The effect of high-intensity interval training (HIIT) on nesfatin, irisin and resistin and gene expression of PGC-1α in Wistar rats

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Abstract

Introduction: The aim of this study was to evaluate the effect of high-intensity interval training (HIIT) on nesfatin, irisin and resistin and expression of peroxisome proliferator-activated receptor 1-alpha (PGC-1α) gene in Wistar rats.
Materials and Methods: In this experimental study, 24 male Wistar rats (weight 300-250 g) were selected and randomly assigned into three groups: baseline control, eight-week control and HIIT training. The experimental group performed training protocol 4 days a week during 8 weeks, while the control group had no training program. To measure the levels of serum irisin, nesfatin, and resistin, the immunoassay method was used. Additionally, the real-time PCR method was applied to evaluate the relative PGC-1α mRNA level in soleus muscle. Independent T-test was used to analyze the data.
Results: The results suggested that there was no significant difference between the concentration of nesfatin, irisin and resistin in the baseline control group compared to the eight-week control group ($P > 0.05$). HIIT increased the concentrations of nesfatin-1 and irisin ($P = 0.0001$), and significantly decreased resistin ($P = 0.0001$). Furthermore, eight weeks of HIIT significantly increased the PGC-1α mRNA ($P = 0.0001$).
Conclusion: According to the findings of the study, HIIT would possibly help to improve the levels of the factors, nesfatin, irisin, resistin and PGC-1α which involved in the energy balance homoeostasis.

Keywords: High-intensity interval training, Nesfatin, Irisin, Resistin, PGC-1α, Rats

Introduction

Although regulating the energy balance looks simply, but it's a very complicated process. Weight loss or weight gain caused by energy imbalance, is the simplest indicator for detecting energy imbalances and energy regulation in the body. Disrupting the process of energy balance in a regular mode would possibly lead to hazardous complications such as obesity, diabetes, cardiovascular complications, or loss of appetite (1). Several hormonal factors influence insulin resistance, which affects energy homeostasis and metabolism. Consequently, the neuropeptide nesfatin-1 secreted from the hypothalamus is responsible for the regulation of appetite and energy homeostasis and metabolism (2).

Nesfatin secretion is also affected by inflammatory cytokines and insulin. In addition to implications of nesfatin-1 in gastrointestinal functions, it inhibits the stimulation of ghrelin and reduction of adipose tissue (3).

It has also been reported that plasma and tissue concentrations of nesfatin are influenced by factors such as fasting, refeeding, diabetes, high blood sugar and

physical activity (4-6). Based on research evidence, resistin plays a vital role in energy metabolism and is associated with metabolic disorders such as diabetes and obesity (7). It has been reported that, resistin regulates various aspects of metabolism (such as lipolysis and gluconeogenesis), along with other metabolic hormones especially insulin (8). Increase of resistin reduces insulin-dependent glucose transport and ultimately leads to enhancing insulin resistance (9). Additionally, it has been suggested that irisin plays an important role in metabolism of energy and glucose tolerance (10, 11).

Irisin is a myokine that is secreted from skeletal muscle in response to PGC-1a and exercise and secretes into blood stream (12). In fact, irisin is a proteolytic cleavage product of the membrane protein FNDC5 Which acts on brown adipose cells and stimulate UCP1 expression (13). Following activation of irisin by exercise which leads to the conversion of white adipose tissue (mainly in subcutaneous adipose tissue and visceral fat) to brown adipose tissue, parallel increase is induced in body temperature (14). On the other hand, skeletal muscle, as an important metabolic organ in the human body, also have multiple mitochondria to meet energy needs (15). Contracting skeletal muscles have a profound capacity for taking up blood insulin-stimulated glucose uptake (16). It has also been recognized that peroxisome proliferator-activated receptor 1-alpha (PGC-1α) plays a key role in regulating cellular energy metabolism and is involved in most of muscle adaptations (17). PGC-1α is a 90-kDa protein and a member of transcriptional activators family in the mitochondria, which has an SR region and a specific RNA adhesion, which can lead to many energy metabolism adaptations (18).

The effect of different training protocols on energy homeostasis and metabolism has been well investigated. It has been reported that endurance and resistance exercises improve the energy balance (19, 20). There was also a significant increase in the expression of PGC-1α mRNA after interval and continuous exercise (21). However, research have suggested that exercise intensity can't significantly improve the levels of factors involved in energy balance homoeostasis (22, 23). In addition, recent studies on the impact of high-intensity interval training (HIIT) on glucose control and metabolic adaptations have wall been understood. (24), however, the effect of these exercises on the factors affecting the regulation of metabolism is not well understood. Considering the important role of exercise and physical activity in the prevention and treatment of diseases, such as metabolic disorders, it was aimed at studying the effects of various exercises, especially HIIT exercises, on the markers affecting metabolic disorders. Therefore, the purpose of this study was to investigate the effect of HIIT on nesfatin, irisin and resistin of serum and gene expression of PGC-1α in soleus muscle of Wistar rats.

Materials and Methods

This study is experimental and the study population consist of healthy Wister male rats weighing 300-250 g and sample size was 24 male rats that were divided into control and exercise groups. In this study, Wistar male rats were recruited at Baqiyatallah University of Medical Sciences (BMSU) and the animals were kept in 12-hour darkness-light cycle, 22 ± 2°C, relative humidity 55%, and with free access to water and food. Animals were randomly grouped and interventions were performed on them. Animal kept based on the Iranian Society of the Animal Protection rules used for laboratory purposes. The rats were kept and trained at the animal house of Baqiyatallah University of Medical Sciences (BMSU). In their groups, the animals were placed in cages made of transparent polyethylene with metal and mesh doors that were marked completely apart. The water was

supplied through special plastic containers placed on the cage's door, and during the research, access to water and food was free for rats. In each cage, four rats were kept. The rats were divided into three groups: baseline control, eight-week control and HIIT. The baseline control group was killed and biopsied at the beginning of the study, and the control group was kept for 8 weeks like the HIIT group, but they did not participate in any exercise program and to create the same conditions, 5 times for 10 to 15 Minutes per session were placed on the turned off treadmill.

After two weeks of adaptation (6 sessions), animals were trained for 8 weeks. Exercise intensity was 5, 10, 15 m/min, and duration 5, 10, 15 minutes. In adaptation phase, rats that prevented running, dropped out of the study. In training groups, warming up was conducted for 3 minutes at 15 to 20 m / min and cooling down for 2 minutes at 15 to 20 m/min. The treadmill slope was zero degrees throughout the experiment. The exercise intensity was set at the speed of 30 m / min and 70% of the maximum oxygen consumption (VO_2 max) (Table 1).

Table 1. High-intensity interval training (HIIT) protocol applied in the present study.

Training weeks	Intense intervals		Slow intervals	
	Number of bouts (One minute)	Speed (m/min)	Number of bouts (One minute)	Speed (m/min)
First	4	28-30	3	12-15
Second	5	30-32	4	12-15
Third	5	32-35	4	12-15
Fourth	6	35-40	5	15-17
Fifth	6	41-45	5	17-20
Sixth	7	46-50	6	20-25
Seventh	7	46-50	6	20-25
Eighth	8	50-55	7	25-30

At 12 h after fasting and following the last exercise, the rats were anesthetized by Ketamine and Xylazine and the surgery was carried out and 5 cc blood sample was taken from the heart of each rat. Then, they were transported to the test tube. Soleus muscle tissue was placed into a liquid nitrogen. The tissue and serum were then stored in a freezer at a temperature of 80 °C.

Evaluation of serum levels of irisin, nesfatin-1 and resistin were performed by the enzyme-linked immunosorbent assay (ELISA) method based on the manufacturer's instructions. For measurement of irisin and nesfatin-1, the ELISA kit was used, (Bioassay technology Laboratory, China), with sensitivities of 0.03 and 16.23 ng/ml, respectively. The serum resistin level was measured by Biovendor kit (Biovendor Research and Diagnostic Products, Czech Republic) with a sensitivity of 0.25 ng/ml. measuring the gene expression of PGC-1α was assessed by Real time-PCR technique and analyzed after the quantification of gene expression values using the formula $2^{-\Delta\Delta ct}$. The considered Primer genes and beta-actin were designed and studied by Allele ID and MEGA 6 software. The specificity of the primers for the target genes was investigated by the BLAST program. In this study, Beta actin gene was used as an internal control. The sequence of primers used in this study are presented in the Table 2.

Statistical Analysis

Assumptions of normal data distribution and homogeneity of variance: were confirmed by the Shapiro-Wilk test and Levene's test. Independent T-test was used to evaluate the data between groups. The statistical analysis was performed using the SPSS v22.0 software (SPSS Inc., Chicago, IL). Significant difference was set at $P < 0.05$.

Table 2. The primer sequences of the gene under study.

Gene name	Primers	Sequence	Amplicon's Length
PGC-1α	Forward	5'- CACCAAACCCACAGAGAACAG -3'	104 bp
	Reverse	5'- GGTGACTCTGGGGTCAGAG -3'	
Beta actin	Forward	5′- TCCTCCTGAGCGCAAGTAC -3′	123 bp
	Reverse	5′- CCTGCTTGCTGATCCACATCT -3′	

Results

The results of one-way ANOVA suggested that there was a significant difference between the groups in the levels of serum irisin (P = 0.001). The results of the LSD post hoc test indicated that HIIT resulted in a significant increase in serum irisin compared to baseline control and 8 weeks' control groups (P = 0.001). There was no significant difference in serum irisin between baseline control and 8-weeks control groups (P > 0.05) (Figure 1).

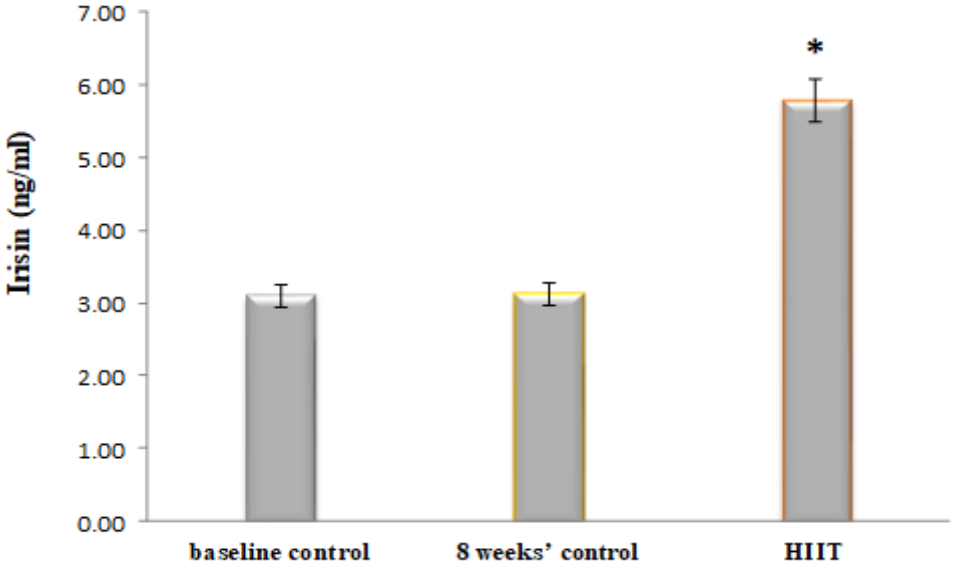

Figure 1. Changes in serum irisin levels male Wistar rats in different groups. *Significant increase rather than baseline control and 8 weeks' control groups. Data are presented as means ± SD. P < 0.05, one-way ANOVA test.

The results of one-way ANOVA suggested that there was a significant difference between the groups in the level of serum resistin (P = 0.001). The results of the LSD post hoc test indicated that HIIT resulted in a significant decrease in serum resistin compared to baseline control and 8 weeks' control groups (P = 0.001). There was no significant difference in serum resistin between baseline control and 8-weeks' control groups (P > 0.05) (Figure 2).

The results of one-way ANOVA suggested that there was a significant difference between the groups in the level of serum nesfatin-1 (P = 0.001). The results of the LSD post hoc test indicated that HIIT resulted in a significant increase in serum nesfatin-1 compared to baseline control and 8 weeks' control groups (P = 0.001). There was no significant difference in serum nesfatin-1 between baseline control and 8-weeks' control groups (P > 0.05) (Figure 3).

Furthermore, significant changes were found in PGC-1α gene expression in the HIIT group (P = 0.001) compared to baseline control and control groups (P = 0.001), hence, eight weeks of HIIT training significantly increased the expression of PGC-1α gene expression (Figure 4).

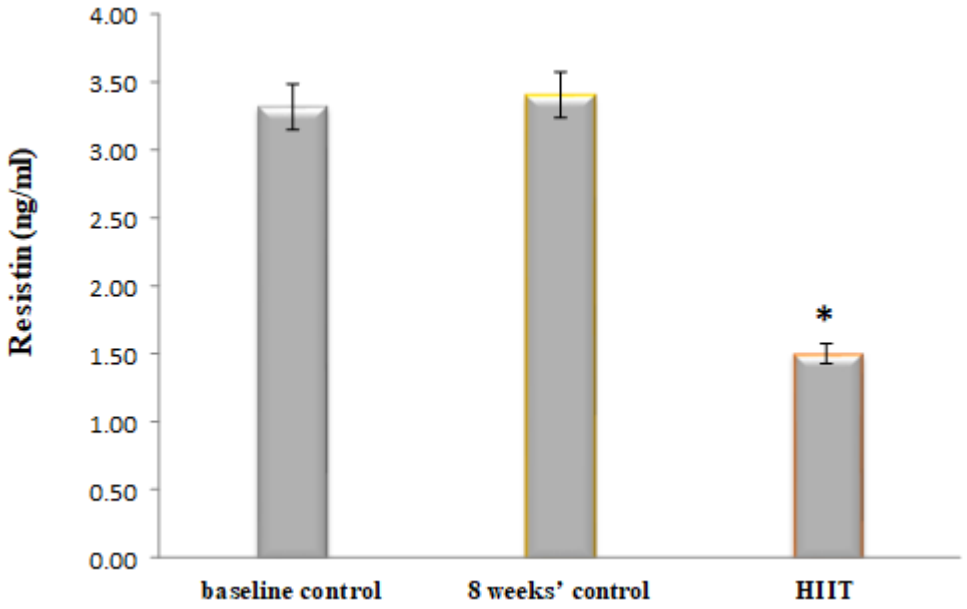

Figure 2. Changes in serum resistin levels male Wistar rats in different groups. *Significant decrease rather than baseline control and 8 weeks' control groups. Data are presented as means ± SD. P < 0.05, one-way ANOVA test.

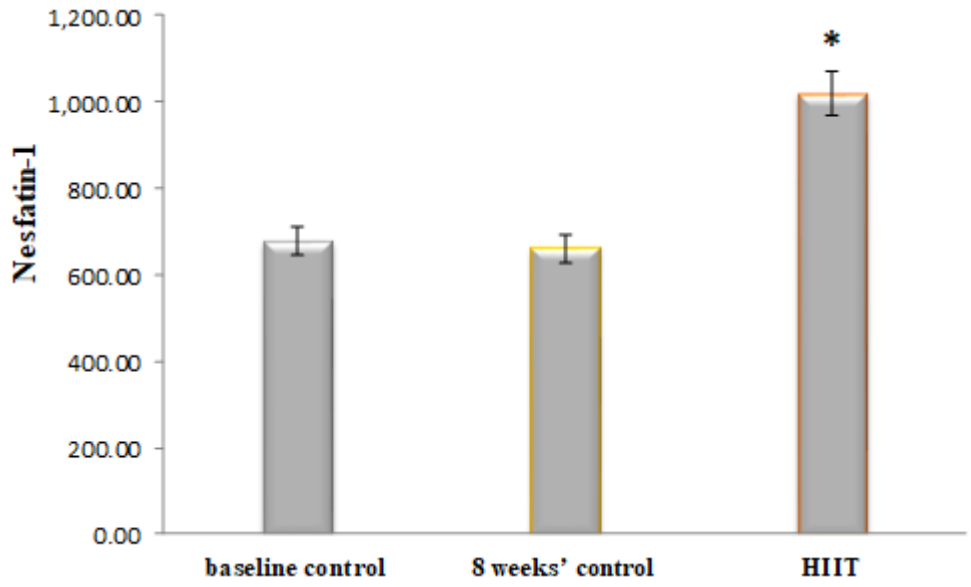

Figure 3. Changes in serum nesfatin-1 levels male Wistar rats in different groups. *Significant increase rather than baseline control and 8 weeks' control groups. Data are presented as means ± SD. P < 0.05, one-way ANOVA test.

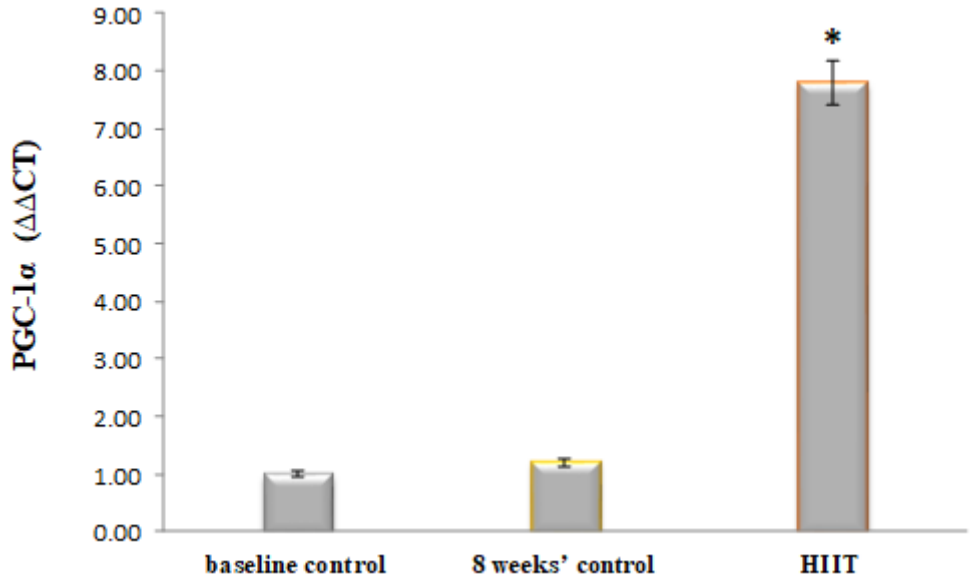

Figure 4. Changes in the gene expression of PGC-1α in male Wistar rats in different groups. *Significant difference than the baseline control and 8-weeks' control groups ($P < 0.05$).

Discussion

The results showed that HIIT exercise significantly increased the concentration of nesfatin and irisin and decreased serum resistin. Consistent with the findings of the study, it has been shown that endurance training increases the plasma levels of nesfatin-1 (25). The serum levels of of adipokine secretion, including nesfatin-1, is affected by diet, inflammatory cytokines and insulin, which play a role in regulating appetite and energy consumption (26).

Based on evidence, a positive correlation between nesfatin-1 concentrations and age, BMI, fat mass, triglyceride and insulin has been observed (27).

Regular physical activity increases the capacity to maintain appropriate plasma glucose and Insulin levels. As a result, it would affect levels of nesfatin-1 and lead to increased level of nesfatin-1 and consequently improves insulin sensitivity (28). Regarding to the role of cytokines and sympathic nerve stimuli in regulating resistin level, the mechanism of reducing resistin is related to decreasing of this factor. (29). It has been reported that inflammatory cytokines stimulate the expression of the resistin genes in blood cells and increase resistin levels (30). The resistin level is also likely to be related to the intensity of exercise. As Jamurtas et al. (2006) reported that aerobic exercise did not cause significant maximum changes in resistin levels (31). In some studies, no significant effect was reported on resistin (32, 33). The differences observed in these results may be due to the difference in age and gender of the statistical samples, the differences in the type, duration, and intensity of training and length of the training intervals. The decrease in resistin levels observed in this study can be attributed to the ability of this exercise to change the energy balance.

As noted in results section, irisin levels increased significantly after the HIIT exercise, which is consistent with the findings of previous studies (34-37). Through increasing contributions of fuel sources and energy production during exercise, HIIT, activates the effective metabolic pathways in regulating the gene expression of this adipokine and increase the level of irisin secretion. On the contrary, there are some researches showing no significant effects of exercise on irisin levels (22, 38).

Different training methods such as exercise intensity and duration, different subjects in studies are of possible reasons

justifying the variation in obtained results. The exercise intensity in the current study seems to be so high that it can make significant changes in irisin. In general, irisin is increased in response to exercise, and that's why irisin increase through HIIT exercise would be justified in PGC-1α activating signals. Moreover, those factors triggering PGC-1α activation are likely to transport a message cascade to change the phenotype of the adipose tissue. In addition. The results indicated that HIIT exercise would significantly increase the expression of PGC-1α gene in male rats.

This finding is consistent with the results of Ruschke et al. (2010) and Taylor et al (2016), which suggested a significant increase in PGC1α after severe endurance and resistant exercises (39, 21). Several signaling pathways have been suggested to regulate the PGC-1 family. These signaling pathways include calcium, calcinin and CaMK, AMPK, and p38 pathways, as well as the activation of adrenergic b2 receptors (40). PGC-1a in response to exercise would be also affected by some other factors (e.g., type, duration, and intensity of exercise). One of the limitations of this study is that it didn't measure other factors related to energy metabolism in skeletal muscle. Measuring signaling pathways such as calcium route pathways, calcineurin, CaMK, AMPK, and p38 as well as adrenergic receptors would also support the possible effects of physical activity on transcription factors involved in skeletal muscle. However, further research is required regarding which types of exercise more are most appropriate.

Conclusion

It's concluded that HIIT significantly increased serum levels of nesfatin, irisin and resistin. The results indicated that there was a significant increase in serum levels of nesfatin, irisin and resistin of male Wistar rats following HIIT training. Besides, eight weeks of HIIT training significantly increased the gene expression of PGC-1α. According to the findings of the present study, high-intensity interval training would possibly help to improve the levels of factors involved in the energy balance homoeostasis.

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Conflict of interest

The authors declare no conflict of interest.

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