosis. Itoh et al. (2013) study examined the physiological role of FGF signaling in the heart[12]. Cardiac reconstruction leads to heart failure, which is the cause of morbidity and mortality. The heart's secretory proteins (Cardiomyokines) may play a role in heart regeneration. Fibroblast growth factors (FGFs) are proteins with a variety of functions, mainly secreted during development and metabolism. However, some FGFs play an important pathophysiological role in cardiac regeneration as cardiomyocytes. FGF21 increases blood pressure and cardiac fibrosis by activating MAPK signaling by activating the FGFR1c receptor. FGF21 improves fat profiles and protects against atherosclerosis in the body. Recent studies show the role of FGF21 in protecting against atherosclerosis. The ApoE / FGF21 (DKO) mice aggravates atherosclerotic plaque formation, hypertension and hypoadiponectinemia, premature death, increased macrophage uptake, smooth muscle cell proliferation, and increased brachiocephalic arterial cholesterol ester levels compared with APE knockout control (KO). ApoE / FGF21 DKO mice treated with FGF21 showed a greater reduction in plaque formation than mice treated with recombinant adiponectin. It has been suggested that FGF21 suppresses adiponectin expression, suppresses smooth muscle cell proliferation, and reduces the uptake of oxidized LDL by macrophages[13]. Angiogenic growth factor levels can change during heart surgery, such as coronary artery bypass graft surgery. Possible changes in the concentration of these factors can be measured in plasma before, during and after surgery[6]. Plasma levels of FGF-21 were determined in patients during and after CABG surgery. They observed that the concentration of FGF-21 increased during surgery and returned to preoperative levels within six hours after surgery. The results were consistent with those of other researchers and showed that the heart could be a potential source of FGF-2. They also agree with other researchers that the administration of exogenous FGF-21 may be useful in patients undergoing coronary artery bypass graft surgery[7]. The fat-reducing, anti-inflammatory, and antioxidant properties of FGF21 suggest that it may play a potential role in atherosclerosis and CVD. FGF21 inhibits key processes in the pathogenesis of atherosclerosis and reduces cardiovascular mechanical factors by direct and indirect mechanisms. It acts on endothelial cells to protect locally against atherosclerosis and also improves lipid profiles and reduces systemic inflammation[14]. For coronary patients, moderate-intensity exercise showed improve functional ability and may provide greater safety. Short-term exercise for patients with CABG demonstrated the benefits of cardiorespiratory function, muscle strength, metabolic profile, heart function, ventilation efficiency, hemodynamic function and quality of life. In addition, exercise may improve transplantation, reduce heart rate and re-hospitalization. Therefore, CR exercise training is an important intervention; it should be recommended to most patients after CABG. In the present study, the levels of FGF21 and FGFR1 in the post-test period and 8 weeks of selected exercises compared to the pre-test

stage, as well as in the experiment group compared to the control group had a significant decrease. Recently, the effect of exercise on FGF21 is considered and there are many published studies about this topic[15]. However, there is no firm conclusion or agreement on the results. The study by Ramos et al. Noted that daily physical activity was positively associated with increased serum FGF21 levels in healthy humans, and a two-week supervised exercise significantly increased serum FGF21 levels, which is consistent with the results of the present study[16].

There are new evidences that exercise reduces serum FGF21 levels in humans[17]. It is possible that the conclusion differences are related to the subjects and the difference in the physical condition of participants. The study results showed 8 weeks of special exercises among the experimental group had a significant increase in the expression levels of FGF21 and FGFR1 among CABG patients, compared to the control group. Physical activity may increase FGF21 levels, which is an important factor in oxidative stress and inflammation.

**Conflict of interest**

Authors declare no conflict of interest.

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