New Approaches in Exercise Physiology (NAEP), Vol 4, No 7, 214-231, Sep 2022

Effect of resistance training on FTO and PPAR-y genes expression in muscle tissue of obese diabetic rats

Mehdi Kushkestani
Ph.D. student, Wellness and lifestyle science initiative group, Ph.D. student of kinesiology and health, school of art and science, Rutgers University New Brunswick, New Brunswick, New Jersey, United States.
Mahsa Moghadassi
M.Sc Student of Exercise Physiology, Department of Exercise Physiology, Islamic Azad University, Tehran North Branch, Tehran, Iran.
Mohsen Parvani
Ph.D. student of Sports Sciences, Faculty of Sports Sciences, University of Coimbra, Portugal.
Raheleh Baradaran*
Allameh Bohlool Gonabadi Hospital, Gonabad University of Medical Sciences, Gonabad, Iran.
Received: December 29, 2022; **Accepted:** February 27, 2023
Doi: 10.22054/NASS.2023.71785.1123

Abstract

Purpose: It has been well proven that type 2 diabetes is one of the most common non-communicable diseases leading to many complications and mortality every year. The aim of this study was to investigate the effect of resistance training on FTO and PPAR-y gene expression in muscle tissue of obese diabetic rats. Study design: This experimental study was performed on 12 male Wistar rats (10 weeks old and 220±20 g bodyweight). **Methods:** Animals received 6 weeks high-fat diet and then in order to induce type 2 diabetes an intraperitoneal injection of a single dose of 30 mg/kg freshly prepared streptozotocin (STZ) (Sigma, USA) solved in citrate buffer (pH 4.5) was performed. Diabetic rats were divided into two (Resistance and control) groups randomly. The resistance program included 6 weeks, 5 sessions per week. The muscle expression of FTO and PPAR-γ was measured using the real-time PCR method. Independent t-test and Analysis of covariance (ANCOVA) were applied to compare the means. **Results:** The muscle mRNA expression of PPAR-γ and body weight significantly increased after 6 weeks of resistance training (p=0.031, p=0.037; respectively) but there was no significant change in the muscle mRNA expression of FTO (p=0.317). Also, blood glucose significantly decreased in the training group compared to the control group (p=0.01). **Conclusion:** According to the results of this study, it can be noted that 6-week resistance training by decreasing glucose levels and

* **Author's e-mail:** mk2084@scarletmail.rutgers.edu, mahsa.kushk@gmail.com, mparva2020@gmail.com, baradaran.r@gmu.ac.ir **(Corresponding Author)**.

increases insulin sensitivity, and the muscle expression of PPAR-γ plays a prominent role in the control and treatment of type 2 diabetes in obese patients.

Keywords: Exercise, Metabolic diseases, Gene expression, Diabetics, Resistance training.

Introduction

Type 2 diabetes (T2DM) is a metabolic disease characterized by insulin resistance and relative deficiency of insulin secretion. It accounts for more than 90% of diabetes mellitus cases (D. Yang et al., 2019). Failure to control and treat it leads to diseases such as diabetic nephropathy, retinopathy, peripheral neuropathy, peripheral vascular disease, and diabetic foot (Chatterjee et al., 2017, p. 2; Kushkestani et al., 2020, 2020; Kushkestani, Parvani, Nosrani, & Rezaei, 2020a, 2020b, 2020a; Kushkestani, Parvani, Nosrani, Rezaei, et al., 2020; Kushkestani, Parvani, Rezaei, & Moradi, 2020; Tartibian et al., 2020). It has been estimated that there are about 422 million diabetes patients worldwide most of whom, unfortunately, live in low- and middle-income countries. In addition, 1.6 million people die annually due to diabetes. Moreover, the prevalence of diabetes and its related mortality have been increasing steadily over the past several decades with the advances in technology (WHO, 2021). Reports suggest that overweight and obesity are predictors of T2DM so that, at present, the obesity dilemma kills more people than hunger worldwide (Kushkestani et al., 2021, 2022; D. Yang et al., 2019). Recent research indicates that serum concentrations of some inflammatory markers including cytokines, TNF-α, IL-1β, Il-6, and C-reactive protein and macrophage accumulation and chemotaxis of skeletal muscle satellite cells in adipose tissue and kidneys of obese people with T2DM are higher compared to healthy individuals (Esser et al., 2014; Tartibian et al., 2019; TARTIBIAN & KUSHKESTANI, n.d.). The obesity activates the various signaling cascades and subsequent inflammatory pathways leading to phosphorylation dysfunction of insulin signal transduction protein (Gleeson et al., 2011; Karstoft & Pedersen, 2016).

Fat mass and obesity-associated protein (FTO) are expressed in the hypothalamus, pituitary gland, adipose tissue, and adrenal glands accompanied by regulation of glucose and fat metabolism in the target tissues including skeletal muscles leading to changes in the expression of genes related to metabolism (Hertel et al., 2011; Liguori et al., 2014). The

exact role played by FTO in metabolic mechanisms of various tissues especially, the skeletal muscles has not been determined yet. FTO expression in adipose and skeletal tissues may be involved in the development of some components of the metabolic syndrome such as dyslipidemia and peripheral metabolic regulation (Yazdanpazhooh et al., 2018). Moreover, studies suggest that reduced expression of this gene is accompanied by improved blood glucose and insulin resistance (Kilpeläinen et al., 2011; Nascimento et al., 2018; Yazdanpazhooh et al., 2018).

Peroxisome proliferator-activated receptor γ (PARA-γ) is activated by fatty acid metabolism leading to the regulation of insulin sensitivity throughout the body (Kim, 2016). The mechanisms of action of PARA-γ in glucose absorption and insulin sensitivity in the target tissues (skeletal muscles, adipose tissue, and kidneys) are not completely clear yet. Nevertheless, the results of some research indicate reduced PARA-γ expression in humans and animals with T2DM (Cha et al., 2008). In one study, it was shown that the PARA-γ protein regulated GLUT4 expression in adipose and skeletal tissues as the main glucose transporter. In addition, PARA-γ activity influences the insulin signaling pathways in several stages accompanied by reduced insulin and glucose levels (Yazdanpazhooh et al., 2019).

At present, physical activity and exercise are introduced as a cost-effective and safe strategy for controlling and treating T2MD that increases muscle mass and reduces fat mass thus decreasing blood sugar in patients with T2DM. In addition, this strategy has extensive benefits for the immune system. Research suggests that the skeletal muscles are responsible for absorbing about 80% of the total blood sugar in the human body by stimulating insulin. Consequently, they play a vital role in preventing insulin secretion disorders. Therefore, the target tissue is considered for the function of insulin in the body (Kim, 2016).

Comprehensive mechanisms are involved in improving T2DM, its complications, and the diseases that it causes. For example, resistance training is accompanied by increased glucose uptake and utilization (Dos Santos et al., 2015), protection of pancreatic β-Cells function (Solomon et al., 2013), increase of lipid hydrolysis oxidation (Ma et al., 2019), and alleviation of systemic inflammation. In addition, increases in the expression of the GLUT4 protein in muscle cells and in its translocation to

the cell membranes enhance the ability of the skeletal muscles to uptake and transport glucose (Hussey et al., 2012). Furthermore, resistance training is accompanied by higher muscle strength and cross-sectional area that increase the number of insulin receptors and improve insulin sensitivity (D. Yang et al., 2019). Moreover, enhancement of insulin signaling is another advantage of strength training for controlling blood sugar in patients with T2DM (Kim, 2016). Izadi et al. reported that insulin resistance and sugar profiles in rats with T2DM improved after 8 weeks of strength training (Eizadi et al., 2019). Considering the lack of study in the field of resistance training and FTO gene expression as well as the beneficial effects of resistance training on markers of diabetes and its consequences, we hypothesized that 6 weeks of resistance training can modify some diabetes-associated genes expression, blood glucose, insulin sensitivity, and body mass. So, the aim of this study was to investigate the effect of resistance training on FTO and PPAR-y gene expression in muscle tissue of obese diabetic rats.

Method

Animals

This experimental study was performed on 12 male Wistar rats (220±20 g bodyweight and 10 weeks old) that were purchased from Iran Pasteur Institute. Before starting the study, all rats were adapted to the living conditions (room with dimensions of 1.60×2.20 meters, 22±3 °C temperature, 30–60 % relative humidity, and a half day light/ half day dark cycle) in the animal house of the Islamic Azad University, Alborz Province within 1 weeks. Animals had open access to standard high-fat food and drinkable water (Sun et al., 2000). All processes were conducted in accord with the Guide of the Care and Use of Laboratory Animals of Islamic Azad University, Alborz Province and was confirmed by ethics committee (96-8-3788).

Induction of type 2 diabetes

To induce diabetes 2 type, animals received high-fat diet within 6 weeks and then was performed an intraperitoneal injection of a single dose of 30 mg/kg freshly prepared streptozotocin (STZ) (Sigma, USA) solved in citrate buffer (pH 4.5) (Vatandoust et al., 2018). For the preparation of high-fat food, to the standard food purchased from company Pars Dam

were added 1% cholesterol powder and 1% pure corn oil. It should be noted that a high-fat diet was continued for all three groups until the end of the study (Sun et al., 2000). One week after establishment of diabetes, fasting blood glucose was measured and blood sugar between 150 to 400 mg/dl was considered as a criterion for ensuring that rats develop type 2 diabetes (Eizadi et al., 2017). Then diabetics rats were distributed randomly into two groups: (A) diabetic+ control group (control group= 6), (B) diabetic+ resistance training group (training group= 6).

Training protocol

Resistance training protocol

Animals of this group were introduced how to climb the ladder within 2 weeks before the start of training protocol. The resistance training type in this group was climbing the ladder that it lasted for a period of 6 weeks. The resistance induction pattern was applied by gradually increasing the resistance using closing a load to the tail of the rats, equivalent to different percentages of body weight. The exercise program was accomplished in 5 sessions per week in the form of 5 sets with 4 repetitions in each period. The rest intervals between sets were 2 minutes and the rest intervals between repetitions in each period were 30 seconds (Yazdanpazhooh et al., 2019) (3-5) (Table 1).

Table1. Resistance training protocol

week	**sets**	**Repetition in each set**	**Intensity of exercise**	**Rest between Rep**	**Rest between sets**	Frequency
1	5	4	30%BW	30 sec	2 min	5 d.w
2	5	4	50%BW	30 sec	2 min	5 d.w
3	5	4	70%BW	30 sec	2 min	5 d.w
4	5	4	90%BW	30 sec	2 min	5 d.w
5	5	4	100%BW	30 sec	2 min	5 d.w
6	5	4	100%BW	30 sec	2 min	5 d.w
Sec; second, min; minute, %; percent, d.w; day/week						

Blood and Tissue sampling

48 hours after the last training session, rats of two groups were anaesthetized with ketamine 10% (50 mg/kg)/xylazine 2% (10 mg/kg) mixture and sacrificed by cervical dislocation, then the thorax cavity was opened and blood sampling was directly done from the heart. Gastrocnemius muscle (Banaeifar et al., 2019) of rats were sampled and

after washing in saline solution, they were immersed in microtubes containing RNA later TM (RNA Stabilization reagent 50mL) with a ratio of 20% and transferred to -70 °C for further genetic testing in Tehran Pasteur Institute, Iran.

Insulin resistance assay

Blood samples were centrifuged at 1000×g within 2 min to separate serum and kept at -80 °C to measure serum glucose and insulin. Glucose level was evaluated by enzymatic colorimetric procedure with glucose oxidase technology and using the glucose kit of Pars Azmoon Company (Tehran, Iran). The changes coefficients of intra-test and extra-test of the glucose were 1.74 and 1.19 percent, respectively, and the sensitivity of the measurement was 5 mg/dl. To measure serum insulin, a Demeditec laboratory kit (Germany) was used by ELISA method. The changes coefficients of intra-test and extra-test and the sensitivity of insulin measuring were 2.6, 2.88 percent and 1.76 unit, respectively. Then insulin resistance was obtained by following formula:

Insulin resistance = (glucose (mmol/l) × insulin (μU/ml)) / 22.5 (Gutch et al., 2015).

Real-time polymerase chain reaction (Real-time PCR)

The sequence of primers was designed by a geneticist and its make order was given to the Pishgam Biotech Company (Tehran, Iran). Meanwhile, RNA-polymerz II gene was applied as the internal control to evaluate the relative quantitation of the mRNA expression. The designed primers are summarized in Table2.

Table 2. Pattern of primers used in this study

Genes	Primer sequence	Product size	Tm	Gene Bank
FTO	For: TACACAGAGGCCGAGATTGC Rev:AAGGTCCACTTCATCATCGCAG	159 bp	60	NM_001191052.1
PPARy	For: ACAACAGGCCACATGAAGAGC Rev:AAGCTTCAATCGGATGGTTCTTCG	159 bp	60	NM_001191052.1
RNA Polymrase II	For:ACTTTGATGACGTGGAGGAGGAC Rev: GTTGGCCTGCGGTCGTTC	164 bp	60	XM_008759265.1

20 mg of the tissue was crushed using a scalper and inserted into a microtube, and then RNA was extracted by applying Rneasy protect mini kit (QIAGEN, Germany) from gastrocnemius muscle according to the manufacturer's guidelines. To ensure from the RNA concentration for the cDNA preparation, its OD was checked by a NanoDrop (2000, USA). Then, cDNA synthesis from RNA was carried out by cDNA synthesis kit (QIAGEN, Germany), and the obtained product was maintained at -20 °C. Determination of FTO mRNA and PPARy mRNA by Real-time PCR was done by Rotorgen 6000 system using One Step SYBR® Green kit (TaKaRa, Japan) according to the company's instructions. Melting curve analysis was performed at the end of the PCR cycle to determine the validity of the PCR product. The used thermal cycle protocol in Real-time PCR included: 1 cycle with 42 °C on 20 min, 95 °C on 2 min to actuate the enzymes, and 40 cycles with 94 °C on 10 sec and 60 °C on 40 sec. Finally, the extracted CTs of reactions were recorded by device software. Then the fold change was calculated using the following formulas:

ΔCt = Ct target gene – Ct polymerase ll

$\Delta\Delta Ct = \Delta Ct$ training group – ΔCt control group

Fold change = $2^{(-\Delta\Delta Ct)}$

Statistical Analysis

SPSS 16 software was used to perform statistical analyses and data were reported as mean± SD. Shapiro-Wilk Test was used to investigate the normality of distributions among the groups. Analysis of variance (ANCOVA) Independent t-test was applied to compare the means. The test's significance level was considered less than 0.05.

Results

The results of statistical analyses showed a significant decrease in PPAR-y mRNA expression ($p<0.05$), fasting blood sugar ($p<0.001$), and HOMA-IR ($p<0.001$) in training group compared to control group (Table3). Although, weight significantly enhanced in training group after resistance training compared to control group ($p<0.001$) (Table4). Further, FTO mRNA expression was decreased in training group but it was not significant ($p<0.317$) (Table3).

Table3. The results of independent t-test among variables between training and control groups.

Variables	Control group	Training group	Mean ± SD
Insulin (μIU/ml)	5.21±0.37	6.38±0.31	0.001**
Glucose (mg/dL)	293±11.07	184±10.46	0.001**
Homa-IR	67.89±5.74	52.29±4.06	0.001**
Gastrocnemius-FTO	1	0.91±0.23	0.317
Gastrocnemius-PPARy	1	1.26±0.27	0.031*
Weight (g)	331.87±8.22	417.75±9.68	0.00001**
**: Correlation is significant at the 0.01 level (2-tailed).			

Table 4. The results of ANCOVA in weight changes between control and training groups

Variable	SS	df	MS	F	p
Weight (g)	1811.026	1	1811.026	35.821	0.000**
**: Correlation is significant at the 0.01 level (2-tailed).					

Discussion

In the present study, we investigated the effect of resistance training on FTO and PPAR-y mRNA expression in gastrocnemius muscle of obese diabetic rats, using real-time PCR method. Our results demonstrated that there was no significant difference in FTO mRNA expression but PPAR-y mRNA expression had a significant difference in the resistance training group compared to the control group.

The results of this study showed that fasting blood glucose and HOMA-IR significantly increased whilst the weight decreased significantly in training group compared to control group. Previous studies indicated that resistance training induces weight increase in diabetic rats through regulation (increment) of circulating FABP4 (Fatty acid-binding protein) levels (Safarzade & Talebi-Garakani, 2014). Resistance training in diabetic rats induces protein synthesis including phenylalanine that which causes muscle hypertrophy and weight gain (Farrell et al., 1999). Some studies showed that muscle mass in response to resistance training was significantly increased that is related to reducing Myostatin levels (Allen et al., 2011; McPherron et al., 2013; Saremi et al., 2010; Shabkhiz et al., 2020). On the other hand, it has been showed that resistance training is efficient in adipose tissue decrease in rats (Corriveau et al., 2008; Pighon et al., 2009). Regarding these two points, increasing of muscle and

decreasing of adipose tissue in response to resistance training, it can be stated that this exercise program can increase muscle tissue, which in turn leads to weight gain. Exercise training decreases glucose through the adiponectin-AMPK pathway (de Bem et al., 2018). In response to muscle contraction and resistant training, AMPK is activated in muscles. Activated AMPK phosphorylate proteins that involved in glucose uptake via increasing GLUT4. Therefore, resistant training decrease circulating glucose (J. Yang, 2014). It has proven that resistance training increases insulin synthesis and secretion through the impact on genes in target tissues such as skeletal muscle, adipose tissue, and liver (Klöting et al., 2008; Tontonoz & Spiegelman, 2008) which is associated with a decrease in serum glucose levels and insulin resistance (Eizadi et al., 2016). For example, Eizadi et al. 2016 revealed resistance training increases serum insulin by decreasing TCF7L2 expression in the pancreas tissue of type 2 diabetic rats (Eizadi et al., 2016). Also, Sohaily et al. 2020 showed that resistance training by reducing the FOXO1 gene in subcutaneous adipose tissue leads to a decrease in serum glucose and insulin resistance in type 2 diabetic rats (Sohaily et al., 2020).

The obtained results from real-time PCR didn't show a noticeable increase in mRNA expression of FTO in the resistance training group compared with control group. In line with our study, Leońska-Duniec et al. 2018 showed that physical activity has no effect on FTO rs 9939609 expression in obese women (20). Another study of Yazdanpazhooh et al. 2018 reported that 6 weeks of resistance training did not influence the expression of FTO in fatty tissue of type 2 diabetic rats, despite of glucose decrement and insulin resistance. They argued that decrease in glucose and insulin resistance may be relevant to changes in other genes or hormones such as the changes in FOXO1, PPAR-y, IRS1, and GLUT4 signaling pathways (Yazdanpazhooh et al., 2018) or due to the reduction in TNF-α and IL-6 inflammatory factors (Abd El-Kader et al., 2013; Yazdanpazhooh et al., 2019). In contrast to our study, Sailer et al. 2016 reported that 9 months aerobic exercise can change FTO rs 8050136 only in those that have the highest maximal oxygen uptake (Sailer et al., 2016). Further, a meta-analyzed study showed that physically active adults can only attenuate minor an allele of FTO rs 9939609 by 27% (Kilpeläinen et al., 2011). Therefore, it can be stated that the response of FTO to exercise

training depends on FTO polymorphisms, exercise type, duration, and/or frequency as well as studied species.

Another part of our study showed that resistance training significantly increases PPAR-y mRNA expression in gastrocnemius muscle of obese diabetic rats. In agreement with this part of our results, Yazdanpazhooh et al. 2019 reported that resistance training can activate insulin signaling pathways. They showed that six weeks resistance training reduced insulin resistance and glucose via increased PPAR-y expression in subcutaneous fatty tissue of type 2 diabetic rats (Yazdanpazhooh et al., 2019). Further, Zheng and Cai 2019 stated 12-week swimming exercise reduced the insulin resistance probably via increased PPAR-γ signaling in mice (Zheng & Cai, 2019). Furthermore, Hu and Chen 2004 reported that aerobic exercise for 8 weeks enhanced the GLUT4 expression in muscle and adipose tissue of mice. They argued that GLUT4 transcription is upregulated by PPAR-y (HU & CHEN, 2004). While it has reported that resistance training can more effectively increase the level of GLUT4 in the muscles that are involved compared to aerobic exercise (Yaspelkis III et al., 2002). Therefore, in our study probably resistance training can increase GLUT4 by upregulating PPAR-y and subsequently decreasing serum glucose levels and insulin resistance. It should be noted that during exercise, muscles not only systemically produce insulin-like growth factor-1 (IGF-1) but also utilize more circulating IGF-1 (Goldspink, 2005). IGF-1 also activates gene expression of L-type calcium channels, leads to an increased intracellular Ca++ concentration (Teppala & Shankar, 2010). This induces cAMP response element-binding protein (CREB) pathway activation, which is a regulatory mechanism for genes expression. On the other hand, Tunstall et al. 2002 demonstrated a significant decrease (20%) in PPAR-y expression after 9 days of training in human skeletal muscle (Tunstall et al., 2002). Besides, results of another study affirmed that the PPAR family gene expression is sensitive to exercise training in skeletal muscle, but is not sensitive to acute periods of resistance exercise. They concluded that changes in the PPAR gene expression are related to the accumulation of repeated periods of exercise as opposed to a short period of activity (Spangenburg et al., 2009). In our opinion, this inconsistency finding may be related to differences in the type, duration, and/or frequency of exercise training as well as studied species.

Conclusions

In brief, our results indicated that the PPAR-y gene expression was significantly higher in the resistance training group compared to obese diabetic group. But there was no significant difference in FTO gene expression in the resistance training group compared to the diabetic group. Alterations observed in PPAR-y gene expression in the resistance training group may lead to an increased in insulin levels and serum glucose levels improvement and insulin resistance suppress in obese diabetic rats. However, future studies are needed to evaluate the effects of resistance training on the expression of other related genes involved in signaling pathways in muscles or other tissues.

Limitation

The shortcoming of our study was that we did not examine muscle weight or the ratio of muscle weight to body weight. Therefore, resistance training should be considered as a treatment for diabetes, which can modulate glucose and insulin metabolism by affecting the expression of some genes regardless of enhancing weight.

Acknowledgment

There was no financial support for this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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