Research Article

The effect of moderate-intensity continuous training versus high-intensity interval training on the lipocalin 2 levels in obese women

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Abstract

Adipose tissue affects the lipid and glucose metabolism by secreting various adipokines such as lipocalin 2. The aim of present study was to compare the effect of 12 weeks' moderate intensity continuous training (MICT) and high intensity interval training (HIIT) on the serum levels of lipocalin 2 in obese women. Thirty-six obese women with average age of 26.3±3.41 years old and body mass index of 31.6±1.27 kg.m2 were assigned to three groups consisting of control, MICT and HIIT groups. Both exercise training program conducted for 12 weeks three sessions per week. The MICT intensity was 60-70 percent of the maximum heart rate and the intensity for HIIT program considered 90 percent of maximum heart rate. Blood samples collected in pre and post-test stages and the levels of desired variables were measured. Data analysis was performed by the analysis of covariance test and Bonferroni post hoc-test ($p<0.05$). The findings indicated that both MICT and HIIT programs result in significant decrease of lipocalin-2 and insulin resistance ($p<0.05$). In addition, significant improvement of lipid profile in MICT and HIIT groups were observed and there was no significant difference between the trained groups. According to the findings, it seems that one of the positive effective mechanisms of exercise training is the decrease in lipocalin2 levels with continuous and high intensity interval training.

Key Words: **Continuous training, High intensity interval training, Adipokine, Lipocalin2**

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Introduction

Obesity is a condition that results from the accumulation of excess fat tissue and has adverse effects on health. Among the complications of obesity diseases, we can mention disability and short life span, insulin resistance, type 2 diabetes, atherosclerotic heart diseases, non-alcoholic fatty liver disease, high blood pressure and hyperlipidemia (Liu et al., 2020). Today, the prevalence of obesity and metabolic syndrome is increasing at an alarming rate among adults and children and has become a global epidemic (Dhasarathy et al., 2017). All these cases have made obesity one of the biggest health problems worldwide in terms of its high prevalence and associated costs. According to the studies conducted in 2014, more than 1/2 billion people around the world, that is, nearly 30% of the world's population, were obese or overweight, and 5% of all deaths in the world were attributed to obesity. If the rate of obesity continues, by 2030, almost half of the world's adult population will be overweight or obese. Adipose tissue secretes various factors called adipokines, which play an important role in the pathogenesis of various conditions, including metabolic syndrome (Kershaw & Flier, 2004).

Yan et al. (2007) introduced lipocalin-2 as a new adipokine secreted in large amounts by the adipose tissue of animal samples. In addition, they showed that lipocalin-2 levels increased by dexamethasone and tumor necrosis factor alpha and decreased by rosiglitazone in mouse adipocytes (Yan et al., 2007). Wang et al. (2007) reported that lipocalin-2 levels increase in obesity and diabetes (Wang et al., 2007). Some researchers have also stated that the expression of lipocalin-2 increases significantly in the fat tissue of obese women and has a positive correlation with inflammatory cytokines such as interleukin-6 (IL-6). Based on the mentioned cases, researchers have introduced lipocalin-2 as an inflammatory factor that has a positive correlation with obesity, insulin resistance, and hyperglycemia in human samples and has a close relationship with chronic inflammation and metabolic disorders it caused leading to a decrease in insulin resistance. Insulin can reduce the levels of lipocalin-2 (Wang et al., 2007).

Based on this, lipocalin-2 can be considered as a therapeutic target to deal with insulin resistance and improve metabolic profile. Researchers showed that three weeks of HIIT on animal samples (male Wistar rats) was associated with a significant decrease in the expression of lipocalin-2 in the soleus muscle. Despite this, Moradi et al. (2019) found that there was no significant effect of eight weeks of intermittent speed training on lipocalin-2 levels in volleyball girls (Moradi & Moradi, 2019). However, less attention has been paid to the positive effects of exercise, including improving insulin resistance, the effect of different types of exercise, especially high intensity interval training (HIIT), on lipocalin levels. Thus, for the first time, this study compared the effects of 12 weeks of continuous training with moderate intensity and intense intermittent training on the serum levels of lipocalin-2 in obese women according to the limited and contradictory findings.

Materials and Methods

Subjects

The current research adopted a quasi-experimental and applied design, implementing laboratory and field tests. The statistical population of the present study consisted of obese women with an age range of 20 to 35 years. Subjects were selected from among the volunteers qualified as the statistical sample and after medical evaluation, 36 people were selected to participate in the study according to the criteria considered by the researchers.

Procedure

In the beginning of the research, an attempt was made to identify the desired subjects for conducting the present study through informing and mentioning the required conditions of the subjects. For this purpose, notification was first made by placing notices in several public places (parks, sports clubs, and streets) in Karaj to find qualified people to participate in the research. People who did not have the desired criteria were excluded from the research. After identifying and selecting the intended subjects, the conditions of the study and how it would be conducted were explained for everyone to inform them about the advantages and disadvantages of exercise for overweight and obese people. Then, 36 subjects were selected based on the entry and exit criteria considered for the research from among those who were willing to continue cooperation. Moreover, an informed consent was obtained from all of them before conducting the research. Finally, the randomly selected people were divided into three groups of 12 including control, high intensity interval training (HIIT), and moderate intensity continuous training (MICT) groups.

The subjects were asked to refrain from any changes in their lifestyle during the 12 weeks of the study in order to accurately control the disturbing and influencing factors during the implementation of the study. Subjects of the exercise group were also justified not to participate except for the exercise program considered by the researcher in another exercise program.

Entry and exit criteria

The inclusion criteria for this study included absence of: cardiovascular diseases, high blood pressure, menopause, diabetes, various types of malignancies (cancer), and regular exercise during the last year. In addition, there should be no consumption of alcoholic beverages, no consumption of processed supplements, and no medical prohibition to participate in sports exercises, no restrictions or physical problems to participate in the training program. The criteria for withdrawing from the research included not agreeing to the conditions considered by the researchers, absence of more than two sessions during the 12- week period, injury and inability to continue the exercise program, any discomfort and heart disease.

Anthropometric measurements

The height and weight of the subjects were measured by a Seca scale and caliper made in Germany. To estimate the body mass index (BMI) of the subjects, dividing weight in kilograms by height in meters to the power of two (2kg.m) was also used. BOCA-X1 body composition analyzer made in Korea was also used to measure body fat percentage.

Exercise training programs

Intermittent and continuous exercise program was implemented for12 weeks and three sessions per week in the form of walking or running on a treadmill. Intense interval training consisted of a 10-minute warm-up with an intensity of 50-60% of the maximum heart rate (walking on the treadmill and at the end of dynamic stretching movements), which was followed by four intense intervals of four minutes with an intensity of 90% of the maximum heart rate. After each intense interval, it performed at 50-60% of maximum heart rate.

At the end of each exercise session, a cool-down was performed, including 5 minutes of low- intensity walking on the treadmill and static stretching. A continuous exercise program was also implemented for 47 minutes with an intensity of 60- 70% of the maximum heart rate (Schjerve et al., 2008) (Table 1). During this period, the subjects of the control group continued their usual daily schedule and did not participate in any regular exercise program until the end of the study.

Laboratory measurements

In the present study, blood sampling was performed in two phases: pre-test and post-test. The subjects were asked to come to the laboratory between 8 and 9 in the morning and after about 12 hours of overnight fasting for blood sampling in the pre-test

Table 1. Continuous and intense interval training program.

Moderate intensity continuous training (MICT)				
Time (minutes)		Intensity (percentage of maximum heart rate)		
47		60		**1-4 Week**
47		65		**5-8 Week**
47		70		**9-12 Week**
High Intense interval training (HIIT)				
Time of interval Rest (minutes)	The number of interval Rest	Time of interval training (minutes)	The number of interval training	
3	4	4	4	**1-12 Week**

phase. Subjects were exposed to the independent variable (HIIT or MICT) for 12 weeks, a few days after measuring anthropometric variables and collecting pre-test blood samples. The subjects were asked to appear in the post-test stage, like the pre-test stage, two days after the last session of the exercise program.

Again, in order to take blood and measure anthropometric variables, the subjects were prohibited from any physical activity or heavy sports after the last exercise training session. In both stages of blood collection, 7 milliliters of blood was taken from each subject in a sitting and resting position from the anterior vein of the right hand. Immediately after blood collection, the blood samples were transferred into the Falcon tube and then the blood samples were placed inside the centrifuge and centrifuged at 3000 rpm for 10 minutes. After this period of time, the tubes were removed from the device and the serum was transferred into the microtube using a sampler and kept in the refrigerator at -80 degrees Celsius until the relevant tests were performed.

Lipocalin-2, insulin, glucose and lipid profile

Blood glucose levels were measured with a Pars Azmoun kit using the glucose oxidase method. Insulin levels were also measured by the ELISA method using the demeditec ELISA kit (DE 2935) with a sensitivity of 1,76 µIU/m. In order to measure the serum levels of lipocalin-2, the Biovendor ELISA kit with catalog number (RD 191102200 R) and a sensitivity of .02 ng/ml was used. Blood lipids (cholesterol, triglycerides, LDL-c and HDL-c) were measured using Pars Azmoun kits, made in Iran. In order to calculate the body mass index (BMI) of the subjects, dividing the body weight in kilograms by the square of the height in meters was also used. In order to calculate insulin resistance, the following formula was used.

Insulin resistance (HOMA-IR): insulin (mU/L) * glucose (mg/dl).

Statistical analysis

Data analysis was done using SPSS-24 software and the level of significance was considered .05 ($p<0.05$). In order to determine the normality of data distribution, the Shapiro-Wilk test was used. Furthermore, in order to determine the significance of the difference between the research groups, the analysis of covariance (ANCOVA) test and in case of a significant difference, the Bonferroni post hoc test was used.

Results

The levels of lipocalin-2, glucose, insulin, insulin resistance, cholesterol, triglycerides, LDL-c, HDL-c, body fat percentage and BMI of the subjects in the control, HIIT and MICT groups are presented as mean ± standard deviation in Table 2 in the pre-test and post-test stages.

Comparison of changes in lipocalin-2 levels between different groups using Bonferroni's post hoc test showed that lipocalin-2 levels decreased significantly in the MICT ($p=0.002$) and HIIT ($p=0.001$) groups compared to the control group. In addition, analysis of covariance test showed a significant difference between groups for levels of insulin resistance, cholesterol, triglyceride, LDL-c, HDL-c, body fat percentage and BMI ($p<0.001$). Bonferroni's post hoc test showed a decrease in insulin resistance in the MICT group ($p<0.001$) and HIIT ($p<0.001$) compared to the control group, a decrease in total cholesterol in the MICT group ($p=0.001$) and HIIT ($p < 0.001$) compared to the control group, the reduction of triglycerides in the MICT group ($p = 0.037$) compared to the control group, as well as a significant decrease in the MICT group ($p = 0.017$) and the HIIT group ($p = 0.001$) compared to the control group.

In addition, a significant increase in HDL-c levels in the MICT group ($p=0.007$) and HIIT ($p<0.001$) was observed compared to the control group and a significant increase in HDL-c levels in the HIIT group compared to the MICT group ($p=0.006$). Also, the current results showed a significant decrease in body fat percentage and BMI in the HIIT and MICT groups compared to the control group ($p<0.001$) (Table 2)

Discussion

The present study was conducted to compare the effect of 12

Table 2. Different variable of study at pre-test and post-test (Mean ± Standard Deviation).

Variable	Groups	Post-Test	Pre -Test	Sig.
Height (cm)	control	160.29± 4.87		
	MICT	159.75± 4.59		
	HIIT	161.62±4.25		
lipocalin-2 (ng/ml)	control	46.53 ± 5.72	45.79 ± 4.19	0.001
	MICT	45.26 ± 6.43	41.12 ± ± 6.22 #	
	HIIT	48.74 ± 5.35	43.55 ± 5.27 #	
Glucose (mg/dl)	Control	91.58 ± 9.19	93.25 ± 8.10	.078
	MICT	94.33 ± 10.75	91.83 ± 9.19	
	HIIT	89.83 ± 8.42	88.08 ± 7.30	
insulin (mU/ml)	Control	8.48± 1.40	8.56 ± 1.31	0.001
	MICT	9.66 ± 1.89	8.47 ± 1.48 #	
	HIIT	9.27 ± 1.38	7.54 ± 1.26 #	
insulin resistance	Control	1.90 ± 0.30	1.96 ± 0.34	0.001
	MICT	2.25 ± 0.54	1.92 ± 0.41#	
	HIIT	2.06 ± 0.40	1.63 ± 0.30 #	
Cholesterol (mg/dl)	Control	194.83± 17.80	201.66 ± 19.30	0.001
	MICT	203.75 ± 16.61	187.58 ± 14.77 #	
	HIIT	198.41 ± 18.48	179.33 ± 13.83 #	
TGL (mg/dl)	Control	142.91 ± 7.64	144.33 ± 9.13	0.029
	MICT	153.16 ± 9.86	141.58 ± 11.87 #	
	HIIT	147.66 ± 12.47	139.83 ± 12.75	
LDL-c (mg/dl)	Control	162.41± 10.29	159.83± 9.48	0.001
	MICT	156.75± 13.30	160.29± 4.87#	
	HIIT	151.66± 11.49	141.83 ± 10.32#	
HDL-c (mg/dl)	Control	54.08± 9.16	55.25 ±7.78	0.001
	MICT	51.41 ± 8.33	56.58 ± 7.42	
	HIIT	49.16 ± 4.21	58.33 ± 5.78 ¥⁕	
Fat %	Control	33.64 ± 2.23	33.91 ± 2.92	0.001
	MICT	35.38 ± 2.74	33.45 ± 2.83 #	
	HIIT	33.25 ± 2.76	31.06 ± 2.71 #	
BMI (kg/m^2)	Control	31.21 ± 1.28	31.16 ± 1.26	0.001
	MICT	32.03 ± 1.16	31.39 ± 1.08 #	
	HIIT	31.54 ± 1.34 #	30.73 ± 1.30 #	

A significant decrease was observed compared to the control group, ¥ significant increase compared to the # control group, ⁕ and a significant increase compared to the MICT group. The results of analysis of covariance showed a significant difference and thus, in order to investigate changes between the groups (control, MICT and HIIT groups) of lipocalin-2 ($p<0.001$), Bonferroni test was used.

weeks of continuous training with moderate intensity and intense intermittent training on the serum levels of lipocalin-2 in obese women. The main finding of the present study was that 12 weeks of continuous exercise with moderate intensity and intense intermittent exercise leads to a significant decrease in serum levels of lipocalin-2. In addition, a decrease in insulin resistance and an improvement in the lipid profile was observed in the trained groups compared to the control group. Lipocalin-2 is a 25kDa glycoprotein that can bind to small lipophilic molecules and transport them. Lipocalin-2 is expressed in many tissues such as neutrophils, macrophages, kidney, liver, lung, thymus and small intestine. In addition, lipocalin-2 is expressed mainly in adipocytes (Luo et al., 2016).

In accordance to the present study findings, Mohammadi et al. (2015) showed that eight weeks of aerobic training (three sessions per week) with an intensity of 65 to 80% of the maximum heart rate leads to a significant decrease in lipocalin-2 levels in obese men. However, the changes were not statistically significant, despite the decrease in insulin resistance. In addition, a decrease in LDL-c levels and an increase in HDL-c levels was observed in the trained group (Mohammadi & Reddy, 2015). These researchers associated decreased lipocalin-2 levels with decreased inflammatory mediators (CRP) and body fat percentage. Perhaps the reason for the contradiction of the findings of insulin resistance in the above study compared to the current study can be attributed to the shorter period of exercise training in the study by Mohammadi et al. (2015) compared to this study (Mohammadi & Reddy, 2015). Some researchers have also introduced lipocalin-2 as an inflammatory factor that is related to metabolic disorders, including metabolic syndrome to confirm the interaction between lipocalin-2 and inflammatory mediators.

In line with the above findings, regarding the relationship between lipocalin-2 levels and insulin resistance, research has showed that lipocalin-2 levels increase in overweight and obese people compared to normal weight people and there is a positive correlation between lipocalin-2 levels and insulin resistance. Rashad et al. (2017) also stated that serum levels and expression of lipocalin 2 in blood cells could be an early predictive factor for type 2 diabetes. These researchers showed that increased serum levels and expression of lipocalin-2 were associated with increased levels of inflammatory mediators such as CRP serum levels and more lipocalin-2 expression in obese women compared to lean women (Rashad et al., 2017). Studies conducted on animal samples have also shown that suppression of lipocalin 2 in mice significantly improves insulin sensitivity. These findings indicate that suppression or downregulation of lipocalin-2 levels or expression is one of the effective mechanisms in improving insulin sensitivity and reducing insulin resistance.

Exercise increases insulin sensitivity through different mechanisms. Muscle contractions cause the translocation of glucose transporter 4 (GLUT-4) to the plasma membrane due to the activation of adenosine monophosphate-activated protein kinase, which is caused by the increase in cytoplasmic calcium concentration caused by depolarization (Santos et al., 2008). It starts through increasing the intracellular ratio of adenosine monophosphate to adenosine triphosphate, which reflects the endangerment of the cell's energy status. Activation of c-Jun N-terminal kinase and IKB kinase/IKB/NF-KB can cause serine phosphorylation of insulin receptor substrate 1 (IRS-1) through stimuli such as cytokines, endoplasmic reticulum stress and fatty acids which leads to impaired phosphorylation of substrate Akt 60, a key step in insulin signaling that regulates GLUT-4 translocation (Mathur & Pedersen, 2008). In addition, the role of exercise in reducing inflammation can also be one of the effective mechanisms in reducing insulin resistance following exercise. One of the present findings was that there was no significant difference in the changes in lipocalin-2 levels after 12 weeks of moderate intensity continuous training and intense intermittent training. Despite this, unfortunately, no similar study has been conducted in this regard.

In a research, Moghadasi et al. (2014) showed a significant decrease in lipocalin-2 levels in both endurance and resistance groups, by examining the effect of eight weeks of endurance and resistance training, but did not show a significant difference in changes in lipocalin-2 levels between two endurance and resistance groups. In addition, a significant decrease in insulin resistance in both trained groups was accompanied by a decrease in lipocalin-2 levels with endurance and resistance training, which confirms the present study findings, indicating a negative correlation between lipocalin-2 and insulin resistance. Despite this, contrary to the present findings, no significant change was observed in the body fat percentage and BMI of the subjects, which shows that the positive effects of exercise training can occur independently of significant changes in the body fat percentage and BMI in reducing the levels of lipocalin-2 and insulin resistance (Moghadasi & Domieh, 2014).

Although contrary to the above findings and in confirmation of this study findings, previous studies have also shown a positive correlation between lipocalin-2 with body weight, BMI, body fat percentage and waist-to-hip ratio (WHR). Ghorbin and Esmailzadeh (2017) stated that there is no significant effect of eight weeks of resistance training (four days per week) compared to the control group on the levels of lipocalin-2 in overweight and obese inactive men. These researchers stated that a significant change in lipocalin-2 levels requires a significant decrease in body fat percentage (Ghorbanian & Esmaelzadeh, 2017). In the present study, a significant decrease in body fat percentage and BMI was observed simultaneously with the decrease in lipocalin levels. In line with these statements, studies have shown that there is a significant positive correlation between visceral fat mass and lipocalin-2 and MCP-1 levels, which indicates that visceral fat mass is one of the main sites of lipocalin-2 secretion into the blood circulation. In this regard, adipocytes have been known as one of the major sites of lipocalin-2 expression.

The expression of lipocalin-2, including visceral fat tissue, is stimulated by various inflammatory stimuli, mainly through the activation of NF-KB-dependent pathways. Based on the available evidence, it has been stated that lipocalin-2 can play a role in various inflammatory diseases. Another finding of the present study was that 12 weeks of continuous moderate intensity and intense intermittent exercise leads to a significant improvement in the lipid profile (decrease in cholesterol, triglyceride and LDL-c levels and a significant increase in HDL-c levels). Wang et al. (2007) showed that there is a significant negative correlation between lipocalin-2 and HDL-c, which was confirmed in the current study (Wang et al., 2007).

In another study, researchers confirmed that the reduction of lipocalin-2 levels after exercise is associated with the improvement of lipid profile. In this regard, Toloui Azar et al. (2018) also reported that eight weeks of selected aerobic exercise in water in overweight middle-aged men leads to a significant decrease in lipocalin-2 levels and a simultaneous decrease in body fat percentage. In addition, a significant decrease in cholesterol, triglyceride and LDL-c levels was observed in the trained group. Despite the non-statistically significant increase in HDL-c levels in the trained group (Toloueiazar et al., 2019).The inconsistency with the current findings regarding HDL-c can be attributed to the shorter duration of the exercise period in the study of Toloui Azar et al. compared to the current study. Nevertheless, further investigation is needed to determine the mechanism of association between lipocalin-2 levels and lipid profile.

Conclusion

The present results showed that 12 weeks of continuous moderate intensity and intense intermittent exercise leads to a significant decrease in lipocalin-2 and insulin resistance, and there was no significant difference between the two types of exercise in the effect on lipocalin-2 and insulin resistance. Based on the present study findings, one of the mechanisms of the positive impact of exercise in obese people is the reduction of lipocalin-2 levels with continuous and intense intermittent exercise.

What is already known on this subject?

Today, the prevalence of obesity and metabolic syndrome is increasing at an alarming rate among adults and children and has become a global epidemic.

What this study adds?

12 weeks of continuous moderate intensity and intense intermittent exercise leads to a significant decrease in lipocalin-2 and insulin resistance, and there was no significant difference between the two types of exercise in the effect on lipocalin-2 and insulin resistance.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol conformed to the declaration of Helsinki and was approved by the Committee of Islamic Azad University, Tehran, Iran.

Informed consent It was obtained from the subjects.

Author contributions

Conceptualization: A.M.S, M.G, H.E.B.; Methodology: H.A.N; Software: A.M.S, M.G.; Validation: H.E.B; Formal analysis: H.A.N; Investigation: A.M.S, M.G.; Resources: A.M.S, M.G.; Data curation: H.A.N; Writing - original draft: H.E.B.; Writing - review & editing: A.M.S, M.G.; Visualization: A.M.S; Supervision: M.G.; Project administration: A.M.S, M.G; Funding acquisition: M.G.

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