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The Effect of 8 Weeks of High-Intensity Interval Training on GLUT4 and GALR2 Gene Expression in Skeletal Muscle Tissue of Obese Female Rats with Type 2 Diabetes

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A B S T R A C T

The present study is an applied, basic, and experimental research that examined the effect of 8 weeks of high-intensity interval training on the gene expression of GLUT4 and GALR2 in the skeletal muscle tissue of obese female rats with type 2 diabetes. To conduct this study, 40 female Wistar rats, aged 8 weeks with an average weight of 200 grams, were obtained from the animal farm of Kerman University of Medical Sciences for use in laboratory experiments at the same institution. After the animals adapted to their new environment, they were divided into four groups, with 10 rats each. The groups were as follows: healthy control (without diabetes and without exercise), diabetic control (with diabetes and without exercise), healthy exercise (without diabetes and with exercise), and diabetic exercise (with diabetes and with exercise). The diabetic control and diabetic exercise groups were induced with type 2 diabetes mellitus (T2DM) and then underwent an 8-week exercise intervention. To induce diabetes in the samples, a single intraperitoneal injection of 35 mg/kg streptozotocin (STZ) was administered. High-intensity interval training was conducted for 8 weeks, three sessions per week. Data analysis was performed using two-way ANOVA, and Tukey's post hoc test was used for intergroup comparisons. The findings showed that 8 weeks of high-intensity interval training led to a significant increase in the expression of GALR2 and GLUT4 in the gastrocnemius muscle tissue. Overall, it can be stated that 8 weeks of high-intensity interval training resulted in significant improvements in metabolism and hormonal function in obese female rats with type 2 diabetes. These exercises increased the expression of genes related to lipid and glucose metabolism, such as GALR2 and GLUT4, in skeletal muscle tissue, indicating enhanced energy consumption and improved metabolic performance in these animals.

Keywords: *High-Intensity Interval Training, Type 2 Diabetes, GALR2, GLUT4*

1. Introduction

Over the past century, obesity has emerged as a major global health concern due to recent environmental and social changes (1). The worldwide prevalence of overweight and obesity has doubled since 1980, with nearly one-third of the global population now classified as overweight or obese. Obesity rates have increased across all ages and both sexes, regardless of geographic location, ethnicity, or socioeconomic status, although the prevalence is generally

higher among older adults and women (2). The primary factors contributing to the development of obesity include the consumption of high-calorie or high-fat foods, insufficient physical activity, and the transition to a sedentary lifestyle (3). The rising prevalence of obesity is the strongest risk factor for developing diabetes. The dual epidemic of obesity and type 2 diabetes mellitus (T2DM) is a major public health issue worldwide, with projections estimating an increase in the number of individuals with diabetes to 642 million by 2040 (4). Type 2 diabetes is rapidly emerging as one of the greatest global health challenges of the 21st century, and the rising epidemic is expected to result in a sharp increase in diabetes-related complications, such as ischemic heart disease, stroke, neuropathy, retinopathy, and nephropathy (5).

Diet plays a crucial role in the induction of diabetes in humans. An increased intake of high-fat diets and Western dietary patterns is associated with insulin resistance, which is linked to a higher risk of diabetes and related metabolic diseases. Over the years, it has become increasingly evident that the development of T2DM is driven by poor dietary habits and unhealthy lifestyles, predominantly high in fat or sugar (6). GLUT4 is one of 13 glucose transporter proteins (GLUT1–GLUT12 and HMIT) encoded in the human genome that catalyze hexose transport across the cell membrane via an ATP-independent facilitative mechanism. These glucose transporters differ in their kinetics and substrate specificities, with GLUT5 and potentially GLUT11 being fructose transporters (7). GLUT4 is highly expressed in adipose tissue and skeletal muscles, but these tissues also express a selective group of other transporters (8). In skeletal muscle, GLUT1, GLUT5, and GLUT12 may significantly contribute to glucose uptake alongside GLUT4, whereas in adipose tissue, GLUT8, GLUT12, and HMIT are also expressed (9). However, GLUT4 uniquely exists in an intracellular state under unstimulated conditions and acutely translocates to the plasma membrane in response to insulin and other stimuli (10). The primary role of GLUT4 in whole-body metabolism is strongly supported by various genetically modified mouse models, where transporter expression is either increased or ablated in muscle or adipose tissue, or both. Whole-body GLUT4 knockout mice may provide less informative data due to compensatory mechanisms that could enhance the survival of these animals (11).

On the other hand, T2DM and depression may increase galanin secretion. Galanin concentrations are higher in individuals with depression or T2DM compared to healthy individuals. In turn, galanin may improve both conditions through central GalR2 activation (11). It is suggested that galanin may directly and/or indirectly affect the relationship between depression and T2DM, although the precise mechanisms are not yet fully understood. Compelling evidence supports the association between galanin levels and both conditions (12). For example, physical exercise may improve symptoms and outcomes of depression and T2DM (13). Physical activity is a significant physiological stimulus that accelerates galanin release, increasing plasma and brain galanin levels, whereas obesity and physical inactivity are associated with disease development and reduced galanin levels (14). Hence, a biological explanation emerges: exercise may enhance galanin secretion, beneficially influencing depression and insulin resistance through GalR2 activation; thus, the beneficial effect of physical activity on both conditions is mediated, at least in part, by the galanin system (15).

In a study examining the effect of swimming exercise on high-fat diet-fed mice, exercise increased insulin sensitivity through PGC-1α and GLUT4, which are key indicators of glucose uptake activity and energy consumption in skeletal muscle (16). Aerobic exercise is considered an essential component in treating T2DM patients to improve cardiovascular health (17). The American Diabetes Association recommends 150 minutes of moderate-intensity aerobic activity (50–70% HRmax) at least three days per week, with no more than two consecutive days between exercise sessions for individuals with diabetes (18). Long-term exercise training is associated with increased muscle mass and capacity, while acute exercise facilitates the use of glucose and lipids as fuel for muscle contractions (19). Given the limited information on the effect of 8 weeks of high-intensity interval training on the gene expression of GLUT4 and GALR2 in the skeletal muscle tissue of obese female rats with T2DM, the aim of this study was to investigate the changes in GLUT4 and GALR2 gene expression following 8 weeks of high-intensity interval

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training in skeletal muscle tissue of obese female rats with T2DM.

2. Methods and Materials

The present study is a funamental research experiment in which subjects are examined in an 8-week design, making it an experimental study. For this study, 40 female Wistar rats, aged 8 weeks with an average weight of 200 grams, were obtained from the animal farm of Kerman University of Medical Sciences for use in laboratory experiments at the same institution. The samples were kept under standard conditions, with a 12-hour light-dark cycle, a temperature of 23 ± 1°C, and adequate food and water. A 10-day acclimatization period without intervention was conducted to allow the animals to adapt to the laboratory environment. After adaptation to the new environment, the 40 rats were divided into four groups of 10 each as follows: healthy control (non-diabetic, no exercise), diabetic control (diabetic, no exercise), healthy exercise (non-diabetic, exercise), and diabetic exercise (diabetic, exercise). The diabetic control and diabetic exercise groups were induced with type 2 diabetes mellitus (T2DM) and subsequently underwent an 8-week exercise intervention. A high-fat diet (HFD) was purchased from Royan Research Institute, Esfahan, containing the following components: 60% fat (245 g of lard and 25 g of soybean oil), 20% carbohydrates (125 g of 10Lodex and 72.8 g of sucrose), 20% protein (200 g of casein and 3 g of cysteine), 50 g of fiber (Solca Floc), 50 g of minerals, 3 g of vitamins, and 0.5 g of coloring agents. The composition of the standard diet was similar to the high-fat diet but with different ingredient proportions. Obesity criteria for each rat in this study were considered to be a weight between 300–400 grams.

Type 2 diabetes (T2DM) induction in this study involved feeding the animals with a 60% caloric HFD for 2 months, followed by a 12-hour fasting period, after which a single intraperitoneal injection of 35 mg/kg streptozotocin (STZ) was administered. Blood glucose levels were measured three days after injection using a glucometer. Rats with fasting blood glucose (FBG) levels above 300 mg/dL were considered diabetic and included in the study (6).

To implement the exercise protocol, the rats in the exercise and diabetic exercise groups initially underwent a familiarization phase, walking on a treadmill twice a day for 5 days, 10 minutes each day at 0° incline and 8 m/min. After the familiarization period, a progressive incremental test was conducted to determine the maximum speed (Vmax) of each rat. In this test, the rats first ran for 2 minutes at 6 m/min, with the treadmill speed increased by 2 m/min every 2 minutes until the rat could no longer maintain the speed. The final speed sustained by each rat was recorded as its maximum speed. The training protocol was then carried out for 8 weeks, with 3 sessions per week. The protocol details are provided in Table 1. At the beginning and end of each session, the rats ran on the treadmill for 5 minutes at 40–50% of their maximum speed for warm-up and cool-down (2). The maximum speed of each rat was re-measured at the beginning of each week to design exercise intensity based on their maximum speed, ensuring adherence to the principle of overload.

Table 1

High-Intensity Interval Training Protocol

Week	Incline	Number of Intervals	Intense Interval Duration (minutes)	Intense Interval Speed	Rest Interval Duration (minutes)	Rest Interval Speed	Total Training Time (minutes)
1	0°	4	2	80% max speed	1	50% max speed	12
2	0°	5	2	80% max speed	1	55% max speed	15
3	0°	6	2	85% max speed	1	55% max speed	18
4	0°	7	2	85% max speed	1	60% max speed	21
5	0°	8	2	90% max speed	1	60% max speed	24
6	0°	9	2	90% max speed	1	65% max speed	27
7	0°	10	2	95% max speed	1	65% max speed	30

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8	0°	11	2	95% max speed	1	65% max speed	33	

For tissue sampling and genetic measurements, the Western blot method was used. To adhere to ethical standards, the rats were sacrificed 48 hours after the last intervention following a minimum of 8 hours of fasting. Anesthesia was induced with chloroform solution, and a 3 cc blood sample was drawn from the left ventricle of the heart to sacrifice the rats. Subsequently, the desired longitudinal sample from the gastrocnemius muscle tissue was rapidly excised with a scalpel, washed with phosphate-buffered saline (PBS), and placed in a microtube. The sample was then frozen in liquid nitrogen and stored at -80°C until analysis.

To analyze the study variables and determine the significance of differences among the groups in each test, two-way ANOVA was used. Additionally, Tukey's test was applied for intergroup comparisons. Statistical analyses were performed at a significance level of $P<0.05$. Data analysis was conducted using SPSS version 22, and GraphPad version 6 was used for charting.

3. Findings and Results

The values (mean ± standard deviation) of the studied variables after 8 weeks of the research design in the four groups—healthy control, diabetic control, healthy exercise, and diabetic exercise—are reported in Table 2.

Table 2

Values (mean ± standard deviation) of the studied indices in rats after 8 weeks of the research design

Variable	Healthy Control (n=10)	Healthy Exercise (n=10)	Diabetic Control (n=10)	Diabetic Exercise (n=10)
GALR2	0.163 ± 0.991	0.379 ± 1.234	0.263 ± 0.461	0.443 ± 0.869
GLUT4	0.199 ± 0.961	0.123 ± 1.066	0.027 ± 0.641	0.297 ± 1.037

To examine the interaction between high-intensity interval training and T2DM after 8 weeks concerning GALR2 levels, two-way ANOVA was used. According to Table 3, two-way ANOVA revealed that the effect of T2DM, regardless of exercise or non-exercise group status, on GALR2 levels was significant, as the diabetic state reduced GALR2 levels ($F_{1,36} = 18.325$, $P = 0.000$). However, irrespective of the T2DM or healthy status, 8 weeks of high-intensity interval training significantly increased GALR2 levels ($F_{1,36} = 9.695$, $P = 0.000$). There was no significant interaction between the effects of T2DM and high-intensity interval training on GALR2 levels, as the interaction group did not show significant changes in GALR2 levels ($F_{1,36} = 0.623$, $P = 0.435$).

Table 3

Two-way ANOVA for GALR2 Levels

Measured Index	Comparison Effect	Sum of Squares	F Value	P Value
GALR2	T2DM	2.003	18.325	0.000 *
	EXERCISE	1.060	9.695	0.004 *
	T2DM × EXERCISE Interaction	0.068	0.623	0.435

*Significant at $P<0.05$.

For pairwise comparisons among the studied groups concerning GALR2 levels, Tukey's post hoc test was used. As shown in Figure 1, Tukey's post hoc test indicated that GALR2 levels in the exercise + diabetes interaction group significantly increased compared to the diabetic control group ($P = 0.000$). Additionally, GALR2 levels in the diabetic group significantly decreased compared to the healthy control ($P = 0.005$), exercise ($P = 0.000$), and interaction groups ($P = 0.043$), while no significant differences were observed in the other groups.

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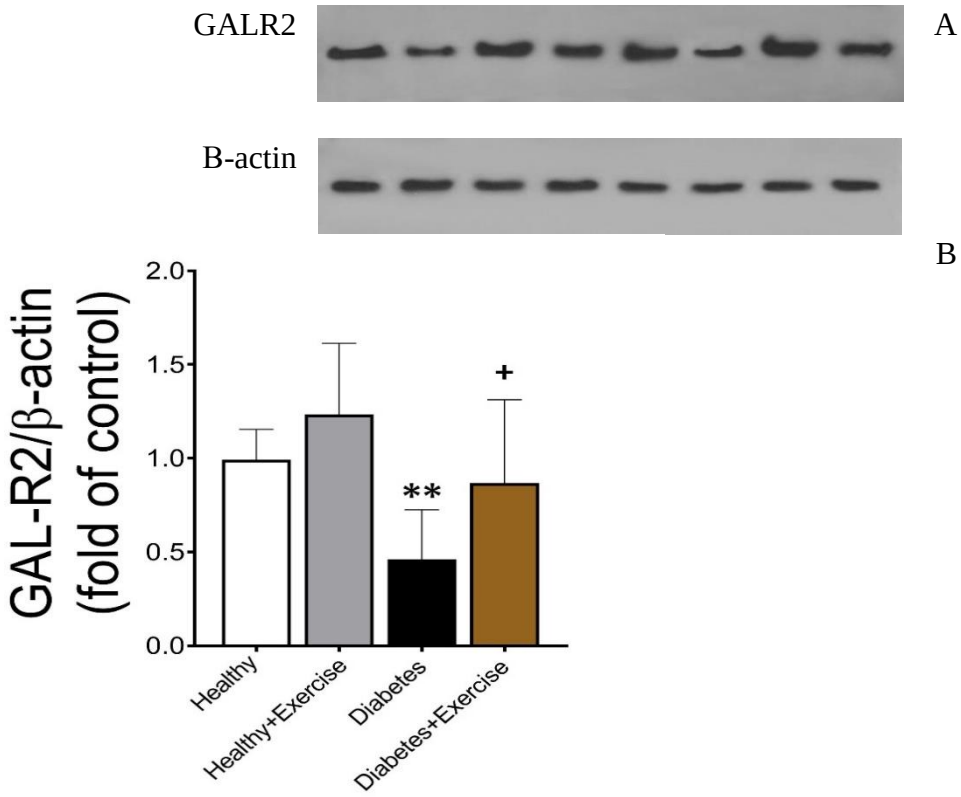
Figure 1

GALR2 Protein Expression in Skeletal Muscle



A: Western blot images of GALR2 protein and beta-actin as the internal control in the skeletal muscle of diabetic rats.

B: Quantified band values of GALR2 protein relative to beta-actin protein (mean and standard deviation).

Note: * indicates comparison with the healthy group; + indicates comparison with the diabetic group; one symbol = P<0.05, two symbols = P<0.01, three symbols = P<0.001.

To examine the interaction between high-intensity interval training and T2DM after 8 weeks concerning GLUT4 levels, two-way ANOVA was used. According to Table 4, two-way ANOVA revealed that the effect of T2DM, regardless of exercise or non-exercise group status, on GLUT4 levels was significant, as the diabetic state reduced GLUT4 levels (F1,36 = 5.555, P = 0.024). However, irrespective of the T2DM or healthy status, 8 weeks of high-intensity interval training significantly increased GLUT4 levels (F1,36 = 11.441, P = 0.002). There was a significant interaction between the effects of T2DM and high-intensity interval training on GLUT4 levels, as the interaction group showed a significant increase in GLUT4 levels (F1,36 = 3.862, P = 0.05).

Table 4

Two-way ANOVA for GLUT4 Levels

Measured Index	Comparison Effect	Sum of Squares	F Value	P Value
GLUT4	T2DM	0.305	5.555	0.024 *
	EXERCISE	0.628	11.441	0.002 *
	T2DM × EXERCISE Interaction	0.212	3.862	0.05 *

*Significant at P<0.05.

For pairwise comparisons among the studied groups concerning GLUT4 levels, Tukey's post hoc test was used. As shown in Figure 2, Tukey's post hoc test indicated that GLUT4 levels in the exercise + diabetes interaction group

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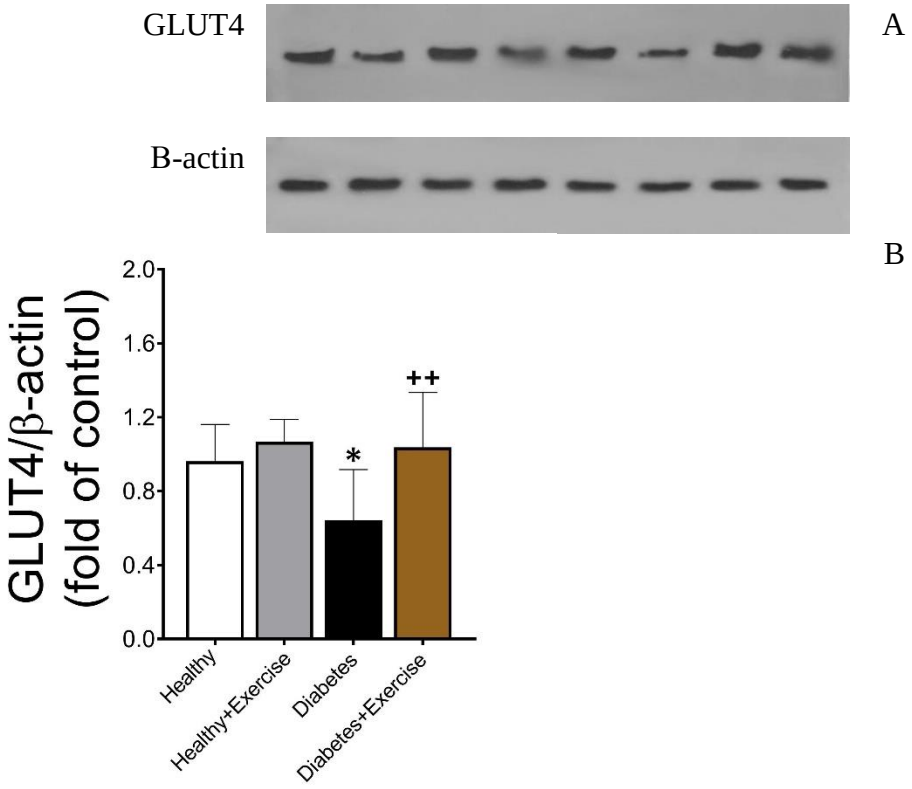
significantly decreased compared to the diabetic control group (P = 0.003). Additionally, GLUT4 levels in the diabetic control group significantly decreased compared to the healthy control (P = 0.021), exercise (P = 0.001), and interaction groups (P = 0.003). GLUT4 levels in the healthy control group significantly increased compared to the diabetic control group (P = 0.001), with no significant differences observed in the other groups.

Figure 2

GLUT4 Protein Expression in Skeletal Muscle



A: Western blot images of GLUT4 protein and beta-actin as the internal control in the skeletal muscle of diabetic rats.

B: Quantified band values of GLUT4 protein relative to beta-actin protein (mean and standard deviation).

Note: * indicates comparison with the healthy group; + indicates comparison with the diabetic group; one symbol = P<0.05, two symbols = P<0.01, three symbols = P<0.001.

4. Discussion and Conclusion

The results showed that the effect of T2DM, regardless of group status concerning exercise, on GALR2 levels was significant, as the diabetic state decreased GALR2 levels. However, irrespective of the T2DM or healthy status, 8 weeks of high-intensity interval training significantly increased GALR2 levels. There was no significant interaction between the effects of T2DM and high-intensity interval training on GALR2 levels, as the interaction group did not show significant changes in GALR2 levels. Pairwise comparisons revealed that GALR2 levels in the exercise + diabetes interaction group significantly increased compared to the diabetic control group. Additionally, GALR2 levels in the diabetic group significantly decreased compared to the healthy control, exercise, and interaction groups, with no significant differences observed in the other groups. The results of this study are consistent with those of Turkel et al. (2024) and Jia et al. (2024). High-intensity interval training increases insulin sensitivity, improving glucose uptake by muscles and enhancing glucose metabolism. These changes in glucose metabolism may influence the expression of genes such as GALR2 in skeletal muscle (20, 21). Furthermore, high-intensity interval training improves lipid oxidation and reduces body fat stores, which may increase

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GALR2 activity, as this gene plays an essential role in regulating energy and lipid metabolism (22).

High-intensity interval training significantly enhances insulin sensitivity. In individuals with T2DM, insulin sensitivity is reduced, making it difficult for muscle cells to absorb glucose from the bloodstream. High-intensity interval training enhances glucose uptake by muscle cells by increasing the activity of metabolic enzymes and improving the function of glucose transporters, such as GLUT4 (23). This process ultimately reduces blood glucose levels and improves glucose utilization in muscle. Increased glucose uptake activates energy metabolism in muscle, stimulating glucose and fatty acid metabolism pathways. One result of these changes is the increased expression of genes involved in regulating these pathways, such as GALR2, which may act as a regulator of metabolic responses to high-intensity interval training, indicating improved energy resource utilization in muscle and metabolic balance enhancement (24).

High-intensity interval training creates an environment that promotes changes in gene expression related to energy metabolism by increasing glucose flow into muscle cells and activating metabolic pathways. GALR2 is one of these genes, playing a crucial role in muscle metabolism and modulating muscle function under metabolically challenging conditions, such as T2DM. High-intensity interval training also directly improves lipid oxidation and metabolism (25). In individuals with T2DM and obesity, fat metabolism is often impaired, leading the body to store fat rather than use it for energy. High-intensity interval training stimulates enzymes and metabolic pathways related to lipid oxidation, promoting greater utilization of fatty acids as an energy source. Active muscles during intense training require more energy, prompting the body, particularly skeletal muscles, to consume fat stores (22).

Increased lipid oxidation, facilitated by activating metabolic pathways like PGC-1α, which regulates energy production and mitochondrial processes in muscle cells, allows muscles to use fats more effectively for energy. These metabolic changes may regulate the expression of various genes, including GALR2. GALR2, as a galanin receptor, plays a key role in energy and lipid metabolism regulation. The increased expression of this gene following high-intensity interval training indicates muscle adaptation to new energy demands, optimizing fat metabolism (18).

High-intensity interval training also reduces chronic inflammation associated with obesity and T2DM. Reducing inflammation can modulate inflammatory and metabolic pathways, improving muscle function. Consequently, the increased expression of GALR2 in muscle may result from the regulation of these pathways. High-intensity interval training has beneficial effects on chronic inflammation reduction in T2DM and obesity. Chronic inflammation in these individuals, particularly in adipose and muscle tissues, exacerbates insulin resistance and metabolic disturbances (13). High-intensity interval training improves the balance between anti-inflammatory systems and inflammatory factors, regulating metabolic and inflammatory homeostasis. Chronic inflammation in T2DM often involves elevated levels of inflammatory cytokines such as TNF-α, IL-6, and CRP, which directly disrupt muscle metabolic pathways, impairing insulin action and glucose and fat utilization. High-intensity interval training reduces these inflammatory markers, enhancing glucose and lipid utilization (12).

Additionally, high-intensity interval training stimulates the production of anti-inflammatory adipokines like adiponectin, which improves insulin sensitivity and regulates lipid metabolism, contributing to a better inflammatory and metabolic status. GALR2 may play a role in these metabolic and anti-inflammatory adjustments. As a galanin receptor, GALR2 can influence inflammatory and metabolic pathways. Galanin, a neuropeptide with anti-inflammatory properties, is regulated by high-intensity training and helps manage chronic inflammation. Increased GALR2 expression indicates the positive impact of high-intensity interval training on regulating these pathways (11).

High-intensity interval training creates a better metabolic environment by enhancing fat utilization instead of storage, increasing the expression of genes like GALR2 involved in these processes. Ultimately, improved lipid oxidation reduces body fat, enhances the metabolic profile, and improves muscle metabolic conditions, allowing muscles to use fats and other energy sources efficiently. Consequently, increased expression of genes like GALR2, related to energy and inflammation regulation, is observed (16). High-intensity interval training also affects neuropeptide and hormonal systems, with galanin being one such

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neuropeptide (5). Galanin regulates various processes, including energy metabolism, food intake, and inflammation. It exerts its effects through different receptors, including GALR2, which influences muscle energy consumption and metabolism. Training intensity can stimulate galanin release, and galanin, via GALR2, helps muscle adapt to energy demands and improve recovery (9). Jurysta et al. (2013) demonstrated in their study on STZ-induced diabetic rats that the expression of GLUT4 and its other isoforms significantly decreases in tissues such as the heart, kidney, parathyroid, and salivary glands upon diabetic induction. Aerobic exercise in their study led to a significant increase in GLUT4 levels in the cardiac muscle of diabetic rats (26). Chou et al. (2004) were the first to show that aerobic exercise increases GLUT4 in the heart (27). Neufer et al. (1992) investigated the effects of one-day, one-week, and six-week treadmill training in Wistar rats (1.9 km/h, two hours per day, six days per week) and compared muscle biopsy samples to those from untrained rats. They found no significant difference in GLUT4 levels between the one-day and one-week training groups, but the six-week training significantly increased GLUT4 levels by 1.7- and 1.4-fold in muscles (28). This increase was also observed in the present study, although our training duration was eight weeks, resulting in a greater increase in GLUT4 levels compared to the diabetic control group. Some studies have shown that the type of exercise (resistance or endurance), duration, and the type of muscle engaged (aerobic or anaerobic) influence GLUT4 level increases (26). Additionally, this part of the present findings aligns with the study by Lehnen et al. (2011), which demonstrated that aerobic exercise (treadmill, one hour per day, five days per week, for ten weeks) significantly increased GLUT4 levels in cardiac muscles, calf muscles, and adipose tissue in different groups of rats (29). Church et al. (2010) also showed in a study on patients with type 2 diabetes that exercise helps control blood glucose, consistent with the findings of the present study (30). Exercise enhances GLUT4 translocation to the plasma membrane through two mechanisms. First, since muscle contraction requires energy from ATP conversion to ADP and AMP, intracellular AMP levels increase, activating AMPK, a cellular energy sensor. AMPK influences GLUT4 translocation via two downstream proteins, AS160 and aPKC. Unlike insulin, which accelerates GLUT4 exocytosis in response to increased plasma glucose, AMPK reduces GLUT4 endocytosis when energy levels are low, promoting glucose uptake for oxidation. Increased insulin sensitivity or higher GLUT4 levels on the cell membrane lead to greater glucose uptake from the blood (17). Second, hypoxia and muscle contraction during exercise release calcium from the endoplasmic reticulum into the cytoplasm, potentially activating aPKC via a secondary messenger (calcium-calmodulin), increasing glucose uptake into the cell independently of AMPK, though this mechanism is not fully understood (Gabryelska et al., 2020). Exercise plays a crucial role in managing both insulin-dependent and non-insulin-dependent diabetes. As discussed above, exercise, like insulin but via different signaling pathways, increases GLUT4 levels on the cell membrane, enhancing glucose uptake into muscle cells (8).

In summary, high-intensity interval training leads to significant metabolic improvements in obese female rats with T2DM. The training increased the expression of genes related to lipid and glucose metabolism, such as GALR2 and GLUT4, in skeletal muscle, indicating enhanced energy utilization and metabolic performance improvement.

Authors' Contributions

H. F., F. F. M., and M. P. collaboratively contributed to the design and execution of the study. H. F. led the experimental procedures, including the administration of high-intensity interval training and sample collection. F. F. M. was responsible for the gene expression analysis and interpretation of molecular data. M. P. managed the overall data analysis, including statistical evaluations, and provided critical insights into the study's metabolic implications. All authors participated in drafting and revising the manuscript, approved the final version for publication, and are accountable for the accuracy and integrity of the research.

Declaration

In order to correct and improve the academic writing of our paper, we have used the language model ChatGPT.

Transparency Statement

Data are available for research purposes upon reasonable request to the corresponding author.

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Declaration of Interest

The authors report no conflict of interest.

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Ethical Considerations

The study adhered to the ethical guidelines for research with human subjects as outlined in the Declaration of Helsinki.

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