JOURNAL OF NUTRITION FASTING AND HEALTH

The Effect of Interval Training on PPARγ-GLUT4 Expression in Subcutaneous Adipose Tissue of Male Wistar Obese Rats

Mohammad Hossein Ghofrani [1*], Mojtaba Eizadi [2]

1. Assistant Professor of Exercise Physiology, College of Physical Education and Sport Sciences, Karaj Branch, Islamic Azad University, Karaj, Iran.
2. Assistant professor of Exercise Physiology, Department of Exercise Physiology, Saveh Branch, Islamic Azad University, Saveh, Iran.

ARTICLEINFO

Article type:
Research paper

Article History:
Received: 09 Dec 2023
Accepted: 07 Feb 2024
Published: 28 Aug 2024

Keywords:
Gene expression
Glucose
High intensity interval training
Obesity
Insulin sensitivity

ABSTRACT

Introduction: Genetic and metabolic dysfunctions are primary contributors to the onset and intensity of type 2 diabetes (T2D) through the promotion of insulin resistance. The objective of this research was to examine the impact of high-intensity interval training (HIIT) on the expression levels of PPARγ and GLUT4 in the subcutaneous adipose tissue, as well as its influence on insulin sensitivity among obese rats.

Methods: Obesity was induced by high fat diet (HDF) in 14 male wistar rats. Then rats were divided randomly into exercise (HIIT, n = 7) or control (n = 7) groups. The exercise group completed an 8 weeks HIIT (5 days / weekly) and the control group received no training. Fasting blood glucose, insulin sensitivity and PPARγ and GLUT4 gene expression in subcutaneous adipose tissue were measured 48 hours after last exercise session. Independent t-test was used to compare variables between groups.

Results: HIIT resulted in a significant decrease in fasting blood glucose (P = 0.001) and increase in insulin sensitivity (P = 0.001), PPARγ expression (P = 0.038) and GLUT4 expression (P = 0.019) in subcutaneous adipose tissue compared with control rats.

Conclusion: HIIT can be improve insulin sensitivity in obese rats. This improvement may be attributed to increased PPARγ and GLUT4 expression in subcutaneous adipose tissue.

▶ Please cite this paper as:
Ghofrani MH, Eizadi M. The Effect of Interval Training on PPARγ-GLUT4 Expression in Subcutaneous Adipose Tissue of Male Wistar Obese Rats. J Nutr Fast Health. 2024; 12(3): 174-180. DOI: 10.22038/JNFH.2024.76733.1488.

Introduction

Over many years, researchers have come to believe that obesity is the result of complex interactions between hormonal and environmental factors acting on fat and glucose metabolism, such as liver and muscle insulin function defects, adipose tissue metabolism, and lipolysis of the whole body (1). Recent research over the past ten years has highlighted the significance of genetic contributors alongside other factors in the development of obesity and its associated metabolic conditions. The alteration in the expression of certain genes or proteins, which act as transcription factors, can impact carbohydrate and lipid metabolism through their effects on lipolysis or insulin function. Notably, genetic components like FOXO1, PPARγ, and FTO are involved in regulating energy balance as well as glucose and lipid metabolism within specific tissues, including skeletal muscle and adipose tissue (2, 3). Moreover, numerous studies have documented a correlation between the levels and expression of these proteins with obesity, lipid profiles, and insulin resistance (3, 4).

Among the genetic components, the effective role of PPARγ in controlling insulin action and glucose homeostasis has been mentioned (3). PPARγ is expressed in white and brown adipose tissue, colon and spleen. Nonetheless, its levels are markedly elevated in adipocytes, where it serves a crucial function in controlling the formation of adipose tissue, maintaining energy equilibrium, and synthesizing lipids (5, 6). The mechanisms responsible for the effect of PPARγ on insulin sensitivity are complex and adipose tissue, skeletal muscles and liver are its target points, but it seems that adipose tissue is the most important target tissue of PPARγ-TZDs, which is manifested by increasing insulin sensitivity (7). Although PPARγ is often expressed in adipose tissue, it is also expressed in some other tissues such as skeletal muscle and liver, which are involved in glucose homeostasis

* *Corresponding authors:* Mohammad Hossein Ghofrani, Assistant Professor of Exercise Physiology, College of Physical Education and Sport Sciences, Karaj Branch, Islamic Azad University, Karaj, Iran. Tel: +98 9121674381, Email: manochehr_ghofrani@yahoo.com.

(3). It has been found that PPARγ activity directly regulates the expression of GLUT4 as the main glucose transporter in adipose tissue and skeletal muscle (8). These evidences somehow support the interaction of PPARγ and GLUT4 in glucose homeostasis in the target tissue. Laboratory studies have revealed that the expression of PPARγ is reduced in obese animal species (9) and the use of PPARγ agonists by increasing its expression in type 2 diabetic rats is associated with the improvement of glucose metabolism and insulin function (10).

During the last two decades, a multitude of research endeavors have explored the impacts of various therapeutic treatments with the aim of improving carbohydrate and lipid metabolism or inflammatory profile in healthy or sick obese populations, but among them, there are few studies aimed at the effect of non-pharmacological interventions such as exercise. It has been done on genetic or transcription factors or their polymorphisms in healthy or sick obese people. In this context, the study of Lee et al (2014) showed that 8 weeks of low-intensity strength training leads to an increase in PPARγ expression in adipocytes of obese Sprague Dawley rats, but glucose response and insulin resistance were not mentioned in this study (11). Rufino et al, (2016) also reported that exercise increases the expression of some genetic markers in macrophages by increasing the activity of the PPARγ transcription factor, which is associated with anti-inflammatory properties and improving insulin sensitivity to prevent insulin resistance and type 2 diabetes. (12). On the other hand, in Garley's study (2016), 4 weeks of aerobic running in obese mice fed a high-fat diet was associated with an improvement in fasting insulin, but did not affect the expression of GLUT4 in skeletal muscle (13). In another study, GLUT4 expression in adipose and muscle tissue of type 2 diabetic rats was not affected by regular aerobic exercises (14). In addition, In Benafar's study (2018), 6 weeks of resistance exercise led to an increase in GLUT4 expression in the biceps muscle of type 2 diabetic rats (15). In Bagheri et al.'s study (2020), 8 weeks of intense interval training led to an increase in hepatic PPARγ expression and hepatic triglyceride content in rats with fatty liver (16).

The review of research evidence on the one hand points to contradictory findings regarding the response of the expression of these transcription factors to exercise training and on the other hand to the lack of sufficient studies regarding their response to high intensity interval training (HIIT) in obese rats. Consequently, the current research was undertaken to ascertain the impact of HIIT over a period of 8 weeks, with a frequency of 5 times per week, utilizing treadmill running, on the expression of PPARγ and GLUT4 in the subcutaneous adipose tissue of rats consuming a high-fat diet (HFD). Additionally, this study evaluated alterations in glucose concentrations and insulin sensitivity.

Materials and Methods

Experimental Animals

The research sample for this controlled experiment comprised exclusively male Wistar rats housed at the Pasteur Institute of Tehran's animal facility. From this population, 14 rats (aged 10 weeks, weighing 220 ± 10 grams) were subjected to a high-fat diet (HFD) for 8 weeks, leading to obesity. Subsequently, these rats were allocated into two groups: a control group (n=7) and a high-intensity interval training (HIIT) group (n=7). The conditions for the rats included a regulated lighting environment with 12-hour cycles of light and darkness, and a stable climate maintained at 22 ± 3°C with relative humidity between 30% and 60%.The high-fat diet for the group continued until the end of the study.

Induction of Obesity

To induce obesity, a HFD 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% pure corn oil (100%) and made into pellets again (17).

Training Protocol

Following the obesity induction, the cohort of 14 obese rats was split into two groups: control and HIIT groups. The HIIT group underwent an 8-week regimen of HIIT, consisting of five weekly sessions that involved treadmill running, as detailed in Table 1. The control group rats were not included in this exercise regimen. Forty-eight hours subsequent to the final exercise session, all rats from both groups were subjected to dissection post an overnight fast.

Sample Collection and Biochemical Assay

48 hours subsequent to their final exercise session, having fasted for a period of 10 to 12 hours, the experimental rats from each group

were anesthetized via intraperitoneal injection with a solution comprising 10% ketamine at a concentration of 50 mg/kg and 2% xylazine at 10 mg/kg. Following this, samples of subcutaneous adipose tissue were collected from the rats, rinsed with saline solution, and then preserved in microtubes of 1.8 ml capacity filled with a 20% solution of RNAlater for subsequent genetic analysis. The extraction of RNA was carried out utilizing the RNeasy Mini Kit provided by QIAGEN. For the quantification of gene mRNA levels, RT-Real Time PCR was conducted using the Rotorgen 6000 system and the One Step SYBR Green Kit by Takara, in accordance with the manufacturer's protocol (17). RNA Polymerase II served as the control gene. The specific sequences of the primers utilized are detailed in Table 1.

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

Exercise session	**Exercise phase**		**Resting phase**	
(weeks)	**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. Primer sequence

Genes	**Primer sequence**
PPARγ	**For**: ACAACAGGCCACATGAAGAGC **Rev**: AAGCTTCAATCGGATGGTTCTTCG
GLUT4	**For**: CTTGGCTCCCTTCAGTTTGG **Rev**: CCTTTCTCTTCCCACCACCTG
RNA Polymerase II	**For**: ACTTTGATGACGTGGAGGAGGAC **Rev**: GTTGGCCTGCGGTCGTTC

Statistical Analysis

The Shapiro-Wilk test was employed to verify the data's normality. Descriptive statistical methods were utilized to characterize the data and graphical representations, while independent t-tests were applied to assess differences between groups concerning the variables under investigation. A significance threshold was set at an alpha level of less than 0.05. All statistical analyses were conducted using the SPSS for Windows, version 22 software.

Results

Alterations in body weight for both groups pre- and post-exercise program are detailed in Table 3. The independent t-test revealed no significant difference in baseline weight between the cohorts (P = 0.632). Conversely, while the paired t-test indicated a significant increase in weight from start to finish of the intervention, the independent t-test demonstrated that this increase did not result in a significant difference in final body weight when comparing the two groups (P = 0.126).

Statistical analysis revealed significant differences between the two groups concerning their glucose levels, insulin sensitivity, and the expression of PPARγ and GLUT4, as detailed in Table 4. In other words, HIIT resulted in significant decrease in fasting blood glucose (P = 0.001) and increase in insulin sensitivity (P = 0.001), PPARγ expression (P = 0.038, Fig 1) and GLUT4 expression (P = 0.019, Fig 2) in subcutaneous adipose tissue compared with control rats.

Table 3. Pre and post-training of body weight of 2 groups (Mean ± SD).

Group	**Pre-training**	**Post-training**	**sig***
Control	295 ± 8.5	370 ± 4.9	*0.001*
Exercise	297 ± 6.6	364 ± 7.5	*0.001*
sig¥	*0.632*	*0.126*	-----

** Significant changed based on paired t test*

***¥** Significant change based on independent t test*

Table 4. Clinical characteristic and genes expression after HIIT intervention of exercise and control groups (Mean ± SD).

Variable	Control group	HIIT group	*sig*
Fasting glucose (mg/dl)	120 ± 4	96 ± 5	*0.001*
Insulin sensitivity (HOMA-IS)	0.56 ± 0.01	0.66 ± 0.05	*0.001*
PPARγ expression	1	1.57 ± 0.65	*0.038*
GLUT4 expression	1	1.26 ± 0.25	*0.019*

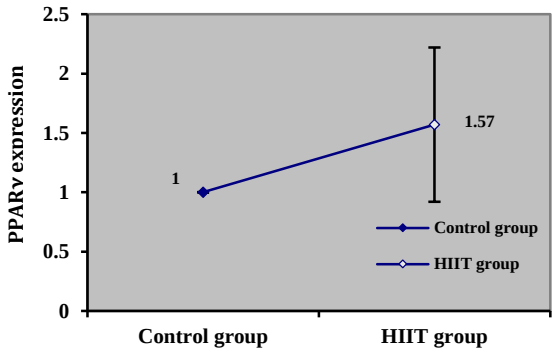

Figure 1. PPARγ expressions in subcutaneous adipose tissue in exercise rats compare to control group.

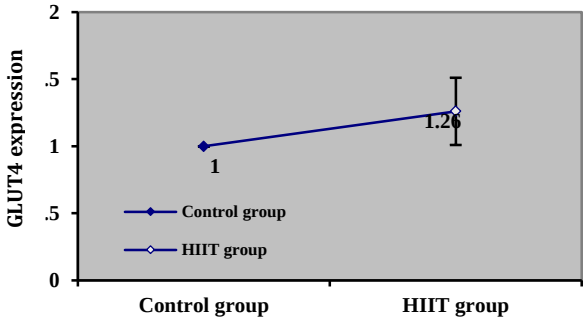

Figure 2. GLUT4 expressions in subcutaneous adipose tissue in exercise rats compare to control group.

Discussion

The research identified a notable elevation in PPARγ and GLUT4 expression in the subcutaneous adipose tissue as a key outcome. Specifically, subjecting obese rats, whose condition was prompted by a HFD, to HIIT five times per week over an eight-week period resulted in enhanced PPARγ and GLUT4 expression in their subcutaneous adipose tissue relative to a control group that did not engage in the exercise intervention. Additionally, the HIIT was linked with a marked reduction in fasting blood glucose levels and an improvement in insulin sensitivity when compared to the control group. This finding of reduced fasting glucose following diverse exercise protocols aligns with the results documented in prior research. In line with the present study, in Bai et al.'s study (2013), 2 months of aerobic exercise led to a significant reduction in fasting blood glucose in overweight male and female students (18). Also, in Di Raimondo's study (2013), 24 weeks of exercise training in the form of 1 hour of brisk walking on a treadmill for 5 sessions per week led to a significant reduction in glucose and glycosylated hemoglobin in patients with metabolic syndrome (19). However, contrary to the findings of this study, in another study, 6-week exercise training with an intensity of 60 to 80% of VO2max did not lead to a significant change in glucose (20). Also, in another study, 20 weeks of sports 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 (21). In the study of Maltais et al. (2016), 4 months of resistance training, although it was associated with a decrease in body fat

mass, did not lead to a change in insulin and glucose in overweight elderly men (22).

Despite the contradictions in the mentioned findings, which are often rooted in differences in the type, duration and intensity of training or differences in the type of population studied, most studies support the improvement of blood glucose or glycemic profiles following exercise, especially those that have continued for a long time. In the meantime, most studies have attributed this improvement to the reduction of insulin resistance following exercise. Thus, in the present study, in addition to improving fasting glucose, insulin sensitivity was also increased in response to HIIT. In confirmation the outcomes of this research, which identifies the enhancement of insulin sensitivity as a key outcome in response to HIIT, a parallel investigation by Ho (2015) explored the impact of a year-long weight loss initiative involving dietary limitations. This study focused on obese and overweight individuals, assessing insulin resistance, insulin sensitivity, and inflammatory indicators. The results indicated that the 12-month regimen led to a significant reduction in insulin resistance and an elevation in insulin sensitivity (23). Drawing from their results, these scholars have highlighted the advantageous therapeutic influence of exercise in diminishing risk factors associated with the development of insulin resistance within obese individuals.

Despite the mentioned evidence, some other studies have reported the non-alignment of their findings with our findings. For example, in Legat's study (2012), 6 sessions of HIIT in a two-week period was not associated with a remarkable change in insulin sensitivity in obese men (24). In Dongz's study (2013), 12 weeks of endurance and resistance training was not associated with significant changes in insulin function and cellular glucose transport in middle-aged obese men (25). Longitudinal studies have also indicated that changes in protein levels or expression of some genes in the target tissue strongly affect insulin action in adipose and muscle tissue. Some of them, such as GLUT4, also affect glucose transport directly or by affecting insulin signaling mechanisms in the target tissue (26). On the other hand, the findings of this study revealed that the expression of GLUT4 and PPARγ is affected by HIIT. In other words, 8 weeks of HIIT increased PPARy and GLUT4 expression in subcutaneous adipose tissue of obese rats. In this context, in the study of Li et al, (2014) the protein and expression of PPARy in subcutaneous adipose tissue of male Sprague Dawley rats were increased in response to 8 weeks of low, moderate and intense resistance training compared to the control group (11). Some other studies have also reported the improvement of blood glucose with an increase in PPARy expression in response to relatively intense aerobic exercise (11).

In the study of Pala et al, (2018) although acute exercise for 30 minutes led to a decrease PPARy expression in liver and muscle tissue of albino Nejard rats, continued exercise for 6 weeks significantly increased PPARy and GLUT4 and GLUT2 in liver and muscle tissue (27). Laboratory evidence has supported the effective role of GLUT4 protein levels in fat and muscle tissue in glucose regulation (28). In patients with insulin resistance, the metabolic process of glucose in adipose and muscle tissue is damaged, and the response of GLUT4 to insulin is impaired (29). In confirmation of our findings, Lennon et al (2010) have mentioned that relatively intense exercise leads to an increase of 34 and 22% of GLUT4 in the heart and adipose tissue of laboratory rats (30). Hashi et al (2011) also lead to a 36 and 20% increase in GLUT4 expression in skeletal muscles and adipose tissue of type 2 diabetic patients (31).

The mechanisms responsible for the effect of PPARy on insulin sensitivity and resistance are complex and adipose tissue, skeletal muscles and liver are its target points, but it seems that adipose tissue is the most important target tissue of PPARy-TZDs, which is manifested by increasing insulin sensitivity (7). In this context, it has been determined that in type 2 diabetic patients, PPARy activity through binding to thiazolidinediones (TZD) leads to a significant improvement in insulin sensitivity of the whole body, which is associated with a decrease in insulin and glucose levels (7). It is also possible that the change in the activity or expression of PPARy in response to exercise due to the effect on other transcription factors effective in insulin signaling pathways, such as GLUT4, leads to a decrease in insulin resistance or an improvement in glycemic profile(8). It should be noted that although measuring the expression of the mentioned genes is the strengths of the present study, this evaluation alone does not represent the response of the glycemic profile to exercise

because many hormonal and genetic components such as inflammatory and anti-inflammatory mediators and stress agents Oxidative agents are effective in this process and their lack of measurement is one of the limitations of the present study.

Conclusion

HIIT improves glucose in obese Wistar rats. This improvement may be attributed to increased GLUT4 and PPARγ expression in subcutaneous adipose tissue along with an increase in insulin sensitivity in response to this training method. However, understanding the mechanisms responsible for changes in insulin action in response to exercise requires more studies.

Declarations

Acknowledgments

The authors extend their gratitude to the Islamic Azad University and genetic laboratory of pastored institute Tehran.

Authors' Contributions

Each author contributed equally to the composition of this article.

Conflict of Interest

The authors have reported no potential conflicts of interest.

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