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Research Paper

The Effect of High-intensity Interval Training and Moderate-intensity Continuous Training on Oxidative Stress Markers in Left Ventricular Tissue of Male Rats

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ABSTRACT

Objectives: The present study aimed to assess and compare the effects of high-intensity interval training and moderate-intensity continuous training on oxidative stress-related markers in the left ventricular tissue of the heart muscle in healthy male rats.

Methods: Fifteen male Wistar rats, aged 50-70 days, were randomly divided into 3 groups: Control group (CON), high-intensity interval training (HIIT), and moderate-intensity continuous training (MICT). After determining the maximum speed of VO_2max, the training program of HIIT (six 2-min periods with 85%-90% VO_2max and five 2-min with 50%-60% VO_2max intensity) and MICT (same distance of running as HIIT with 70% VO_2max intensity) groups were performed for 8 weeks, 5 days per week. Forty-eight hours after the last intervention session, the animals were anesthetized, and their heart tissue was removed and stored at -80°C. Then, the expression rates of peroxisome proliferator-activated receptor-γ coactivator-1α (*PGC-1α*), AMP-activated protein kinase (*AMPK*), and superoxide dismutase (*SOD*) genes were measured by real-time PCR, and the concentration of malondialdehyde (MDA) in left ventricular tissue of heart was measured by colorimetry method. One-way analysis of variance and Tukey post hoc test were used for data analysis at the significance level of P<0.05.

Results: There were significant differences between the groups' expression rates of AMPK, PGC-1α, and SOD (P<0.05). The expression rates of *AMPK* and *PGC-1α* were higher in the MICT group than in the CON group (P<0.05). No significant difference was observed between HIIT and MICT groups regarding *AMPK* and *PGC-1α* (P>0.05). *SOD* expression was significantly higher in the HIIT group than CON and MICT groups (P<0.05). SOD expression was also higher in the MICT group compared to the CON group (P<0.05). MDA concentration was not significantly different between the studied groups (P>0.05).

Discussion: HIIT and MICT induce positive adaptations in the expression of *AMPK, PGC-1α*, and *SOD* in the heart tissue of healthy male rats. However, HIIT stimulates *SOD* gene expression more than MICT.

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Introduction

The cardiovascular system plays a crucial role in the health of mammals. Accordingly, cardiovascular diseases (CVDs) are among the leading causes of death worldwide. According to the World Health Organization (WHO), about 17.9 million people die annually from cardiovascular diseases. Moreover, based on epidemiological studies, this figure will increase to 23.3 million by 2030 worldwide because of the aging population [1, 2]. Therefore, investigating effective strategies for preventing cardiovascular diseases is particularly important [3].

Although different mechanisms are involved in developing cardiovascular diseases, molecular, oxidative stress and overexpression of reactive oxygen species (ROS) have been suggested as significant influencers of cardiovascular diseases or dysregulation of cardiovascular adaptation [3].

In summary, oxidative stress is an imbalance between the formation and removal of ROS. Most mammalian cells' metabolism, especially cardiomyocytes, depends on aerobic energy production and mitochondrial respiration pathways. Although most of the oxygen consumed in the mitochondria for water production is reduced, some can be incompletely reduced, giving rise to ROS. While low amounts of ROS significantly regulate cellular homeostasis, including cell growth, proliferation, differentiation, and survival, excessive ROS formation can lead to cellular and tissue damage. For example, excessive ROS levels in the heart are associated with cardiometabolic disorders such as hypertension, atherosclerosis, cardiac hypertrophy, myocardial infarction, and cardiac arrhythmias [4, 5].

In confronting ROS, cells, including cardiomyocytes, use antioxidant mechanisms. These mechanisms reduce ROS levels by specific antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), working to maintain to redox balance state [4, 5]. Thus, understanding cellular and molecular mechanisms that strengthen the innate antioxidant defense plays a significant role in preventing and combating cardiovascular diseases [4, 5].

In heart tissue, AMP-activated protein kinase (AMPK) is one of the proteins that can directly and indirectly affect the regulation of oxidative stress [4, 6]. Although AMPK is classically recognized as a cellular energy sensor and regulator [4, 6], it has demonstrated additional roles in regulating growth, angiogenesis, cell survival, and perceiving oxidative stress in the heart [4]. AMPK has also been reported to protect cardiac cells against oxidative stress by increasing the expression of antioxidant enzymes and peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) [7]. Also, the effect of AMPK on regulating *PGC-1α* expression is fundamental. PGC-1α activity and concentration affect many cellular interactions, including mitochondrial biogenesis, regulation of antioxidant gene expression, and cell survival. For example, low levels of PGC-1α in inflamed tissues have been reported to increase ROS production and cause oxidative damage [3]. Left ventricular dysfunction and abnormal heart rate after training have also been observed in rats deficient with PGC-1α [8].

Several human and animal studies have indicated that regular training improves cardiovascular function and health by strengthening the antioxidant defense system and increasing *PGC-1α* expression. In other words, regular training through AMPK and PGC-1α upregulation improves cardiovascular function and reduces oxidative stress in heart tissue [4, 9]. Also, according to Hormesis theory, the increase in ROS at physiological levels, usually induced by moderate-intensity training, can act as a significant stimulus to regulate cellular function and increase antioxidant capacity [9, 10]. However, little information is available on the role of different training protocols in regulating oxidative stress-related adaptations and related molecular mechanisms.

A study on male rats with myocardial infarction showed that after intermittent training with three different intensities, the PGC-1α protein content increased only in the moderate-intensity continuous training group, and no significant changes were observed with other intensities [11]. In contrast, other studies have shown that 8 weeks of high-intensity intermittent training significantly increases the protein content of AMPK and PGC-1α [12, 13]. Also, two studies support that high-intensity interval training significantly increases PGC-1α in heart tissue compared to the control group or low-intensity training [14, 15]. Moreover, the AMPK activity of the heart in response to short-term high-intense training has a higher upward slope than moderate-intensity training [6].

Lu et al. also reported that moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT) reduce oxidative stress in infarcted heart tissue by decreasing malondialdehyde (MDA) and increasing SOD and GPx [16]. In this study, GPx concentration and heart function were higher in the HIIT group than in the MICT group [16]. Paes et al. also showed that high-

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intensity aerobic training is a stronger stimulant than MICT in fortifying the antioxidant defense system [17]. However, to our knowledge, no study has ever compared the effect of HIIT and MICT on the important factors of SOD, AMPK and PGC-1α. Thus, due to the significant role of ROS and oxidative stress in the regulation of adaptations and cardiovascular diseases, as well as its complex interaction with many intracellular signaling pathways and the potential importance of PGC-1α and AMPK proteins in regulating cardiomyocyte function, the present study was conducted to compare the effect of 8 weeks of HIIT and MICT on the expression of AMPK, PGC-1α and oxidative stress markers in left ventricular tissue of healthy male rats.

Materials and Methods

The subjects of the present study consisted of 15 male rats (Wistar) with an age range of 50-70 days. The rats were purchased from the Pasteur Animal Breeding Center in Iran. After 2 weeks of habituation and testing their maximum speed, they were randomly divided into three study groups: Control (CON), high-intensity interval training (HIIT), and moderate-intensity continuous training (MICT). The number of animals in each group was calculated as 5 based on the analysis of variance (ANOVA) requirements [18].

Housing and tissue removal methods

The rats were kept in cages (3 rats per cage) at 25˚C, under 30% humidity, with a 12:12 hours of dark: Light cycle and free access to water and food. The animals were weighed on the first day of each week with a digital scale for animals. The diet of rats included the standard feeding pattern of rats prepared from the Behparvar Food Industry (consisting of a total of 16.6 kj/g: Carbohydrate 66.40%, fat 10.60%, and protein 23%).

Forty-eight hours after the last intervention session, the animals were anesthetized with xylazine (10 mg/kg) and ketamine (75 mg/kg) while fasting for 12 hours. After complete anesthesia, pain test, and ensuring lack of consciousness, blood was taken from the heart's left ventricle. Then, an incision was made in the chest with a surgical razor, and the heart tissue was quickly removed and washed with phosphate buffer saline. Next, the tissue was placed inside the coded microtube. Afterward, the tissue was placed inside the coded microtube and kept at -80˚C until molecular analysis.

Familiarization to training

Familiarization was performed for both HIIT and MICT groups for two weeks, with rats running on a treadmill 5 days a week for 15 minutes at a speed of 5 to 15 m/min with a 0˚ slope.

Maximum oxygen consumption test

After familiarization, to determine the speed of maximum oxygen consumption, the rats underwent a standard Bedford et al. incremental test [19], standardized by Leandro et al. on Wistar rats [20]. The trial included ten 3-min steps. The speed in the first step was 0.3 km/h and 0.3 km/h, which increased in the following steps. Based on a study conducted by Leandro et al., a 0˚ slope was used in this study to determine the maximum speed of oxygen consumption [20]. The speed of animals in the last step that they could not run was considered the maximum speed of the animal [19, 20].

Training protocol

The training protocol for HIIT and MICT groups was performed for 8 weeks, 5 days per week, starting 72 hours after the test to determine the maximum speed of VO_2max. HIIT group training in each session included 5 minutes of warm-up with an intensity of 40%-50% VO_2max, then six 2-min sessions with an intensity of 85%-90% VO_2max and five 2-min sessions with an intensity of 50%-60%. Finally, there was 5 minutes of cool down (40%-50% VO_2max) [21]. The MICT group training program also included 5 minutes of warm-up (40%-50% VO_2max), then running on a treadmill with an intensity of 70% VO_2max). Then, a 5-minute cooling down was implemented with an intensity of 40%-50% VO_2max. The running distance in each MICT session was similar to that of the HIIT group [21]. The training intensity in the present study was estimated using the treadmill's speed, and the relevant graphs were used to convert VO_2 max to the maximum speed [19].

Measurement of biochemical variables

After the biopsy, the left ventricle of the rats was removed and kept at -80˚C until laboratory studies. The tissue was then homogenized using an RNA extraction column kit (FavorPrep™ Tissue Total RNA Mini Kit, made in Hong Kong) according to the cell RNA content (total RNA) guidelines. Then, the extracted RNA was stored at -80˚C. Also, cDNA synthesis was prepared according to the guidelines in the Fermentas kit (K1621). The reverse transcription reaction was performed using Re-

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vertAid™ M-MuLV Reverse transcriptase enzyme. Then, the prepared cDNA was used for RT-PCR. To evaluate the expression of genes using real-time PCR, all primers were designed by Allele ID software, version 7.8 and *β2m* gene (beta 2 microglobulin) was used as the internal control (Table 1). All primers were designed as exon-exon connections. To investigate the expression of genes, PCR mixture, RealQ 2 x Master mix Green Dye (made by AMPLQON Germany) was used according to the kit guidelines. Then, the program of the real-time PCR device was set. After completing the apparatus activity and observing the graphs and the amount of fluorescence propagation, the rate of change in the expression of the desired gene was measured by calculating ΔΔCt compared to *β2m* and the control group. Afterward, the gene expression rate was calculated using the formula of $\Delta\Delta Ct^{-2}$. Also, MDA concentration was measured by Zellbio laboratory kits (Made in Germany) using the colorimetry method.

Data Analysis

All statistical analyses in the present study were performed using the SPSS software, version 26. After confirming the normal distribution of the data by the Shapiro-Wilk test, the one-way ANOVA test was used to compare data in the study groups at the level of P<0.05. Regarding significant results, the Tukey post hoc test was used for pair wise comparison of the groups.

Results

The results of the one-way ANOVA test showed significant differences in the expression of *AMPK, PGC-1α,* and *SOD* genes between the studied groups (P<0.05) (Table 2). The findings showed that the expression of *AMPK* was higher in both HIIT (relative difference [RD]=+168%) and MICT (RD=+242%) groups than in the CON group. Still, these differences were significant only between MICT and CON (P=0.041) (Figure 1). Also, *AMPK* expression was non-significantly lower in the HIIT group than in the MCT group (P>0.005; RD=-21.63%). In addition, the expression of *PGC-1a* was higher in the HIIT (RD=+100) and MICT (RD=+273%) groups than in the CON group. Still, only the difference between MICT and CON was statistically significant (P=0.035). The expression of *PGC1-α* was non-significantly lower in the HIIT group than in the MCT group (P>0.05, RD=-46.38%).

Also, *SOD* expression was significantly higher in the HIIT group than in CON (P=0.000, RD=+405%) and MICT groups (P=0.019, RD=+54.43%) (Figure 1). In addition, MICT showed higher *SOD* expression than the CON group (P=0.004, RD=+227%) (Figure 1). Although the relative differences of MDA in the HIIT (RD=-1.37%) and MICT (RD=-27.11%) groups were lower than the CON group, no significant differences were observed between the groups (P>0.05) (Table 2).

Discussion

The present study showed that 8 weeks of MICT significantly increased the expression of *AMPK* and *PGC-1α* genes in the left ventricular tissue of healthy male rats (P<0.05). HIIT also significantly increased SOD values compared to MICT (P<0.05). However, no significant effect of HIIT and MICT training on MDA concentration in heart tissue in healthy male rats was observed (P>0.05). These results suggest that the antioxidant adaptability induced by HIIT and MICT training in heart tissue may be different. In general, this result is consistent with the results

Table 1. List of primers used in this study

Genes	Primer Sequences	Sizes (bp)
AMPK	Forward: 5′-ACTATCAAAGACATACGAGAGCA-3′ Reverse: 5′-CTTGAGGGTCACCACTGTATAA-3′	181
PGC-1a	Forward: 5′-CAGAAGCAGAAAGCAATTGAAGA-3′ Reverse: 5′-GTTTCATTCGACCTGCGTAAAG-3′	230
SOD	Forward: 5′-CAAGGAACCACAGGCCTTAT-3′ Reverse: 5′-GGCTAACATTCTCCCAGTTGA-3′	133
β2m	Forward: 5′-CGTGCTTGCCATTCAGAAA-3′ Reverse: 5′-ATATACATCGGTCTCGGTGG-3′	244

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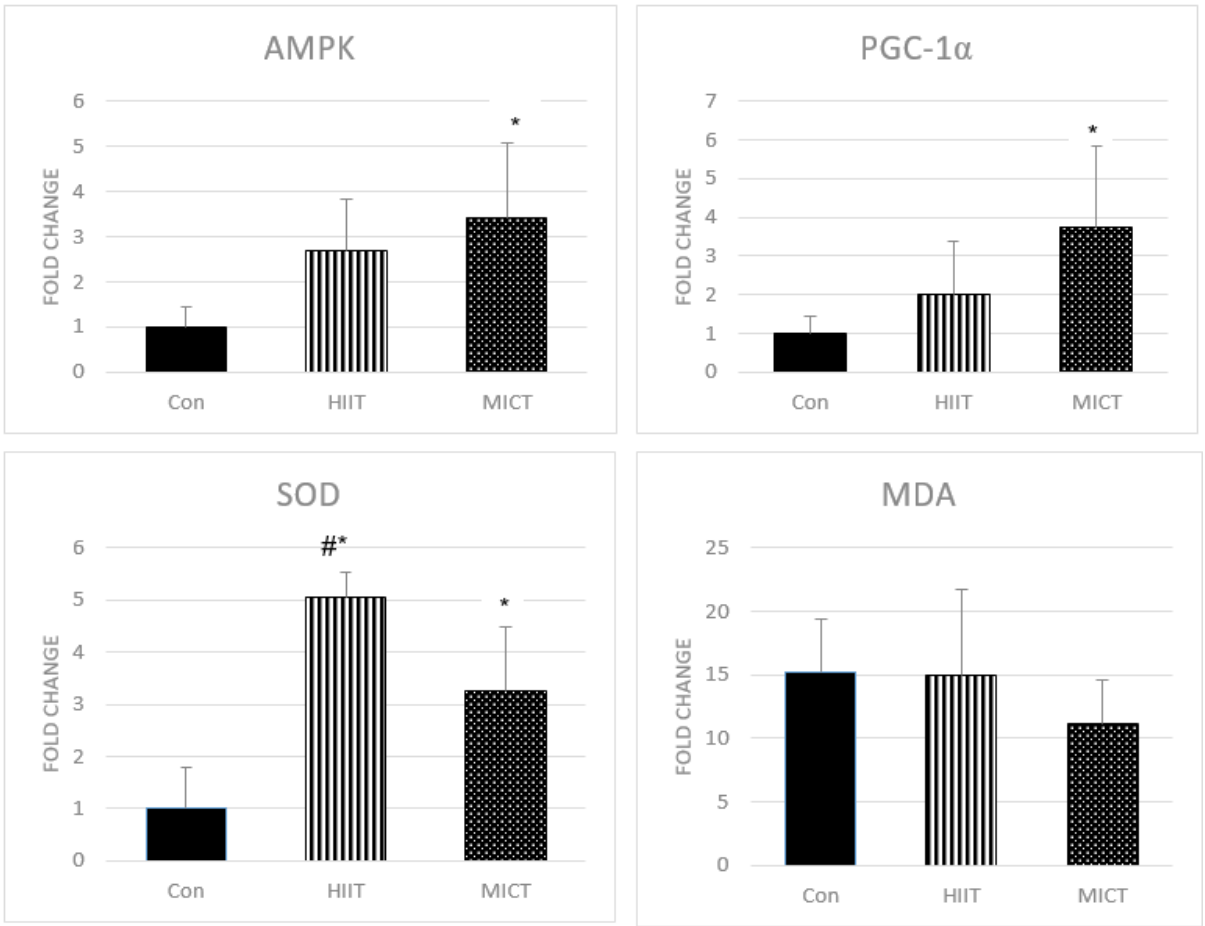


Figure 1. Changes in *AMPK, SOD, PGC-1a* gene expression and MDA concentration in left ventricular tissue after 8 weeks in the study groups

Abbreviations: HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training; ANOVA: Analysis of variance; AMPK: AMP-activated protein kinase; PGC-1a: Peroxisome proliferator-activated receptor-γ coactivator-1α; SOD: Superoxide dismutase; MDA: Malondialdehyde.

*Significant difference with the control group, #Significant difference between the HIIT and MICT groups. P<0.05.

of some previous studies [13, 17, 22, 23] and inconsistent with others [11, 12, 14, 15, 24, 25]. The discrepancies might be attributed to differences in the type of samples, research methodology, and the length of training courses. Consistent with this study, Chen et al. showed that 8 weeks of continuous swimming training (20 to 60 minutes per session, 5 sessions per week) significantly increased AMPK protein, PGC-1α, and SOD of heart tissue [22].

Another study revealed that HIIT and MICT training make the body more resistant to oxidative stress by beneficial adaptations in the antioxidant system and heart tissue [23]. Based on this study, MICT significantly affects the regulation of AMPK, PGC-1α, and SOD in the heart tissue. The results revealed that HIIT, similar to MICT, induced positive adaptations in regulating AMPK and PGC-1α in the left ventricular tissue of healthy male rats. Also, HIIT increased SOD levels more than MICT. Thus, increasing the intensity of training stimulates more antioxidant adaptations in the heart tissue. This outcome is noteworthy due to the time saving of HIIT compared to MICT.

Previous studies have indicated that upregulation of AMPK, PGC-1a, and SOD by training activates anti-aging signaling pathways and suppresses its related inflammatory cytokines [22]. In addition, studies have indicated that HIIT provides greater functional adaptations in the cardiovascular system than MICT. For example, Lu et al. reported that MICT and HIIT decreased oxidative stress in infarcted heart tissue by decreasing MDA and increasing SOD and GPx concentrations in female Sprague-Dawley rats [16]. In their study, GPx concentration and heart function were higher in the HIIT group than in the MICT group [16].

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Table 2. Comparing the main effects of the HIIT and MICT on research variables (one-way ANOVA test)

Variables	Group	Mean±SD	df	F	Sig.
AMPK	Control	1.00±0.46	(12, 2)	4.04	0.045
	HIIT	2.68±1.14			
	MICT	3.42±2.04			
PGC-1a	Control	1.00±0.44	(12, 2)	4.19	0.042
	HIIT	2.00±1.40			
	MICT	3.73±2.10			
SOD	Control	1.00±0.78	(12, 2)	26.91	0.000
	HIIT	5.05±0.47			
	MICT	3.27±1.20			
MDA	Control	15.23±4.10	(12, 2)	1.09	0.36
	HIIT	15.02±6.71			
	MICT	11.10±3.48			

Abbreviations: HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training; ANOVA: Analysis of variance; AMPK: AMP-activated protein kinase; PGC-1a: Peroxisome proliferator-activated receptor-γ coactivator-1α; SOD: Superoxide dismutase; MDA: Malondialdehyde.

$P<0.05$.

These results confirm the crucial role of training intensity in regulating redox responses in cardiac muscle tissue. Paes et al. (2020) also showed that high-intensity aerobic training is a stronger stimulant than MICT for strengthening the antioxidant defense system [17]. Although high-intensity training significantly increased GPx and SOD, the group's level of carbonyl protein (a marker of oxidative damage to proteins) increased significantly. In contrast, MICT caused a significant increase in antioxidant enzymes and a smaller increase in carbonyl protein content in rat heart tissue [17].

Although the MDA concentration in the MICT group was lower than those in the HIIT and CON groups in the present study, these differences were not significant. Thus, the results of the present study are somewhat inconsistent with the results of the study conducted by Paes et al. [17]. This inconsistency might also be due to differences in the training protocols. Thus, due to these inconsistencies, more comparative studies on the effect of HIIT and MICT on heart tissue oxidative stress markers are needed.

Another study also revealed that after 6 weeks of interval training with three different intensities (high, moderate, and low), the protein content of PGC-1α increased only in the moderate-intensity training group, and no significant changes were observed with other intensities [11]. However, the samples studied in this study were infarcted rats [11], different from the healthy samples in the present study. Also, the training period was not similar in the three groups. While in the present study, the distance traveled by the MICT and HIIT groups was the same.

Some existing mechanisms can theoretically explain the increased expression of PGC-1a, AMPK, and SOD after HIIT and MICT training. One of the proposed mechanisms is bioenergetic, redox, and mechanical stress caused by training, affecting the regulation of gene expression in the myocardium [4, 9]. During exercise, an increase in intracellular calcium activates calcium/calmodulin-dependent protein kinase, thereby triggering cyclic AMP-response element binding protein (CREB) or AMPK [3].

It has also been stated that increased ROS activates the AMPK protein complex. The activation of these molecules increases transcription of the *PGC-1α* gene [4]. Furthermore, *PGC-1α*, aside from improving the function of heart muscle cells, stimulates the expression of antioxidant genes, including *SOD*, *GPX*, and *CAT* [3,

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26, 27]. Thus, the increase in *AMPK*, *PGC-1α*, and *SOD* in the present study confirms the role of these signaling pathways in regulating adaptations resulting from training. It also suggests that a greater increase in SOD in the HIIT group than in the MICT group and higher intense training may play a role in the upregulation of SOD because AMPK and PGC-1α levels are not significantly different between the MICT and HIIT groups.

An important limitation of the present study was that only the expression of *PGC-1α* and *AMPK* were measured, with the activity, protein levels, and location of these proteins left unexplored. Thus, their measurement is recommended for future studies to determine the role of the AMPK/PGC-1α pathway in regulating *SOD* expression and activity. Another limitation was not assessing the role of these adaptations caused by training in relation to cardiac function.

In conclusion, the present study showed that 8 weeks of aerobic training stimulated the expression of *AMPK*, *PGC-1α*, and SOD, implying that aerobic training strengthens the antioxidant defense system of heart cells, especially in the heart's left ventricular tissue, and consequently prevents heart disease. Both HIIT and MICT seem to induce positive adaptations in strengthening the antioxidant defenses of heart tissue. However, more studies are needed to reach a certain conclusion about the effect of training intensity on oxidative stress-related cardiac adaptation.

Ethical Considerations

Compliance with ethical guidelines

All study procedures, including housing, care, anesthesia, and sacrifice of animals, were performed according to the Iranian National Committee for Ethics in Biomedical Research guidelines for animal research. The study proposal was approved by Shiraz University of Medical Sciences (Code: IR.SUMS.REHAB.REC.1400.005).

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Authors' contributions

Study design and data analysis: All authors. Investigation and drafting the manuscript: Saeede Yazdani; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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