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The Effect of a HIIT Training Course on the Expression of PGC-1α, SIRT1, and SIRT3 Genes in the Cardiac Tissue of Elderly Female Rats

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ABSTRACT

Background and Aim: Exercise improves the function of mitochondrial proteins and enzymes in old age. This study aimed to investigate the effect of a high-intensity interval training (HIIT) training course on the expression of PGC-1α, SIRT1, and SIRT3 genes in the cardiac tissue of elderly female rats.

Materials and Methods: In this experimental study, 14 female Sprague-Dawley rats with a mean age of 16-18 months and a weight range of 280-320 g were randomly divided into 2 groups of 7, including the control group and the HIIT training group. The experimental group performed HIIT training for 8 weeks and 5 days a week with an intensity of 85%-110% VO_{2max}. Forty-eight hours after the last training session, rats were anesthetized by intraperitoneal injection of ketamine and xylazine, and the target tissue was immediately removed for examination. Shapiro-Wilk statistical test and one-way analysis of variance in SPSS software v. 22 analyzed the findings ($P \geq 0.05$).

Results: The results showed that the expression of PGC-1α, SIRT1, and SIRT3 genes increased in the cardiac tissue of the experimental group compared to the control group after 8 weeks of HIIT training, but this increase was not significant ($P \leq 0.05$).

Conclusion: It seems that in elderly conditions, exercise from pathways other than PGC-1α improves mitochondrial function. However, further research is needed on the effect of HIIT exercise on the expression of these genes in cardiac tissue.

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1. Introduction

The world's aging population is growing rapidly, with statistics showing that the elderly population over 65 will increase from 9.09% in 2019 to 16.67% in 2050 [1]. Aging leads to increased treatment costs for physical and mental illnesses which is a major problem for healthcare organizations globally [2]. Mortality from cardiovascular diseases is also one of the leading causes of death in the elderly, and approximately 20% of deaths in the elderly are due to cardiac diseases [1]. Many factors are involved in the pathology of cardiac disease in the elderly. However, studies show that a decrease in the efficiency of the antioxidant system and an increase in reactive oxygen and nitrogen species (RONS) decreases mitochondrial capacity in energy production, and is associated with apoptosis, inflammation, and increased oxidative stress ultimately leading to dysfunction of the cardiac muscle [3].

Due to advances in laboratory science, in a variety of ways, such as decreasing the ratio of ATP to ADP and decreasing nicotinamide dinucleotide (NAD), studies have shown that increased oxidative stress can reduce NAD+ -dependent deacetylation proteins such as Sirtuin 1 (SIRT1) in the cell nucleus, Sirtuin 3 in the mitochondria (SIRT3), gamma receptor activated by 1-alpha coactivator (PGC-1α), proteins responsible for nuclear respiration factor, reduction of mitochondrial superoxide dismutase 2, and mitochondrial dysfunction in cardiac tissue [4, 5]. Also, due to the increase in the elderly population, it seems necessary to provide effective strategies to prevent cardiovascular disease in the elderly; therefore, researchers believe that regular and long-term activities as the least costly way to improve the metabolism of fats and sugars and ameliorate aerobic capacity, physical function, and elderly's life quality [2, 6]. It is believed that exercise activity with the mechanism of increasing catecholamine causes AMP phosphorylation and continually activates the protein kinase activated by AMP (AMPK). In response to the activation of protein kinases, PGC-1α is phosphorylated, after which this protein can be directly involved in improving mitochondrial function. This protein can also accelerate the process of mitochondrial biogenesis by changing the ratio of NAD+ to NADH to activate SIRT3 in mitochondria and activate SIRT1 [7]. However, the impact of exercise depends on the type, intensity, and duration of exercise, and the mechanism of the type of exercise on this molecular-cellular mechanism is not yet well understood [6]. In this regard, researchers have shown that six weeks of high-intensity interval training (HIIT) increased muscle levels of SIRT1, citrate synthetase, beta-hydroxyl coenzyme A dehydrogenase, cytochrome C oxidase, and PGC-1α in human subjects [8]. Also, 12 weeks of swimming training increased levels of SIRT1, PGC-1α, AMPK, and Forkhead box protein-3A (FOXO3a) in gastrocnemius and soleus muscle of 3-month-old, 12-month-old, and 18-month-old rats [9]. Moreover, in a study comparing eight weeks of HIIT training, the researchers showed that SIRT1 increased, but the increase in SIRT3 and PGC-1α was not significant in the liver of rats with type 2 diabetes [10]. Meanwhile, a very intense interval program has been introduced that has a greater impact on cardio-respiratory capacity use than traditional exercises. Very intense interval training has intense work-up and low-intensity rest intervals. This training program consists of interval periods of intense sports activity with a period of passive or active recovery from low to moderate intensity. One of the most important benefits of this training program is maintaining strenuous exercise for a longer time than regular exercise. Therefore, HIIT causes more training stimulation, which increases the maximum aerobic capacity. The physiological benefits of HIIT are realized in less time than traditional continuous training. HIIT results in increased VO_{2max}, maximal cardiac rate, glucose transporters, fatty acid oxidation enzymes, and anabolic hormones [11]. Given the existing background, it can be concluded that studies on the role of various sports activities and PGC-1α, SIRT1, and SIRT3 proteins and mitochondrial biogenesis, especially in elderly specimens, are still in their infancy. Although interval training in comparison with other training on the mentioned factors has been investigated in different samples [12, 13], there is no consensus on the timing, intensity, and type of exercise that can highly affect these factors. Given the importance of SIRT1 and SIRT3 in the aging process and related disorders and diseases, as well as the regulatory role of SIRT1 and SIRT3 in mitochondrial biogenesis proteins such as PGC-1α, this study aimed to investigate the effect of a course of HIIT training on the expression of PGC-1α, SIRT1, and SIRT3 genes in the cardiac tissue of elderly female rats.

2. Materials and Methods

The present study is an experimental-basic study conducted with training and a control group. In this study, 14 elderly female Sprague-Dawley rats with a mean age of 16-18 months and a weight range of 280-320 grams were prepared from the Laboratory

Animal Breeding Center of Marvdasht Islamic Azad University and were transferred to the specialized physiology laboratory of this university. The present study was performed accord ing to the National Institute of Health (NIH) instructions and was approved and conducted by the ethics committee of the Islamic Azad University, Marvdasht Branch, with the code of ethics (IR.IAU.M.REC.1400.023). All rats were kept in clean, sterile cages under standard conditions with a 12-hour cycle of darkness and light and a temperature of 19-22°C. Animals with standard laboratory diet of rodents (crude protein 19.50%-20.50%, fat 4.5%-5.3%, fiber 4%-4.5%, calcium 0.95%-1%, phosphorus 0.65%-0.7%, salt 0.55%-5%, lysine 1.15%, methionine 0.33%, threonine 0.72%, tryptophan 0.25%, and calories 16.16-17 mg/kg) were with fed tap water, unlimited access. After one week of adaptation to the laboratory environment, rats were randomly divided into 2 groups of 7: control (C) and HIIT training (TH).

HIIT training protocol

To design the training, the rats first walked on a treadmill at 8 m/s 5 days for 5 minutes to get acquainted with the treadmill. Then, to obtain the maximum speed, the rats were first heated to 8 m/min for 5 minutes, then two meters were added to the treadmill every 3 minutes until the speed reached 18 m/min, after which for every 2 minutes, 3 meters per minute was added to the treadmill speed to make the rats exhausted. It is noteworthy that exhaustion in rats was a condition in which rats could not continue to run due to extreme fatigue and hit the end of the treadmill three times in a row in one minute. Then, after determining the maximum running speed, HIIT training for 8 weeks and 5 days a week, with an intensity of 85% to 110% VO_{2max}, the equivalent of seven attempts for a minute, the speed of 31 m/min active rest between intervals of six attempts, and the pace of 15 m/min in the first week was done, which gradually increased by an average of 2 m/min per week to ten one-minute attempts at 55 m/min and active rest with 9 one-minute attempts (between intervals) at 25 m/min in the eighth week.

Measurement of PGC-1α, SIRT1, and SITR3 gene expression values

First, to measure the variables, the cardiac tissue was homogenized using a mortar and centrifuge, and then the instructions of the RNA extraction column kit (FavorPrep ™ Tissue Total RNA Mini Kit) made in Hong Kong were operated for extracting the entire RNA contents of the cell, and 5 µl of the solution was placed on agarose gel electrophoresis to ensure RNA quality. Using its absorption property at a wavelength of 260 nm with a Sigma PicoDrop device (made in the USA), the purity of RNA was measured to check its quality using the open formula (Equation 1):

1. $(C\ (\mu g/\mu l)=A260\times\varepsilon\times d/1000)$

Then, cDNA synthesis was performed according to the protocol in the fermentate kit (K1621). The synthesized cDNA was used for reverse transcription reaction using RevertAid ™ M-MuLV Reverse transcriptase enzyme. First, the primer was designed by Allele IDv7.8 software and used to check the specificity and performance of the primers using the software available on the NCBI site. Then, to check the gene expression of variables, samples were placed in the device. After completing the activity of the device and viewing the graphs, regarding the increase in the number of desired fragments and fluorescence emission, by calculating $\Delta\Delta C_t$, the amount of change in gene expression was calculated, compared to the internal control gene and the control group, using the following formula. The sequence of primers used in the study is presented in Table 1.

Statistical analysis method

Shapiro-Wilk test was used to investigate the normality of the distribution of findings and a one-way analysis of variance was used to analyze the data in SPSS software v. 22 ($P\geq0.05$).

3. Results

The weight of rats in the study groups is presented in Table 2. Gene expression levels of PGC-1α, SIRT1, and SIRT3 are shown in Figures 1, respectively. The one-way analysis of variance showed that the expression of the PGC-1α gene in the TH group was 1.2 times higher compared to group C, but this increase was not statistically significant (F=0.79, F=16.3). The expression of the SIRT1 gene in the TH group was 1.4 times higher than in group C, which showed a non-significant increase (P=0.29, F=18.05). Also, the expression of the SIRT3 gene in the TH group was 1.8 times higher than in group C, which was not statistically significant (P=0.89, F=12.5).

Table 1. Sequence of primers designed in this research

Genes	Primer Sequences	Sizes (Bp)
B2m	Forward: 5′-CGTGCTTGCCATTCAGAAA-3′ Reverse: 5′-ATATACATCGGTCTCGGTGG-3′	244
SIRT1	Forward: 5′-TCCTGTGGGATACCTGACTT-3′ Reverse: 5′-AAAGGAACCATGACACTGAATGA-3′	300
PGC1a	Forward: 5′-CAGAAGCAGAAAGCAATTGAAGA-3′ Reverse: 5′-GTTTCATTCGACCTGCGTAAAG-3′	230
SIRT3	Forward: 5′-CCCAATGTCGCTCACTACTTCC-3′ Reverse: 5′-CGTCAGCCCGTATGTCTTCC-3′	199

4. Discussion

The present study results showed no increase in the expression of PGC-1α, SIRT1, and SIRT3 genes in the cardiac tissue of elderly female rats after 8 weeks of HIIT training. According to previous studies, one of the main causes of deaths over 65 years is the cardiac aging phenomenon and one of the key mechanisms of this incident is the abnormal expression of non-coded RNAs, which can lead to defective expression of many vital proteins within the cell, telomere damage, mitochondrial DNA mutations, mitochondrial protein oxidation, decreased mitochondrial volume and number, decreased ATP synthesis, increased reactive oxygen species, and in general, defective cardiac cell function. Also, increased ROS following biological defects synergistically with other disorders of cardiac aging causes an excessive increase in autophagy and apoptosis of the cardiac cell [1]. In addition, researchers believe that cell dysfunction in the synthesis of

Table 2. Pre-test and post-test levels of rat weight in the study groups

Groups	Mean±SD	
	Pre-test (gr)	Post-test (gr)
Control	295.4±31.57	305.4±57.64
HIIT training	300.3±14.59	280.2±23.41

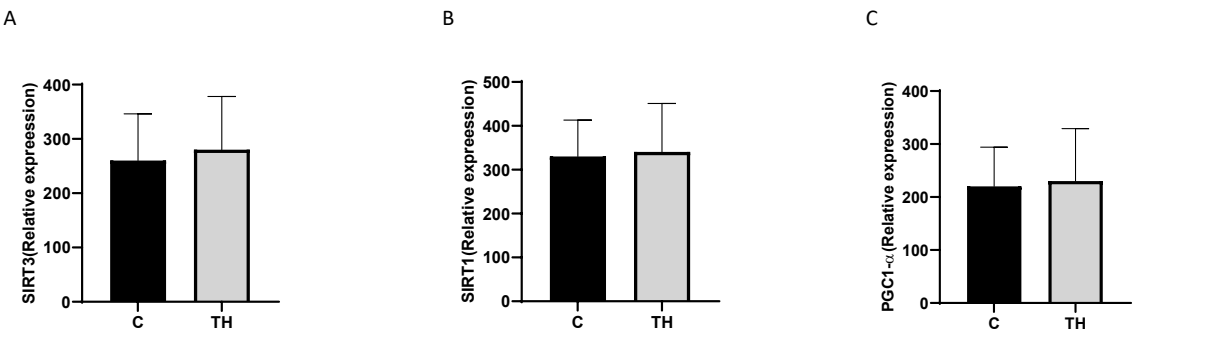

Figure 1. Expression levels

A. PGC-1α, SIRT1, and SIRT3 genes in the heart tissue of elderly rats in research groups, B. SIRT1 genes in the heart tissue of elderly rats in research groups, **C.** SIRT3 genes in the heart tissue of elderly rats in research groups.

metabolic proteins, such as changes in PGC1 subunits with decreasing PGC-1α and increasing PGC-1β subunits, as well as decreasing cell energy charge in the sarcoplasmic reticulum, NAD+levels that decrease the activation of SIRT1 in cell DNA, and SIRT3 in mitochondria stop different pathways of mitochondrial biogenesis such as AMPK, calcium/calmodulin, and distillation proteins [15].

The activation pathway of PGC-1α is also dependent on the activation of the p38γ subunit in the AMPK protein, which is drastically reduced under autophagy and oxidative stress induced by diseases [16]. Considering the optimal role of sports activities, it seems that endurance activities are involved in the mechanism of upregulation of cAMP, phosphorylation of protein kinases, AMPK, activation of p38γ MAPK subunit, and PGC-1α. Furthermore, PGC-1α is involved in activating proteins such as calcium, SIRT1, and SIRT3 in cardiac tissue [16, 17]. However, the available data suggest that activation of the PGC-1α pathway following training is dependent on insulin sensitivity and the pathway of glucose metabolism, the type of PGC-1α subunit activated by training, and the type of training [18].

The results of the present study suggest that the non-increase in PGC-1α, SIRT1, and SIRT3 compared to the control group can be justified by the fact that in the elderly, training from pathways other than PGC-1α can also improve mitochondria, and its non-expression can also depend on the length of the training period [18]. In this regard, researchers showed that training in elderly rats, which was associated with the genetic deletion of PGC1 subunits, increased mitochondrial function by increasing electron transport chain proteins [18]. Also, training can activate the pathway MAPK-2/ERK1, δ subunit of protein kinase C (PKC-δ), protein kinase A, calcium-calmodulin kinase 2 (CaM-KII), and adjust the amount of calcium, which can play a role in the acetylation amount and affect the distillation proteins and the expression of Sirtuins [19]. Since the present study is one of the first studies on the long-term effect of HIIT training on the expression of PGC-1α, SIRT1, and SIRT3 genes simultaneously in the cardiac tissue of elderly subjects, similar studies can be compared with the findings of this study. However, in line with the results of this study, Shabani et al. (2016) examined the effect of 8 weeks of intense interval training on the expression of PGC-1α and VEGF genes in the cardiac muscle of healthy male rats. They concluded that intense interval training insignificantly increases the expression of PGC-1α and VEGF in the cardiac muscle [20]. Nourshahi et al. (2019) also found that 8 weeks of fast-paced interval training did not significantly affect the expression of the muscular SIRT3 gene in elderly mice [21]. In contrast to the results of the present study, Bakhtiyari et al. (2019) reported that 12 weeks of very severe interval training had a significant impact on the increased expression of PGC-1 and SIRT1 proteins in the gastrocnemius muscle of elderly rats [22]. MacInins et al. (2017) also showed that 6 sessions of HIIT training increased mitochondrial proteins more than moderate training [23]. Also, Edgett et al. (2016) and Mehrabi et al. (2021) showed that interval training or HIIT increases SIRT3 gene expression in human skeletal muscle and frontal lobe of the brain of elderly rats [24, 25]. These contradictions appear to be rooted in the severity, duration, and type of training used in the studies. Other reasons for the contradiction of the findings include the tissue and age of the subjects studied. The present study was performed on cardiac tissue and elderly female rats, but Mohsenzadeh et al. (2020) studied the horseshoe muscle of young male rats, Cheng et al. (2016) hippocampal neurons, Jokar et al. (2020) the left ventricular tissue of rats with type 2 diabetes, and Little et al. (2010) studied the skeletal muscles of young men, whose results were not consistent with the present study [12, 26-28]. Due to non-compatible adaptations of PGC-1α, Sirt1, and Sirt3 caused by training in aging conditions, the lack of capacity and performance of the electron transfer chain and its associated enzymes are among the limitations of the present study. Therefore, it is suggested that the variables of the Krebs cycle and the electron transfer chain be also evaluated. Due to the challenges of aging and the complex mechanisms of exercise, it is suggested that future studies evaluate the lack of effective proteins in the PGC-1α, SIRT1, and SIRT3 axes on variables such as AMPK, p38γ MAPK, FOXO3a.

5. Conclusion

The present study's findings showed that HIIT training did not significantly increase the expression of PGC-1α, SIRT1, and SIRT3 genes in the cardiac tissue of elderly female rats. It seems that the training protocol in the present study is one of the training activities that shows its function more on the peripheral muscles and puts less pressure on the heart. Furthermore, protocol training to improve cardiovascular diseases such as atherosclerosis can have good results without too much pressure on the heart. This issue has been confirmed by studies on the helpfulness and applicability of HIIT training for cardiovascular patients [20]. It can also be said that training from paths other than PGC-1α improves mitochondrial

capability in old age. However, further research is needed on the effect of HIIT training on the expression of these genes in cardiac tissue.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee in Biomedical Research in the Islamic Azad University. (Code: IR.IAU.M.REC.1400.023).

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Authors' contributions

Conceptualization: Bahram Abedi, Khadija Hassanpour; Methodology: Bahram Abedi, Lida Moradi, Investigation: Bahram Abedi, Khadija Hassan Pour, and Lida Moradi; Writing drafts: Khadija Hassan Pour, Bahram Abedi; Collection and analysis of data: Bahram Abedi, Lida Moradi; Editing and finalizing: All authors.

Conflict of interest

The authors declared no conflict interest.

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