



Comparison of the Effects of Two Different Intensities of Combined Training on Irisin, Betatrophin, and Insulin Levels in Women with Type 2 Diabetes

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Abstract

Background: Betatrophin is a β -cell proliferation marker produced as a result of irisin expression. It is regarded as a therapeutic indicator of diabetes due to elevated insulin secretion.

Objectives: The purpose of this study was to compare the effects of 2 different intensities of combined training on the levels of irisin, betatrophin, and insulin in women with type 2 diabetes.

Methods: In this study, 26 female patients with type 2 diabetes were divided into 3 groups of combined high-intensity training, combined moderate-intensity training, and control. The training groups participated in combined training at high or moderate intensities for 8 weeks. The variance analysis test and the Duncan post-hoc test were applied to analyze the data ($P > 0.05$).

Results: Combined training at 2 intensities of moderate and vigorous led to a rise in the levels of irisin, betatrophin, and insulin. Exercise intensity was a determining factor for these elevated levels insofar as combined high-intensity training resulted in higher levels of these hormones than combined moderate-intensity training.

Conclusions: It appears that participating in relatively high-intensity training programs may be beneficial for diabetic patients inasmuch as they increase the levels of irisin, betatrophin, and then, insulin.

Keywords: Irisin Hormone, Betatrophin Hormone, Insulin Hormone, Combined Exercises, Type 2 Diabetes

1. Background

Diabetes is one of the most common endocrine disorders and one of the greatest challenges facing public health in the present century. It is estimated that over 100 million individuals globally suffer this disease each year. Unfortunately, the complete treatment of this disease has hitherto proven elusive. Generally, taking different medicines is allied to adverse effects and that is why the medical community at large seeks solutions other than medication. Of these non-pharmacological solutions, it appears that participation in a regular and systematic training program may play an important role in alleviating diabetic complications and insulin injection (1). Researchers have proposed combined exercises as the best training method for diabetes control. According to the American Diabetes Association, aerobic activities together with resistance training are more effective in controlling the blood sugar level, improving insulin function, and reducing the risk factors of cardiovascular disorders than

aerobic activities and resistance training individually (2). Regular physical activity confers improved glucose and lipid metabolisms by increasing insulin sensitivity and high-density lipoproteins and reducing triglycerides and low-density lipoproteins. Moreover, physical activity could increase the body's response to insulin and insulin sensitivity and prevent diabetes and its adverse effects by increasing glucose transmitters in muscle cells, insulin receptor substrates, and muscle mass. (More than 21% of the insulin taken is due to insulin stimulation related to the muscle tissue.) The main role of physical activity in individuals with type 2 diabetes is to enable skeletal muscles to take glucose with no insulin requirement. Accordingly, regular physical activity could have a remarkable effect on disease management (3). The American Diabetes Association has proposed moderate aerobic exercises for 30 minutes over 5 days or 150 minutes per week as well as endurance exercises for 2 days per week (2). Research shows that aerobic physical activity could be effective in controlling diabetes by activating the adenosine monophosphate-

activated protein kinase (AMPK) pathway and increasing glucose uptake and endurance training could also enhance glucose uptake and consumption by activating the pathways of phosphatidylinositol-4,5-bisphosphate 3-kinase (PL3K), followed by protein kinase B (Akt) and the mechanistic target of rapamycin (mTOR). These improvements in controlling the level of blood sugar could reduce the prescription of drugs (4). It is, therefore, advisable that the cellular/molecular mechanisms activated by combined training be thoroughly investigated. One of the factors secreted from the muscle tissue upon physical activity is the irisin hormone, which is capable of controlling and treating diabetes. Injecting irisin results in increased oxygen consumption, weight loss, decreased fasting insulin levels, and augmented expression of uncoupling protein 1 (UCP1) in fat rats. Research has indicated that UCP1 expression could convert the white adipose tissue into brown adipose tissue, thereby controlling blood sugar, insulin sensitivity, and lipid metabolism (5). Kurdiova et al. showed that insulin sensitivity was able to increase irisin secretion due to its role in increasing energy consumption, resulting in weight loss, body fat drop and consequently, increased insulin sensitivity (5). Irisin has been identified as a glucose homeostasis, energy, and insulin-sensitivity regulator. Indeed, most of the relevant studies such as those conducted by Abu-Farha et al. (6), Fu et al. (7), Huh et al. (8) have indicated that since irisin expression is increased in diabetic patients and insulin-resistant individuals, it could act as a metabolic controlling factor and a regulatory factor for blood sugar. In light of the aforementioned evidence, it appears that increased levels of irisin in diabetic patients may be associated with the body's compensating adjustments, resulting in increased insulin sensitivity and improved glucose metabolism (8). On the other hand, irisin may be effective on glucose metabolism by expressing the betatrophin hormone. The findings of the recent studies have indicated the presence of the P38-PGC-1 α -irisin-betatrophin-beta cell signaling pathway. Accordingly, the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-a) pathway causes the expression of irisin before irisin causes the release of the betatrophin hormone. Betatrophin is a factor in the reduction of blood sugar levels and a key factor in diabetes treatment. According to the research concerning this hormone, betatrophin may probably manifold the β -cell proliferation in the pancreas and consequently, the production of the insulin hormone by 17 times (9). As one of the goals to treat diabetes is a proper dose of insulin in the bloodstream, betatrophin could be an essential factor in controlling diabetes by expressing the insulin hormone. Researchers believe that when betatrophin is present, patients tend to inject insulin

weekly, monthly and in the best state, yearly instead of its daily injection. The administration of a proper therapeutic dose needs much time and research, but some other ways could be found to increase the expression of this hormone. Therefore, it appears that irisin could not only control diabetes by expressing UCP1 but also prevent the onset of diabetes through β -cell proliferation by increasing betatrophin. There is currently a dearth of data on the effects of regular physical activity on changes in the serum levels of irisin and betatrophin in individuals with diabetes. Insulin injection is associated with a large number of complications, while combined moderate-intensity training is deemed the best type of physical training for diabetics. Exercise intensity can augment the expression of irisin.

2. Objectives

In view of the aforementioned evidence, we sought to study the serum levels of the irisin, betatrophin, and insulin following combined high- and moderate-intensity training in order to answer the following questions:

- 1- Can combined training result in increased irisin expression and consequently, betatrophin and insulin and finally, diabetes control?
- 2- Can these exercises lower insulin injection and consequently, the complications of this therapeutic procedure?
- 3- What is the mechanism of the impact of these combined exercises on insulin secretion?

3. Methods

3.1. Subject

26 type 2 diabetes patients in Jannan Diabetes Center, in the Iranian city of Najaf Abad aged between 35 and 45 years participated in this study. The inclusion criterion was current diabetes based on the criteria of the World Health Organization (WHO). Recently, the American Diabetes Association recommended the following 4 criteria for the diagnosis of diabetes: (1) a minimum 6.5% rate of glycosylated hemoglobin, (10) a fasting glucose level higher than 126 mg/dL, (11) a 2-hour plasma glucose level higher than 200 mg/dL during the oral glucose tolerance test using 75 g of glucose, and (2) symptoms of elevated blood glucose levels such as increased urine volume, excessive thirst, and weight loss without any reason (12). In addition, having a history of diabetes with insulin injection for more than 5 years was another inclusion criterion in the current study. Patients unable to continue combined training due to conditions such as high hyperglycemia during the exercise

were excluded. The subjects received comprehensive explanations about the study, including the purpose of the study, the combined exercises, blood sampling, and the time, place, and schedule of the research. Thereafter, they were asked to fill in and sign a personal and medical information questionnaire and sign a written consent form for study participation.

3.2. Hormonal Assessments

Irisin was measured using an EASTBIOPHARM kit (China) (Lot: E 2014, 08, 3; sensitivity = 0.023; detection rate = 0.05 - 15 $\mu\text{g/mL}$; unit = $\mu\text{g/mL}$; and EXP: 08/29/2018), beta-trophin was measured using an EASTBIOPHARM kit (Lot: E 2014, 08, 3; sensitivity = 5.21 ng/L; detection rate = 10 - 2000 ng/L; unit: ng/L; and EXP: 08/29/2018), and insulin was measured via the enhanced chemiluminescence method with a Cobas e411 device and a Roche kit (Germany).

3.3. Training Protocol

The training program comprised 8 weeks of combined exercises (aerobic and resistance training), 5 sessions per week. The patients received full instructions in a gym for 3 sessions before commencing the training program. The combined moderate-intensity training group performed aerobic exercises, comprised of walking at 55% to 69% of the maximum heart rate (HR_{max}) over the 8 weeks. These exercises were performed at 12 to 13 ratings of perceived exertion (RPEs) for 150 minutes per week, each session for 30 minutes. Resistance training was performed using colored resistance bands 2 days per week for 8 weeks. The subjects were recommended to take 10 to 15 g of carbohydrate before training to prevent hypoglycemia. The combined high-intensity training group performed aerobic exercises, comprised of walking or running fast at 70% to 89% HR_{max} and at 14 to 16 RPEs for 75 minutes for 5 days. In each training session, the aerobic exercises lasted for 15 minutes. Resistance training was performed using colored resistance bands for 2 days per week for 8 weeks (13, 14).

3.4. Resistance Exercise Protocol Using Colored Resistance Bands (Total-Body Resistance Exercise)

This training method is recommended by the American Diabetes Association because it is easy to perform, possible to do with no device and special environment, inexpensive, and safe. First, yellow resistance bands, classified as light resistance, were used and the subjects were asked to perform a maximum of 15 to 20 repetitions. The stretching rate was determined for the first time using a tape measure for each person. The difference in intensities for the subjects of the 2 training groups was determined

by using different elasticity in the range generally permitted for joint movements, so that the rate of elasticity was considered to be 25% for both of the high- and moderate-intensity training groups (Table 1). The resistance of the elastic bands was different between the 2 groups based on the tables of the elastic force. Within the first 4 weeks, the combined moderate-intensity training group performed their exercises at a rate of 100% elasticity and the combined high-intensity training group at 125%. In the second 4 weeks, the researcher hypothesized that if the elasticity was increased by 25% and a subject could perform more than 20 repetitions, the moderate-intensity training group subjects might be able to perform their exercises at a rate of 125% elasticity and the high-intensity training group subjects at a rate of 150%. Nonetheless, none of the subjects could perform more than 20 repetitions. Each exercise was performed by both groups in 2 sets of 12 repetitions, and the groups rested between the sets for 90 seconds and between the exercises for 30 seconds (15). The exercises were hip abductions, crunches, shoulder abductions, elbow flexion, elbow extensions, hip adductions, hip flexion, hip extensions, and row extensions.

3.5. Statistics

The Kolmogorov-Smirnov test was applied to determine whether the data were normally distributed. After the normal distribution of the data was established, the variance analysis test (ANOVA) was employed to compare the study variables. The significance level in all the measurements was a P value less than 0.05, and the data analyses were conducted using SPSS, version 17.

4. Results

The mean level of the irisin hormone had an incremental increasing trend in the posttest by comparison with the pretest in the 2 training groups of moderate- and high-intensity training (Table 2). The mean of the difference between the 3 groups of control, moderate-intensity training, and high-intensity training was significantly different ($P < 0.05$). The Duncan post-hoc test was employed to perform 2-by-2 comparisons between the 3 study groups concerning the mean score of irisin and it demonstrated that whereas there was no significant difference between the control group and the moderate-intensity training group, there was a significant difference between the control group and the high-intensity training group and also between the moderate-intensity group and the high-intensity training group. In other words, the moderate- and high-intensity training groups each had a statistically

Table 1. Rate of Force (Pound Based on the Stretching Rate)

Percentage of Stretching	Golden	Silver	Black	Blue	Green	Red	Yellow
100	21.6	13.2	9.7	7.1	5	3.9	2.9
125	24.6	15.2	11	8.1	5.7	4.4	3.4
150	27.5	17.1	12.3	9.1	6.5	4.9	3.9

significant difference with the other 2 groups. Moreover, the mean level of the betatrophin hormone exhibited an incremental trend in the 2 training groups of moderate- and high-intensity exercises in the posttest relative to the pretest.

The mean of the difference between the 3 study groups of moderate-intensity training, high-intensity training, and control had a statistically significant difference ($P < 0.05$). The mean level of the betatrophin hormone was compared between the 3 groups 2 by 2 using the Duncan post-hoc test, which revealed no significant difference between the control group and the moderate-intensity training group. Additionally, no significant difference was seen between the moderate-intensity training group and the high-intensity training group, while there was a significant difference between the high-intensity training group and the control group.

Apropos of the effects of combined training on the level of the insulin hormone, the mean level of insulin had an incremental trend in both of the training groups of high-intensity and moderate-intensity exercises.

The mean of the difference between the 3 study groups of high-intensity training, moderate-intensity training, and control was significantly different ($P < 0.05$). In addition, the mean of the insulin score was compared between the 3 groups 2 by 2 using the Duncan post-hoc test, which demonstrated a significant difference between the control group and the moderate-intensity training group, but not between the high- and moderate-intensity exercise groups. In other words, the control group had a statistically significant difference with the other 2 groups. Moreover, the mean of the insulin hormone had an incremental trend from the pretest to the posttest in the 2 training groups of moderate- and high-intensity exercises; this difference in the mean between the pretest and the posttest was statistically significant.

5. Discussion

In summary, the results of the present research showed that combined aerobic and resistance training led to elevated irisin hormone levels ($P < 0.05$): by 88.4% in the high-intensity training group and by 36.7% in the moderate-

intensity training group. Additionally, combined training resulted in a rise in the betatrophin hormone level ($P < 0.05$). The serum level of the betatrophin hormone rose by 67.3% in the high-intensity training group and by 1.6% in the moderate-intensity training group. The level of insulin also increased as a result of combined training in our 2 training groups ($P < 0.05$): by 100.2% in the high-intensity training group and by 56.7% in the moderate-intensity training group.

Bostrom et al. showed that the plasma irisin level increased by twofold in their human subjects after endurance exercise for 10 weeks (16). The results of the studies by Bostrom et al. (16) is consistent with those of the present study. In contrast to our results, Norheim et al. reported that the irisin level was reduced in their study population as a result of physical activity (17). The authors concluded that the irisin level rose immediately after exercising and reduced 2 hours afterward. They also reported that the serum irisin level was reduced among their inactive prediabetic male subjects after 12 weeks of endurance and resistance training. One of the reasons for this nonalignment is the gender difference and the length of the subjects' diabetes history. Moreover, Norheim et al. believed that the cause of the drop in the irisin level might be related to genetic factors, which were out of the researchers' control (17). The results of a study by Kurdiova et al. demonstrated no change in the irisin level after physical activity (5). The discrepancy between our findings and the results of these studies is due to differences in the experimental and measurement methods and the intensities and methods of the training protocols. Kurdiova et al. in their study concluded that physical activity did not affect irisin expression and that irisin was affected by muscle mass, power, and metabolism (5). In this study, irisin was measured from the adipose tissue and muscle; different sampling methods from tissues may be the reason behind the inconsistencies between our results. What may also have resulted in the divergence in our findings are the differences between in vivo and in vitro approaches and the durations of the physical training.

We found that irisin expression was affected by the intensity of training inasmuch as there was a more pronounced rise in the level of irisin after combined

Table 2. Descriptive Indices of the Research Variables in the Study Groups and Inter-Group Comparisons Using the Variance Analysis Test (ANOVA)

Variable	Group			F	P Value
	Control	Training (Moderate-Intensity Exercise)	Training (High-Intensity Exercise)		
Irisin, $\mu\text{g/mL}$				5.93	0.010
Pretest	3.47 \pm 0.40	3.80 \pm 0.96	4.50 \pm 1.45		
Posttest	3.69 \pm 0.32	7.16 \pm 2.07	21.03 \pm 9.11		
Betatrophin, $\mu\text{g/mL}$				6.65	0.006
Pretest	524.56 \pm 47.22	508.95 \pm 37.33	601.50 \pm 347.58		
Posttest	400.7 \pm 36.89	517.34 \pm 27.63	1006 \pm 565.99		
Insulin, $\mu\text{g/mL}$				8.17	0.003
Pretest	16.86 \pm 6.56	9.22 \pm 5.20	9.51 \pm 5.65		
Posttest	27.57 \pm 18.78	19.04 \pm 8.67	14.45 \pm 7.68		

high-intensity training relative to combined moderate-intensity training. This result is consistent with the results of investigations by Loffler et al. (18), Tsuchiya et al. (19), Pekkala et al. (20), and Hakimi and Hosseini (21). Loffler et al. pointed out that high-intensity training resulted in high levels of blood irisin in comparison with moderate-intensity training and concluded that the level of irisin expression was affected by the level of consumed oxygen (18). Tsuchiya et al. measured the serum irisin level in their study subjects while they were on treadmills at 2 different intensities of VO₂ max 40 and VO₂ max 80 and concluded that serum irisin responded to high-intensity training more than training at moderate intensity (19). Pekkala et al. compared the level of irisin expression between high-intensity aerobic training and combined moderate-intensity training (20). In their study, the high-intensity aerobic training protocol consisted of working on an ergometer bicycle for between 60 and 90 minutes at 70% to 80% HRmax twice a week for 21 weeks and the combined moderate-intensity training protocol comprised 2 sessions of aerobic exercises per week for 21 weeks and 2 sessions of resistance training per week for 60 to 90 minutes. The authors reported that the serum level of irisin exhibited a rise immediately after both of the exercise protocols and that this elevation was higher after high-intensity aerobic training, indicating that irisin expression was affected by the intensity of training (20). Likewise, Hakimi and Hosseini demonstrated that low-intensity aerobic exercise for 8 weeks led to no significant change in serum irisin in spite of significant weight loss as well as a reduction in body mass and body fat percentages (21). The reason reported for this inconsistency is the inadequate training intensity for boosting irisin expression.

However, in the present study, we found that the increase in the level of the betatrophin hormone as a re-

sult of combined training was more remarkable after high-intensity training than training with moderate intensity. A few investigations have thus far been conducted on changes in the betatrophin level following a training program. Yi et al. reported the occurrence of a considerable proliferation in pancreatic β -cells in rats resistant to insulin due to betatrophin expression. The investigators concluded that betatrophin caused the proliferation of β -cells and improved glucose tolerance (22), which is consistent with the results of the studies by Chen et al. (23), and Fu et al. (7). Based on the reports of Xie et al. an increased betatrophin serum level in metabolic patients is probably associated with β -cell proliferation, insulin secretion and consequently, fasting blood sugar regulations and reduced insulin resistance in the liver cells (24). Their results concerning increased insulin production are consistent with the results of the present study, which show that as a result of a combined training period, the level of insulin is increased in diabetic patients. Zheng and Liu et al. posited that although the effects of betatrophin on different body organs and cells were not completely known yet, this matter was a promising pharmaceutical target for proliferating β -cells, with the current results concerning this betatrophin specification being encouraging as well (25).

Combined training also had significant effects on the insulin level in the current study in that it was increased in our 2 training groups. This finding confirms the effects of the betatrophin hormone on the proliferation of β -cells, followed by insulin expression. The results of a study by Kadoglou et al. showed that all their active groups significantly experienced insulin improvement compared with their control group (26). Rawal et al. showed that running on the treadmill at moderate intensity for 7 weeks led to increased insulin levels in diabetic rats (27).

In the present research, we measured the insulin in-

jection dose and recorded it in our 3 groups at the pretest and posttest. The results showed that this dose was reduced by 52% in the moderate-intensity training group and by 84% in the high-intensity training group, demonstrating the necessity of the application of a combined training approach aimed at augmenting the expression of irisin, betatrophin, and insulin and consequently, reducing insulin injection in patients with type 2 diabetes. Kurdiova et al. showed that irisin released into the bloodstream was able to improve insulin resistance by increasing UCP1 expression (5). Irisin amplifies UCP1 expression by linking to unknown receptors and boosting the expression of PPAR- γ (peroxisome proliferator-activated receptor gamma). Then, UCP1 converts the white adipose tissue into brown adipose tissue through the ERK and MAPK P38 (P38 mitogen-activated protein kinases) pathways. Additionally, irisin transfers GLUT4 (glucose transporter type 4) to the cell plasma membrane by activating the P38 MAPK pathway. It affects glucose homeostasis by affecting the expression of genes like GLUT4, hexokinase 2, and PPARA (peroxisome proliferator-activated receptor-alpha), involved in glucose and lipid metabolism, as well as regulatory factors like glycogenolysis (PCK1) and gluconeogenesis (PYGM) (muscle glycogen phosphorylase) (8). Most of the studies have indicated that betatrophin expression is enhanced in diabetic and insulin-resistant individuals, so that it could be considered a metabolic control factor and a regulatory factor for blood sugar. This specification of betatrophin was confirmed in studies by Abu-Farha et al. (6), Fu et al (7), and Huh et al. (8). Based on the results obtained by the abovementioned researchers, increased levels of irisin in diabetic patients may be related to the body's compensating adjustment, resulting in increased insulin sensitivity and improved glucose metabolism and ultimately, it may be regarded as an adjustment factor on increased fasting blood glucose and hepatic insulin resistance. However, based on the views of some researchers, betatrophin does not induce the proliferation of the pancreas β -cells per se, and some other factors may also be involved in this event (24). This hormone probably induces insulin secretion via the phosphorylation of AKt, glycogen synthase kinase-3, or FoxO1 and has, thus, been recommended for diabetes as a factor for reducing insulin injection complications and an important potential therapeutic factor because of producing insulin several times. Some studies have suggested that betatrophin is transcribed via the interface pathway RAS/c-RAF/MAPK and activated through ERK phosphorylation in the liver cells, adipocytes, and pancreatic β -cells (23). Hence, based on the signaling pathway of P38-PGC-1 α -irisin-betatrophin-beta cell, skeletal-muscle stimulation increases the expression of PGC-1 α and subsequently

FNDC5, irisin, and betatrophin in turn. Betatrophin affects the pancreas β -cells and, consequently, expresses the insulin hormone several times. Since insulin injection can cause severe complications such as hypoglycemia, tachycardia, edema and even, death in addition to creating financial burden, the expression of irisin and betatrophin may be considered an effective technique instead of insulin injection for diabetes control.

5.1. Conclusions

In sum, the results of the present research showed that combined aerobic and resistance training led to elevated irisin hormone levels additionally, combined training resulted in a rise in the betatrophin hormone level. The level of insulin was also increased as a result of combined training in our 2 training groups. Thus, it appears that participating in relatively high-intensity training programs may be beneficial for diabetic patients in as much as they increase the levels of irisin, betatrophin, and then, insulin.

Footnotes

Authors' Contribution: All authors have same contribution.

Conflict of Interests: It is not declared by the authors.

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