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The effect of different intensity circuit resistance training on the level of the hepatokines, FGF-21, ANGPTL3 and ANGPTL4 in obese postmenopausal women

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ABSTRACT

Introduction: Hepatokines play an important role in the regulation of lipid and glucose metabolism, and hepatokines dysregulation can be associated with different pathological conditions such as obesity and type 2 diabetes. The present study conducted aimed to examined the effect of 12-week circuit resistance training with different intensities on the level of the insulin resistance related hepatokines, FGF-21, angiopoietin-like proteins 3 (ANGPTL3) and ANGPTL4 in obese postmenopausal women.

Materials and Methods: Forty-four postmenopausal women with average age of 56.07 ± 3.18 years participated in the present study, which randomly divided into four groups (11 subjects in each group) including control groups, low (LT), moderate (MT) and severe (HT) intensity circuit resistance training groups. The training program conducted for 12 weeks and three sessions per week. Blood samples collected before and after training interventions and the levels of desired variables were measured by ELISA method. The findings were analyzed with Graphpad Prism software and significance considered at the level of $P < 0.05$.

Results: A significant decrease of FGF-21 levels was observed in the HT compared to control group ($P = 0.015$), but there were no significant changes in FGF-21 levels in the other groups ($P < 0.05$). ANGPTL3 levels decreased in LT, MT and HT groups compared to the control group ($P < 0.001$). In addition, decrease in the levels of ANGPTL3 in the HT group was significant compared to the LT ($P < 0.001$) and MT ($P = 0.002$) groups. The reduction of ANGPTL4 levels was significant in the three trained groups compared to the control group ($P < 0.001$), and also in the HT compared to the LT group ($P = 0.025$).

Conclusion: High intensity circuit resistance training compared to its low and moderate intensities can have a greater role in modulating insulin resistance by further reducing the levels of insulin resistance related hepatokines.

Keywords: Obesity, Hepatokine, Menopause, Inflammation

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Introduction

It has been reported that the liver can control the whole-body energy homeostasis by regulating the lipid and glucose metabolism through the secretion of hepatokines, which are liver derived proteins (1). Lipid accumulation in the liver is closely related to visceral fat, type 2 diabetes and cardiovascular diseases, all of which are associated with changes in the secretion patterns of hepatokines (2). In this regard, upregulation of some hepatokines including angiopoietin-like proteins 3 (ANGPTL3) and 4 (ANGPTL4) has been reported in obese compared to normal weight individuals, which enhance its levels can increase the risk of type 2 diabetes and metabolic syndrome (3). ANGPTLs are a family of proteins that are structurally similar to angiopoietins, which eight members of the ANGPTLs family have been identified so far, which play an important role in various physiological and pathological processes (4). Among ANGPTLs family, ANGPTL3 and ANGPTL4 attracted a lot of attention.

ANGPTL3 is mainly expressed in the liver tissue during embryonic development and also in adulthood, which is known as a strong modulator for triglyceride, LDL-c and HDL-c levels, as well as endothelial lipase activity (5). Since the liver tissue is the main expression cite for ANGPTL3, its known as a true hepatokine (6). The ANGPTL3 upregulation has been observed in the type 2 diabetic patients compared to non-diabetic subjects, a significant increase in the levels of ANGPTL3 has been also reported in the obese non-diabetic compared to non-obese non-diabetic individuals. In addition, ANGPTL3 levels increase in the insulin resistance status and can affect carbohydrate metabolism (7). Unlike ANGPTL3, its suggested that ANGPTL4 is synthesized by different tissues and cells, including adipose tissue, liver, skeletal muscle, heart, intestine, and macrophages (8).

In human subjects, ANGPTL4 is expressed most highly in liver tissue, although a remarkable expression of ANGPTL4 in adipose tissue and pancreatic islets has also been observed (9). ANGPTL4 affects lipid and glucose metabolism, ANGPTL4 suppresses the clearance of circulating triacylglycerols (TAGs), which is achieved by inhibiting LPL, the enzyme that hydrolyses TAGs in lipoprotein particles. Accordingly, deletion of ANGPTL4 causes lowering of circulating TAGs, whereas ANGPTL4 overexpression leads to an increase in TAGs (10). In addition, overexpression (3-4 times) of ANGPTL4 in the peripheral tissues of transgenic mice leads to a 2-3-fold increase in the plasma levels of triglyceride (11). Moreover, ANGPTL4 levels are positively correlated with circulating free fatty acid (FFAs) levels and waist-to-hip ratio (WHR), suggesting a ANGPTL4 role in the fat storage (12).

Some researchers indicated that ANGPTL4 levels increased in type 2 diabetic compared to healthy subjects (13). On the others hand, the expression of ANGPTL4 as well as its levels in the blood circulation of diabetic patients is higher compared to healthy people, that its upregulation and interaction with inflammation and oxidative stress is due to a compensatory mechanism in order to limit the further dysfunction in adipose tissue (14). Moreover, higher levels of ANGPTL4 were observed in obese individuals with normal glucose tolerance compared to lean individuals, and ANGPTL4 levels were higher in obese individuals with impaired glucose tolerance compared to individuals with normal glucose tolerance, which increased ANGPTL4 levels was associated with higher levels of inflammatory mediators including CRP (15). The plasma levels of ANGPTL4 in human are relatively stable, but it has been reported that its levels increase (80%) after fasting (2 days). In addition, increased levels of ANGPTL4 have been observed after chronic calorie restriction and exercise (12, 13). Fibroblast

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growth factor 21 (FGF-21) is another hepatokine, which is mainly synthesized in the liver. However, the expression of FGF-21 in other tissues such as white and brown adipose tissue, skeletal muscle, cardiac endothelial cells and hypothalamus has also been observed (16).

FGF-21 exert many biological effects consist of increasing glucose uptake due to the promotion of glucose transporter 1 (GLUT-1) independent from insulin action and thermogenic activation of brown adipose tissue (17). Higher serum levels of FGF21 have been observed in insulin resistance status such as impaired glucose tolerance, diabetes mellitus and obesity (18). Therefore, obesity known as an FGF21-resistant condition (19). The health benefits of exercise training attracted a lot of attention, and regular exercise has been recognized as a therapeutic strategy for the prevention and treatment of a wide range of chronic disorders such as obesity, insulin resistance, and type 2 diabetes (20). Exercise training is known as an important intervention that influence the levels of hepatokines (21). Some researchers have suggested that positive effects of exercise training on the body exerted by hepatokines partly, and modulating the levels of hepatokines following exercise training can play a significant role in improving metabolic diseases such as obesity and insulin resistance (22). Positive effects of circuit resistance training have been investigated in the different studies, and cardiovascular benefits and increased strength have been reported following this type of training (23), and is associated with enhancing the maximum oxygen consumption, maximum pulmonary ventilation, functional capacity and improvement of body composition (24). In fact, circuit resistance training can exert a combination of the positive effects of endurance and resistance training, although the increase in strength and muscle mass in response to traditional circuit resistance training is moderate. However, its approved that higher intensities circuit resistance training can magnify neuromuscular and cardiovascular adaptations in the elderly (25). Despite this, the effect of different intensities of circuit resistance training on the levels of different hepatokines, such as FGF-21, ANGPTL3 and ANGPTL4 is unknown. Therefore, the effect of different intensities of circuit resistance training on the levels of FGF-21, ANGPTL3 and ANGPTL4 have been investigated in the present study.

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 age ranging the 48-65 years old (average BMI: 33.43±1.29 kg.m2) were chosen 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. The subjects' physical characteristics has been reported in the Table1.

The inclusion criteria for the study were as follow: The participants should have passed at least 12 months after the last menstrual period, did not addict to drugs or alcohol, did not take part in regular exercise training in last year, and having no kidney, liver, cardiovascular disease and diabetes. Their body mass index must be equal or greater than 30 kg/m2, and have not any injuries or physical problems. In addition, 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 were considered as exclusion criteria.

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Table1. Demographic characteristics of the subjects participated in the study.

Variable	Controls	LT	MT	HT
Age (years)	56.72 ± 3.91	54.90 ± 2.68	57.41 ± 2.82	55.36 ± 3.24
Height (cm)	163.95 ± 3.22	164.21 ± 2.71	162.38 ± 2.67	163.23 ± 1.71
Weight (kg)	89.82 ± 2.16	88.92 ± 2.84	88.49 ± 1.91	89.21 ± 2.22
BMI (kg/m^2)	33.47 ± 1.58	33.05 ± 1.44	33.55 ± 1.34	33.72 ± 0.73

Data are shown as mean ± SD. LT; low, MT; moderate and HT; severe intensity circuit resistance training groups.

Study Design

Because the subjects of the study included obese menopausal women and were examined in a 12-week research period, so the research is considered as a semi-experimental study. After checkup by a gynecologist and confirming the menopause, subjects were qualified to enter in the 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 participant's 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 (LT), 3) moderate intensity circuit resistance training (MT) and 4) High-intensity circuit resistance training (HT). 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 circuit 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 (26, 23). The training group consist of 1) HT: Three sets with 10 repetitions at 80% 1RM, 2) MT: Three sets with 13 repetitions at 60% 1RM, 3) LT) 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) (27). The between sets rest considered two minutes and was inactive (28). The subjects 1RM was calculated using Brzycki equation (29) 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

Commercial immunoassay kits were used for measurement of the plasma levels of FGF-21 (Biovendor, catalog number: RD191108200R, sensitivity level: 7 pg/ml), ANGPTL3 (Biovendor, catalog number: RD191092200R, sensitivity level: 1.08 ng/ml), ANGPTL4 (Biovendor, Catalog number: RD191073200R, sensitivity level: 0.173 ng/ml), and insulin (Demeditec, catalog number: DE2935, sensitivity level: 1.76 µIU/ml). Moreover, a specialized kit of Pars Azmoun company

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with a sensitivity of 5 mg/dL was used to measure glucose levels. In order to calculate insulin resistance, the following formula was used (30):

Fasting insulin {µU/mL} × fasting glucose {mg/dL} /405

Statistical Analysis

In order to present study 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 insulin resistance, body fat percentage, body mass index (BMI) and body weight of participants in the different groups, before and after the 12-week intervention of circuit resistance training have been depicted in the Table 2.

Table 2. Changes in the insulin resistance, body fat percentage, BMI and body weight in different groups of subjects participated in the study.

Variables		Control	LT	MT	HT	Between group P value
Insulin Resistance	Before	4.48 ± 0.70	4.58 ± 0.46	4.61 ± 0.24	4.79 ± 0.38	< 0.001
	After	4.27 ± 0.30	3.68 ± 0.25	2.94 ± 0.26	2.73 ± 0.31	
Intragroup P value		0.27	0.001	< 0.001	< 0.001	-
Body Fat (%)	Before	31.51 ± 1.03	30.62 ± 0.79	30.94 ± 1.14	31.44 ± 1.06	< 0.001
	After	31.53 ± 1.12	29.30 ± 0.61	28.25 ± 0.80	27.81 ± 1.04	
Intragroup p value		0.98	0.004	0.001	< 0.001	-
BMI (kg/m^2)	Before	33.4 ± 1.50	33.1 ± 1.40	33.6 ± 1.30	33.7 ± 0.61	< 0.001
	After	33.1 ± 1.60	32.2 ± 0.87	33.2 ± 1.40	31.9 ± 1.10	
Intragroup P value		0.26	0.027	0.003	< 0.001	-
Body weight (kg)	Before	89.88 ± 2.11	88.92 ± 2.88	88.42 ± 1.95	89.72 ± 2.22	< 0.001
	After	88.82 ± 1.70	86.81 ± 1.84	84.82 ± 1.61	83.10 ± 2.41	
Intragroup P value		0.126	0.026	0.003	< 0.001	-

Data are shown as mean ± SD. LT; low, MT; moderate and HT; severe intensity circuit resistance training groups.

The present findings indicated that the BMI in the HT group compared to the control ($P < 0.001$), LT ($P = 0.003$) and MT ($P = 0.036$) groups decreased significantly, but BMI changes between other groups wasn't significant ($P > 0.05$). In addition, a significant decrease in body fat percentage was observed in the LT, MT and HT groups compared to the control group ($P < 0.001$). On the other hand, body fat percentage represented a significant decrease in the MT ($P = 0.023$) and HT ($P = 0.002$) groups compared to the LT group. In addition, insulin resistance decreased significantly in the LT, MT and HT groups compared to the control group ($P < 0.001$). Observed insulin resistance reduction in the MT and HT groups was also significant compared to the LT group ($P < 0.001$) (Table 2).

Repeated measures analysis of variance test with intergroup factor for FGF-21 levels indicated that the effect of time ($P < 0.001$) and group-time interaction ($P = 0.021$) is significant. The Bonferroni post hoc test findings showed no significant difference between the control group with LT ($P = 0.99$) and MT ($P = 0.57$) groups, but significant difference was observed between the control and HT groups for FGF-21 levels ($P = 0.015$). However, there was no significant difference between different intensities of circuit resistance training ($P < 0.05$). Intra-group analysis with paired t-test showed that the changes of FGF-21 levels after 12-week circuit resistance training in control ($P = 0.13$) and LT ($P = 0.07$) groups wasn't significant. On the other hand, FGF-21 levels significantly decreased in the MT ($P = 0.03$) and HT (P

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< 0.001) groups. The FGF-21 levels in the different groups reported in the Figure 1.

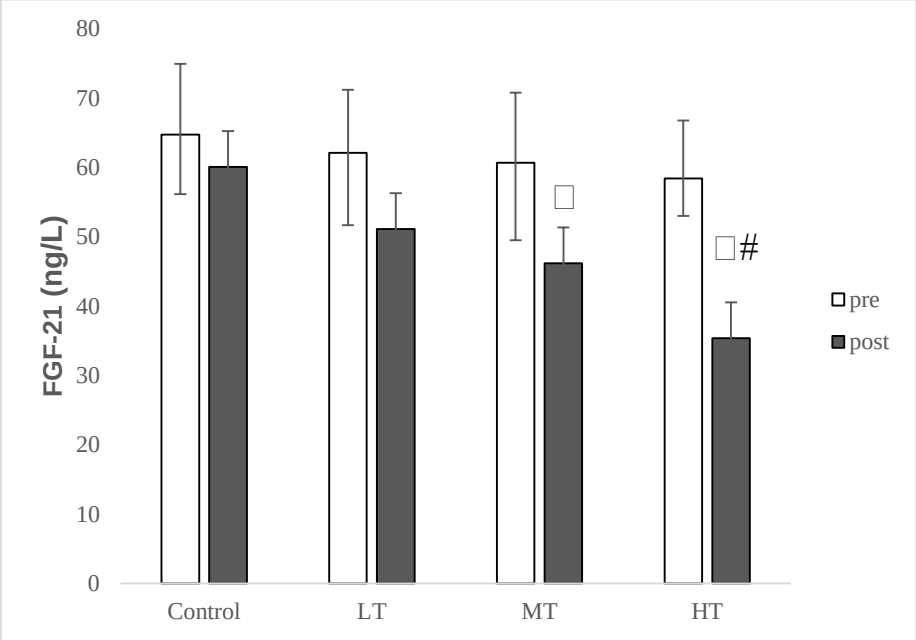

Figure 1. Plasma levels of FGF-21 in different groups of the study. LT; low, MT; moderate and HT; severe intensity circuit resistance training groups. # Significant difference with the control group. Significant decrease compared to the pre-test group.

The effect of time (P < 0.001) and group-time interaction (P < 0.001) were also significant for ANGPTL3 levels. Bonferroni post hoc test results indicated a significant difference between the control group with the LT, MT and HT groups (P < 0.001), and significant difference was observed between the LT and HT groups (P < 0.001), but observed difference between the LT and MT groups wasn't significant statistically (P = 0.081). In addition, the ANGPTL3 levels was significantly difference between the MT and HT groups (P = 0.002). Paired t test showed a significant decrease of ANGPTL3 levels in LT (P < 0.001), MT (P < 0.001) and HT (P < 0.001) groups and a significant increase in the control group (P = 0.016) (Figure 2).

The effect of time (P < 0.001) and group-time interaction (P < 0.001) was significant for plasma levels of ANGPTL4. The results of Bonferroni post hoc test indicated a significant difference between the control with LT (P = 0.005), MT (P = 0.001) and HT (P < 0.001) groups. In addition, a significant difference was observed between the LT and HT groups (P = 0.025), but the difference between the LT and MT groups (P = 0.99) and between the MT and HT groups (P = 0.105) wasn't significant statistically for plasma levels of ANGPTL4. Intra-group data analysis represented a significant decrease in the plasma levels of ANGPTL4 in the LT (P = 0.027), MT (P = 0.017) and HT (P < 0.001) groups, and ANGPTL4 levels significantly increased in the control group (P = 0.004) (Figure 3).

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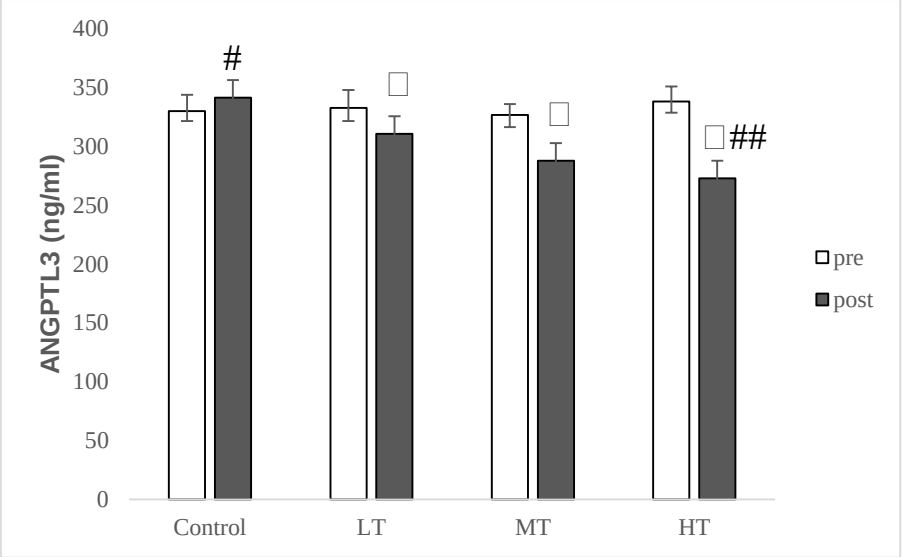

Figure 2. Plasma levels of ANGPTL3 in different groups of the study. LT; low, MT; moderate and HT; severe intensity circuit resistance training groups. # Significant difference with the LT, MT and HT groups. ## Significant difference with the LT and MT groups. □ Significant decrease compared to the pre-test group.

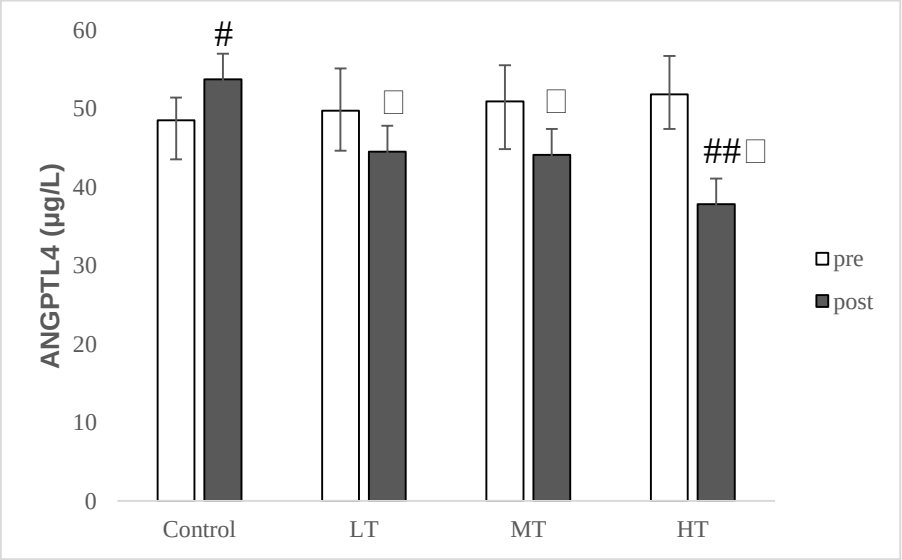

Figure 3. Plasma levels of ANGPTL4 in different groups of the study. LT; low, MT; moderate and HT; severe intensity circuit resistance training groups. # Significant difference with LT, MT and HT groups. ## Significant difference with LT group. □ Significant decrease compared to pre-test.

Discussion

The present study conducted aimed to compare the effect of low, moderate and high intensity circuit resistance training on the plasma levels of FGF-21, ANGPTL3 and ANGPTL4 in obese postmenopausal women. This research main finding was that the levels of ANGPTL3 significantly decreased in the LT, MT and HT groups compared to the control group and also in the HT group compared to the LT and MT groups. In addition, a significant decrease in ANGPTL4 levels was observed in the LT, MT and HT groups compared to the control group, as well as in the HT group compared to the LT group. These results emphasized the effect of various intensities circuit resistance training in reducing the levels of ANGPTL3 and ANGPTL4, with a

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further effect of higher intensity compared to low and moderate intensities on the levels of these hepatokines. Exercise training can affect the levels of ANGPTL4, and significant increase in the levels of ANGPTL4 after (immediately and 90 minutes after) mountain ultra-marathon running have been reported in healthy trained men (31). These findings suggested that ANGPTL4 can also be secreted from skeletal muscles and can be considered as a myokine. Supporting this hypothesis, it has been reported that ANGPTL4 in addition to liver tissue, is produced and secreted by adipose tissue, skeletal muscle, heart, intestine and macrophages (8).

Consistent to the present findings, Khosravi et al (2018) reported a significant decrease in the levels of ANGPTL4 after 12-week endurance training in obese women, which downregulation of ANGPTL4 was associated with weight loss and body fat percentage reduction (32). Since the inflammatory adipokines such as TNF-α and IFN-γ play an important role in the up-regulation of circulating ANGPTL4 levels (33), the observed reduction in ANGPTL4 levels can be explained by decreasing TNF-α and IFN-γ levels, which unfortunately their levels have not been investigated in the current research. In addition, because the ANGPTL4 is known as adipokine (34), observed decrease in the levels of ANGPTL4 in the trained groups can be attributed to the reducing body fat. Confirming this hypothesis, a greater decrease of body fat percentage in the HT group was associated with a further reduction of ANGPTL4 levels in this group. In another study, Smol et al (2015) investigated the changes in the levels of ANGPTL3 after 12-week regular exercise (recreational exercise such as football, swimming, walking, and resistance exercise training) and reported that ANGPTL3 levels in the active compared to inactive people (men and women) are lower non-significantly (35). Moreover, these researchers suggested that ANGPTL3 levels were significantly higher in women compared to men, which emphasizes the role of gender in the observed changes in circulating levels of ANGPTL3 (35).

In contrast to our findings, it's reported that 10 weeks of sprint interval or combined aerobic and resistance training don't have a significant effect on ANGPTL4 levels, but consistent with the present research indicated that sprint interval or combined training can't affect the FGF-21 levels (36). In this regard, our findings showed that the reduction of FGF-21 levels was significant only in the HT group compared to the control group, but low and moderate intensity circuit resistance training did not have a significant effect on the levels of FGF-21, although a relative decrease of FGF-21 levels was observed in the low and moderate intensity training groups. Despite the present results, there was a contradictory finding about exercise training effects on the levels of FGF-21, and decrease (37), increase (38) and no change (39) of FGF-21 levels after different type of exercise training have been reported. These contradictory finding can be attributed to the difference in age, gender, physical fitness level, subjects' physical condition (healthy, sick, lean, normal weight or obese) and the duration of exercise training program. Despite the effect of FGF-21 in stimulating lipolysis, it is very surprising that obese diabetic mice and obese human have higher levels of FGF-21 and its levels increases due to obesity (40). The FGF-21 levels are up-regulated in obese people due to high levels of FFAs, increased glucose and disruption of the downstream signaling pathway (19). Although, the FGF-21 levels increase in obese individuals, the effect of FGF-21 is probably reduced due to the downregulation of b-Klotho receptor expression, which its reported that b-Klotho and PPAR-γ expression decreased in obese diabetic rat islets treated with high levels of glucose, and the expression of FGFR1 and b-Klotho is significantly suppressed in the white adipose tissue of diet induced obese mice with high levels of FGF-21 (40).

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Consistent to the current findings regarding the reduction of FGF-21 levels, especially with high intensity circuit resistance training, Yang et al (2011) reported that 12 weeks combined training (endurance-resistance) in obese women result in significant reduction in FGF-21 levels (37). In the current study, FGF-21 levels reduction was observed in all trained groups, although statistically significant decrease was observed only in the high intensity circuit resistance training group. The reduction of FGF-21 levels with exercise training in obese people can be related to the decrease in FGF-21 resistance. In supporting this idea, the researchers indicated that like other hormonal resistance, the resistance to FGF-21 is also can occurred in obese people, and probably the upregulation of FGF-21 levels in obese individuals is a protective response against the metabolic pressure caused by obesity (19). In fact, the positive effects of exercise training in obese people are partly exerted by reduction of resistance to FGF-21. The enhancing FGF-21 levels in obese subjects is related to the decrease of local expression of β-klotho (FGF co-receptor) in obesity induced pro-inflammatory conditions. In addition to obesity, pathological conditions such as type 2 diabetes, lipodystrophy, metabolic syndrome or insulin resistance cause to increased FGF-21 levels, and based on this evidence, the FGF-21 considered as a marker for metabolic syndrome and type 2 diabetes in the different researches, which enhancing its levels can be associated with a disturbance in the lipid profile (41). Collectively, the present findings showed that different intensities of circuit resistance training have an effective role in improving insulin resistance and modulating the levels of different hepatokines such as FGF-21, ANGPTL3 and ANGPTL4, and there is a positive correlation between the observed changes in above mentioned hepatokines with the intensity of circuit resistance training. These findings, emphasis the greater effectiveness of higher intensity of circuit resistance training in obese postmenopausal women, which identify its responsible signaling pathways and molecular mechanisms requires further investigation, which should be determined in future studies.

Conclusion

According to the present study findings, it can be concluded that observed decrease in the levels of hepatokines including FGF-21, ANGPTL3 and ANGPTL4 can partly illustrated the positive effect of different intensities circuit resistance training on body composition and insulin resistance in obese postmenopausal women, and in order to increase the effectiveness of circuit resistance training, higher intensities can be recommended.

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Conflict of Interest

The authors declare that no conflict of interest exists.

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