Cardiac rehabilitation in coronary artery bypass grafting patients: Effect of 8-week of moderate-intensity continuous training versus high-intensity interval training

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Abstract

Purpose

The aim of the present study was to investigate the effects of traditional moderate-intensity rehabilitation training and interval training on some angiogenesis factors in coronary artery bypass graft (CABG) patients.

Methods

Thirty CABG patients (mean age ± SD, 55 ± 3 years) were randomly assigned to one of three groups: high-intensity interval training (HIIT) or moderate-intensity continuous training (MICT) or the control group. After the initial assessments, eligible patients in the experimental groups (HIIT and MICT) performed exercise training for 8 weeks, while the control group did not. Angiogenesis and angiostatic indices, including pro-adrenomedullin (pro-ADM), basic fibroblast growth factor (bFGF), and endostatin, were then measured.

Results

The results showed no significant difference between pro-ADM in the HIIT and MICT groups ($P = 0.99$), but a significant difference was found between MICT and the control group and between HIIT and the control group ($P = 0.001$). There is also no significant difference between the bFGF levels in the HIIT and MICT training groups ($P = 1.00$), but the changes in this factor between the training groups and the control group were significant ($P = 0.001$). There was a significant difference between the levels of endostatin in all three groups.

Conclusion

Two methods of cardiac rehabilitation (HIIT and MICT) may be useful for the recovery of patients with coronary artery bypass grafting. This improvement manifested itself in changes in angiogenesis and angiostatic indices in this study. However, more extensive studies are needed to investigate the effects of these two types of rehabilitation programs on other indicators of angiogenesis and angiostatic.

Introduction

One of the causes of ischemic coronary heart disease is coronary artery occlusion (Schoen and Levy, 2005). With the growing prevalence of cardiovascular disease, non-surgical and surgical interventions and, consequently, cardiovascular rehabilitation programs have become extra crucial. One of the important components of the cardiac rehabilitation program is physical exercise which may reduce the spread of atherosclerosis in the coronary arteries (Leon et al., 2005). Rehabilitation programs for cardiovascular patients are a priority within the first days of discharge from the hospital till going back to normal (Razaghi and Sadeghi, 2020). Based on previous studies, exercising in patients with coronary heart failure is closely associated with hemodynamic, cardiac, and angiogenesis parameters (Esposito et al., 2018). Various factors are involved in the process of angiogenesis. Certainly, one of them involved in angiogenesis is adrenomedullin (ADM). Adrenomedullin is a 52 amino acid vasoactive peptide that plays an important role in microcirculation and endothelial dysfunction. it is especially expressed in the adrenal medulla and adipose tissue, in addition to endothelial and vascular smooth muscle cells, immune cells, and numerous endocrine glands(Lippi et al., 2015). It has many physiological roles such as angiogenesis in ischemic situations, vasodilation, apoptosis, bronchodilation, increase regulation, and antimicrobial activity (Nagaya et al., 2005, Pérez-Castells et al., 2012). Measuring ADM degrees is challenging because of their short half of-life and the presence of a binding protein. Even though, the ADM pro fragment has a long half of-life and represents ADM levels (Geven et al., 2018, Florin et al., 2020). Elevated ADM synthesis in response to chronic hypoxia may additionally cause progressed left ventricular regeneration, induction of pre-angiogenic factor, stimulation of regulatory cytokine secretion, and vasodilation(Hamid and Baxter, 2005). Physical activity can alter ADM levels. ADM levels seem to increase after acute exercise (KOC Yildirim et al., 2021). Also, an increase in the mid-region a part of pro-ADM was observed after 60 km of running (Hamid and Baxter, 2005). ADM suppresses the activity of the renin-angiostatin-aldosterone, endothelin-1, and angiostatin II systems and prevents an increase in environmental resistance. It seems that the increase in ADM increase during exercise may be a compensatory mechanism against in enhance in blood pressure and play an essential role in maintaining healthy function(KOC Yildirim et al., 2021, Charles et al., 2003). Similarly, exercising has been proven to stimulate phosphorylation of the enzyme nitric oxide synthase and increase nitric oxide production, and increasing ADM is one of the factors increasing nitric oxide production (Higashi and Yoshizumi, 2004). Another factor involved in angiogenesis the is basic fibroblast growth factor (bFGF), which impacts endothelial cells and smooth muscle cells and promotes the proliferation of fibroblasts and epithelial cells, leading to the induction of angiogenesis. This growth factor, by binding to receptors expressed on the cell surface, activates tyrosine kinase, transcriptional changes, and biological responses in endothelial cells (Seyedi et al., 2020, Gibala and McGee, 2008). Capillary network proliferation and angiogenesis due to prolonged physical activity have been demonstrated but the results are somewhat contradictory (Currie et al., 2013, Gibala and McGee, 2008). As an instance, a decrease in bFGF was observed in young athletes after eight months of prolonged training (Members et al., 2003). It was also shown that running for 30 minutes on a treadmill at 75% VO2max did not alter bFGF levels in healthy active and inactive men (Landers-Ramos et al., 2014). While, in another study, an increase in bFGF factor and a development in capillary beds due to high-intensity exercise were reported (Fukai et al., 2005).

On the other hand, angiostatic factors prevent the occurrence of angiogenesis. Endostatin is one of the angiostatic factors that is a fragment isolated from the collagen XXVII and has a molecular volume of 20 kDa that is produced by the tissues within the body (Ruge et al., 2017). Endostatin inhibits angiogenesis in numerous ways: First, endostatin inhibits fibroblast growth factor activity by binding to its receptor; second, endostatin inhibits the migration and proliferation of fibronectin-induced endothelial cells by binding to the α5β1 integrin receptor (Lippi et al., 2015, Higashi and Yoshizumi, 2004). Under normal conditions there is a balance between angiostatic factors and factors involved in angiogenesis, however, this balance changes to angiostatic factors during some exercises. An increase in angiostatic factors following an exhausting exercise of 1.5 to 2.6 times has been demonstrated (Linscheid et al., 2005). The mechanisms by which exercise affects the amount of endostatin within the tissue are uncertain and controversial. Endostatin, a proteoglycan of heparin sulfate and an epithelial component and endothelial basement membrane, exerts its action with the aid of inhibiting the proliferation and migration of endothelial cells and the formation of tubules, lowering angiogenesis(Suhr et al., 2010). Exercise may additionally lessen the adhesion of endostatin to active tissue, that exercise will increase blood flow to active muscle and that endostatin is transported from active tissue into the general circulation. As a result, the amount of endostatin within the circulation will increase and decreases in the active tissue(Gu et al., 2004). Decreasing endostatin with increasing vascular endothelial growth factor (VEGF) results in a change in the stability between angiogenic and angiostatic factors and will increase the ratio of blood vessels to muscle fibers (Isaacs-Trepanier et al., 2020). Despite the effect of exercise on inhibitory and stimulatory factors of angiogenesis and due to the importance of angiogenesis in improving the condition of cardiovascular patients and the unknown effect of various exercise intensities on angiogenic and angiostatic indices in these patients, the present study was conducted to determine the effect of moderate-intensity continuous training and high-intensity interval training on these variables.

Materials And Methods

Subjects

The target population of this study was coronary artery bypass graft patients and a selected sample of this population was available from patients referred to Amirkabir Hospital in Arak, Iran. All patients underwent coronary artery bypass graft surgery, rested at home for at least a month, and then returned to the center for a cardiac rehabilitation program. Inclusion criteria included: one month after surgery and no exclusion criteria such as irreversible heart failure, myocardial infarction over the past month, persistent ventricular arrhythmias, unstable angina, or any exercise restrictions. After initial evaluations, 30 patients were divided into three equal groups: moderate-intensity continuous training, interval training, and, control. All subjects gave written informed consent and the ethical committee of the institution approved this study.

Measurements

Patients first participated in an introductory session with practice and test procedures. To determine the intensity of training, the peak of patients' ability was measured in the first session. To determine the intensity of training based on peak power output, people first cycled for 20 minutes on a 20-watt Ergoline bicycle ergometer (German SELECT100, ECG mountable) to warm up. Then, the initial resistance was set to 60 watts and 15 watts were added every minute. In the case of voluntary exhaustion, significant abnormalities in the ECG (drop of ST-segment more than 2 mm, or abnormal blood pressure response) and high exercise training pressure (Borg scale: 7 or more) were stopped. The training program was planned based on the percentage of peak output. The HTT training intervention was the common method in previous studies(Gibala and McGee, 2008). Also, based on literature subjects randomized to MICT began with 20 minutes of continuous activity at ∼a 65% HR peak (Jung et al., 2015, Hannan et al., 2018). The control group had an active lifestyle (daily walking) as recommended by the physician but did not participate in the rehabilitation program. All dependent variables of the study were measured in two stages (24 hours before the first training session and 24 hours after the last training session). At each turn, 10 ccs of blood were taken from each person in the fasting state (12 hours) from the brachial vein. All measurements were performed under the same conditions (8 am to 10 am). Blood samples were centrifuged at 10 rpm for 10 minutes. The obtained serum was then poured into numbered microtubess and stored in a -80 ° C freezer for further measurements. Serum concentrations of pro-ADM were measured by ELISA and China Cusabio kit, bFGF by ELISA by Quantikine kit according to manufacturer's instructions (Minneapolis, USA, R&D Systems Inc), and endostatin by kit (Chemicon, UK).

Statistical analyses

Results are expressed as the mean ± standard deviation and were analyzed using the SPSS (version 28). Analysis of covariance was used to examine the differences between groups and if there was a significant difference to determine the location of the differences, Bonferroni post hoc test and correlated t-test were used for differences within the group. A *p*-value of less than 0.05 was considered significant.

Results

The results showed that the significance level obtained in all groups: MICT, HIIT, and control, for three variables pro-ADM, bFGF, and endostatin in pre-test and post-test is more than 0.05. Which indicates the normal distribution of data and homogeneity of variance (p>0.05). The general characteristics of the subjects are given in Table 1. Table 2. shows the mean and standard deviation of pre-test and post-test variables in the three groups, as well as the differences between group and intra-group variables.

Analysis of covariance (ANCOVA) was used to compare the effect of 8 weeks of MICT and HIIT on the dependent variables. The results showed that there was a significant difference in pre-test and post-test of MICT and HIIT in the two variables pro-ADM and bFGF. Also, the intergroup results in pro-ADM (F = 36/76, Sig = 0/001) and bFGF (F = 18/62, Sig = 0/001) indicate a significant difference between the three groups MICT, HIIT, and control. In this regard, the results of the Bonferroni test showed that there is no significant difference in the level of pro-AMD and bFGF in the MICT and HIIT (P = 0.99). But there was a significant difference between the MICT and the control group and also between the HIIT and the control group (P = 0.001). Regarding Endostatin, the results showed that there was a significant difference in the pre-test and post-test of MICT, HIIT, and control groups. The results between groups also show a significant difference between MICT, HIIT, and control in the variable Endostatin (F = 43/09, Sig: 0/001). Bonferroni test results showed that for endostatin values there is a significant difference between MICT and HIIT (P = 0/004), MICT and control (P = 0/001), HIIT and control (P = 0/001).

Table 1
Descriptive characteristics of the subjects.

Variables	Groups		
	Control	HIIT	MICT
Age (year)	52/12 ± 5/4	51/5 ± 6/2	54/01 ± 4/2
Height (cm)	174/4 ± 15	176/1 ± 9/1	173/2 ± 4/1
Weight (kg)	84/5 ± 12/3	85/1 ± 10/2	87 ± 7/2
BMI (kg/m^2)	27/72 ± 2/3	27/5 ± 2/9	29/04 ± 3/27
Resting HR (beat/min)	79/1 ± 10/33	79/7 ± 9/129	82/8 ± 8/23
Resting SBP (mm Hg)	133/5 ± 5/87	134/3 ± 4/27	130/07 ± 3/86
Resting DBP (mm Hg)	81/1 ± 3/60	80/9 ± 3/51	81/7 ± 3/02

Values are expressed as mean ± standard deviation. HIIT, high-intensity interval training; MICT, moderate-intensity continuous training, HR, heart rate; SBP, systolic blood pressure; DBP; diastolic blood pressure.

Table 2
Mean ± standard deviation and difference between groups and within the group

Variables		Groups				
		Control	HIIT	MICK	*F*	*Sig*
Pro-ADM	Pre	0.714 ± 0.029	0.718 ± 0.023	0.696 ± 0.032	36.76	0.001*
	Post	0.756 ± 0.036	0.778 ± 0.020	0.773 ± 0.027		
	Sig (within-group)	0/270	0/001†	0/001†		
bFGF	Pre	13.62 ± 1.72	14.43 ± 1.49	13.66 ± 1.41	18.62	0.001*
	Post	16.72 ± 3.17	18.14 ± 1.83	18.79 ± 2.10		
	Sig (within-group)	0/652	0/001†	0/001†		
Endostatin	Pre	14.53 ± 1.74	14.88 ± 1.11	15.86 ± 1.49	43.09	0.001*
	Post	13.13 ± 1.26	12.04 ± 0.86	13.73 ± 1.02		
	Sig (within-group)	0/005†	0/001†	0/001†		

†, Sig (within-group), Values are expressed as mean ± standard deviation. HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; Pro-ADM, Pro-adrenomedullin; bFGF, basic fibroblast growth factor.

Discussion

Adrenomedullin (AM) is a new member of adipokines that is also stimulated in inflammatory processes. The results of the present study showed that after performing MICT and HIIT rehabilitation in patients with coronary artery bypass graft, pro-ADM levels increased ($p < 0.05$). A significant increase in serum concentrations of pro-ADM and AM in the middle part after the r activity has been identified in most studies(Lippi et al., 2015, Hudlicka et al., 1992). As the results of the present study showed that there is a significant difference between both the training groups and the control group. However, no significant difference was observed between the MICT and HIIT groups, which probably indicates that the type of exercise did not affect the variability of pro-ADM. Exercise stimulates phosphorylation of the enzyme endothelial nitric oxide synthase and thus increases the production of nitric oxide and one of the factors to increase the production of nitric oxide is an increase in AM (Krzeminski, 2016). But Yildirim et al. observed a decrease in AM after 6 weeks of swimming activity in 8-week-old rats. The reason for this decrease is probably the insufficient duration and volume of exercise to change AM (KOC Yildirim et al., 2021). On the other hand, AM activates the PI3K-dependent pathway in vascular endothelial cells, which is crucial for angiogenesis. In vitro, AM increases endothelial cell migration and the formation of new blood vessels(Jensen et al., 2004). AM enhances endothelial regeneration through PKA-dependent Akt activation and PI3K. Improved blood flow and new capillary formation induced by AM gene transfer have been shown in mice with chronic ischemic conditions(Jensen et al., 2004). Taken together, these findings suggest the possibility that AM plays an important role in regulating angiogenesis and neovascularization(Laufs et al., 2004). Another finding of our study was a significant increase in serum bFGF levels in the training groups compared to the control group. But there was no significant difference between the two groups of HIIT and MICT. bFGF, through the JAK/STSTE/RAS protein pathway, stimulates processes such as cell proliferation, differentiation, adhesion, and migration during angiogenesis(Karnoub and Weinberg, 2008). Expansion of the capillary network and angiogenesis due to long-term activity have been demonstrated in healthy individuals. Increasing the number of capillaries allows for better oxygen exchange and more nutrient delivery, as well as reducing the O2-to-mitochondrial release distance and helping to increase aerobic capacity and muscle function. (Yamashita et al., 1993). Ryan et al. showed that exercise-induced capillary formation was higher in young men(Ryan et al., 2006). In addition, duration and intensity (above or below the lactate threshold, as well as the type of exercise (resistance or endurance), appear to be effective in inducing angiogenesis(Members et al., 2003). Among endurance exercises, exercises that are above the lactate threshold promote the growth of blood vessels; but exercise under the lactate threshold can also lead to angiogenesis if done regularly(Yamashita et al., 1993, Shono et al., 2002). On the other hand, based on the study of Jensen et al., Intense intermittent endurance training caused endothelial cell proliferation and capillary growth within 4 weeks(Jensen et al., 2004). However, the training period requires more than 8 weeks because in the 7 weeks after training, the number of endothelial cells multiplying is not significantly different from before training(Isaacs-Trepanier et al., 2020). These findings indicate the importance of angiogenesis in the early stages of adaptation to exercise(Members et al., 2003). The results of our study showed that HIIT and MICT - both - reduced endostatin as an angiostatic factor. There was a significant difference between MICT and HIIT groups (p

= 0.004), MICT and control groups (p = 0.001) and HIIT and control groups (p = 0.001). According to the research literature, aerobic exercise can have a positive effect on endothelial function, especially in cardiovascular patients, by increasing shear stress in circulating vessels, increasing endothelial nitric oxide activity, and increasing antioxidant capacity(Laufs et al., 2004). Brixius et al. reported that endostatin levels decreased after prolonged aerobic activity in obese men(Brixius et al., 2008). On the other hand, Rullman et al. showed that one session of resistance activity has no significant effect on reducing endostatin (Rullman et al., 2007). Reasons for differences in results include differences in subjects, type, and duration of exercise. Endostatin is a spherical protein with two pairs of disulfide bonds that connect the central nucleus and peripheral structures. This disulfide bond may be responsible for the anti-angiogenic effects of endostatin, which binds to VEGF and bFGF to inhibit angiogenesis. Endostatin also prevents the destruction of the capillary basement membrane, which prevents the migration of endothelial cells. Endostatin inhibits the growth of the capillary network by preventing the proliferation and migration of endothelial cells (Wen et al., 1999, O'Reilly et al., 1997, Felbor et al., 2000). However, the mechanism of endostatin reduction response to physical exercise is still unknown.

Conclusion

The results of the present study, due to the increase in adrenomedullin and bFGF and the decrease in plasma levels of endostatin, showed that continuous and interval exercise training has a significant effect on reducing the complications of cardiovascular disease, which is probably a positive point for coronary heart disease patients. According to the results of this study, which examined the effect of eight weeks of MICT and HIIT training on the factors involved in the process of angiogenesis and showed that these exercises increase blood flow to the myocyte due to increased angiogenesis factors. On the other hand, reducing antiangiogenic factors in the bloodstream has a significant effect on reducing the complications of cardiovascular disease. Also, according to the results of similar studies, it is suggested that in patients with coronary artery bypass graft as well as patients with cardiovascular disease, exercise along with other clinical therapies, as a non-pharmacological method and even an effective prevention method and efficient be considered. One of the limitations of this study is the lack of control over the amount of rest and sleep, the lack of accurate control of patients' mental and emotional states and rest, as well as the variety of drugs (according to the physician's prescription) used patients.

Declarations

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Author Contribution Statement

All authors have been fully involved in all stages of the work as well as in writing and editing the article. All authors read and approved the manuscript.

Declarations

The authors have no relevant financial or non-financial interests to disclose. The Author(s) declare that there is no conflict of interest.

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Abbreviations

CABG	Coronary artery bypass graft
HIIT	High-intensity interval training
MICT	Moderate-intensity continuous training
bFGF	Basic fibroblast growth factor
pro-ADM	pro-adrenomedullin
ADM	Adrenomedullin
VEGF	Vascular endothelial growth factor
BMI	Body mass index
HR	Heart rate
SBP	Systolic blood pressure
DBP	Diastolic blood pressure

Figures

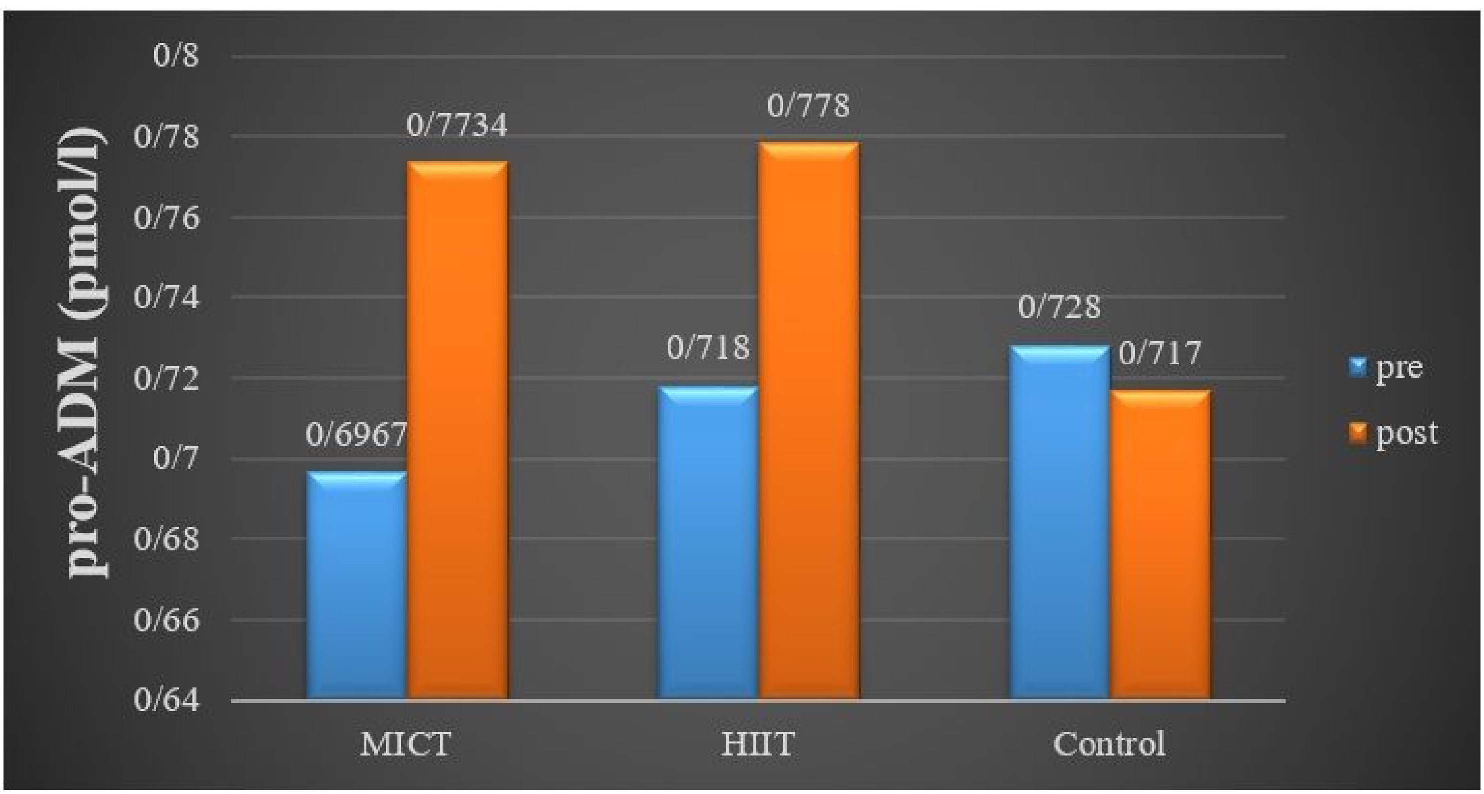

Figure 1

Pro-ADM changes. Pro-ADM changes levels in the three groups of MICT, HIIT, and control before and after 8 weeks of exercise training. Data are mean ± standard deviation (SD). $P < 0.05$. Pro-ADM, Pro-adrenomedullin; MICT, moderate-intensity continuous training; HIIT, high intensity interval training.

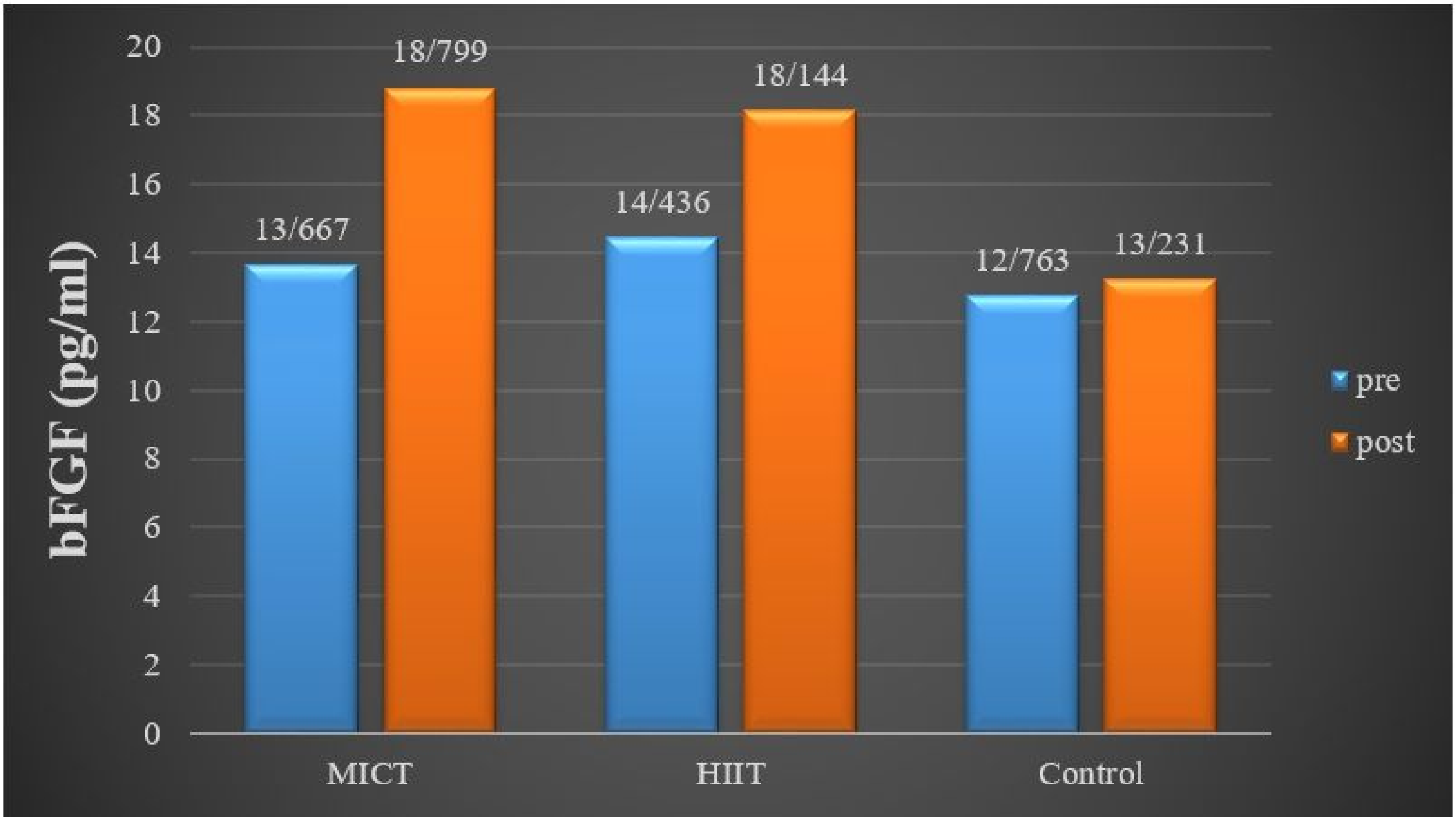

Figure 2

bFGF changes. bFGF levels in the three groups of MICT, HIIT, and control before and after 8 weeks of exercise training. Data are mean ± standard deviation (SD). $P < 0.05$. bFGF, basic fibroblast growth factor; MICT, moderate-intensity continuous training; HIIT, high intensity interval training.

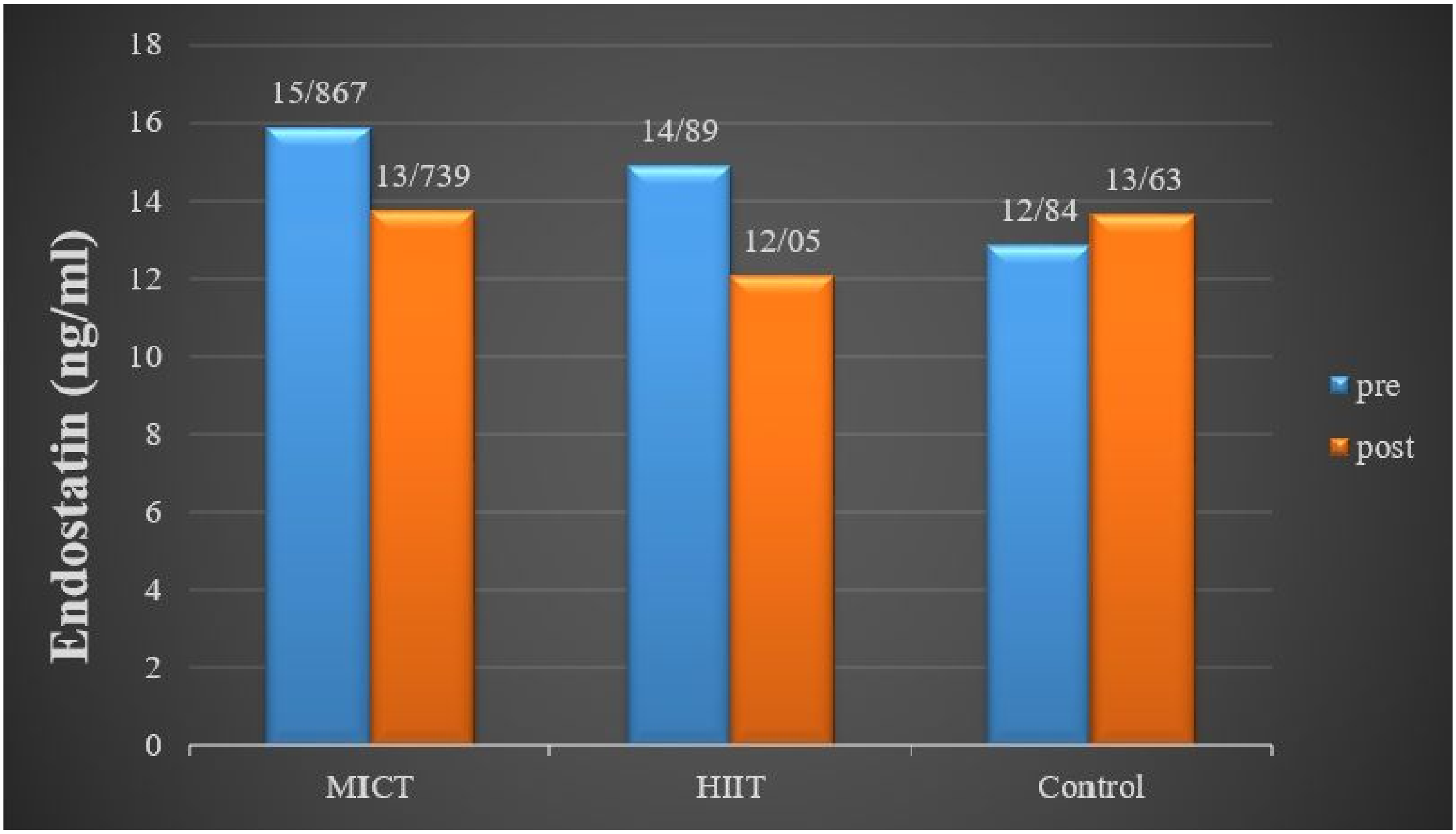

Figure 3

Endostatin changes. Endostatin levels in the three groups of MICT, HIT, and control before and after 8 weeks of exercise training. Data are mean ± standard deviation (SD). $P < 0.05$. MICT, moderate-intensity continuous training; HIIT, high intensity interval training.