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The Effect of Interval and Resistance Training on Insulin Resistance with Emphasis on FTO Gene Expression in Subcutaneous Adipose Tissue of Wistar Rats with Obesity Induction

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Abstract

Background and Aim: Clinical evidence highlights the critical role of transcription factors in insulin action within adipose and muscle tissues. This study aimed to evaluate the effects of **high-intensity interval training (HIIT)** and **resistance training** on **FTO expression** in subcutaneous adipose tissue, as well as on **glucose metabolism** and **insulin resistance** in obese rats.

Methods: Obesity was induced in **21 male Wistar rats** via a **high-fat diet (HFD)**. The rats were then randomly assigned to three groups: **HIIT group** (8 weeks, 5 sessions/week; n=7); **Resistance training group** (8 weeks, 5 sessions/week; n=7); **Control group** (no training; n=7). At **48 hours after the final exercise session**, the following parameters were measured: Fasting glucose, Serum insulin, Insulin resistance (HOMA-IR), **FTO expression** in subcutaneous adipose tissue. Statistical analysis was performed using **one-way ANOVA** followed by **Tukey's post hoc test** for between-group comparisons.

Results: Both **HIIT** and **resistance training** led to significant reductions in: **Fasting glucose** (P = 0.001), **Insulin resistance** (P=0.001), **FTO expression** in subcutaneous adipose tissue (P=0.001), **Serum insulin levels** (P= 0.001) compared to the control group.

Conclusion: The observed improvements in **glucose metabolism** and **insulin resistance** following HIIT and resistance training may be attributed to the **downregulation of FTO expression** in subcutaneous adipose tissue. These findings suggest that **both exercise modalities** could be effective strategies for metabolic regulation in obesity.

Laboratory Highlights & Technical Implications:

- Both HIIT and resistance training significantly reduced fasting glucose, insulin levels, and insulin resistance (HOMA-IR) in obese rats.
- Downregulation of FTO expression in subcutaneous adipose tissue may be a key mechanism behind improved insulin sensitivity.
- Both exercise modalities showed similar metabolic benefits, supporting their efficacy in obesity management.
- These findings highlight structured exercise (HIIT or resistance training) as a non-pharmacological strategy for metabolic regulation.
- Future research should explore long-term FTO modulation and combined training effects for clinical translation.

Keywords: Gene Expression; Glycemic Profile; Exercise; Obesity; Obesity Induction; Insulin Resistance; Interval Training; Resistance Training; FTO Gene Expression; Subcutaneous Adipose Tissue; Wistar Rats; Animal Model.

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Introduction

Laboratory studies have indicated that almost 70% of the predisposition to obesity depends on genetic differences. (1, 2). Nearly 2,000 genetic loci related to obesity and related diseases have been discovered (3), and at least 75 of them have been identified as obesity-prone genes (4, 5).

In the meantime, disturbances in protein levels or the expression of some genetic components such as Fat mass and obesity associated (FTO) are among the most important of them. So that it has been introduced as the first and most important gene causing obesity in all races during life (6, 7).

The FTO gene was first discovered in a European study in 2007 on a large group of type 2 diabetic patients. In the mentioned study, researchers have observed that a group of single nucleotide polymorphisms in the first intron of this gene is strongly related to type 2 diabetes. It should be noted that in later studies, it was found that the close relationship between FTO and the occurrence of type 2 diabetes was revealed in response to the effect of FTO on body mass index (6).

FTO gene has been introduced as one of the effective genetic candidates in obesity and related diseases in both children and adults (8). A positive and significant relationship between FTO expression and visceral fat deposits has been reported (9). FTO is located on the long arm of chromosome 16 (10) and in addition to adipose tissue, it is strongly expressed in the hypothalamus, pituitary and adrenal glands, which are involved in the control of energy homeostasis in the brain (10). Disturbance in protein levels and its expression increases the tendency to obesity and, in turn, diabetes in obese people (11).

Several studies have supported the association of its polymorphisms with BMI and the risk of overweight at different ages (12, 13). It has been found that the allele that increases the body mass index in FTO single nucleotide polymorphisms increases the energy intake along with decreasing satiety and increasing appetite and accelerating the absorption of fat from consumed food, the desire for obesity and body fat mass (14, 15).

Clinical reports have indicated that protein levels and FTO expression in muscle cells and adipose tissue of diabetic and non-diabetic obese people increase compared to people with normal weight and severely affects fat metabolism (15). However, its direct effects on insulin action and glucose metabolism in obese or diabetic subjects are less reported. Based on the above evidence, it seems that decreased protein levels or FTO expression are associated with decreased lipid levels.

In this context, many studies in the last two decades, have been conducted on the effect of different therapeutic interventions with the aim of improving carbohydrate and fat metabolism in healthy or sick obese populations, but among these, limited studies have been conducted with the aim of the effect of non-pharmacological interventions such as exercise. It has been done on protein levels or FTO expression in adipose tissue of healthy or diseased obese individuals. Thus, in the study of Kraff et al (2017), physical activity led to a 30% adjustment of the effect of FTO on indicators of obesity such as abdominal circumference, body mass index compared to inactive people (16).

In Karoli et al.'s study (2012), 30 minutes of aerobic exercise led to the reduction of 2 FTO single nucleotide polymorphisms (rs8044769 and rs3751812) (17). However, so far, few studies have followed the effect of HIIT and resistance training on FTO expression in obese rats. Therefore, in the present study, the effect of 8 weeks of resistance and high intensity interval training (HIIT) training were measured on FTO expression on subcutaneous adipose tissue, fasting glucose and insulin resistance of obese Wistar rats.

Methods

Experimental animals

Twenty-one Male Wistar rats (10 weeks old) with a weight of (220 ± 10 g) were prepare from the animal house (Pasteur Institute of Tehran, Iran), and were housed in ventilated cages (1 mouse/cage) under controlled conditions (22°C, 12-h light cycle; & humidity 45 to 55%).) with ad libitum access to food and water.

All procedures were approved by the Committee of Ethics in Research of Islamic Azad University of Karaj Branch (Alborz, Iran) and carried out in accordance with CPCSEA (Committee for the Purpose of Control and Supervision of Experiment on Animal) guidelines. Then, after induction of obesity, they were randomly divided into 3 groups: 1) control, 2) HIIT, and 3) resistance training.

Induction of obesity: To induce obesity, a high-fat diet was used for 8 weeks. In order to prepare high-fat food, first, standard food was prepared from Pars Animal Feed Company, then it was kneaded and added to 1% cholesterol powder and 1% corn oil (pure 100%) and made into pellets again (19).

Training protocol: After obesity induction, the rats of HIIT group experienced HIIT for 8 weeks, 5 sessions

weekly in the form of running on a treadmill (19) (Table 1).

The resistance group underwent a structured training program involving **climbing a 26-step ladder at an 85% slope** while carrying an external load (weights attached to the tail). The protocol consisted of:

- **Frequency:** 5 sessions per week for 8 weeks.
- **Sets/Reps:** 3 sets × 6 repetitions per set.
- **Rest Intervals:**
  - 3 minutes between sets.
  - 45 seconds between repetitions within each set (20; modified).

Table 1. Interval training protocol according to speed and time of running in interval obese group

Exercise Session (weeks)	Exercise phase		Resting phase	
	Time (S)	Speed (m/min)	Time (S)	Speed (m/min)
1-2	40	20	120	14
3-4	40	25	120	14
5-6	40	30	120	14
7-8	40	35	120	14

*Running time in the exercise phase is 40 seconds and in the active rest phase is 2 minutes and the speed is in meters per minute.

Table 2. Resistance training protocol based on body weight percentage

Exercise Session (week)	1	2	3-4	5-6	7-8
Resistance (body weight%)	20	40	60	80	100

The rats of control group did not participate in this training program. Finally, 48 hours after the last training session, the studied rats in all groups were dissected after an overnight starvation.

Sample Collection and Biochemical Assay

Forty-eight hours after the last training session (10 to 12 hours of fasting), the studied rats in each group were fainted by injected intraperitoneally with a mixture of 10% ketamine at a dose of 50 mg/kg and 2% xylazine at a dose of 10 mg/kg. Next, the subcutaneous adipose tissue of rats was sampled and after washing in physiological serum, it was immersed in 1.8 microtubes containing 20% RNAlater liquid to perform genetic tests. RNA extraction was performed using the commercial kit RNeasy mini kit of QIAGEN Company. Determination of gene mRNA by RT-Real time PCR by Rotor Gene 6000 system using One Step SYBR TAKARA kit from Takara Company was used according to the company's instructions. RNA Polymerase II was used as a control gene. The sequence pattern of the primers is shown in Table 1.

Statistical analysis

Data were analyzed by the Statistical Package for Social Sciences (SPSS) for Windows, version 22.0 and are expressed as mean ± SD. One way ANOVA with Tukey post hock test were used to compare each parameter between groups. Differences were considered to be statistically significant when p-value<0.05.

Table 3. Primer sequence

Genes	Primer Sequence	Product Size	T_m	Gene Bank
FTO	**Forward**: TACACAGAGGCCGAGATTGC **Reverse**: AAGGTCCACTTCATCATCGCAG	159 bp	60	NM_001191052.1
RNA Polymerase II	**Forward**: ACTTTGATGACGTGGAGGAGGAC **Reverse**: GTTGGCCTGCGGTCGTTC	164 bp	60	XM_008759265.1

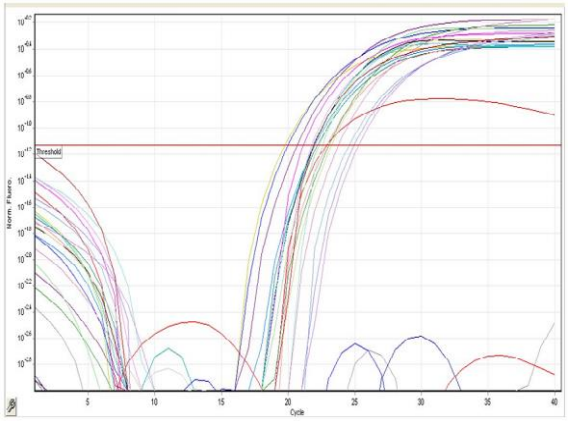

Figure 1. The cycling A Green of FTO gene expression

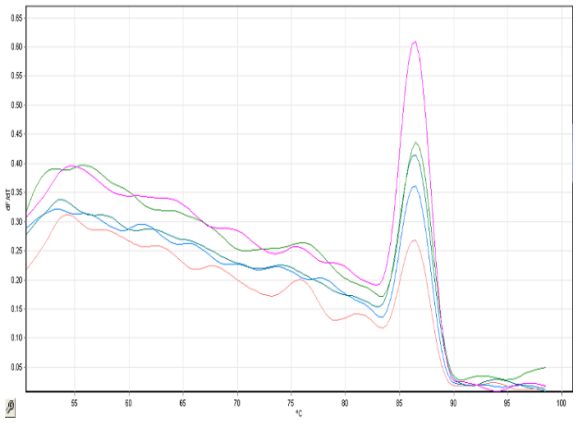

Figure 2: The melting curve of FTO gene expression

Results

Biochemical markers of 3 group are showed in Table 4. Based on one way ANOVA, there are a significant difference in serum insulin, glucose and insulin resistance between the study groups. On the other hand, based on the findings of Tukey's test, both HIIT and resistance training led to a significant decrease in serum insulin (P=0.001) and significant decrease in fasting glucose (P=0.001) and insulin resistance (P=0.001) compared to the control group. However, there was no significant difference in serum insulin (P=0.974), glucose (P=0.600) and insulin resistance (P=0.989) between HIIT and resistance groups.

Table 4. Mean and standard deviation of diabetes determinants of studied groups

Group	Control	HIIT	Resistance	Sig (ANOVA)
Glucose (mg/dL)	120± 3.62	96 ± 5.38	94 ± 1.38	0.001
Insulin (µIU/ml)	9.04 ± 0.72	6.37 ± 1.15	6.47 ±0.59	0.001
Insulin resistance (HOMA-IR)	2.68 ± 0.22	1.53 ± 0.34	1.51 ±0.15	0.001

Table 5. Pattern of changes in gene expression in response to HIIT and resistance training

Group	Control	HIIT	Resistance	Sig (ANOVA)
FTO relative expression	1	0.69±0.27	0.63±0.23	0.007

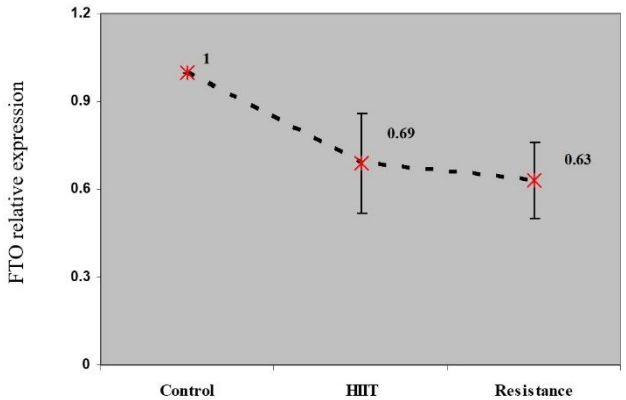

Figure 3: FTO gene expression in subcutaneous adipose tissue of studied groups. HIIT and resistance training led to a significant decrease in FTO gene expression compared to the control group.

Determining the effect of HIIT and resistance training on FTO expression in subcutaneous adipose tissue is main aims of this research. There is a significant difference in FTO expression in subcutaneous adipose tissue between the study groups.

On the other hand, based on the findings of Tukey's post hoc test, both HIIT and resistance training led to significant decrease in FTO expression compared to the control group (P=0.031, P= 0.008; respectively). However, there was no significant difference in FTO expression between HIIT and resistance groups (P= 0.974).

Discussion

Decreased FTO expression in subcutaneous adipose tissue in response to exercise interventions is the main findings of the present study. In other words, 8 weeks of HIIT and resistance training for 5 sessions per week led to a decrease in FTO expression in the subcutaneous adipose tissue of obese rats compared to the control group that did not participate in the training program. HIIT and resistance training were also associated with a decrease in glucose and insulin resistance and an increase in serum insulin.

Improvement of glycemic profile in response to exercise interventions has been reported in most previous studies. As Eizadi et al (2016) have reported a decrease in blood glucose along with an increase in serum insulin following 12 weeks of resistance training in type 2 diabetic rats (21).

In Karimi et al.'s study (2019), 8 weeks of HIIT led to the improvement of blood glucose along with the reduction of insulin resistance in obese rats (22). Nevertheless, in another study, 20 weeks of physical activity in the form of 3 to 5 sessions with an intensity of 70% of VO2max per week did not lead to a change in glycosylated hemoglobin as a result of long-term glucose changes (23). In the study of Maltais et al (2016), 4 months of resistance training did not lead to a change in glucose and insulin levels in 26 overweight elderly men, although the body fat mass decreased significantly (24).

Meanwhile, most studies have attributed this improvement to the reduction of insulin resistance following exercise. So, in the present study, in addition to improving fasting glucose, insulin resistance was also reduced in response to HIIT and resistance training. In other words, 8 weeks of HIIT and resistance training led to a decrease in insulin resistance in obese rats. It should be noted that several

factors such as increasing the levels of lipid profiles and decreasing HDL, disturbances in metabolic components such as blood lipids and hormonal components such as cortisol, thyroid hormones have a potential contribution to the dysfunction of insulin in target tissues (25). Some researchers have also attributed the reduction in blood glucose levels or glycemic profile to the improvement of inflammatory components in response to exercise. As these studies have indicated that the improvement of insulin function at the tissue levels is rooted in the improvement of the inflammatory profile. For example, research has indicated that improvements in glucose levels and HbA1C following 12 weeks of HIIT (at 70 to 90 percent of maximum heart rate) are associated with reduced pro-inflammatory interleukins and increased IL-10 levels (26).

Researchers believe that exercise increases insulin sensitivity by activating the AMP protein kinase pathway, thereby reducing insulin resistance. Apart from the metabolic and hormonal components effective in glycemic profile and insulin resistance, today the map of transcription factors and genetic factors in insulin signaling pathways in target tissues, especially skeletal muscles and subcutaneous and visceral fat tissue, have been introduced much more colorfully. In the present study, HIIT and resistance training were associated with a decrease in FTO expression in subcutaneous adipose tissue. In this context, it has been found that FOXO1, PPAR-y and FTO genetic components affect energy homeostasis and glucose and fat metabolism in target tissues such as skeletal muscles and adipose tissue (27). So that the relationship between protein levels and their expression with lipid profile and insulin resistance has been reported many times (28).

Researchers believe that FTO is a type 2 diabetes susceptibility gene independent of BMI. Thus, the FTO intronic variant is associated with both insulin resistance in the cerebral cortex (28) and peripheral insulin resistance (29). This relationship has been reported in some studies after BMI adjustment (29,30) and in some studies without BMI adjustment (31). The FTO expression in several key tissues such as pancreatic alpha and beta cells, liver, skeletal muscle and adipose tissue affects the tendency to type 2 diabetes, glucose levels and the rate of glucose oxidation (16). FTO expression with some genes involved in liver gluconeogenesis process (32), TNF and NF-kB expression in subcutaneous adipose tissue (33) and insulin and KCNJI1 expression in pancreatic beta cells (34) and signaling pathways related to these genes. It is involved in the regulation of glucose homeostasis. FTO overexpression in the myotubes of muscle cells leads to an increase in AKT phosphorylation, an increase in lipogenesis and oxidative stress, and a decrease in mitochondrial oxidative function in people with type 2 diabetes (16). On the other hand, the removal of FTO in laboratory mice leads to a significant improvement in insulin sensitivity (35). Laboratory studies have revealed that overexpression of FTO leads to increased resting phosphorylation of some transcription factors effective in the insulin signaling cascade, such as PDK1, PKB and p70/85s6k. However, FTO did not appear to inhibit the effect of insulin on PKB activity in muscle cells, suggesting that changes in FTO expression do not lead to acute changes in upstream IRS1/PI3K pathways in muscle cells. However, FTO inhibits insulin-dependent PKB phosphorylation in muscle cells (HEK293), supporting that FTO directly or indirectly affects transcription factors involved in the insulin signaling cascade (16).

Based on the effective role of FTO in insulin function and the findings of the present study, the reduction of glucose and insulin resistance in response to HIIT and resistance training is probably rooted in the reduction of FTO expression in subcutaneous adipose tissue. On the other hand, the findings of the study indicate that there is no difference in FTO between HIIT and resistance groups. Since the studies regarding the responsiveness of FTO to various exercise training are limited, especially in the subcutaneous adipose tissue, it is difficult to provide a general conclusion regarding the responsiveness of its expression to HIIT and resistance training and the need for other studies in this field is pointed out. In summary, exercise training regardless of interval or resistance leads to the improvement of signaling pathways affecting insulin action in subcutaneous adipose tissue of obese Wistar rats.

Conclusion

HIIT and resistance training leads to improvement of glucose in obese Wistar rats. Based on the effective role of FTO in insulin signaling pathways, this improvement is probably rooted in the reduction of FTO expression in subcutaneous adipose tissue in response to these exercise interventions.

The findings of this study showed a decrease in FTO expression in the subcutaneous adipose tissue along with a decrease in insulin resistance following HIIT and resistance training. Nevertheless, understanding the mechanisms responsible for changes in insulin action in response to exercise calls for more studies in this field.

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Conflict of Interest

The authors declare no conflict of interest.

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Ethics

This study was approved by Committee of Ethics in Research of Islamic Azad University of Karaj Branch, Alborz, Iran (Ref. IR.IAU.PIAU.REC.1400.010) and carried out in accordance with CPCSEA (Committee for the Purpose of Control and Supervision of Experiment on Animal) guidelines.

Authors' Contributions

All authors were involved in conception and design of the study as well as in data generation, data analysis, and drafting the manuscript. Also, all authors approved the final draft.

AI Use Declaration

This article was written without the use of artificial intelligence.

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