Research in Molecular Medicine

Effect of Aerobic Exercise on the Expression of *Ppargc-1α* and *SIRT1* in Cardiac Muscle of Diabetic Male Wistar Rats

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ABSTRACT

Background: Type 2 diabetic patients have an abnormally high rate of mortality due to cardiovascular diseases. Given the adverse impact of diabetes on mitochondrial biogenesis in heart cells and the role of exercise on mitochondrial biogenesis signaling, this study investigated the effect of eight weeks of aerobic exercise on *PGC-1a* and *SIRT1* gene expression in the myocardium of diabetic male Wistar rats.

Materials and Methods: This experimental study was conducted on 24 adult male Wistar rats (eight weeks old and weighing 278.26±18.06g), which were randomly assigned to three groups of healthy control (n=8), diabetic control (n=8), and diabetes+aerobic exercise (n=8). The exercise protocol consisted of eight weeks of exercise, three sessions a week, starting with 10 minutes of running at a speed of 10m/s in the first week and ultimately reaching 40 minutes of running at a speed of 18m/s in the eighth week. The changes were analyzed using the one-way analysis of variance and Tukey's post hoc test.

Results: Significant differences were observed between the groups in terms of body mass (P=0.0001), fasting glucose (P=0.004), serum insulin (P=0.023), and myocardial *Ppargc-1α* expression (P=0.031). The post hoc test represented a notable weight decrease in the diabetic control group (P=0.001) and the diabetic exercise group (P=0.001) compared to the healthy control group. The results also showed a significant increase in the glucose level of the diabetic control group compared to the healthy control group (P=0.008) and a notable decrease in the diabetic exercise group's glucose level in comparison with the diabetic control group (P=0.001). A significant decrease was also observed in the insulin level of the diabetic exercise group compared to the diabetic control group (P=0.034). The results of the post hoc test for *Ppargc-1α* expression changes showed significantly increased myocardial *Ppargc-1α* expression in the diabetic exercise group compared to the diabetic control group (P=0.009). No significant change was detected in the expression of *SIRT1* (P=0.075).

Conclusion: The findings suggest that exercise positively affects insulin resistance and weight changes by regulating genes related to mitochondrial biogenesis.

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Introduction

Type 2 diabetes mellitus (T2D) is not only the most common endocrine disorder but also the most important cardiovascular risk factor [1]. It has been shown that diabetic patients are almost three times more likely to develop cardiovascular diseases than their healthy counterparts [2]. Recent studies have shown that mitochondrial biogenesis plays a major role in the development of cardiovascular diseases. There is also evidence showing that diabetes significantly reduces the mitochondrial biogenesis of heart cells [3].

Regulation of mitochondrial biogenesis is essential for proper cardiac adaptation, and any disruption of this pathway can have irreversible consequences for the heart [4]. The most important regulator of mitochondrial biogenesis is *Ppargc-1α*, which is a cellular receptor to facilitate the release of mitochondrial proteins [5].

The most common treatment for diabetes is taking a diabetes medicine called insulin, β-blockers, and herbal remedies. However, there are many reports of medication non-adherence (X), drug interactions [6], and limited and contradictory effects of herbal remedies [7] in diabetic patients.

SIRT1 is a deacetylase protein with an essential role in counteracting oxidative stress and controlling homeostasis [8]. Sirtuinsare is involved in many vital functions, including the inhibition of the production of free radicals, lipid oxidation, and mitochondrial biogenesis by deacetylating transcription factors, like *Ppargc-1α* [9, 10]. Many studies have examined the exercise effects on *Ppargc-1α* and *SIRT1* [11, 12]. In one of these studies, Suwa et al. reported that acute endurance exercise increased *Ppargc-1α* gene expression immediately after the exercise, but did not change the expression of *SIRT1* [13]. In another study, both high-intensity and low-intensity endurance exercises increased *SIRT1* expression, but *Ppargc-1α* expression increased only after high-intensity exercise [14]. Also, Gurd et al. declared that interval training for six weeks at high intensity led to an increase in the expression of *Ppargc-1α*, the activity of antioxidant enzymes, such as catalase, and *SIRT1* activity. These researchers suggested that increased *SIRT1* nuclear activity may increase *Ppargc-1α* [15]. Findings on the effect of exercise on *Ppargc-1α* and *SIRT1* are inconsistent, which highlights the necessity of further research in this field. Considering the key role of *Ppargc-1α* in mitochondrial biogenesis and the upstream regulatory role of *SIRT1*, any change in the expression or function of these molecules can contribute to cardiovascular dysfunction or affect the pathogenesis of cardiovascular diseases in diabetics. Therefore, this study was conducted to investigate the effect of eight weeks of aerobic exercise on the expression of *PGC-1a* and *SIRT1* genes in the myocardium of male diabetic Wistar rats.

Materials and Methods

Animal preparation and maintenance

This study was designed as experimental research. In all stages of the study, the animals were maintained and handled according to the CONSORT guidelines for animal research [16]. Also, the experimental design and treatment protocols of the study were approved by the research ethics committee of Islamic Azad University, Najafabad Branch with the code IR.IAU.NAJAFABAD.REC.1400.061. The study was performed on 24 male Wistar rats (two weeks old and weighing 278.26±18.06g) purchased from the Pasteur Institute of Iran. The rats were kept in groups of 4 in 1×1×1m fiberglass cages placed in a light-controlled room (12 light/12 dark cycle) with free access to water and standard rat feed (containing 23% protein, 3.5-4.5% crude fat, 4.5-4% crude fiber, and sufficient amounts of minerals and vitamins; manufactured by Behparvar Co., Iran) [16]. In the first two weeks, the rats were familiarized with the laboratory environment and running on the treadmill by the practice of 5-10 minutes per day (min/day) for five days (speed= 4 to 5 m/min).

Study design

The animals were randomly divided into three groups of eight rats: healthy control, diabetic control, and diabetic with aerobic exercise. Both diabetic groups were prepared by a single intraperitoneal (IP) injection of STZ (manufactured by Sigma Aldrich, USA, S0130). To simulate the stress of injection in healthy control animals, they were injected with normal saline in the same volume of STZ solution administered to diabetic groups.

Induction of type 2 diabetes

Type 2 diabetes was induced by an IP injection of streptozotocin at a dose of 60 mg/kg dissolved in 0.1M citrate buffer with pH=4.5 [17]. To reduce mortality, the rats were given 5% glucose solution instead of water for 48 hours after STZ injection. Blood glucose concentration was measured with a Glucocard 01 sensor 72 hours after STZ injection. It was performed following 12-hour overnight fasting using a lancet by a

Table 1. Aerobic exercise protocol

Exercise Variables	1st Week	2nd Week	3rd Week	4th Week	5th Week	6th Week	7th Week	8th Week
Speed (meters per minute)	4-5	4-5	10	10	14-15	14-15	17-18	17-18
Duration (minutes)	5	5	10	20	20	30	30	40

small incision in the tail area [17]. The rats with blood glucose higher than 300mg/dL were considered as diabetic animals. The day when the blood sugar was recorded was considered day zero.

Exercise protocol

The exercise protocol was taken from Chae et al. [18]. Briefly, animals of the exercise group were subjected to running on the treadmill three sessions a week for eight weeks when the speed and time of aerobic exercise gradually increased to maintain the exercise intensity at 50-55% of maximum oxygen consumption [19]. The speed and duration of aerobic exercise gradually increased concomitant with the program, which is detailed in Table 1. Each session started with 3 minutes of warming up and ended with 3 minutes of cooling down both at a speed of 4-5 m/min. To minimize stress during the exercise, no electric shock was applied to simulate running on the treadmill.

Sample collecting and biopsy

At the end of eight weeks of exercise, the animals were sacrificed for collecting biological samples 48 hours after the last exercise session. To provide the least stressful condition, they were first anesthetized by IP injection of ketamine (90 mg/kg body weight) and xylazine (10 mg/kg body weight) following 12-hour overnight fasting. Blood samples were collected from the tail vein of the rats and then the animals were sacrificed prior to awakening from anesthesia. A sampling of heart tissue was performed with appropriate surgical instruments (scissors and forceps) so that the samples were immediately immersed in liquid nitrogen (-196°C) for 10 minutes and then stored at -80°C until the molecular analysis of *Ppargc-1α* and *SIRT1* genes.

Molecular analysis

Cardiac tissues of the animals (*Rattus norvegicus*) were evaluated for quantitative RT-PCR analysis of PPARG coactivator1 alpha (*Ppargc-1α* or *PGC-1α*) and sirtuin 1 (*SIRT1*), in which actin alpha 2 (α-act) was used as reference gene. For this purpose, total RNA was extracted from the tissues by applying Mini Kit (Qiagen RNeasy™) in accordance with the manufacturer›s instructions. Then, isolated RNA was quantified and qualified using a Thermo Scientific NanoDrop 2000 UV-Vis Spectrophotometer instrument. A certain amount of normalized RNA (≈200 ng) was used to synthesize cDNA by RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific) according to the manufacturer's manual. RT-PCR analysis was carried out by Applied Biosystems StepOnePlus Real-Time PCR System. The PCR reaction containing primers and template cDNA was prepared by Applied Biosystems® SYBR® Green PCR Master Mix. The program of thermocycler was set as an initial denaturation of 95°C for 10 min followed by 40 cycles of 95°C, 57°C, and 72°C, for 10, 15, and 30 sec, respectively. Primers were designed for intron spanning targets as listed in Table 2.

Table 2. The primers used in molecular analysis of cardiac tissue

Gene	Sequence	Tm (°C)	Product Size (bp)
Ppargc1a	F:AAGAGCGCCGTGTGATTTAC R:TAGCTGTCTCCATCATCCCG	58 58	130
SIRT1	F:AGTGATGACGATGACAGAGCA R:AGGATCGGTGCCAATCATGA	59 59	111
α-Actin	F: CATCATGCGTCTGGACTTGG R: TCTCACGCTCAGCAGTAGTC	59 59	101

Tm: melting temperature of primers which is represented in Celsius (°C); bp: base pair of nucleotides in PCR products based on the primer blast result in NCBI; F and R: forward and reverse primers, respectively.

Statistical methods

After recording the raw data, the normality of the data distribution was checked by the Shapiro-Wilk test and the equality of variances was assessed by Levene's test. Since these tests showed that the data had a normal distribution with equal variances, descriptive statistics (mean and standard deviation) were used to create a quantitative summary of the data. The statistical analysis of biochemical variables and the intergroup comparisons were done by applying one-way analysis of variance (ANOVA) and Tukey's post hoc test. All statistical tests were performed by the software SPSS v.23 at the P≤0.05 significance level.

Results

The results of one-way ANOVA for intergroup comparisons showed significant changes in weight (P=0.0001), glucose (P=0.0001), insulin (P=0.023), and *Ppargc-1α* (P=0.031) but not in *SIRT1* gene expression (P=0.075) (Table 3). The results of the post hoc test for weight changes showed significant weight loss in the diabetic control group (P=0.001) and the diabetic exercise group (P=0.001) compared to the healthy control group. The results of the post hoc test for glucose changes showed a notable enhancement in the glucose level of the diabetic control group in comparison with the healthy control group (P=0.008) and a considerable decrease in the glucose level of the diabetic exercise group in comparison with the diabetic control group (P=0.001). The results of the post hoc test for insulin changes represented a considerable reduction in the insulin level of the diabetic exercise group in comparison with the diabetic control group (P=0.034) (Figure 1). The results of the post hoc test for *PGC-1α* changes showed significantly increased *PGC-1α* expression in the diabetic exercise group compared to the diabetic control group (P=0.009) (Figure 2).

Discussion

This study aimed to investigate the effect of eight weeks of aerobic exercise on mitochondrial biogenesis indices in the heart tissue of rats with STZ-induced diabetes. The findings showed that while the induction of type 2 diabetes decreased the expression of *PGC-1α* in the myocardium of rats, aerobic exercise significantly increased this gene expression in diabetic rats. This is consistent with the results of Shabani et al., who observed a significant increase in the *PGC-1α* expression and VEGF genes in healthy male rats' heart muscle after eight weeks of high-intensity interval training [19]. A study by Fathi et al. on the chronic effect of endurance training on *PGC-1α* gene expression in the soleus muscle of male rats also reported significantly increased *PGC1-α* expression in the experimental group compared to the control group [20]. In diabetic conditions, high glucose levels due to insulin deficiency or inactivity can cause elevated oxidative stress accompanied by inflammation and apoptosis. However, exercise can enhance the activity of antioxidant enzymes and decrease the lipid peroxidation level, which will have beneficial effects in terms of preventing diabetes-related complications and limiting the tissue damage caused by diabetes-induced oxidative stress [21]. In the present study, exercising rats also showed a significant decrease in body weight, glucose, and insulin levels. It has been shown that exercise increases the expression and activity of *PGC-1α* via various signaling pathways, such as adenosine monophosphate-activated kinase and mitogen-activated protein kinase, which cause the muscle function to shift from glycolytic to oxidative, resulting in improved muscle endurance [22]. In people with type 2 diabetes or a sedentary lifestyle, the muscular *PGC-1α* expression tends to be lower than normal. Therefore, it can be concluded that aerobic exercise performed in

Table 3. Changes in weight, blood glucose, insulin, and the expression of *PGC-1α* and *SIRT1* genes

Variables	Mean±SD				
	Healthy Control (C)	Diabetic Control (D)	Diabetic+Exercise (DT)	F	P Intergroup
Weight (g)	343.49±23.43	227.22±32.03	218.98±29.58	40.474	0.0001
Glucose (mg/dL)	99.01±5.21	625.50±32.18	524.33±60.00	46.147	0.0001
Insulin (µg/L)	0.367±0.299	0.105±0.106	0.052±0.053	4.867	0.023
PGC1-α ($2^{-\Delta CT}$)	427.38±221.97	147.30±105.75	480.90±39.56	5.960	0.031
SIRT1 ($2^{-\Delta CT}$)	17.83±8.09	6.77±5.69	19.83±6.93	3.828	0.075

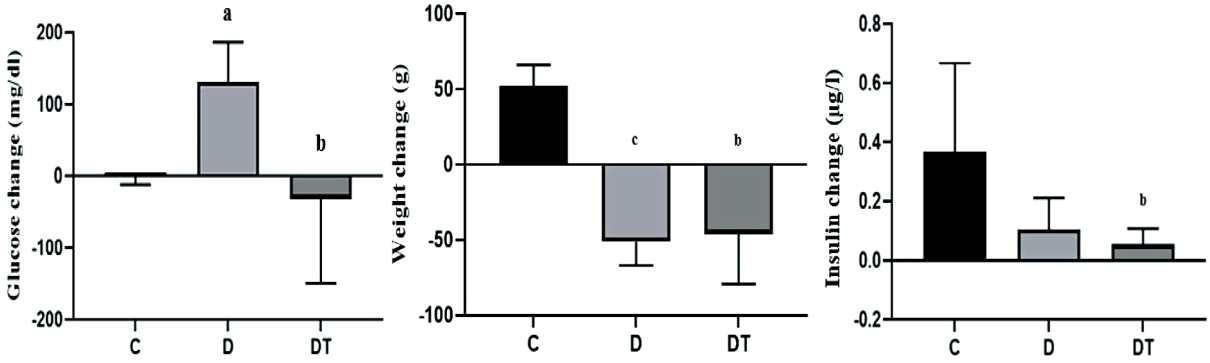

Figure 1. Changes in weight, blood glucose, and insulin levels of diabetic male Wistar rats

Following eight weeks of aerobic exercise. C: control group, D: diabetic group, DT: diabetic exercise group, a: Considerable increase in comparison with the control group, b: notable decrease in comparison with the control group, c: considerable decrease in comparison with the control group.

this study not only led to improved body composition, reduced fat mass, and improved insulin resistance, especially in visceral fat, but also improved the expression of several key proteins, including glucose carriers (GLUT4,5,1) and enzymes, like hexokinase and glycogen synthase [23]. Thus, changes in glucose uptake and consumption in response to the protocol have been another mechanism of action for the improvement of insulin resistance and the reduction of serum glucose. In contrast, some previous studies in this area have cited the reduced expression of *PGC-1α* as a reason for the development of insulin resistance [24]. Also, the level of *PGC-1α* may decrease or remain unchanged because of defects in energy metabolism and increased oxidative stress [25, 26].

Physical activity activates *PGC-1α* in skeletal and myocardial muscle tissues via factors, such as nitric oxide, P38 AMPK, calcium/calmodulin-dependent protein kinase (CaMK), and AMPK, which in turn increases the expression of nuclear respiratory factors (NRFs) and estrogen receptor alpha (α-ERR), thereby increasing the expression of mitochondrial enzymes, such as cyclooxygenase (COX) and the activity of carbohydrate and fat oxidation enzymes [27]. In vitro studies have shown that the increased expression of *PGC-1α* increases the expression of oxidative isoforms and decreases the expression of myosin heavy chain (MHC) isoforms, eventually leading to fiber formation. Research has also shown that the expression of *PGC-1α* in skeletal muscle increases two hours after exercise and remains at its peak for up to 6 hours [28], and continuous endurance training affects the expression of this gene for 52 days [29]. In addition, swimming has been shown to increase *Ppargc-1α* expression and decrease HIF-1 in rat heart muscle under hypoxia [30]. *PGC-1α* has also been shown to increase the expression of glucose transporter type 4 (GLUT4), which results in higher glucose uptake and energy production in muscle [31]. *PGC-1α* also suppresses

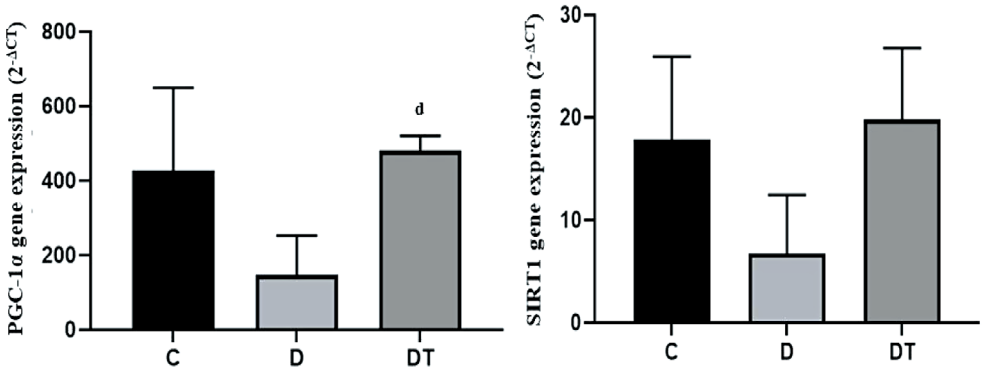

Figure 2. Expression of *PGC-1α* and *SIRT1* genes following eight weeks of aerobic exercise in the myocardium of diabetic male Wistar rats

C: control group, D: diabetic group, DT: diabetic exercise group, d: significant increase compared to the diabetic group.

insulin signaling by increasing the expression of Tribbles homolog 3 (TRB 3). One study has also reported a decrease in the mitochondrial capacity of skeletal muscle in insulin resistance in type 2 diabetics, stating that since muscle oxidation capacity is a predictor of insulin sensitivity, a rapid increase in mitochondrial content following chronic aerobic exercise could be an important factor for the reduction of insulin resistance and the improvement of blood sugar control [32].

The findings of the present study showed no significant change in the expression of the *SIRT1* gene in rats with type 2 diabetes compared to the control group. It is observed no significant change in *SIRT1* expression and mitochondrial biogenesis of insulin-resistant rats after eight weeks of moderate-intensity exercise. In another study, it was reported that eight weeks of swimming exercise at an intensity of 46% of VO_2max, despite improving the metabolic condition of the subjects, had no effect on serum levels of *SIRT1* [33]. However, exercise is associated with decreased adipocytes in adipose tissue, decreased fat content, increased level of enzymes involved in fat oxidation, and also increased level of anti-inflammatory cytokines, and decreased level of pro-inflammatory cytokines. Consistent with this finding, decreased mitochondrial content (skeletal muscle and fat tissue) in several insulin-resistant models has been reported [34]. Overall, the evidence aligning with the findings of the present study suggests that while regular exercise tends to increase sirtuins, some of the positive effects of such exercise on the body's metabolic conditions are not realized via the signaling of this protein. As a regulatory protein controlling the metabolism of lipids and sugars, *SIRT1* is widely expressed in various tissues of the body [35]. It plays its different roles by deacetylating PPAR, FOXO, and *PGC-1α* factors, which have different functions in different tissues, such as gluconeogenesis regulation, glucose release from the liver, insulin secretion from pancreatic beta cells, mitochondrial activity regulation, oxidation of fatty acids, and insulin activity regulation in muscle cells [36]. However, sirtuins are sensitive to nutrient depletion and limitation and regulate metabolic pathways in response to low energy. This is why therapeutic interventions (such as *SIRT1* activators) and exercise activities that activate *SIRT1* should be considered as a treatment for obesity and many metabolic diseases [37]. Therefore, possible mechanisms for the beneficial effect of exercise on insulin resistance and mitochondrial biogenesis could be as follows: 1- increased expression of GLUT4 in the cell membrane through the activation of intracellular signal transmission pathway following contractions; 2- increased activity of insulin receptors glycogen synthetase and protein kinase B; 3- up-regulation of factors involved in the insulin signaling cascade [38]. The findings of previous studies in this field have also shown significantly reduced *SIRT1* expression and AMPK activity in cardiac tissue following insulin resistance and inflammation [39]. Therefore, not changing *SIRT1* in response to the exercise protocol defined in this article can also be due to the reasons mentioned above. In a study on adaptation to aerobic and endurance training, Sin et al. also observed no significant change in *SIRT1* levels in muscle tissue after 14 weeks [40].

Regarding the limitations of the present study, it should be stated that while the findings showed the impact of chronic aerobic exercise on some of the factors affecting mitochondrial biogenesis and cellular metabolism, more extensive studies must still be conducted on other signaling pathways to further elucidate the involved mechanisms. It is clear that chronic aerobic exercise increases the activity of antioxidants, thus decreasing ROS. However, the *SIRT1* enzyme deacetylates FOXO3, which leads to disrupted transcription and down-regulation of cell death by the activity of inflammatory proteins, thus promoting cell survival. The up-regulation of these enzymes and *PGC-1α* could therefore be the upstream mechanism responsible for the extensive suppression of FOXO3 and FOXO1 gene expression [36]. Hence, one of the limitations of this study was that given the role of FOXO1, 3, their effects on the metabolic function of the cell were not investigated. Also, since the study aimed to investigate the effect of exercise on the prevention or inhibition of the adverse effects of diabetes on rats, it is recommended to further study the changes in these transcription factors in combination with supplementation and assess the mechanisms and extent of the interactive effects of physical activity and supplementation under experimental conditions on the tissues of various organs including the liver, pancreas, and skeletal muscle of diabetic rats.

Conclusion

The present study found that aerobic exercise significantly increased the expression of *PGC-1α* in myocardial tissue and resulted in weight loss and improved insulin resistance in type 2 diabetic rats. However, the results showed no significant change in *SIRT1* expression. From these results, it can be concluded that exercise positively affects insulin resistance and weight changes by regulating genes related to mitochondrial biogenesis.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article.

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Authors contribution's

Conceptualization, Methodology, Investigation, Writing the Original Draft, Review & Editing, Funding Acquisition, Resources, and Supervision: Elham Mehrpouya; Conceptualization, Methodology, and Supervision: Saeed Keshavarz; Methodology, Writing of the main Draft, Review & Editing, Resources, and Supervision: Ebrahim Banitalebi; Methodology, Investigation, and Supervision: Hasan Naghizadeh; Methodology and Supervision: Javad Ramezani.

Conflict of interest

The authors declared no conflict of interest.

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