

Effect of Different Training Methods on *SIRT1* Gene Expression in Subcutaneous Adipose Tissue of Male Wistar Rats

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Abstract

Objective: *SIRT1* is a key regulator of adipose tissue's energy balance, inflammation, and mitochondrial function. This study was designed to investigate the effect of different training modalities, Moderate-Intensity Aerobic Training (MIAT), High-Intensity Aerobic Training (HIAT), and High-Intensity Interval Training (HIIT), on *SIRT1* gene expression in subcutaneous adipose tissue of male Wistar rats.

Materials and Methods: Thirty-two 8-week-old male Wistar rats (237 ± 33 g) were randomly assigned to four groups (n= 8): Control, MIAT, HIAT, and HIIT. Animals were housed under controlled conditions and had free access to food and water. Training protocols were performed five times per week for eight weeks. After 12 hours of fasting and 24 hours post-intervention, subcutaneous abdominal adipose tissue was collected. *SIRT1* gene expression was analyzed using RT-PCR. Data were statistically evaluated using one-way ANOVA and LSD post hoc test ($P < 0.05$) in SPSS-22.

Results: The results showed that all three training models - MIAT ($P = 0.023$), HIAT ($P = 0.001$), and HIIT ($P = 0.003$) - significantly increased *SIRT1* gene expression compared to the control group.

Conclusion: Although all training modalities significantly increased *SIRT1* gene expression compared to the control group, the HIAT group showed the highest mean expression level. However, no statistically significant difference was observed between the training groups.

Keywords: Aerobic exercise training, Adipose tissue, Gene expression, *SIRT1*

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Introduction

Physical inactivity and poor dietary habits are major contributors of the global rise in metabolic disorders such as obesity, type 2 diabetes (T2DM), cardiovascular disease, and MSFLD (1,2). Insulin resistance, a hallmark of these conditions, is characterized by impaired cellular response to insulin and is prevalent in nearly all patients with T2DM (3,4). Although the molecular mechanisms underlying insulin resistance are not fully understood, energy imbalance and mitochondrial dysfunction are central to its development (4). Skeletal muscle, with its high metabolic flexibility, plays a key role in maintaining energy homeostasis, partly through AMPK activation during exercise-induced ATP depletion (5,6).

Among metabolic regulators, *SIRT1*-a NAD⁺-dependent deacetylase-has emerged as a key modulator of lipid metabolism, inflammation, oxidative stress, and insulin signaling (7-13). *SIRT1* interacts with transcription factors such as *PPAR-γ*, *p53*, and *FOXO*, and influences insulin sensitivity through regulation of *IRS2*, *Akt*, and *PTP1B* (12,13). These properties make *SIRT1* a promising therapeutic target for metabolic diseases.

Exercise training, particularly high-intensity interval training (HIIT), has gained attention for its ability to activate *SIRT1*-related pathways and improve mitochondrial function (14-19). Studies have shown increased *SIRT1* expression in skeletal muscle, heart, liver, and kidney following regular exercise (20-22). However, findings remain inconsistent across tissues and protocols, highlighting the need for further investigation (23,24).

Since *SIRT1* activation is closely linked to AMPK signalling and adipose tissue remodelling, and given that AMPK is activated by energy depletion during intense exercise (23-25), understanding how different exercise modalities affect *SIRT1* expression in adipose tissue is essential. Subcutaneous adipose tissue (scWAT) is a metabolically active organ

involved in hormone and cytokine production and plays a critical role in systemic energy regulation (7).

Given the potential of *SIRT1* to modulate adipose tissue function and insulin sensitivity, this study aimed to investigate the effects of different aerobic training protocols-moderate-intensity aerobic training (MIAT), high-intensity aerobic training (HIAT), and high-intensity interval training (HIIT)-on *SIRT1* gene expression in scWAT of male Wistar rats. Clarifying these molecular adaptations may help guide more effective strategies for preventing and managing obesity-related metabolic dysfunction.

Material and methods

Experimental animals

This experimental laboratory study was conducted using a post-test control group design. Thirty-two male Wistar rats (8 weeks old, 237 ± 33 g) were obtained from the Razi Institute (Tehran, Iran). The animals were housed in standard polycarbonate cages under controlled conditions: temperature $22 \pm 1.4^{\circ}\text{C}$, humidity $55 \pm 4\%$, and a 12:12 h light-dark cycle. All rats had free access to water and standard chow (Behparvar Animal Feed Co.). After one week of environmental adaptation and treadmill familiarization, the rats were randomly assigned into four groups ($n=8$): Control, MIAT, HIAT, and HIIT (26).

Aerobic capacity was assessed using the protocol described by Høydal et al. and initial training intensities were adjusted accordingly. Training was performed five days per week for eight weeks, in the morning and in a fixed sequence. After the final training session, and following 12 hours of fasting and 24 hours of rest, the animals were anesthetized using intraperitoneal injection of ketamine and xylazine. Abdominal subcutaneous adipose tissue was harvested immediately and stored in liquid nitrogen for molecular analysis. Body weight was measured at baseline and at the end

of the intervention. All procedures were conducted in accordance with institutional guidelines for the care and use of laboratory animals.

RNA Extraction and cDNA Synthesis

Total RNA was extracted from 70 mg of subcutaneous adipose tissue using Chiasol reagent. The tissue was homogenized and lysed, followed by chloroform phase separation and centrifugation at 12,000 RPM for 15 minutes at 4°C. The aqueous phase containing RNA was transferred to a new microtube, and RNA was precipitated using isopropanol and 1 µL glycogen (10 mg/mL). After incubation and centrifugation, the RNA pellet was washed twice with 75% ethanol to reduce phenolic contamination, air-dried, and dissolved in 20-30 µL DEPC-treated water.

To remove genomic DNA, DNase I treatment was performed by adding 1 µL DNase buffer and 0.5 µL DNase enzyme to 1 µg of RNA, followed by incubation at 37°C for 30 minutes. The reaction was terminated with 1 µL EDTA and heated at 65°C for 10 minutes. RNA samples were stored at -70°C until use.

For cDNA synthesis, the Easy cDNA Synthesis Kit (Pars Toos, Iran) was used. All reagents were thawed, vortexed, and briefly centrifuged. The RT mix was prepared using 5

µL RT buffer with enzyme, 1 µL specific primer (Table 1) and 3 µL DEPC water. The mix and RNA sample were combined in 0.2 mL microtubes and incubated in a dry block heater (Kiagen, Iran) according to the thermal program outlined in Table 2. Synthesized cDNA was stored at -20°C for subsequent gene expression analysis.

Aerobic power assessment protocol

Due to the lack of access to direct instruments, the animals' maximal oxygen consumption was assessed indirectly by an incremental treadmill test according to the protocol of Høydal et al. (2007) (27). First, a 10-minute warm-up was performed at an intensity of 40 to 50% of VO₂max. Then, the rats started running at a speed of 15 m/min for two minutes, and the speed was increased by 2 m/min every two minutes until exhaustion.

Training protocol

Rats were subjected to a 5-minute warm-up (5 m/min) for 8 weeks. They trained five times per week (28). The MIAT training protocol consisted of running at 65% of VO₂max for 47 minutes. The training consisted of a 5-minute warm-up, a 5-minute cool-down, and 37 minutes of main exercise at 65% of VO₂max (Figure 1).

Table 1. *SIRT1* primer sequences with the control gene *GAPDH*

Genes	Primer sequence
<i>SIRT1</i>	For: 5'- ATGCTGAGGAAGAAGATGTGGA -3'
	Rev: 5'- ATGAACTGCGTGGATGGGA -3'
<i>GAPDH</i>	For: 5'- GACATGCCCGCCTGGAGAAAC -3'
	Rev: 5'- AGCCCAGGATGCCCTTTAGT -3'

Table 2. Real-Time PCR Protocol

Step	Temperature (°C)	Time (min)	Number of cycles	Step
Hold	95	15	1	---
	95	15	40	1
Cycling	60	30	40	2
	60	30	40	3
Melt	60-95	---	1	---



Figure 1. MIAT training protocol

The HIAT training protocol consisted of running at 20 m/min for 40 min on an increasing incline treadmill. The training consisted of a 5-min warm-up, a 5-min cool-down, and a 30-min main body workout at 65% of maximal oxygen consumption. The treadmill incline was zero in the first week and increased by 2% every two weeks until it reached 8% in the eighth week (28) (Figure 2).

The HIIT training protocol consisted of four high-intensity intervals with four minutes of running at an intensity of 90–100% VO₂max followed by three minutes of active rest at 50–60% VO₂max (29). The workout consisted of a 5-minute warm-up, a 5-minute cool-down, and 28 minutes of the main body of the workout. It lasted a total of 38 minutes (Figure 3).

To ensure that the training was isolated in all four groups, the exercise training was performed according to the method of Rognmo et al. (2004). Based on this method, the net training time in each group was calculated and equalized based on the time, intensity, and repetition of the work steps. Therefore, with this method, 28 minutes of interval training at average intensities of 95 and 55% VO₂max was calculated to be equivalent to 38 minutes of continuous training at an intensity of 65% VO₂max. Similarly, the intensity of constant high-intensity training was also equalized (Figure 4).

All values are reported as mean $\pm$ standard deviation (SD). The Shapiro-Wilk test was used to determine the normality of the data distribution. Homogeneity of variances was assessed using Levene's test prior to post hoc analysis. Since variances were homogeneous and group sizes equal, the LSD test was applied to maximize statistical power at the significance level ($P < 0.05$). SPSS-22 software was used to analyze the data.

Ethical considerations

This study was approved by the Research Ethics Committee of Payam Noor University with the ethics code IR.PNU.REC.1400.052.

Results

Descriptive characteristics of the research samples are presented as mean ($\pm$ SD) in the research groups (Table 3). The results of a one-way analysis of variance test showed that there was a significant difference in the expression level of the *SIRT1* gene in subcutaneous adipose tissue of male Wistar rats among the study groups ($P = 0.001$, $F = 10.232$). The effect size (η^2) for the ANOVA was 0.523, indicating a large effect. Based on the results of LSD's post-hoc test, a significant difference was observed between all experimental groups compared to the control group, MIAT ($P = 0.023$), HIAT ($P = 0.001$), and HIIT ($P = 0.003$).

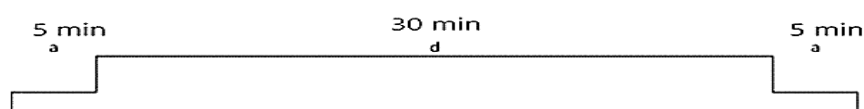


Figure 2. HIAT training protocol

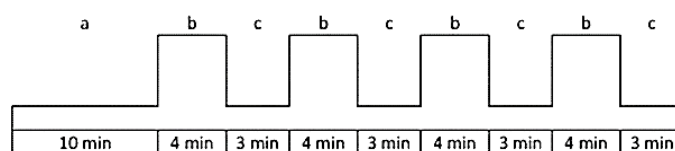


Figure 3. HIIT training protocol

(Activity intensity in heavy intervals * Total activity time in heavy intervals) + (Activity intensity in light intervals * Total activity time in light intervals)

Duration of training in the continues group =

Activity intensity for continues activity

Figure 4. Equivalence formula

No significant difference was observed between the experimental groups ($P > 0.05$).

Discussion

The present study demonstrated that all three exercise protocols-MIAT, HIAT, and HIIT-significantly increased *SIRT1* gene expression in subcutaneous adipose tissue compared to the control group. *SIRT1* is a nutrient-sensitive histone deacetylase that plays a central role in regulating adipose tissue inflammation, mitochondrial function, and systemic metabolic health (30). These findings support the hypothesis that aerobic exercise, regardless of intensity pattern, can positively modulate *SIRT1* expression in metabolically active tissues.

Although previous studies have suggested that HIIT may induce superior metabolic adaptations due to greater energy stress and activation of mitochondrial pathways (23,31), our results showed no statistically significant differences between the exercise groups. This suggests that moderate-to-high intensity continuous training (MIAT and HIAT) may be equally effective in enhancing *SIRT1* expression, at least at the gene level. Soltani et

al. (2018) similarly reported increased *SIRT1* levels following submaximal aquatic exercise in overweight men (32), while Khalafi et al. (2020) found that HIIT led to greater *SIRT1* protein expression and mitochondrial biogenesis markers (*PGC-1 α* , *CD36*, *CPT1*) in scWAT compared to MICT (31). Akbari et al. (2020) also showed that both HIIT and MICT increased *SIRT1* in visceral fat, with HIIT being more effective (33).

These studies collectively suggest that exercise intensity may influence the magnitude of *SIRT1* activation, but tissue type, duration, and metabolic status are important modulators. In our study, although the HIAT group showed the highest mean *SIRT1* expression, the lack of statistical significance between exercise groups indicates that this numerical advantage should be interpreted cautiously and not overstated. *SIRT1* activation is closely linked to the *AMPK/SIRT1/PGC-1 α* axis, which regulates mitochondrial function and promotes adipose tissue browning.

Exercise-induced activation of this pathway enhances oxidative capacity and suppresses adipogenesis through mechanisms such as Wnt/ β -catenin signaling (31). Increased *SIRT1*

Table 3. Mean ($\pm$ SD) of body weight and maximal oxygen consumption

Variable / group	Control	MIAT	HIAT	HIIT
Body weight (gr)	312.8 ($\pm$ 25.8)	313.7 ($\pm$ 28.6)	310.3 ($\pm$ 31.4)	295.6 ($\pm$ 27.2)
VO2max (ml/kg/min)	47.7 ($\pm$ 3.2)	69.1 ($\pm$ 3.5)	64.2 ($\pm$ 4.5)	65.7 ($\pm$ 6.9)

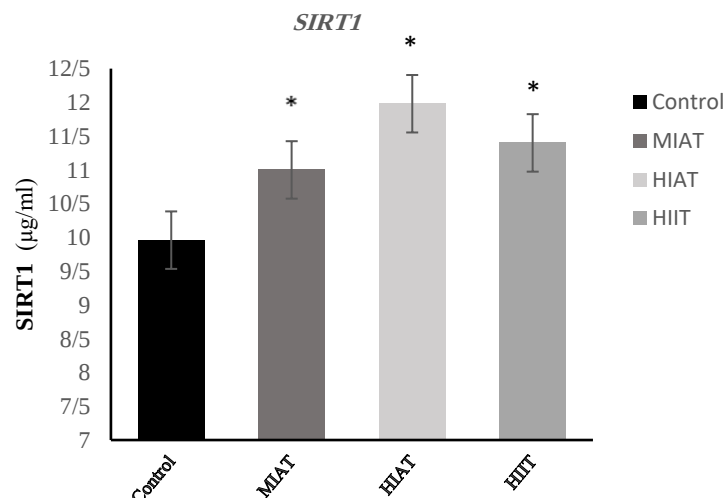


Figure 5. *SIRT1* gene expression in abdominal subcutaneous adipose tissue across the study groups

* Significant difference compared to the control group, MIAT ($P = 0.023$), HIAT ($P = 0.001$), and HIIT ($P = 0.003$).

expression may also reduce obesity-induced inflammation and macrophage infiltration in adipose tissue (33,34), contributing to improved metabolic flexibility.

Proteomic studies in mice have shown that both MICT and HIIT reduce subcutaneous fat mass and alter metabolic pathways related to mitochondrial activity and ribosomal function (35). Although *SIRT1* was not directly measured in those studies, the observed changes are consistent with its known effects. While no studies have directly examined MIT's effect on subcutaneous fat *SIRT1*, evidence from visceral depots suggests a likely increase in expression or activity (33,34).

Despite the strengths of this study-including its controlled animal model and focus on a key metabolic gene-limitations remain. The narrow focus on a single gene, absence of protein-level data, and lack of downstream or functional markers restrict the mechanistic interpretation. Future studies should incorporate additional molecular targets, protein analyses, and functional outcomes to provide a more comprehensive understanding of exercise-induced adaptations.

Conclusions

This study showed that moderate-to-high intensity aerobic training and HIIT significantly increased *SIRT1* gene expression in subcutaneous adipose tissue of male Wistar rats. Although the HIAT group exhibited the highest mean expression, no statistically significant differences were found between the exercise groups. These findings support the role of aerobic exercise in modulating *SIRT1*-

related pathways and improving metabolic health.

Given the central role of *SIRT1* in regulating inflammation, mitochondrial function, and insulin sensitivity, exercise-induced upregulation of this gene may contribute to the prevention or mitigation of obesity-related metabolic dysfunction. However, measuring only gene expression limits the scope of interpretation. Future research should include protein-level assessments, downstream targets such as *PGC-1 α* , and functional markers to better elucidate the biological impact of different exercise modalities.

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Conflict of Interest

No conflict of interest has been declared by the authors.

Authors' contributions

J.R laid out the main idea and participated in the design of the study. A.T, M.ShJ participated in the data collection, and analysis, and drafted the manuscript. All authors read and approved the final manuscript. They agreed to be fully accountable for the integrity and accuracy of the study.

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