Original Article

The effect of combination training program on the expression of placental growth factor and vascular endothelial growth factor receptor 1 indicators among coronary artery bypass graft patients

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Abstract

Context: Short-term exercise can increase cardiorespiratory function, hemodynamic function, and quality of life in patients with coronary artery bypass graft (CABG).

Aims: The aim of this study was the evaluation of combination training program influence on the placental growth factor (PIGF) and vascular endothelial growth factor receptor 1 (VEGFR-1) indicators among CABG patients.

Setting and Design: The study method was semi-experimental; the statistical population was some patients who had heart disease, after CABG at Babol city hospitals, Iran.

Materials and Methods: 16 patients were selected by convenience sampling method.The expression levels of the PIGF and VEGFR-1 genes were measured by the Real Time PCR method.

Statistical Analysis Used: The covariance analysis method and the dependent t-test were used.

Results: The results showed that changes in PIGF and VEGFR-1 gene expression in the experimental group had a significant decrease in the posttest stage compared to the pretest stage; While changes in PIGF and VEGFR-1 gene expression in the control group were not significantly different in the posttest stage compared to the pretest stage; also, data analysis showed that changes in gene expression of PIGF and VEGFR-1 factors had a significant decrease in the experimental group compared to the control group.

Conclusion: The study results showed 8 weeks of combination exercises among the experimental group had a significant decrease in the expression levels of PIGF and VEGFR1 genes among CABG patients compared to the control group. Physical activity may decrease PIGF levels, which is an important factor in oxidative stress and inflammation.

Keywords: Coronary artery bypass graft patients, Combination training program, Placental growth factor, Vascular endothelial growth factor receptor 1

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INTRODUCTION

Cardiovascular disease (CVD) is one of the main causes of death all over the world, now.[1] According to the WHO, this disease will be the main cause of death worldwide by 2020. CVD is a global health problem, despite widespread advances over the past decades. Atherosclerosis is usually diagnosed after a cardiovascular problem such as a myocardial infarction or stroke which can leave vital organs in critical condition.[2,3] It is vitally important that post-coronary artery bypass graft (CABG) complications be reduced and cardiac output be increased in patients undergoing this surgical modality. Cardiac rehabilitation (CR) programs could prevent readmission and reduce health-care costs.[3] Hence, checking clinical atherosclerosis biomarkers and the pharmacological reduction of cardiovascular risk factors are still common in every research center.[4] Chronic diseases, in Iran, are the main causes of 70% of known deaths; 42% of them are CVDs. Among CVDs, coronary artery disease is the first and most common cause of death. As many as 1.5 million people suffer from myocardial infarction annually; more than 600,000 die each year from this disease complications. Previous studies in Iran showed 25-45 percent of deaths were due to CVDs.[5,6,2] No measures to treat CVD as much as heart surgery affected the patients' quality of life. CABG may have been the most significant innovation in the development of heart surgery by pulmonary heart transplantation techniques.[7] Coronary artery bypass grafting and coronary angioplasty are performed through the skin in order to get rid of angina that does not respond to medical treatment and are useful for prolonging life in some subgroups. PlGF, with a sequence similar to the vascular endothelial growth factor, is a primary pleiotropic cytokine that is able to stimulate angiogenesis and atherosclerosis induction by connecting and activating the receptor attached to Soluble fms-like tyrosine kinase-1.[8] PlGF expression through atherosclerotic lesions regulates and activates monocytes and macrophages, which subsequently cause inflammatory and vascular mediators; increasing the risk of plaque rupture.[9] On the other hand, inhibition of PlGF through genetic approaches and the use of PlGF antibodies reduces the atherosclerotic plaques size. There is a probability that vascular inflammation plays an important role in atherosclerosis. General inflammatory markers such as C-reactive protein, interleukin 6 (IL-6), and serum amyloid are associated with different results of coronary heart disease (CHD).[10] However, a placental growth factor (PIGF) in a family member showed to be vascular endothelial, which has a sharp increase in early atherosclerotic lesions. Evidence and medical documents suggest that PlGF acts as a major cause of atherosclerotic plaque inflammation. PlGF has recently showed to be an independent symptom of short-term side effects among those with chest pain suspected of having acute coronary artery syndrome (ACS).[11] Atherosclerotic inflammatory processes are stable after acute or medical intervention and cardiovascular events. It should be noted that PIGF baseline levels were also associated with an increased risk of cardiovascular complications during long follow-up among those who survived at first six months. The usefulness of it showed as a determinant of long-term results. It is important to note the baseline prognosis value of PlGF was independent of bioactive plaques activation and myocardium necrosis.[6] The growth factor PIGF, produced by stromal and tumor cells by binding to their receptors on endothelial cells, can directly cause the survival, migration and proliferation of endothelial cells. PIGF can also bind to its receptor as autocrine on stromal and tumor cells, producing MMF-9, insulin growth factor 1 receptor, platelet-derived growth factor (PDGF), stromal cell derived factor 1, granulocyte colony-stimulating factor, IL-8, vascular endothelial growth factor-a (VEGFA), and other angiogenic factors. They are involved in the survival, migration, and proliferation of endothelial and tumor cells. PIGF glycoprotein binds to FIT1 or vascular endothelial growth factor receptor 1 (VEGFR1), NP-1, and NP-2 receptors (neurofilins).[12] PIGF prevents the binding of VEGF (VEGFA) to VEGFR1 by binding to VEGFR1 and VEGFR1 solution (sVEGFR1). It can also detach the connection between VEGFR1 and VEGF. Finally, the concentration of VEGF increased, activating VEGFR2 and signaling the angiogenesis, cell growth, and proliferation. Furthermore, the binding of PIGF to VEGFR1 mediates the interaction between VEGFR1 and VEGFR2, ultimately increases the signaling pathway of angiogenesis, cell growth, and proliferation.[13] Vascular stenosis is a common side effect after CABG. One of the most important factors leading to transplant blockage is neo-intimal hyperplasia following systemic disorders (metabolic diseases, atherosclerosis, and hypertension) and local (adaptation to left-sided blood circulation).[14] It observed that most vascular (both venous and arterial) transplants lose the intima endothelium earlier than the coronary artery bypass grafting. The vascular (VEGF) family of peptides is regenerated. Exercise is a key point of CAD patients. CR usually begins during hospitalization (first stage, hospitalization), followed by a supervised outpatient program that lasts 3-6 months (second stage), and another stage is the maintenance of longevity with minimal or no monitoring (Step III).[15] According to the American College of Sports Medicine (ACSM), CABG patients should do aerobic exercises 3–5 times a week, for 20–60 min for each

session, with an intensity of 40%–80% vO2peak. It is also recommended strength training be performed 2–3 times a week with an intensity of 40%–50% of voluntary contraction with a maximum of 10–15 repetitions.[16] For coronary artery disease patients, moderate-intensity exercise was effective to improve performance ability; it may provide greater safety during unsupervised exercises. Low-intensity exercises also increase the acceptance of exercise programs,ecombinationly among unhealthy and elderly patients. Heart rate rehabilitation exercise without significant side effects or other side effects increases activity and performance.[17] For CABG patients, previous studies showed an increase in vO2peak; also, the increase in absolute value depends on the different exercise protocol and the initial level of fitness. In line with the above process, the importance of angiogenic factors in the extent of vascular graft should be considered from two different perspectives.[16] The initial activity of VEGFs, defined by ECs repair, should be considered as a desirable factor. In addition, prolonged VEGF activity in vascular bonds may lead to proliferation of smooth muscle cells and/or neo-intimal formation.[18] It can also cause joint failure and blockage. Monitoring the activity of VEGF peptides after CABG is not possible because transplantation is not available.[19] Plasma VEGFs concentration assessment does not provide information that is relevant to the actual vascular transplant status.[20] Therefore, determination of the status of the tissue before CABG vascular transplantation is important to assess the most accurate pattern of protein expression that can then be used to predict its future status. Given the above, the present study seeks to answer the question of what effect a combination training program course has on the expression of PIGF and VEGFR genes among CABG patients?.

MATERIALS AND METHODS

The statistical population of this study was those, after coronary artery bypass graft surgery, who had undergone surgery for at least 3 months. After calling to operate and after the initial clinical evaluations (history, previous CVD, clinical examinations and diagnostic procedures of electrocardiogram, echocardiography and exercise test were as follows: resting LVEF ≥30%, no complications during hospitalization, stable medication regimen, and study physician's approval), the combination is selected 16 patients, voluntarily, according to the results of exercise test into two groups. The sample size of was determined according to previous study and the framework of 2-month rehabilitation study;[21] also, the available facilities and equipment at rehabilitation centers. The inclusion criteria of the patients were the physician's permission, lack of movement ban, and individual permission. The exclusion criteria: physician diagnosis, the absence of patients for more than three sessions in the exercise program, and lack of interest to participate in the study, In case of abnormal heartbeat and blood pressure during exercise, chest pain,dizziness and nausea.

Data collection

After informing the individuals, and before the start of the exercise program, all subjects participated in a joint training session based on a pre-determined schedule, and the study process was fully explained. During the session,while introducing specific exercises and its benefits, a brief description of the program, was discussed. Then, the pre-test stage was taken from the subjects. They were then randomly divided into two groups. They did combination exercises three sessions a week. After eight weeks (3 sessions per week), they were tested again and the exercise effects, on each group, were evaluated.

Combination training protocol

Periodic aerobic exercise program

The sports program was similar to Wislowf *et al.* And the American Sports Medicine College of Design. Depending on the patient's initial condition and the results of the exercise test recorded on the patient's file, the heart rate, level, and intensity or speed of the treadmill for each patient were recorded on the exercise control sheet. Between periods of use, patients rested for 5–10 min, depending on individual circumstances. The sports program of this group was designed and implemented similar to the program of Wisloff *et al.* and the ACSM standards. Depending on the patient's initial condition and the results of the exercise test recorded on the patient's file, the heart rate and its intensity, the treadmill speed for each patient was recorded on the control sheet. Between sessions, patients rested for 5–10 min, depending on individual circumstances.

Strength training protocol

For the experimental group, strength training program was performed three times a week for 8 weeks (24 sessions). The study used strength training recommendations from the ACSM for those with CABG. They did a program based on the RM-1 level. First day, they performed the RM-1 test for six exercises. Lift training started at 50% RM-1 and gradually increased to 75% RM-1. Six exercises focused on arm, shoulder and leg strength. Strength training includes bench press, arm curls, lateral raise, leg curl, leg extension, and triceps kickback. Patients began strength training with one set of 10 repetitions and gradually increased to two and three sets with a 2-min break between each set [Figure 1].

Data implementation

All participants admitted to the medical diagnosis laboratory on an empty stomach between 8 and 9 in the morning. Following 12 h of fasting and 48 h of inactivity, the blood sampling process was performed by three relevant laboratory experts, under the supervision of a researcher, from the right arm vein and sitting position. In order to separate the plasma from the blood, the test tubes are placed inside a 3000 rpm centrifuge for 10 min. The resulting plasma will then be frozen to assess the desired variables at -80°C. The quantity and quality of extracted RNAs were calculated by the Nano Drop spectroscopy method ND-1000 (Thermo Sci., Newington, NH). Additional DNA (cDNA) was synthesized from RNA samples, using Revert Aid Reverse Transcriptase (Thermo science, Germany) at 42 C for one hour and random hexamer initiators (Thermo science, Germany). A Rotor-Gene 6000 thermo-cycler and a Real Q-PCR 29 Master Mix Kit were used in 40 cycles to amplify the process. Each reaction consisted of 5 microliter micron master and 100 nanometer primers. The RT-PCR maintenance phase was 95 C in 10 min. The cycle steps were as follows: 40 cycles, 95.0 C for 15 s; 60. C for 1 min. The initial sequences were synthesized as follows:

PIGF: 5'-TCATCTTCGTGCCCTTCAAT-3 forward (forward)

5'-GAGCGCGATAGTTGTCGAAGT-3 reve (reverse)

VEGFR1: 5'-ATCAATCAGCCCAGATGGAC-3 forward (forward)

5'-TTCACGGGCAGAAAGGTACT-3 reve (reverse)

Delta Ct (ΔCT) was calculated by the following formula:

(ΔCT = CT [target]-CT). The level of gene expression was determined, using the ΔCt 2–method.

Test performance considerations

At the beginning and end of the program, patients' blood pressure and heart rate were assessed to assess the patient's physical and physiological condition. In case of abnormality and acute abnormality during exercise, the patient's electrocardiogram would be printed at the same time and the intensity of exercise would be reduced. The patient was referred to a rehabilitation physician and if necessary, a cardiologist, along with the record and history of the session. Consent to attend the research process was obtained from all patients.

Statistical analysis

The Levene test is used to determine the variance homogeneity test and the Shapiro–Wilk test used to find the data distribution is normal. In order to study intragroup changes, used t-statistical model for dependent groups. Also, for statistical hypotheses, the parametric test of analysis of covariance is used; subsequently, the Bonferroni test was used. The significance level was considered to be $P < 0.05$ for all calculations.

RESULTS

The descriptive characteristics of the subjects are shown in Table 1.

The dependent *t*-test results, to determine intragroup changes in the PIGF expression indicator in control and experiment groups, showed the level of the desired factor in the post-test stage was not significant compared to the pre-test stage in the control group ($P = 0.181$) [Table 2]; however, a significant decrease in the level of PIGF expression was observed among the experiment group in the post-test stage compared to the pre-test ($P = 0.001$) [Table 2].

The results of the dependent *t*-test to determine intragroup changes in the VEGFR1 expression indicator in the control and experiment groups showed the level of the desired factor in the post-test stage was not significant compared to the pre-test stage among the control group ($P = 0.363$); however, a significant decrease in the level of VEGFR1 expression among the experiment group was observed in the post-test stage compared to the pre-test ($P = 0.045$) [Table 3].

Data analysis by covariance analysis test showed there was no significant difference in the rate of change in

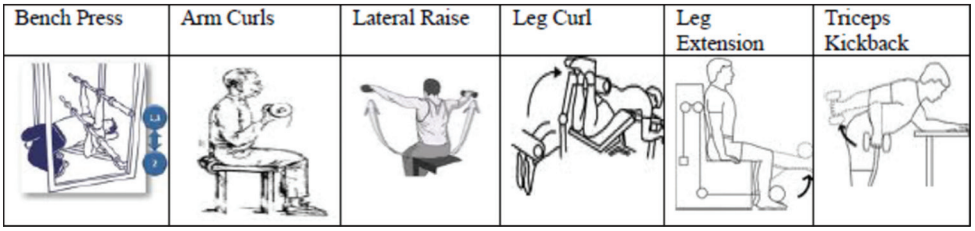


Figure 1: Intended sports programs[22]

Table 1: Mean and standard deviation of the individual characteristics

Group	Variables	Experiment	Control
Pretest	Age	50.60±6.14	51.60±5.07
Pretest	Height	177.40±2.88	166.40±10.69
Pretest	Weight	71.72±8.73	91.12±8.63
Posttest		71.72±8.73	91.12±8.63
Pretest	Heart rate at rest (number per minute)	77.60±6.56	82.60±5.70
Posttest		72±7.51	80±4.89
Pretest	Systolic blood pressure (millimeters of mercury)	127.40±4.66	132.40±7.36
Posttest		123±5	129±6.55
Pretest	Diastolic blood pressure (millimeters of mercury)	79.2±6.41	80.2±7.95
Posttest		73.8±9.23	79.4±5.54
Pretest	Total fat percentage	24.42±4.76	29.12±4.12
Posttest		20.90±3.92	31.14±3.8
Pretest	Total body strength (kg)	160.8±28.15	135.4±55.06
Posttest		166±25.34	131.4±13.4

PIGF expression between control and experiment groups ($P = 0.004$) [Table 4]. Also, the results of the Covariance analysis test regarding the VEGFR1expression showed there is a significant difference between control and experiment groups ($P = 0.028$) [Table 5].

DISCUSSION

Combination training program effects on the expression of PIGF and VEGFR-1 indicators among CABG patients was investigated in this study. Data analysis showed changes in the expression of PIGF and VEGFR-1 gene expression in the experiment group (post-test stage) were significantly reduced in comparison to the pretest. However, these changes in the control group (post-test stage) were not significantly different from the pretest Graph 1. Data analysis also showed changes in the expression of those factors among the experiment group decreased significantly in comparison to the control group Graph 2. Lenderink *et al*. (2003) in a study examined the level of PIGF in patients with acute coronary syndrome. In patients with ACS, increased plasma levels of PIGF are associated with adverse cardiac outcomes during long-term follow-up. These data suggest that PIGF as a specific marker of vascular inflammation should be considered for risk classification of patients with ACS rather than general markers of inflammation.[23,6] Cassidy *et al*. in a study investigated the possible role of plasma PIGF in predicting the risk of coronary artery disease in women. The results suggest that PIGF may be strongly associated with long-term prognosis of CHD, which is consistent with a possible role in early plaque formation and growth.[21] The biological roles of both PlGF and its specific receptor, Flt-1 (VEGFR-1) are currently unclear, with different mechanisms involved in explaining physiological and pathophysiological effects. Evidence suggests its pathophysiological role relates more to vascular inflammation than to angiogenesis, while its effects in healthy individuals relate to its role in the promotion of macrophage infiltration and/or mobilization of bone marrow-derived progenitors for macrophages or plaque neovessels in early plaque formation and growth.[24] PlGF has other known mechanisms of action including stimulation of vascular smooth muscle growth, recruitment of macrophages into atherosclerotic lesions and up regulation of production of TNFα and MCP1 by macrophages.[4] The PIGF produced by stromal and tumor cells, by binding to their receptors on endothelial cells, can directly cause the survival, migration and proliferation of endothelial cells. PIGF can also bind to, as autocrine, its receptor on stromal and tumor cells, producing PDGF, VEGFA and other angiogenic factors. These factors play a role in the survival, migration and proliferation of endothelial and tumor cells. PIGF glycoprotein binds to VEGFR1, NP-1 and NP-2 receptors.[25] Jones *et al*. Examined the concentration of VEGF-A in peripheral vascular patients as a result of physical activity and compared them with normal individuals. The results indicate an increase in VEGFR1.[26] PIGF prevents the binding of VEGF (VEGFA) to VEGFR1 by binding to VEGFR1 and sVEGFR1. It can also detach the VEGF which is connected to VEGFR1. Eventually, the concentration of VEGF increases, which activates VEGFR2 and signals the vasodilation, cell growth and proliferation. Moreover, the binding of PIGF to VEGFR1 mediates the interaction between VEGFR1 and VEGFR2; it ultimately increases the signaling pathway of angiogenesis, cell growth and proliferation.[13] PIGF, as an intrinsic mediator of vascular inflammation, is responsible for promoting angiogenesis and destabilizing plaques through the macrophages accumulation in atherosclerotic lesions via Flt-1[27] PIGF generally may play an important role in the pathogenesis of malnutrition-inflammation (atherosclerosis) syndrome; it helps to explain the high mortality rate among CKD patients. In the VEGF family system, the VEGF is another powerful ligand for Flt-1.[20] Although, VEGF was not associated with CKD severity and was less associated

Table 2: *t*-test information related to placental growth factor expression indicator in two groups

Group	Posttest		Pretest		Significance	*t*
	SD	Mean	SD	Mean		
Control	1.79	30.12	1.38	30.32	0.181	-1.553
Experiment	0.95	30.41	1.18	32.44	0.001	-6.674

SD: Standard deviation

Table 3: *t*-test information related to vascular endothelial growth factor receptor 1 expression indicator in two groups

Group	Posttest		Pretest		Significance	*t*
	SD	Mean	SD	Mean		
Control	1.74	30.29	1.98	30.06	0.363	1.000
Experiment	5.72	28.45	1.76	33.43	0.045	-2.656

SD: Standard deviation

Table 4: Covariance analysis test results related to placental growth factor expression indicator in different groups

	Total	Degree of Freedom	Mean	*F*	Significance
Modified model	18.071	2	9.036	28.947	0.000
PIGF (pretest)	17.816	1	17.816	57.076	0.087
Group	4.508	1	4.508	14.442	0.004

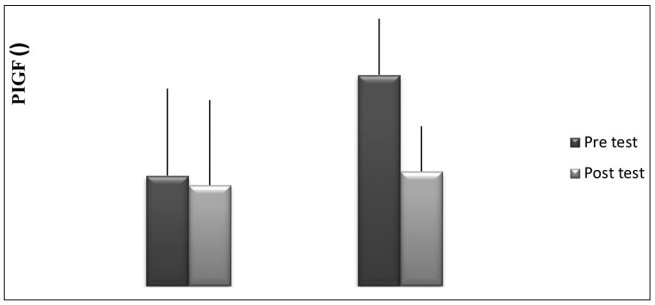
PIGF: Placental growth factor

Table 5: Covariance analysis test results related to vascular endothelial growth factor receptor 1 expression indicator in different groups

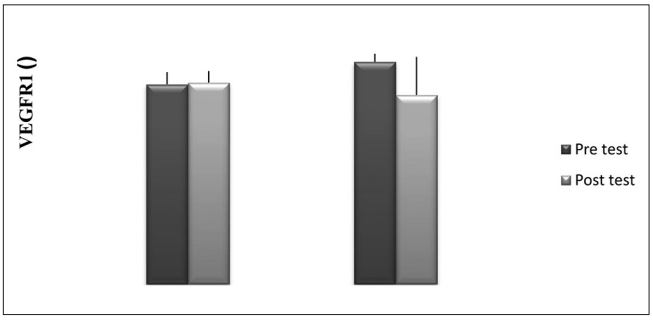
	Total	Degree of freedom	Mean	*F*	Significance
Modified model	91.888	2	45.944	4.244	0.05
VEGFR1 (pretest)	81.732	1	81.732	7.549	0.068
Group	74.161	1	74.161	6.850	0/028

VEGFR1: Vascular endothelial growth factor receptor 1

with mortality and cardiovascular causes in this study, it suggests PIGF could be a more important predictor. The effect of mortality and CVD among CKD patients from VEGF and therefore, clinically, related to the pathology of atherosclerosis associated with CKD.[25] The expression of PIGF in atherosclerotic lesions regulates and activates monocytes and macrophages. It subsequently causes inflammatory and vascular mediators; and increasing the risk of plaque rupture. In contrast, the inhibition of PIGF, through genetic approaches and the use of PlGF antibodies, reduces the size of atherosclerotic plaques.[1] However, PIGF, as a family member of vascular endothelial growth factor, showed to be highly increasing in premature atherosclerotic lesions. The evidence suggest PlGF acts as a major cause of platelet atherosclerotic plaque inflammation. Therefore, PlGF recently showed to be an independent trademark of short-term side effects among patients with chest pain who are suspected to have ACS. Atherosclerotic



Graph 1: Comparison of placental growth factor expression changes among control and experiment groups



Graph 2: Comparison of vascular endothelial growth factor receptor 1 expression changes among control and experiment groups

processes are stable after acute or medical intervention and cardiovascular events. The PIGF prediction value was independent from hsCRP, which indicates general inflammation.[28] The present study showed the expression levels of PlGF and VEGFR1 genes among the experiment group had a significant decrease compared to the control group. According to the recommendations of the ACSM , CABG patients should play Aerobic exercises 3–5 times a week for 20–60 min per session, with 40%–80% intensity of Vo2Peak. Therefore, CR exercise is an important intervention; it should be recommended to most patients after CABG. Previous studies showed moderate-intensity exercise may significantly increase muscle strength for those with heart diseases. It is recommended these patients start with low barbells; doing 8–10 different exercises, repeating 10–15 times. Some studies showed strength training may increase aerobic strength, but other researches showed strength training can only improve muscle strength. Sumid *et al*. reported a 6-month aerobic exercise and strength training programs are beneficial for CABG patients,[29] which is in consistent with the results of the present study.

CONCLUSION

The results of the present study showed 8 weeks of combination exercises among the experiment group caused a significant decrease in the PlGF expression levels and VEGFR1 genes among CABG patients, compared to the control group.

PIGF, as an intrinsic mediator of vascular inflammation, is responsible for promoting angiogenesis and destabilizing plaques through the accumulation of macrophages among atherosclerotic lesions and through Flt-1. It sounds physical activities can reduce PIGF levels, which is an important factor of oxidative stress and inflammation production.

Conflicts of interest

There are no conflicts of interest.

Authors' contribution

All authors contributed equally to this manuscript, and approved the final version of manuscripts.

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REFERENCES

1. American College of Sports Medicine: Guidelines for Exercise Testing and Exercise Prescription. 8th ed. Philadelphia: Lea & Febiger; 2010.
2. Khurana R, Moons L, Shafi S, Luttun A, Collen D, Martin JF, *et al*. Placental growth factor promotes atherosclerotic intimal thickening and macrophage accumulation. Circulation 2005;111:2828-36.
3. Lenderink T, Boersma E, Heeschen C, Vahanian A, de Boer MJ, Umans V, *et al*. Elevated troponin T and C-reactive protein predict impaired outcome for 4 years in patients with refractory unstable angina, and troponin T predicts benefit of treatment with abciximab in combination with PTCA. Eur Heart J 2003;24:77-85.
4. Cassidy A, Chiuve SE, Manson JE, Rexrode KM, Girman CJ, Rimm EB. Potential role for plasma placental growth factor in predicting coronary heart disease risk in women. Arteriosclerosis, thrombosis, and vascular biology. 2009;29:134-9.
5. Selvaraj SK, Giri RK, Perelman N, Johnson C, Malik P, Kalra VK. Mechanism of monocyte activation and expression of proinflammatory cytochemokines by placenta growth factor. Blood 2003;102:1515-24.
6. Denizot Y, Leguyader A, Cornu E, Laskar M, Orsel I, Vincent C, *et al*. Release of soluble vascular endothelial growth factor receptor-1 (sFlt-1) during coronary artery bypass surgery. J Cardiothorac Surg 2007;2:38.
7. Loghmani L. Jariyani A. Borhani F. Effect of preoperative instruction on postoperative depression in patients undergoing open heart surgery. Daneshvar 2006;14:33-42.
8. Domouzoglou EM, Naka KK, Vlahos AP, Papafaklis MI, Michalis LK, Tsatsoulis A, *et al*. Fibroblast growth factors in cardiovascular disease: The emerging role of FGF21. Am J Physiol-Hear Circ Physiol 2015;309:1029-38.
9. Luttun A, Tjwa M, Moons L, Wu Y, Angelillo-Scherrer A, Liao F, *et al*. Revascularization of ischemic tissues by PlGF treatment, and inhibition of tumor angiogenesis, arthritis and atherosclerosis by anti-Flt1. Nat Med 2002;8:831-40.
10. Wang S, Lu J, You Q, Huang H, Chen Y, Liu K. The mTOR/AP-1/VEGF signaling pathway regulates vascular endothelial cell growth. Oncotarget 2016;7:53269-76.
11. Fischer C, Mazzone M, Jonckx B, Carmeliet P. FLT1 and its ligands VEGFB and PlGF: Drug targets for anti-angiogenic therapy? Nat Rev Cancer 2008;8:942-56.
12. Heeschen C, Dimmeler S, Fichtlscherer S, Hamm CW, Berger J, Simoons ML, *et al*. Prognostic Value of Placental Growth Factor in Patients with Acute Chest Pain. J Am Med Assoc 2004;291:435-41.
13. Dalleck LC, Tischendorf JS. Guidelines for Exercise Testing and Prescription (ACSM). Encycl Lifestyle Med Health 2012;doi.org/10.4135/9781412994149.n165.
14. Smith KM, McKelvie RS, Thorpe KE, Arthur HM. Six-year follow-up of a randomised controlled trial examining hospital versus home-based exercise training after coronary artery bypass graft surgery. Heart 2011;97:1169-74.
15. Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, *et al*. Low grade inflammation and coronary heart disease: Prospective study and updated meta-analyses. Br Med J 2000;321:199-204.
16. Dashwood MR, Loesch A. Inducible nitric oxide synthase and vein graft performance in patients undergoing coronary artery bypass surgery: Physiological or pathophysiological role? Curr Vasc Pharmacol 2014;12:144-51.
17. Hosseinian A, Kasayi V, Mohammadzade AR, Habibzadeh S, Saghi F, Davari M. Evaluation of Early Complications of Coronary Artery Bypass Grafting Surgery (CABGS) in the First Month After Operation in Imam Khomeini Hospital of Ardabil During 2013-2014. Journal of Ardabil Unive Med Sci 2014;14:18-27.
18. Carmeliet P, Moons L, Luttun A, Vincenti V, Compernolle V, De Mol M, *et al*. Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. Nat Med 2001;7:575-83.
19. Roncal C, Buysschaert I, Gerdes N, Georgiadou M, Ovchinnikova O, Fischer C, *et al*. Short-term delivery of anti-PlGF antibody delays progression of atherosclerotic plaques to vulnerable lesions. Cardiovasc Res 2010;86:29-36.
20. Naghibi S, Kordi MR, Maleki MJ. Effect of concurrent training on hemodynamic responses in male patients with coronary artery. Rehabilitation 2008;8:6-11.
21. Jones WS, Duscha BD, Robbins JL, Duggan NN, Regensteiner JG, Kraus WE, et al. Alteration in angiogenic and anti-angiogenic forms of vascular endothelial growth factor-A in skeletal muscle of patients with intermittent claudication following exercise training. Vasc Med 2012;17:94-100.
22. Kon ZN, White C, Kwon MH, Judy J, Brown EN, Gu J, et al. The role of preexisting pathology in the development of neointimal hyperplasia in coronary artery bypass grafts. J Surg Res 2007;142:351-6.
23. Autiero M, Waltenberger J, Communi D, Kranz A, Moons L,Lambrechts D, *et al*. Role of PlGF in the intra-and intermolecular cross talk between the VEGF receptors Flt1 and Flk1. Nat Med 2003;9:936-43.
24. Kasper D, Braunwald E, Fauci A, Hauser S, Longo D, Jameson J. Approach to the Patient with Cardiovascular Disease: Disorders of the Cardiovascular System: Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill; 2008. p. 1301.
25. Liu Y, Coresh J, Eustace JA, Longenecker JC, Jaar B, Fink NE, *et al*. Association between cholesterol level and mortality in dialysis patients: Role of inflammation and malnutrition. J Am Med Assoc 2004;291:451-9.
26. Biasucci LM, Liuzzo G, Colizzi C, Rizzello V. Clinical use of C-reactive protein for the prognostic stratification of patients with ischemic heart disease. Ital Heart J 2001;2:164-71.
27. Sabzmakani L, Hazavoiy M, Rabiy M. Predisposing, Reinforcing, Enabling Causes in Educational Diagnosis and Evaluation (PRECEDE). Payesh, J Iran Inst Health Sci Res 2009;8:76.
28. Fallahi A A, Nejatian M, Etemadi S. Effect of rehabilitation continuous and interval aerobic exercise on depression and anxiety in patients with cardiac diseases after coronary artery bypass surgery. IJPCP 2019;25:136-49.
29. Sumide T, Shimada K, Ohmura H, Onishi T, Kawakami K, Masaki Y, *et al*. Relationship between exercise tolerance and muscle strength following cardiac rehabilitation: Comparison of patients after cardiac surgery and patients with myocardial infarction. J Cardiol 2009;54:273-81.