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The Effect of Resistance Training on Serum Levels of NT-proBNP, GDF-15, and Markers of Cardiac Damage in the Elderly Males

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ABSTRACT:

Resistance training (RT) has beneficial effects on the cardiovascular (CV) system and potentially can be an effective treatment for a variety of clinical conditions, such as heart disease (HD). However, the impacts of RT on cardiac risk factors in older men are less known .The current study was investigated the effect of RT on serum levels of NT-proBNP, GDF-15, and markers of cardiac damage (CK and CK-MB) in the elderly men. 24 elderly men (aged 72.1 ± 5.3 years, height 164.3 ± 5.5 cm, and BMI 27.2 ± 4.3 kg/m2) were randomly assigned to one of the two intervention groups: RT (n=12) and control (n=12). The RT protocol included eight movements (3 × 10 repetitions with ∼70% of one repetition maximum [1RM], 1-min rest intervals) for eight weeks and three sessions per week. Serum levels of NT-proBNP, GDF-15, CK and CK-MB were tested at baseline as well as after eight weeks of intervention. All analyses were performed with SPSS version 24 at a significance level of P≤ 0.05. Serum levels of NT-proBNP significantly decreased in the RT group after 8 weeks ($p \leq 0.05$). Moreover, resistance training significantly increased serum levels of CK and CK-MB ($p \leq 0.05$). However, GDF-15 changes were not significant after eight weeks of RT ($p > 0.05$). Therefore, our data confirm that resistance training May be improve cardiac risk factors in older men.

KEY WORDS : Resistance Training, NT-proBNP, Growth Differentiation Factor 15, cardiovascular risk factors, Aging

INTRODUCTION

Aging is associated with a rapid decline in physiological processes that result in an increased risk of health threatening factors and diseases. Aging has a significant impact on the CV system, which results in an increase in cardiovascular diseases (CVD) including atherosclerosis, hypertension, and myocardial infarction (1). Age increase causes an increase in the incidence of heart failure (HF). To such an extent that HF is the first cause of hospitalization in the elderly; its prevalence is associated with high morbidity and mortality, as well as significant health care costs (2). Clinically, HF syndrome has symptoms (e g, shortness of breath and fatigue) and signs (e g, increased jugular vein pressure and lung crackles) that is associated with decreasing or maintaining the left ventricular ejection fraction (LVEF). It is difficult to detect HF due to its not very sensitive or specific features; hence, no gold standard to detect HF is introduced in any of the studies (3). Several indicators were monitored to diagnose and classify cardiac damage and

impairment of the function. CK-MB (creatine kinase-muscle/brain) isoenzyme is one of the most important markers of cardiac muscle damage. Totally, 15%-25% of CK in heart cells is as MB (CK-MB), while it is about 3% in skeletal muscles. The overall activity of CK and its isoenzymes is directly related to its bounding site (4). The total CK and CK-MM activities in the skeletal muscles are significantly higher than those of myocardium. While the CK-MB activity of the skeletal muscles is significantly less than that of the myocardium (5). Changes in the level of CK-MB is particularly useful to detect myocardial necrosis up to 48 hours after the onset of acute myocardial infarction (AMI) (6). Although CK-MB cytosolic enzyme is a marker to diagnose myocardial damage, it has diagnostic limitations. So that it increases after exercise and other events that are not related to the heart. Since CK-MB is not just specific to the heart, its increase may not indicate a cardiac damage (7). The total CK activity also increases following the intensive physical activities. After the muscle damage, total CK is released into the blood stream through the cell membrane (8). The levels of CK and CK-MB isozymes in the crowd of athletes or people who are working or suffering from muscle damage have been suspiciously observed (9). Several studies indicated the CK-MB as a marker of AMI in people with a history of exercise and reported that such histories can be considered as a major highlight point in the diagnosis. Weippert et al., (2016) studied the effect of intensive interval training on CK and CK-MB levels in young males. The results indicated a significant increase in the variables studied in all participants (10). However, release of CK-MB in the serum is of different origin and cannot be considered as the only marker for AMI diagnosis (11). Therefore, other markers such as NT-proBNP and GDF-15 should be considered in order to more accurately assess AMI and provide effective therapeutic strategies.

N-terminal pro–brain natriuretic peptide (BNP) and NT-proBNP are widely introduced in clinical guidelines as biomarkers to diagnose heart failure and monitor the disease progression. The NT-proBNP and BNP hormone peptides are synthesized and released as a proactive protein in response to increased stress on the cardiac wall due to excessive volume or pressure and other conditions such as ischemia or myocardial inflammation (12, 13). Plasma levels of these hormones both increase in patients with left ventricular dysfunction (LVD) (systolic and diastolic) and are often used in the clinical diagnosis of myocardial infarction (14). NT-proBNP increases in response to various signals including excessive myocardial tension (15). Used to predict HF both in the elderly and non-elderly populations. also, NT-proBNP predicts HF with/without preserved ejection fraction (HFpEF) (16) after moderating common clinical risk factors and structural and functional cardiac impairment in the elderly and non-elderly population (17, 18) Therefore, appear to be, people without HF, but increased NT-proBNP, are at high risk for CV events and mortality (18). Accordingly, it is recently reported that screening strategy based on NT-proBNP levels can improve the classification of the risk of CV diseases and results in identification of patients with heart attack, As NT-proBNP is a useful marker for Silent heart damage (19). Therefore, measurement of BNP in blood and other related peptides is considered as a marker for cardiac function. The guidelines recommended in the articles suggest addressing such markers to identify patients with acute and chronic heart diseases (20, 21).

In addition to NT-proBNP as a diagnostic and prognostic tool for all types of chronic cardiovascular diseases, including heart failure and coronary artery disease, the growth differentiation factor15 (GDF-15) also provides prognostic information for such groups (22, 23). GDF-15 is a member of transforming growth factor (TGF) / bone morphogenic protein (BMP) family expressed in the placenta and prostate, as well as in the heart, pancreas, liver, and kidney (24-26). GDF-15 is highly expressed in cardiomyocytes secondary to ischemia / perfusion (27). Increasing the expression of GDF-15 in the human and rat heart is observed within a few hours after myocardial infarction, which remains for several days. Although there are different ideas about the site of GDF-15 secretion from cardiomyocytes, however, the infarction region is identified as the main source of GDF-15 release (28). GDF-15 plays an important preservative role in the adults heart through activating Smad2, Smad3, and ALK4 / 5.7 receptors (29). This factor is not normally expressed in the heart; however, it rapidly increases in response to injuries such as high blood pressure, cardiac failure, ischemia / reperfusion, and atherosclerosis (30). GDF-15 is a predictor of side effects in patients especially the ones with myocardial infarction and chronic angina (31, 32); it is also an emerging biomarker for subclinical diseases and prognosis for cardiovascular events and mortality (33). Recent findings indicate that GDF-15 levels are associated with lower LVEF, worse diastolic function, more inductive ischemia, and lower exercise capacity. Also, GDF-15 is associated with NT-proBNP, concentric left ventricular hypertrophy, coronary artery disease, and heart failure (33, 34). Expression of GDF-15, as a growth factor, increases with age increase, which can be due to indicators such as oxidative stress, protein glycosylation, inflammation, and age-related hormone changes. Many of such stresses induce the expression of GDF-15 by the transcription factors p53 or early growth response protein (EGR)-1 (35, 36). In recent years, GDF-15 is identified as a predictive marker and its increase is associated with chronic diseases such as CVD, especially in the elderly (37). GDF-15 and NT-proBNP as the predictors of CVD such as HF, are under the influence of exercise and physical activity. Accordingly, Hager et al., (2012) showed that levels of NT-proBNP increase after a session of exhausting aerobic activity in patients with HD (38). However, in another study, Normandin et al., (2012) did not report significant changes in NT-proBNP levels in response to an aerobic exercise session in patients with HF (39). Probably, exercising

may reduce NT-ProBNP levels through improving hemodynamic balance in the heart muscle, cleansing NT-ProBNP by renal receptors, improving systolic function of the heart, reducing sympathetic tone, and improving oxygenation in the heart muscle tissue (40-42). There are a few studies regarding GDF-15; for instance, Galleria et al (2014) reported an increase in GDF-15 level alongside the increase in NT-ProBNP in rugby players in response to intensive physical activity (43). Aging is associated with pathologic changes, leading to an increased risk of HD, such as HF. With this in mind, some blood-based biomarkers have been suggested for clinical diagnosis of association between sarcopenia and CVD. On the other hand, the potential role of RT is known as a therapeutic strategy and effective preventive to cardiovascular risk factors even in a variety of clinical conditions such as HD (44). However, the role of RT on new predictive biomarkers of cardiac disorders (GDF-15 and NT-ProBNP) has not been understood in elderly people. Therefore, considering the effective role of resistance training for elderly people, the objective of this study was investigated the effect of RT on serum levels of NT-proBNP, GDF-15, and markers of cardiac damage (CK and CK-MB) in the elderly men. Our hypothesis is that RT improves serum levels of NT-proBNP and GDF-15 in elderly men.

METHODS

The present study is a semi-experimental method and in terms of data collection, a field trial is a pre-test with a post-test with the control group. The target population of this study was the elderly men (aged 65-78) who were disabled in the Kahrizak elderly center of Alborz province (Karaj) Which, according to the statement itself, did not have a history of regular physical activity during the past year and had no prohibition on the exercise program. After obtaining primary permissions from the head of Kahrizak Charity Center, a briefing session was held for the elderly of the center in order to familiarize them with the exercise protocols of the current study. The inclusion criteria were lack of CVD, diabetes, hypertension, no smoking and alcohol consumption, no drug abuse, not regularly attending exercise sessions within the last year, and age 65-78 years. The exclusion criteria for both the resistance training and control groups included illness, smoking, drug abuse and sport supplements consumption, and absence more than two sessions from the course. After approval of the study protocol by the Ethics Committee of the institute (IRCT20180819040831N1), and obtaining written consent and being sure of the health status of the subjects (confirmed by the physician), in order to assess any problems for attending the regular exercise program, 24 individuals were selected as the sample size and randomly divided into two groups of resistance training (n = 12) and control (n = 12). Meanwhile, subjects were free to withdraw from the study at any time for any reasons, and there was no compulsion in this regard. One week before implementation of the study protocols, pre-test including body compositions, physical fitness, and biochemical evaluations were performed. For this purpose, after 12 hours night fasting, 6-mL venous blood samples were collected in Venoject tubes free from anticoagulant or anticoagulant agent, By laboratory expert. Then it was centrifuged with 2000 rpm for 10 minutes and the sera were frozen at -70° C until evaluation of biochemical variables. Then, body composition variables including height (using a wall-mounted stadiometer) and weight were measured and body mass index (BMI) was calculated by Inbody230 device (South Korea).

Serum measurements

To measure serum levels of CK-MB and CK, the creatine kinase-myocardial band, creatine, kinase, CK, ELISA kit, TOYO CK-MB, ELISA Kit (Pars Azmun Co., Iran), with a sensitivity of 1 U/L, were used in the Hitachi 917 apparatus (Japan). To measure serum levels of NT-proBNP and GDF-15, sandwich ELISA (the enzyme-linked immunosorbent assay) using Human N-terminal pro-brain natriuretic peptide, ELISA KIT, and Human growth differentiation factor 15, ELISA Kit (ZellBio Co., Germany), with a sensitivity of 2.5 pg/mL and 5 ng/L, were employed according to the manufacturer's instruction in the Hiperion apparatus model MPRFOURPLAS (the United States). All the tests, including body components and biochemical evaluations assessed in pretest, were performed twice 48 hours after the last session of the current study protocol implementation.

Exercise protocol

Resistance training was performed On single days and at the place of Kahrizak Gym for eight weeks, three sessions per week as described previously (45-47). The exercise protocol included five minutes of warming-up (jagging or cycling), followed by the main part of the training, and five minutes of cooling-down (stretch movements). The main exercise included three sets with 10 repetitions with 70% 1RM in eight movements of leg press, leg Extensions, Best back leg, leg(shank), Bench press, Lat Pull-down, Biceps, and Triceps. The exercise protocol had a gradual increase in the intensity and duration of exercise for the 1st two weeks in order to minimize muscle pain and reduce damage. There was one minute rest between the sets and two minutes rest between the movements. The resistance increased as soon as the subjects could complete 10 repetitions correctly in the 3rd set for two consecutive sessions. The percentage of 1RM at the end of the 4th week was measured to provide overload again and the intensity of exercise was adjusted accordingly (45-47).

Statistical analysis

To analyze the results of the current study, intergroup and intragroup comparisons were made. For this purpose, time as an intragroup variable (pre-test and post-test) and a variable of the level of activity or group (resistance training and control groups) were included in the study. Therefore, Independent t-test and paired t-test were used to check the possible differences between the groups and the measurement steps. All calculations were performed using SPSS software version 24 at a significant level ($p < 0.05$).

Ethics Statement: The Human Research Ethics Committee of Guilan University of Medical Sciences (Approval ID: 3/132/5252) and Iranian

registry of clinical trials (IRCT: IRCT20180819040831N1) approved the study protocol in conformity with the Declaration of Helsinki, and all experiments were carried out in accordance with approved guidelines of the Guilan University of Medical Sciences.

STATISTICAL RESULTS

Table 1 shows the mean and standard deviation of subjects' demographic characteristics, including height, weight, age, and BMI based on the study groups. Both the control and resistance training groups were homogeneous in terms of the demographic characteristics such as age, height, weight, and BMI, and the differences were not statistically significant.

Table 1. Mean and Standard Deviation of Subjects' Demographic Characteristics

Characteristics of subjects	Control Group	Training Group	P Value
Age (year)	70.9 ± 5.8	73.2 ± 4.7	0.128
Height (cm)	165.9 ± 6	162.6 ± 5.1	0.243
Weight (kg)	74.1 ± 13.1	72.8 ± 13.6	0.087
BMI (weight divided by height squared)	26.6 ± 4.9	27.7 ± 3.7	0.225

Table 2. Shows the Serum Levels of NT-proBNP, GDF-15, CK, and MB-CK in the Pretest and Posttest in the Study Groups

	Control Group		Training Group	
	Pre-test	**Post-test**	**Pre-test**	**Post-test**
NT-proBNP (pg/ml)	165.73 ± 41.49	171.39 ± 39.26	168.66 ± 32.65	138.76 ± 35.2
GDF-15 (ng/l)	153.94 ± 38.18	162 ± 43.86	147.08 ± 21.68	151.26 ± 44.53
CK-MB (unit/l)	23.50 ± 8.76	25.51 ± 8.62	21.83 ± 5.30	34.75 ± 13.85
CK(unit/l)	124.83 ± 43.11	131 ± 39.70	131.91 ± 39.33	219.83 ± 87.85

Data in table are presented as Mean ± SD

The results of correlation T-test showed that resistance training resulted in significant reduction of NT-proBNP serum levels compared to pretest ($t_{(11)}$ = 4.11, P=0.001). Also, based on the independent T-test, NT-proBNP levels had a significant reduction in the resistance training group when compared to control group ($t_{(22)}$ = 2.148, P=0.043).

The results of correlation T-test showed that changes in serum levels of GDF-15 (post-test with pre-test) were not significant in training group ($t_{(11)}$=0.74, P=0. 33). Also, based on the results of independent T-test, there was no significant difference in serum levels of GDF-15 between the two groups of resistance training and control ($t_{(11)}$=0.641, P=0.528).

The results of correlation T-test showed that resistance training resulted in significant increase of serum CK-MB ($t_{(11)}$ = 3.70, P=0.003) and CK($t_{(11)}$= 3.35, P=0.006) levels compared to pretest. Also, independent t-test showed that there was no significant difference between two groups of resistance training and control in CK-MB levels ($t_{(22)}$ = 1.96, P=0.062). Also, based on the independent T-test, CK levels had a significant difference between the resistance training and control group ($t_{(22)}$ = 3.192, P=0.04).

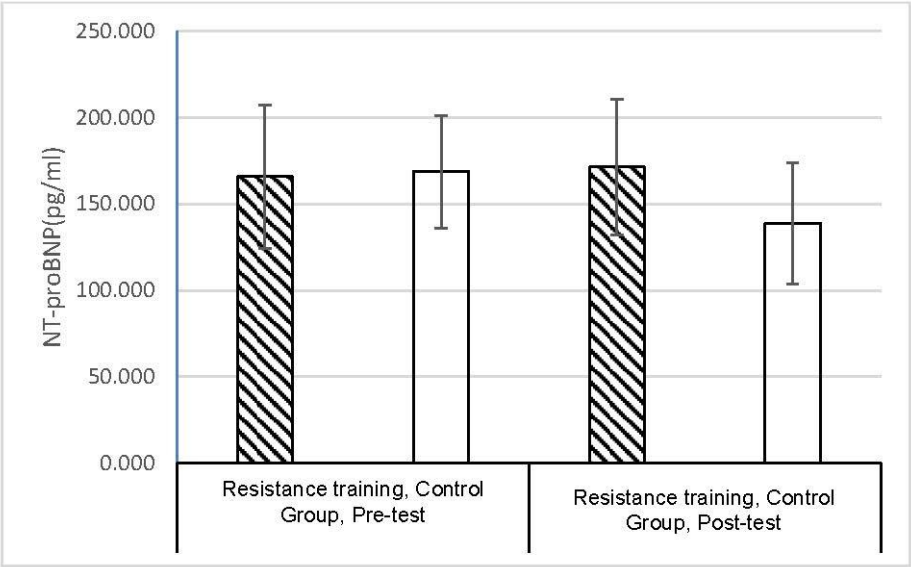

Figure 1. The Trend of NT-proBNP Serum Level Changes in the Pretest and Posttest in the Study Groups

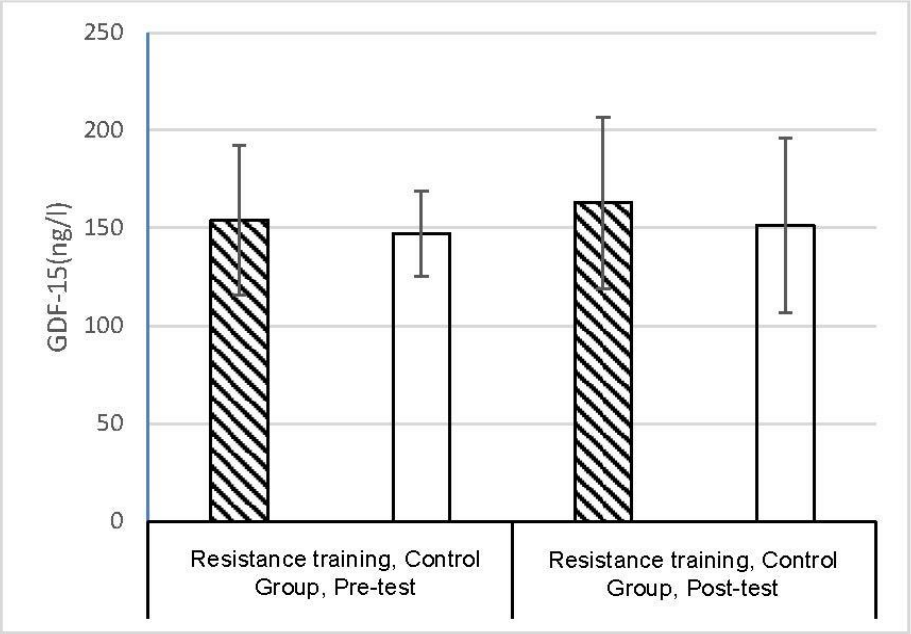

Figure 2. The Trend of GDF-15 Serum Level Changes in the Pretest and Posttest in the Study Groups

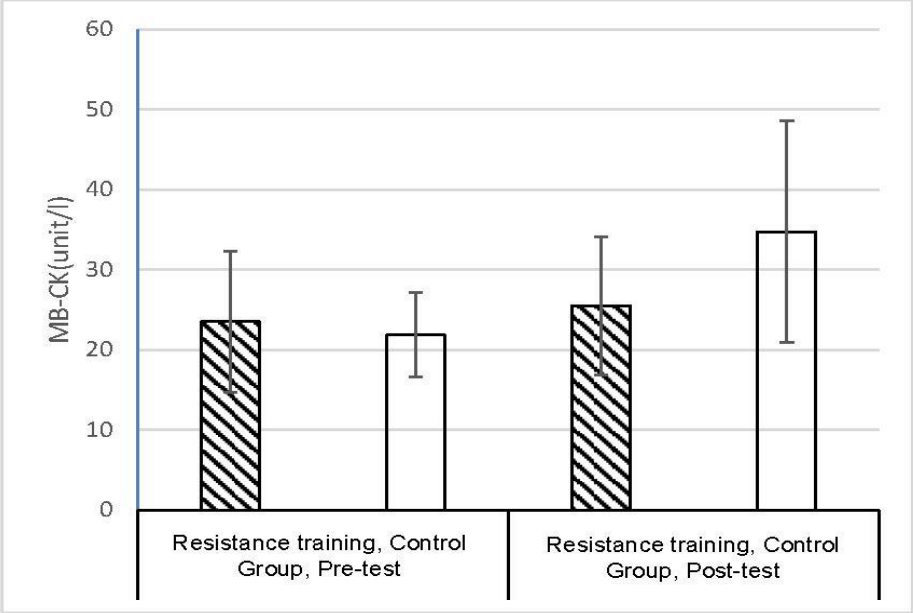

Figure 3. The Trend of CK-MB Changes in the Pretest and Posttest in the Study Groups

Figure 4. The Trend of CK Changes in the Pretest and Posttest in the Study Groups

DISCUSSION

The results of the current study showed that the CK and CK-MB serum levels significantly increased after eight weeks of resistance training. In line with the results of the current study, Rodriguez et al., (2010) examined serum levels of CK and lactate dehydrogenase (LDH) after two sessions of resistance training with 80% 1RM. The serum levels of both CK and LDH enzymes after 24 and 48 hours of training were significantly higher than the baseline (48). Previous studies reported an increase in CK-MB serum levels after endurance exercise and noted that such exercise can cause heart damage. However, the increase in serum CK-MB levels after long-term activities is not credible to diagnose cardiac injury (49, 50). The CK-MB increase in skeletal muscles of endurance runners may be due to an increase in satellite cells that repair damaged skeletal muscles (51). Therefore, it is possible that individuals

with excessive training have a relatively high MB-CK levels in the skeletal muscles released after activity-induced muscle injury. Shave et al., (2004) also examined the changes in cardiac function and heart injury caused by long-term activities. They investigated nine males that practiced triathlon following a half triathlon; blood samples were collected at baseline and after each step, as well as 24 hours after practicing, and then, CK-MB, CK, and CTnT were measured. The results showed a significant increase in CK-MB and CK serum levels during and after the practices, as well as CTnT increase in four subjects during the practices; they concluded that the physiological pressure imposed during the half triathlon reduced the contraction of the left ventricle and caused changes in diastolic filling associated with minimum heart damage to a few athletes that well practiced triathlon (52). Researchers comparing the responses of cardiac troponins and CK-MB serum levels after exercise reported that despite the increase in CK-MB level, cTnT and cTnI levels had no changes. Therefore, only the increase in CK-MB level does not address myocardial damage (7) and to assess cardiac damage caused by activity, the focus should be shifted from MB-CK levels to other factors such as CTn or NT-proBNP, which despite significant damage to the musculoskeletal system, are the specific markers for heart muscle injury. Results of the current study showed that eight weeks of resistance training significantly reduced the serum levels of NT-proBNP in the elderly males. In this regard, Carranza et al., (2011) examined the effect of a heavy resistance training session and soccer match on the release of cTnI, cTnT, and NT-proBNP in experienced athletes. Heavy resistance trainings significantly increased NT-proBNP levels and cardiac troponins. The results of the study showed that intermittent exercise leads to different disturbances in cardiac biomarkers with very limited evidence of myocyte injury or tumor (53). Some studies evaluated the effects of resistance training on NT-proBNP serum levels, in which, in particular, the chronic effects of training on NT-proBNP levels are more than the acute ones. Bordbar et al., (2012) examined the effect of an eight-week resistance and aerobic exercise program on NT-proBNP release. The levels of NT-proBNP showed a significant increase immediately after aerobic exercise, but dropped after eight weeks. In other words, NT-proBNP levels increased significantly after eight weeks of resistance training, although the NT-proBNP levels did not change immediately after the resistance training. They believed that myocardial injury can be a result of long-term resistance training (54). An increase in NT-ProBNP levels after exercise may indicate excessive myocardial activity (55). Waltz et al., (2014) also evaluated the effects of a 12-week moderate-intensity and low-frequency resistance training program on muscle performance and strength of healthy elderly. NT-proBNP levels did not change after the resistance training program (56). However, there seems to be a difference between response and compatibility of NT-ProBNP to exercise to such an extent that previous studies reported a decrease in NT-ProBNP levels as a result of exercise (40, 42, 57). Probably, exercise by improving hemodynamic balance in the heart muscle, cleansing NT-ProBNP by the kidney receptors, improving systolic function of the heart, reducing the sympathetic tone, and improving the oxygenation to the heart muscle tissue lead to a decrease in the levels of hs-CTnI and NT- ProBNP (40-42). The results of different studies in this field are controversial to such an extent that in the study by Waltz et al. (2014), the effect of a 12-week moderate-intensity and low-frequency resistance training on muscle strength and NT-proBNP levels in the elderly could not change NT-proBNP levels after the resistance training (56).Therefore, a moderate-intensity resistance training can be a healthy and safe strategy to improve muscular fitness in the elderly without causing cardiac stress. However, the results of a cross sectional study showed an independent and inverse relationship between muscle mass and BNP levels (58). Part of the results of the present study is inconsistent with the findings of Caranza (2011), Bordbar (2012), and Wollter (2017) (37, 53, 54). It seems that a significant decrease in NT-ProBNP levels in the current study may also be due to increased muscle

mass and/or the type and intensity of exercise, gender, age, or physical condition of the subjects. Therefore, even if NT-proBNP level increase due to excessive exercise, they do not necessarily indicate myocardial injury.

The current study results showed that after eight weeks of resistance training, GDF-15 had no significant changes. Resistance training prevents age-related functional and cardiac and skeletal muscle mass loss (59). In a study by Hoffman et al. (2015), serum levels of GDF-15 were assessed in young people (aged 22-28 years) and elderly females (ages 65-92 years); the results showed that serum levels of GDF-15 in the elderly were higher than those of the young people. They also showed that GDF-15 level had inverse relationship with muscle mass and direct relationship with age increase (60). Galliera et al. (2014), evaluated the impact of an intense rugby training session on NT-ProBNP and GDF-15 levels in 30 rugby players and reported a significant increase after an intensive training session in GDF-15 and NT-ProBNP levels (43). Measuring GDF-15 levels in professional athletes can be a useful tool to monitor their cardiovascular status during training and competition in order to prevent the onset of cardiovascular side effects or heart injury due to intense training, which lets early detection of the disease. Due to the availability of few studies on the effect of resistance training on serum levels of NT-ProBN and GDF-15 in the elderly, and considering the factors such as intensity and duration of training and health problems of the elderly, further standard studies are required to obtain more conclusive results.

Conclusion

In general, the findings of this study showed that resistance training can improve some cardiac risk factors in elderly men.

The limitations of this study include the lack of measurement of lipid profiles and other cardiac risk factors, including inflammatory biomarkers. Therefore, other studies in this field are required with the elimination of the limitations of the present study.

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Conflict of Interest

All authors confirms that there is no conflict of interest with this study or authors.

Financial Disclosure

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