The effect of high, low and moderate intensity circuit resistance training on the levels of hepatocyte-derived fibrinogen-related protein 1 (HFREP1) and lipid profile in obese postmenopausal women

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Abstract

Introduction: Different hepatokines including the hepatocyte-derived fibrinogen-related protein 1 (HFREP1) are secreted by liver tissue, which can affect the lipid metabolism. The aim of present study was to investigate the effect of 12 weeks circuit resistance training with different intensity on the levels of HFREP1 and lipid profile in obese postmenopausal women.
Materials and Methods: Subjects of the study consisted of 44 postmenopausal women with average age of 56.07 ± 3.18 years old, dividing into the circuit resistance training with low (L-RT), moderate (M-RT), high (H-RT) intensity and the control groups (11 subjects in each group). Training program was conducted for 12 weeks and three session per week. Blood samples collected in pre and post-test stages and the levels of HFREP1 were measured by ELISA method and finally data was analyzed by Graphpad Prism software.
Results: Analysis of HFREP1 data indicated that there were significant differences between different groups ($P < 0.001$). The results of Bonferroni post hoc-test showed that there was no significant difference between the control and L-RT groups ($P > 0.05$). However, HFREP1 in M-RT and H-RT groups significantly decreased compared to control group ($P < 0.001$). In addition, HFREP1 decrease in M-RT and H-RT groups was significant compared to L-RT group ($P > 0.05$). Lipid profile also improved in all trained groups, which further improvement observed in the H-RT group.
Conclusion: It seems that, higher intensity circuit resistance training is associated with further decrease in the levels of HFREP1, and improving the lipid profile can be attributed partly to downregulation of HFREP-1 levels.

Keywords: Menopause, Circuit resistance training, Hepatokines, HFREP1

Introduction

Obesity, in terms of prevalence, incidence, as well as economic costs, has become a public health problem worldwide, and according to available evidence in 2014, about 2.1 billion people or nearly 30% of the world's population have been overweight or obese and five percent of all deaths in the world have attributed to obesity (1). Obesity is major risk factor for various diseases, especially cardiovascular disease, hypertension and type 2 diabetes mellitus (2). It has been reported that in adipose tissue and liver, increased energy availability causes lipid accumulation as well as infiltration and activation of immune cells (3). In this condition, inflammatory factors and cytokines are secreted from the liver into blood circulation, which are termed hepatokines and can affect various body functions (4). Accordingly, liver tissue by secreting

hepatokines can affect metabolic pathways, including insulin resistance and lipid metabolism (5).

Hepatocyte-derived fibrinogen-related protein 1 (HFREP1), also known as Fgl1 or Hepassocin, is a new hepatokine involved in insulin resistance through ERK1/2-related mechanisms (6). HFREP1 protein is expressed in adipose tissue, and regulates lipid metabolism (7). It is reported that, plasma HFREP1 levels independently is associated with fasting glucose, insulin resistance, prediabetes, and diabetes (6). In addition, HFREP1 appears to be associated with inflammation, and also HFREP1 is known as an acute-phase reactant that responds to inflammatory cytokines such as interleukin-6 (IL-6) (8). Nevertheless, the effects of inflammation-induced HFREP1 expression are still largely unknown. In contrast, regular exercise training remarkably decreased obesity and its related disorders, and it is suggested that exercise training result in improve the insulin sensitivity in healthy obese individuals or type 2 diabetic patients (9). However, few studies have been conducted about the effect of exercise training on the levels of hepatokines and their association with insulin resistance, and contradictory results have been reported. In a study, the effect of eight weeks resistance and aerobic training on HFREP1 levels and insulin resistance in obese type2 diabetic men was investigated, and researchers reported that both resistance and aerobic training led to decrease the levels of HFREP1 and insulin resistance (10).

HFREP1 significantly disrupts insulin signaling including insulin receptor phosphorylation, IRS1, and AKT in hepatocytes. In addition, serum HFREP1 levels result in disruption of insulin signaling and increase insulin resistance in peripheral tissues by activating ERK1/2 (11). However, its reported that exercise training play an important role in counteracting the pathological effects of obesity and improving insulin resistance. According to previous evidences, resistance training by increasing blood flow and blood pressure leads to improved blood circulation in various tissues and stimulates the tissue oxygen deficiency and modulate inflammatory conditions, adipokine, myokines and insulin resistance related factors (12). Moreover, resistance training improves the insulin sensitivity through skeletal muscle growth (13). The american diabetes association recommends three sessions per week high-intensity (8-10 reps) resistance training for major body muscle groups (14). Physiological and biomechanical responses to resistance training are different from endurance training, and it has been shown that resistance training like endurance training result in improve blood glucose levels, increase insulin function in skeletal muscle, and improve glucose tolerance (15).

Despite the well-known effects of aerobic training, there are some limitations to conducting this type of exercise, especially due to orthopedic and cardiopulmonary limitations in obese people, whereas some researchers have suggested the positive effects of resistance training in obese individuals (16). Circuit training as a new training method, decrease the exercise training associated complications such as overtraining, and circuit resistance training can be considered as a resistance-endurance training which involve the muscles locally and simultaneously improve the cardiovascular system. Therefore, circuit resistance training leads to an increase in people's desire to participate in training (17). Because of HFREP-1 important role in lipid metabolism and few conducted studies, especially about the exercise training effect on the levels of HFREP-1, the present study aimed to investigate the effect of 12 weeks of circuit resistance training with different intensities on the levels of HFREP-1 and lipid profile in obese postmenopausal women.

Materials and Methods

Subjects

This research was performed based on pre-test and post-test design. The study participants consist of obese postmenopausal women who were selected among the recruited subjects. All subjects voluntarily participated in the present study and finally 44 postmenopausal women with age ranging the 48-65 years old (with average BMI: 33.43±1.29 $kg.m^2$) were chosen as a subject to participate in the present research. All of study stages conducted according to ethical guidelines of the Helsinki Declaration and Islamic Azad University, Central Tehran Branch ethics committee.

Present research inclusion criteria consisting of: at least 12 months have passed after the last menstrual period, non-addiction to drugs or alcohol, don't take part in regular exercise training in last year, no kidney, liver, cardiovascular disease and diabetes, body mass index equal or greater than 30 $kg.m^2$, and the absence of any injuries or physical problems. In addition, Exclusion criteria including the absence of regular participation in exercise training sessions, injuries during the exercise training, unwillingness to continue research protocol, medical prohibition to participate in exercise training, and forced to take certain drugs or supplements.

Study Design

Because the present subjects were obese menopausal women and were examined in a 12-week research period, so the present study is semi-experimental. After checkup by a gynecologist and confirming the menopause, subjects were qualified to enter in present study. Menopause was confirmed by menopausal levels of estradiol (<120 pmol/l) and follicle-stimulating hormone (FSH> 30 IU / L). Before conducting the present study, all steps and research methods were explained to subjects and after full knowledge and completion of the medical questionnaire, all of them signed written consent. In the first session, the participants height and weight were measured and in the second session, subjects one-repetition maximum (1RM) determined. The subjects were then matched based on weight, height and BMI and divided into four equal groups (11 persons in each group). The study groups including: 1) control (C), 2) low intensity circuit resistance training (L-RT), 3) moderate intensity circuit resistance training (M-RT) and 4) High-intensity circuit resistance training (H-RT). Three training groups completed their research protocol, but the control group was asked to continue daily routine lives and don't take part in regular training.

Circuit Resistance Training Program

The circular resistance training protocol consisted of eight movements (squat, biceps curl, chest press, knee extension, knee curl, shoulder press with barbell, leg press, underhand cable pulldowns) for upper and lower limb, which conducted as a circuit at different intensities (18). The training group consist of 1) H-RT: Three sets with 10 repetitions at 80% 1RM, 2) M-RT: Three sets with 13 repetitions at 60% 1RM, 3) L-RT) Three sets with 20 repetitions at 40% 1RM. Training volume was calculated based on the Baechle et al (1994) formula (training volume= Weight × number of repetitions × number of sets) (19). The between sets rest considered two minutes and was inactive (20). The subjects 1RM was calculated using Brzycki equation (21) which reported in following:

1-RM = weight (kg)/1.0278 – (number of repetitions to fatigue × 0.0278)

Blood Samples Collection

The first fasting blood sample was taken 72 hours before and the second blood sample was taken 72 hours after a 12-week intervention from the subject's forearm

vein. Blood samples were transferred to special test tubes for serum and plasma (tubes containing sodium citrate) preparation, and then centrifuged at 3000 rpm for 10 minutes. The obtained serum and plasma samples were stored at -70 °C. Then, the circulating variables were measured using kits and special laboratory methods.

Biochemical Analysis

Plasma levels of HFREP-1 were measured by ELISA method (HFREP-1 ELISA kit, Cusabio, catalog number: CSB-EL008653HU, sensitivity: 5.86 pg.ml, Intra-assay CV%<8%, Inter-assay CV%<10%). Blood lipid profile (Cholesterol, Triglyceride, LDL-c, HDL-c) determined by diagnostic Pars Azmoun (Iran) kits.

Statistical Analysis

In order to data analysis, graph pad prism statistical software was used and Excel software was used to draw the graphs. Between group differences were analyzed by repeated measures analysis of variance and Bonferroni post hoc test. In addition, intragroup changes were also analyzed by means of paired t-test. Significance level for all stages of data analysis was considered $P < 0.05$.

Results

The HDL-c data analysis indicated a significant effect of time ($P < 0.001$, $F_{1,40} = 179.6$) and group-time interaction ($P < 0.001$, $F_{3,40}= 3.40$). Bonferroni post hoc test showed significant difference between M-RT ($P = 0.044$) and H-RT ($P < 0.001$) group with control group. Moreover, significant difference between L-RT with H-RT group ($P < 0.001$), and also between M-RT with H-RT group ($P < 0.001$) were observed. The effect of time ($P < 0.001$, $F_{1,40}= 113.5$) and time-group interaction ($P < 0.001$, $F_{3,40}= 22.1$) was significant for LDL-c. LDL-c levels don't change significantly in the L-RT group compared to the control group ($P = 0.34$). However, LDL-c levels in the M-RT and H-RT groups were significantly decreased compared to control group ($P < 0.001$). In addition, M-RT ($P = 0.032$) and H-RT ($P < 0.001$) groups indicated a significant decrease of LDL-c compared to the L-RT group.

Analysis of cholesterol findings also showed a significant effect of time ($P < 0.001$, $F_{1,40}= 26.1$) and time-group interaction ($P < 0.001$, $F_{3,40}= 7.4$). The results of Bonferroni post hoc test indicated a significant decrease of cholesterol in L-RT ($P = 0.039$), M-RT ($P = 0.002$) and H-RT ($P = 0.001$) groups compared to the control. Repeated measures analysis of variance test for triglyceride levels indicated that the effect of time ($P < 0.001$, $F_{1,40} = 99.6$) and also the time-group interaction ($P < 0.001$, $F_{3,40}= 11.4$) was significant, and there is a significant difference between different intensities training for triglyceride levels. The results of Bonferroni post hoc test showed that there was no significant difference between control with L-RT group ($P < 0.05$), but a significant decrease of triglyceride in the M-RT ($P = 0.003$) and H-RT ($P < 0.001$) groups were observed compared to control group. In addition, decrease in triglycerides levels in M-RT ($P = 0.047$) and H-RT ($P = 0.001$) groups compared to L-RT group was significant. But no significant difference was observed between the M-RT and H-RT groups ($P > 0.05$) (Table 1).

Analysis of HFREP-1 levels by repeated measures analysis of variance test with intergroup factor indicated that the effect of time ($P < 0.001$, F1,40 = 153.1) and group-time interaction ($P < 0.001$, F3,40= 34.1) was statistically significant. Therefore, the 12 weeks circuit training with different intensities has a significant effect on the levels of HFREP1 in obese postmenopausal women. Bonferroni post hoc test showed that there was no significant difference between the control group with L-RT group ($P > 0.05$).

However, decrease of HFREP1 levels in M-RT P < 0.001) and H-RT (P < 0.001) groups was significant compared to control and L-RT groups. Moreover, there was no significant difference between M-RT and H-RT groups (P > 0.05). In addition, paired t-test for intragroup analysis indicated no significant changes for control group (P = 0.67). However, a significant decrease of HFREP-1 levels was observed in L-RT (P = 0.021), M-RT (P < 0.001) and H-RT (P < 0.001) groups (Figure 1).

Table1. Changes of cholesterol, triglyceride, LDL-c and HDL-c levels in pre and post-test stages in different groups of the study.

Variables		Control	L-RT	M-RT	H-RT	Between group P value
HDL-c	Pre	31.76 ± 6.42	32.85 ± 4.67	33.23 ± 4.31	30.19 ± 5.88	P < 0.001
(mg/dl)	Post	33.67 ± 6.76	38.39 ± 5.35	39.23 ± 7.44	44.23 ± 5.47	
Paired t test		P = 0.11	P = 0.001	P < 0.001	P < 0.001	-
LDL-c	Pre	164.02 ± 13.75	162.72 ± 13.90	164.34 ± 10.63	166.40 ± 16.82	P < 0.001
(mg/dl)	Post	163.51 ± 13.49	155.98 ± 11.87	148.23 ± 8.55	141.84 ± 13.86	
Paired t test		P = 0.76	P = 0/006	P < 0.001	P < 0.001	-
Cholesterol	Pre	249.28 ± 16.22	241.91 ± 20.06	247.37 ± 13.02	243.92 ± 15.77	P < 0.001
(mg/dl)	Post	254.75 ± 12.24	230.73 ± 18.30	230.03 ± 15.01	225.02 ± 11.14	
Paired t test		P = 0.25	P = 0.019	P < 0.001	P = 0.003	-
Triglyceride	Pre	247.91 ± 15.50	249.88 ± 16.75	248.47 ± 20.77	252.83 ± 19.17	P < 0.001
(mg/dl)	Post	245.97 ± 12.88	245.81 ± 13.47	239.01 ± 18.47	240.83 ± 16.48	
Paired t test		P = 0.17	P = 0.014	P < 0.001	P < 0.001	-

L-RT: Low intensity circuit resistance training; M-RT: moderate intensity circuit resistance training and H-RT: high intensity circuit resistance training intensity.

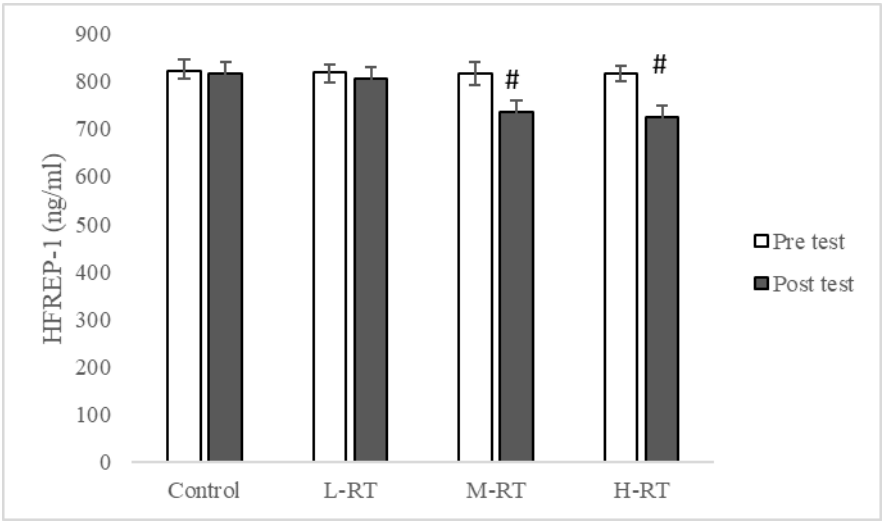

Figure 1. Hepatocyte-derived fibrinogen-related protein 1 (HFREP1) level in the different groups of postmenopausal women under study, before and after 12 weeks intervention. L-RT: Low intensity circuit resistance training; M-RT: moderate intensity circuit resistance training and H-RT: high intensity circuit resistance training intensity.
[#] Significant decrease compared to the control and L-RT groups.

Discussion

The main finding of present study was that 12 weeks low-intensity circuit resistance training don't have a significant effect on HFREP1 levels. However, moderate and high intensity circuit resistance training (60 and 80% of RM, respectively) was associated with a significant reduction in the levels of HFREP1. Among the different types of hepatokines, HFREP1 has attracted a lot of attention that exert

mitogenic activity in animal and human hepatocytes, and is up-regulated during liver regeneration (22, 23). HFREP1 binds not only to fibrin but also to fibrinogen, which may potentially mediate the growth-regulating functions of HFREP1 (24). Upregulation of HFREP1 levels has been reported in different types of malignancies such as hepatocellular carcinoma (HCC) (25). In addition, HFREP1 play an important role in development of insulin resistance (26), and its overexpression in liver tissue, increases the hepatic lipid accumulation and HFREP1 levels in the type 2 diabetic patients is significantly higher compared to healthy individuals (27). Researchers have suggested that HFREP1 levels are positively correlated with obesity (obesity markers such as BMI and waist circumference) and fat accumulation in visceral and subcutaneous adipose tissue, and therefore HFREP1 has been recognized as a therapeutic target in obesity (28). In this regard, the present findings indicated that circuit resistance training can be an effective strategy for decreasing the HFREP1 levels. Due to upregulation of HFREP1 expression in obese individuals' adipose tissue (28), decreased HFREP1 levels with exercise training can be attributed to decreased adipose tissue and thus decreased expression of HFREP1 in adipose tissue.

The effect of exercise training on the levels of HFREP1 is remarkably unknown. Keihaniyan et al (2018) investigate the effect of eight weeks resistance and aerobic training on lipid profile and serum levels of HFREP1 in obese men with type 2 diabetes, and suggested that both aerobic and resistance training was associated with significant decrease of HFREP1 and insulin resistance, which consistent with present findings, the decrease in HFREP1 levels was associated with a decrease in triglyceride, cholesterol and LDL-c levels and a simultaneous increase in HDL-c levels (10). This study results indicated that resistance training was more effective in decreasing HFREP1 levels compared to aerobic training. In general, in all factors except insulin resistance, HDL-c and LDL-c, resistance training was associated with more changes compared to aerobic training (10). Another finding of present study was that lipid profile was significantly improved in all trained groups (decreased triglyceride, LDL-c and cholesterol, and increased HDL-c levels). In addition, between group analysis showed that despite decrease of cholesterol levels in the L-RT group compared to control group, there is no significant difference for triglyceride, LDL-c and HDL-c levels in the L-RT compared to control group.

It has been reported that exercise training is associated with improvement the lipid profile, depending on the type, duration and intensity of exerted training program (29). Jorge et al (2011) compared the effect of 12 weeks different exercises training (endurance, resistance and combined training), and suggested that all exercise training type result in significant decrease in total cholesterol and LDL-c (30). Contrary to the present findings, Mahdirejei et al (2015) reported that four weeks endurance and resistance training don't have a significant effect on lipid profile in obese men (31). Contradiction with the present study findings, can be attributed to shorter training period in the Mahdirejei et al (2015) study, which the non-significant improvement of lipid profile, in the Mahdirejei et al (2015) study confirms this hypothesis.

Consistent with the present findings regarding the greater effect of higher intensities of circuit training in improving lipid profile, Paoli et al (2013) compared the effect of 12 weeks low and high intensity circuit training and reported that despite the increase in HDL-c levels and significant decrease of cholesterol, LDL-c and triglycerides in the high-intensity training group, the low intensity training only was associated with decreased LDL-c levels (32). It seems that total energy consumption can be one of the

determining factors on the lipid profile, and the changes in the lipid profile with exercise training is largely dependent on the total calories consumed (33), which these items confirm the further observed changes in lipid profile with higher intensity of circuit resistance training in the present study. Exercise training effects on lipid profile exert by different mechanism, it has been suggested that increasing the lipoprotein lipase activity during exercise result in breakdown of triglycerides, which is known as a molecular mechanism for increasing HDL-c (34). In addition, PPAR-γ and PGC1-α can be another pathway through which exercise training led to improve lipid profile (35). Based on the present findings, it seems that positive effects of exercise training in obese people is partly exerted by decreasing the levels of HFREP1, which in turn can improve the lipid profile. However, determined the mechanism by which changes in the HFREP1 levels affect the lipid profile needs further study. Therefore, especially due to few conducted studies regarding the effect of different exercises training on HFREP1 levels, it is not possible to conclude about the signaling pathways by which exercise training affect the levels of HFREP1.

Conclusion

The present study findings indicated that higher intensities circuit resistance training was more effective in decreasing the metabolic risk factors such as HFREP1, and further decrease of HFREP1 levels in the intense circuit resistance training group was associated with further improvement in lipid profile. It seems that higher intensities of circuit resistance training in obese postmenopausal women can be an effective strategy to maximize the exercise training induced physiological adaptations.

Acknowledgments

The present study written based on exercise physiology Ph. D thesis and was approved by Islamic Azad University, Central Tehran Branch ethics committee.

Conflict of interest

The authors declare that no conflict of interest exists.

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