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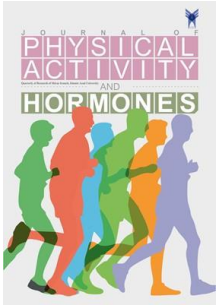

The Effects of 8 Weeks of High and Moderate Intensity Interval Training on Irisin and Adipolin Levels in Type 2 Diabetic Male Rats

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Abstract

Introduction: The purpose of this study was to compare the effects of high and moderate intensity interval training on Irisin and Adipolin levels in type 2 diabetic male rats.

Material & Methods: Thirty-two male Wistar rats were divided into two groups: healthy and diabetic, diabetic rats were randomly divided into three subgroups of diabetic control and two HIIT and MIIT groups; so that the present study was performed on four groups (8 per each group). The training was performed with 65-70% and 85-90% of the maximum oxygen consumption in MIIT and HIIT groups, respectively. Twenty-four hours after the last training session, the mice were removed by intraperitoneal injection of a combination of anaesthetic ketamine and xylazine. The levels of Irisin and adipolin were measured by ELISA method. Data were analysed by one-way ANOVA and Tukey's post hoc test.

Results: The results of the post hoc test indicated a significant increase in irisin and adipolin in the HIIT and MIIT groups compared to the control group ($p = 0.001$). There was no significant difference between HIIT and MIIT groups ($p = 0.274$).

Conclusion: HIIT and MIIT could lead to a significant increase in irisin and adipolin in diabetic rats.

1. Introduction

Diabetes is the most common disease, the fourth leading cause of death in high-income countries, and one of the greatest health challenges in the world today (1). According to IDF reports, in 2015, 415 million people had diabetes, which will increase to about 642 million people by 2040 (2). Unbelievably, Iran ranks third in the total number of adults with diabetes in the entire Middle East and North Africa region (3). One of the prominent characteristics of diabetes is an increase in blood sugar and disturbance in carbohydrate and fat metabolism (4). Adipose tissue plays an essential role in regulating the body's metabolic conditions, especially maintaining blood glucose levels, by secreting pro-inflammatory and anti-inflammatory adipokines. Adipolin (CTRP12) is an anti-inflammatory adipocytokine secreted from fat tissue that plays a role in improving insulin sensitivity and decreases in conditions of obesity, diabetes and other pathological conditions caused by obesity (5). Adipolin is found in blood in both intact (fCTRP12) and cleaved (gCTRP12) forms. The results of studies have shown that only the fCTRP12 isoform of adipolin improves insulin resistance. Therefore, any factor that affects the synthesis of adipolin or causes the breakdown of adipolin can reduce insulin sensitivity (6). Insulin does contribute to the breakdown of adiponectin and its ineffectiveness, so reducing insulin levels is one approach to enhance adiponectin's function by improving insulin resistance (7). Various studies have emphasized the role of physical activity in improving glucose metabolism and insulin secretion levels (8). Aerobic

physical activities are effective in controlling diabetes by activating the AMPK pathway and increasing glucose uptake, while interval training activates the PI3K pathway, followed by AKt and mTOR, resulting in increased glucose uptake and utilization (9). During physical activity, the expression of PGC1a leads to the secretion of factors from skeletal muscle that can influence the function of other tissues. One of the most important of these factors is FNDC5, which is cleaved and secreted into the blood as irisin (10). Irisin induces the expression of the UCP1 gene in brown adipose tissue. The expression of UCP1 leads to the conversion of white adipose tissue to brown adipose tissue, and brown adipose tissue has beneficial effects on blood glucose control, insulin sensitivity, mitochondrial density, and lipid metabolism (11). Researchers consider the PGC1a-irisin-UCP1 pathway, which may be expressed in response to insulin resistance or excessive fat accumulation, as a pathway for controlling diabetes, obesity, and related complications (12). In their studies, Cardiavo et al. (2016) demonstrated that insulin resistance increases irisin secretion due to its role in increasing energy expenditure, leading to weight loss, reducting body fat, and consequently, increasing insulin sensitivity (13). Therefore, based on the available evidence, irisin is recognized as a regulator of glucose homeostasis, energy, and insulin resistance (13). Confirming this, most studies indicate that irisin expression increases in diabetic patients and insulin-resistant individuals, acting as a metabolic regulator and a factor in controlling blood glucose (14, 25, 26). This feature has also been confirmed by other researchers. According to the findings of these researchers, the increase in irisin levels in individuals with diabetes may be associated with compensatory regulation of the body, leading to improved insulin sensitivity and glucose metabolism (15, 27, 28). Therefore, based on the available evidence, irisin is recognized as a regulator of glucose homeostasis, energy, and insulin resistance. Most studies indicate that irisin expression increases in diabetic patients and insulin-resistant individuals, acting as a metabolic regulator and a factor in controlling blood glucose (16, 29). According to the results of studies, physical activity appears to be one of the most important factors influencing irisin secretion and its effects on energy metabolism (17). Huh and colleagues (2015) reported an increase in irisin concentration on adult diabetic patient (40-70 years old) following high-intensity interval exercise protocol. Considering the beneficial effects of irisin and adiponectin, as well as their impact on insulin resistance, white adipose tissue, and thermogenic properties, these myokines have been recognized as therapeutic targets for metabolic patients (18). Intensity and type of exercise has a special importance in the effect of exercise on the expression of irisin and adipolin (19). In this regard, Joyang Hoo and colleagues (2015), Shirvani and colleagues (2019), Loofler (2015) reported that irisin is expressed by physical activity, but the expression of adipolin may be dependent on the intensity of exercise (20, 30,31). However, there is uncertainty about the optimal intensity and type of exercise for metabolic syndrome patients. According to the study by Nazan (2017), plasma irisin increases after moderate and intense aerobic exercises. The maximum level of irisin expression was reported to be 11.9% after moderate activity and 12.3% after intense activities, but irisin levels remained elevated up to 125 minutes after mild intensity exercise, while returning to baseline levels after 15 minutes of high-intensity activity. The results of this study indicated that the greatest increase in irisin concentration occurs immediately after physical activity. However, some studies have reported that plasma irisin levels are higher after intense exercises compared to moderate exercises (21). According to Pekala (2013) and colleagues, it was found that serum irisin immediately increased after both exercise protocols, and a greater increase was reported after intense aerobic exercises, indicating that irisin expression is influenced by exercise intensity (21).

Given that adiponectin levels decrease in individuals with diabetes and physical activity may improve the reduced adiponectin levels associated with diabetes, the effect is likely dependent on the type of exercise performed at different intensities. Additionally, with an understanding that (HIIT) promotes skeletal muscle adaptations and insulin sensitivity development, leading to fat oxidation, and fat oxidation reaches its peak during MIIT, it is hypothesized that mild intensity interval training may have a greater impact on myokines compared to HIIT. Furthermore, since irisin and adiponectin are among the important proteins involved in fat storage and utilization, and it has been shown that impaired utilization and storage of triglycerides are associated with insulin resistance and the development of diabetes, there have been contradictory findings in previous studies regarding this matter. Based on these premises, the present study aimed to investigate the effects of 8 weeks of HIIT and MIIT on adiponectin and irisin levels in type 2 diabetes male rats.

2. Materials and methods

The present study was an experimental study conducted on 32 male rats with a mean age of 8 weeks and a weight range of 204±42 grams. After obtaining ethical code IR.IAU.RASHT.REC.1400.008 and completing the training course on laboratory animal handling principles (with a focus on ethics), the rats were housed in an environment with a temperature of 22±2 degrees Celsius, a 12:12 light-dark cycle, and polycarbonate cages for adaptation to the new environment. After 2 weeks, the rats were randomly divided into two groups: a healthy control group (HC) consisting of 8 rats and a type 2 diabetic group (D) consisting of 24 rats. Subsequently, the diabetic group received a high-fat diet for 10 weeks, while the healthy control group received a standard diet. After the completion of the 10-week period, height, weight, and Lee index were calculated for both groups. The rats that had become obese (based on the Lee index) were included in the study (6). At the end of the twelfth week, 8 rats from the healthy control group (HC) were euthanized after a 12-hour overnight fasting period. In the diabetic group, a single dose of streptozotocin (STZ) dissolved in sodium citrate buffer with a pH of 4.5 was injected intraperitoneal (IP) at a dose of 30 mg/kg (23).

To confirm diabetes, 48 hours after injection, a small incision was made in the tail of the animals, and a drop of blood was placed on a glucose meter strip (Burr model GL42, manufactured in Germany) with a measurement range of 5-700 mg/dl and a sensitivity of 10 mg/dl. The blood glucose levels higher than 250 mg/dl were considered as indicators of diabetes (22). Subsequently, the diabetic rats were randomly divided into three groups: High Intensity Interval Training (HIIT), Mild Intensity Interval Training (MIIT), and Diabetic Control (DC) groups. The HIIT and MIIT groups engaged in physical exercise for a duration of 8 weeks. During the

8-week period, the control group did not engage in any form of activity within their cages. After the completion of the eighth week and 48 hours after the last exercise session, all rats were anesthetized by intraperitoneal injection of a combination of ketamine (30-50 mg/kg) and xylazine (3-5 mg/kg). Once the animals were confirmed to be anaesthesia, their chests were opened, and 10 millilitres of blood was directly collected from their hearts and transferred to tubes containing EDTA solution. The collected samples were centrifuged at a speed of 3000 revolutions per minute for 15 minutes, and their plasma was separated and transferred to a freezer at a temperature of -80 degrees Celsius for further use in the research stages. Plasma adiponectin levels were measured using the ELISA kit "Family with sequence similarity 132" (FAM134G) from My Bio Source, manufactured in the United States. The sensitivity of the measurement method for irisin hormone using the ELISA method and the EASTBIOPHARM kit, manufactured in the United States, was 0.23 ng/mL. One-sided analysis of variance (ANOVA) and post-hoc Tukey's test were performed for data analysis. All statistical operations were conducted using SPSS software version 21, and the significance level for the tests was set at $P \leqslant 0.05$.

The HIIT and MIIT protocols were modified versions of the protocol developed by Hafstad and colleagues (2013) and were implemented for 8 weeks with 5 sessions per week on a treadmill (0% incline) (24). The HIIT protocol consisted of performing 4-minute bouts of HIIT at 85-90% of maximum oxygen consumption (VO2max) with 2-minute active recovery periods. The treadmill speed progressively increased from 25 meters per minute in the first week to 31 meters per minute in the sixth week, and this speed was maintained during the final two weeks. The active recovery periods started at a speed of 11 meters per minute in the first week and increased to 16 meters per minute in the sixth week.

The MIIT protocol also included performing 13 bouts of 4-minute activity at 65-70% of VO2max intensity, with 2-minute active recovery periods. The distance covered with the MIIT protocol was made equivalent to that of the HIIT protocol. Accordingly, the treadmill speed for the MIIT protocol started at 16 meters per minute in the first week and increased to 25 meters per minute in the sixth week, and this speed was maintained during the final two weeks. It should be noted that a 10-minute warm-up and a 5-minute cool-down were performed at the beginning and end of each training session (9). In order to measure VO2max, after a 10-minute low-intensity warm-up, the running test for rats was initiated, and the treadmill speed was increased by 0.3 m/s (1.8 m/min) every 2 minutes until the animals were no longer able to run. The speed at which VO2max is achieved is defined as the maximum speed (10)..

3. Results

The weight changes and data analysis results showed that the body weight of the rats increased continuously in all groups. However, induction of type 2 diabetes led to a greater increase in body weight compared to the standard diet ($P \leqslant 0.001$). The body weight values of the rats in the standard diet group changed from 48.11±20.166 to 58.08±27.277, and in the type 2 diabetic groups, the body weight changed from 55.17±25.197 to 67.19±22.331. At the end of the study, data analysis using ANOVA test indicated that there was no significant difference in body weight among the research groups, including the exercise groups (HIIT and MIIT) and the DC group (P=0.001).

The distribution of data in all variables was normal. In the preliminary analysis, no significant differences were observed between the groups in any of the indicators. The results of the one-way analysis of variance (ANOVA) test showed a significant effect of diabetes on the indices of irisin and adiponectin. These indices changed in the diabetic groups compared to the healthy group (P=0.001). (Table 1).

Table 1. *Average data related to research variables*

Groups	Irisin (Mg/ml)	Adiponectin (Ng/ml)
High Intensity Interval Training	٤/٨٩±١/٠٥	٠/٤٦±٠/٠١٢
Mild Intensity Interval Training	٥/١١±١/٠٦	٠/٦٥±٠/٠١٦
Diabetic Control	١/٤±٠/٢٥	٠/١٠±٠/٠١٨
Health Control	٢/١±٠/٥٦	٠/٢٥±٠/٠١٠

The results showed that there was a significant difference in the mean expression of irisin and adiponectin among the four research groups (Figure 1 and 2). The results of the prosecution test indicated a significant increase in irisin and adiponectin levels in the high intensity interval training (HIIT) and mild intensity interval training (MIIT) groups compared to the diabetic control and healthy control groups (P=0.001). Furthermore, no significant difference was observed between the high-intensity interval training (HIIT) group and the mild-intensity interval training (MIIT) group. However, there was a significant difference between the two control groups, the healthy control and the diabetic control groups (P=0.001).

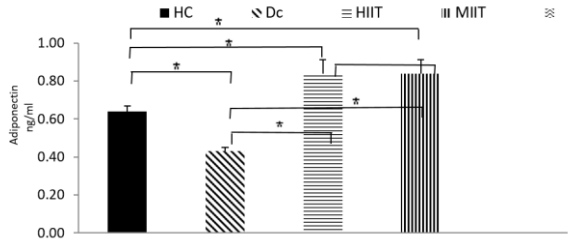

Fig 1. *Changes in adiponectin levels in different groups. HC: Healthy Control, DC: Diabetic Control, MIIT: Mild Intensity Interval Training, HIIT: High Intensity Interval Training (P<0.05)*

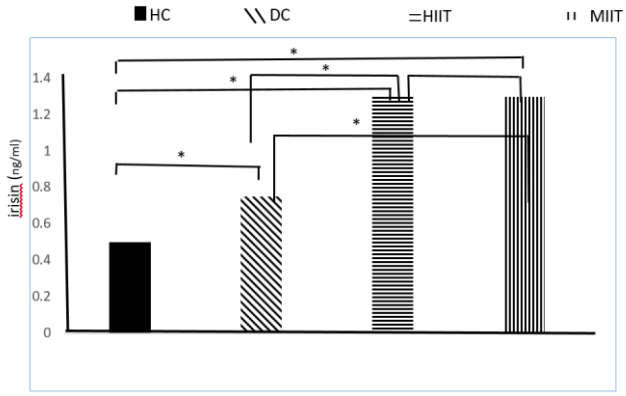

Fig 2. *Changes in irisin levels in different groups. HC: Healthy Control, DC: Diabetic Control, MIIT: Moderate-Intensity Interval Training, HIIT: High-Intensity Interval Training (P<0.05)*

4. Discussion

The results of the one-way analysis of variance (ANOVA) showed that there was a significant difference in the means of the research groups in terms of irisin. The results of the follow-up test indicated a significant increase in irisin levels in both HIIT and MIIT groups compared to the diabetic control group (P = 0.001). Furthermore, no significant difference was observed between HIIT and MIIT groups (P = 0.001). This finding is consistent with the results of previous studies, such as the study by Shirvani and colleagues (2019) on combined exercises in diabetic rats (30), Loofler (2015) identified a clear and immediate increase in serum irisin levels after acute strenuous exercise (cycling ergometry) and a 30-minute bout of intensive exercise in children and young adults (31). In the study by Kraemer and colleagues (2014), it was reported that there was no significant increase in irisin levels by 90 min of prolonged aerobic exercise in young women and men (32). Indeed, the lack of consistency in the findings could be attributed to various factors such as the duration and intensity of exercise, age of participants, ethnicity, individual differences, physical fitness level, weight, muscle mass, and laboratory methodology. Physical activity stimulates the secretion of PGCI-A, which activates PPAR and causes the secretion of FNDC5 and finally the hormone irisin. Irisin leads to the expression of UCP1. UCP1, by facilitating increased permeability of the inner mitochondrial membrane, prevents the coupling of protons and reduces the electrochemical potential, thereby inhibiting ATP synthesis. As a result, the energy derived from electrons is dissipated as heat, leading to the induction of brown fat-like characteristics in white adipose tissue and an increase in thermogenesis. This process is beneficial for preventing obesity and metabolic syndrome (5). Examining the effects of exercise on irisin concentration and determining the type and intensity of exercise that can benefit patients with metabolic syndrome in controlling and managing the disease is effective.

Furthermore, the results of this study demonstrated a significant increase in adiponectin levels after 8 weeks. However, no significant changes were observed in the control group. These findings are consistent with the results of the study by Mogharnasi and colleagues (2021), which reported significant changes in adiponectin levels after 6 weeks of aerobic exercise and black cumin consumption in 24 obese male rats (33). They are also in line with the study by Rahmatollahi and colleagues (2017), which showed changes in plasma adipolin levels after 8 weeks of Low-Intensity Continuous Training in fatty rats. The inconsistent results can also be attributed to the study by Souri and colleagues (2016), which examined the effects of 10 weeks of aerobic exercise on sedentary overweight men (aged 35-50) and reported no significant changes in adiponectin levels (35). Factors such as age, weight, exercise intensity, duration of exercise, and laboratory methods can contribute to the inconsistency of results. Research indicates that serum adiponectin levels decrease in obese and diabetic human and animal samples, as adiponectin is negatively regulated by obesity-related stressors such as TNF-α. TNF-α decreases with weight loss and exercise, which leads to an increase in adiponectin secretion (26). Another factor that plays a role in regulating adiponectin and undergoes changes after exercise is insulin. Insulin has a dual effect on adiponectin, and in conditions of obesity and diabetes, insulin leads to a decrease in adiponectin levels. However, engaging in exercise and reducing insulin levels can result in an increase in adiponectin levels.

5. Conclusion

Periodic exercise can potentially make it possible to achieve health in an effective and efficient time, there are many studies in healthy people where interval training results in a range of cardiovascular and metabolic benefits that are similar in quantity or equal to those who have gained these benefits with regular aerobic exercise, including increases in biogenesis. Muscle mitochondria and GLUT4 levels are the development and improvement of insulin sensitivity (12). Finally, mild and high-intensity interval training may have a greater effect on the metabolic rate of irisin and adipolin. The findings of this study showed that both protocols of high- and medium intensity interval training can lead to an increase in irisin and adipolin in type 2 diabetic rats.

6. Acknowledgment

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Conflict of interests: The authors declare that there is no conflict of interest in the research.

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