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Research Article

High-intensity interval training increases thermogenesis and metabolism through changes in regulatory proteins

Amir Hosein Jafari[1], Moein Fasihiyan[2], Maryam Taheri[2], Maryam Nourshahi[2*]

Abstract

The present study aimed to investigate the effect of 4 weeks of high-intensity interval training on the amounts of metabolic proteins like Sarcolipine, PGC1α and FNDC5 in SOL and EDL muscles of male Wistar rats. In the present study, 14 adult male Wistar rats were randomly divided into experimental (n = 7) and control (n = 7) groups. The training group performed high-intensity interval training for 4 weeks and 5 sessions per week, including high-intensity (90% vVO2max) and low-intensity (45% vVO2max) two-minute intervals. Finally, the SOL and EDL muscles of the research groups were extracted, and also independent statistical t-test ($p < 0.05$) was used for statistical analysis. The results showed that the amounts of SLN, PGC1α, and FNDC5 proteins in the experimental group were significantly different from the control group in SOL muscle, but the amounts of FNDC5 protein in the EDL muscle of the HIIT group were not significantly different from the control group. The results showed that by observing the changes in the amounts of regulatory proteins related to cellular metabolism due to high-intensity interval training, this training method could be suggested to increase metabolism and improve the lipid oxidation process in a short time.

Key Words: **Metabolism, High-intensity interval training, Sarcolipin, PGC1α, FNDC5**

Introduction

Sedentary lifestyle and the reduction of physical activities, which is considered the main reason for reducing the primary metabolism of people, has become a global epidemic. One of the most critical health problems is obesity, which subsequently, according to the statistics of the World Health Organization (WHO), the number of people suffering from diseases related to metabolic factors such as diabetes, blood pressure, cancer, etc., has increased significantly in recent years (Torres et al., 2022). Obesity will be created as a result of the imbalance between calories consumed and calorie expenditure, in the meantime, the role of energy consumption by muscles in physical activities is very important, which will be associated with an increase in basic metabolism (Siedler et al., 2023). Skeletal muscles are included 40% and 32% of the body weight of men and women and also account for about 30% of a person's basic metabolism, which is the main platform for using energy-generating substrates in the body's metabolism (Bosy et al., 2015).

Exercise by using skeletal muscles will increase the amount of energy consumption, which according to different types of exercises, studies have shown that the involvement of different muscles as well as types of the phenotype of muscle fibers have different effects on the cellular-molecular changes of the different organs (Ndahimana et al., 2017; Fasihiyan et al., 2023). As a result of physical training and subsequent adaptations, the amounts and gene expression of all three groups of contractile, structural, and regulatory proteins in skeletal muscles will undergo changes, in the meantime, in terms of metabolic factors of regulatory proteins. which are present in various organelles inside the muscle cell, they play the main role in the adaptations created compared to the metabolic and mechanical stresses of training (Frontera & Ochala, 2015). In muscle contractions during training, the calcium cycle in muscle cells will release and reabsorb calcium from the cytosolic space according to the intensity of the physical activity, in which the sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) plays an important role. Wh-

1. Department of Biological Sciences in Sport and Health, Faculty of Sport Sciences and Health, Tehran University, Tehran, Iran 2. Department of Biological Sciences in Sport and Health, Faculty of Sport Sciences and Health, Shahid Beheshti University, Tehran, Iran.

*Author for correspondence: m_nourshahi@yahoo.com

M F: 0000-0003-4479-0393; M H J: 0009-0009-1474-9489; M T: 0000-002-4455-4529; M N: 0000-002-5064-8599

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-ose regulatory protein is sarcolipin (SLN) (Wang et al., 2021). Sarcolipin plays an important role in skeletal muscle thermogenesis by reducing the efficiency of calcium ion transport by the SERCA pump, and studies have shown that increasing the expression of this protein can increase the energy consumption by the SERCA pump during exercise nearly 50% (Trinh., 2013). In this regard, a study showed that inhibition of sarcolipin protein increased the efficiency of the SERCA pump and decreased the metabolism of skeletal muscles compared to the control group (WT) (Fajardo et al., 2017). On the other hand, increasing the expression of sarcolipin increases the need for ATP produced by mitochondria, and for this reason, the expression of PGC-1α increases when the expression of sarcolipin increases (Liu et al., 2022). And in addition, the changes made in the muscle cells due to physical exercise and diet supplementation cause the release of myokines that are released from the muscles into the blood, among which irisin is one of the newest known myokines. It is considered that it changes the phenotype of white adipose tissue and turns it into brown fat. This myokine is originally in the form of FNDC5 protein in the muscle and is released into the blood after breaking the peptide bonds. which will eventually increase thermogenesis and metabolism (Gheit et al., 2022; Taheri et al., 2023).

In a research, it has been reported that in the group in which the expression of sarcolipin was increased, compared to the control group and the sarcolipin inhibition group, the white fat tissue was greatly reduced, and it was also shown that the expression of sarcolipin protein levels increased in the slow-twitch fibers. (SOL) and fast-twitch fibers (EDL) cost more energy for muscles, which can be related to changes in molecular cellular factors associated with increased metabolism (Maurya et al., 2015). In addition, it was reported in another study that excessive expression of sarcolipin protein can be associated with an increase in energy consumption, and as a result of this phenomenon, mitochondrial biogenesis will increase, and muscular dystrophy will also be prevented, which will ultimately increase the metabolism of sick people (Bal et al., 2021).

However, there is a need for more extensive research in this field in order to determine the effect of these types of proteins on the body's metabolic factors as a result of exercise. Therefore, the current research aim is to investigate the effect of 4 weeks of high-intensity interval training on some factors related to increasing cell metabolism such as SLN, PGC1α, and FNDC5 in the SOL and EDL muscles of male Wistar rats.

Materials and Methods

Animals

After transferring to the laboratory environment and familiarization with the new environment (first week) and adopting to exercise with a treadmill (five sessions in the second week), the animals were randomly divided into 2 intermittent training groups (n=7) and control (n=7). became During the research period, food and water were ad libitum. rats in the animal laboratory of the Faculty of Physical Education of Shahid Beheshti University under controlled conditions of light (12 hours of light and 12 hours of darkness, light starts at 8 in the evening and darkness starts at 8 in the morning), temperature (22 ± 4 °C) and humidity (about 55 ± 4 percent) were kept. The training protocol lasted for four weeks, and during this period the animals of the control group did not have any physical activity. The training time was fixed on all days, from 9 am to 12 am. All stages of keeping and killing rats were done according to the Animal Ethics Committee of Shahid Beheshti University. This study has been approved by the Ethics Committee of the Research Institute of Physical Education and Sports Sciences with code IR.SBU.REC.1401.039.

Maximal speed test

It was done by using the standard incremental test of Bidford et al., which was standardized by Carol Guise et al. (2007) for Wistar rats (Qin et al., 2020). Each rat was tested individually and the incremental test was such that the rats started walking on the treadmill at a speed of 5 meters per minute and then every three minutes the speed of the treadmill increased by 5 meters per minute. It was found that the test continued until the moment the rat reached paralysis. The final speed of the rat was used as the maximum speed at the time of reaching the maximum oxygen consumption to calculate the training intensities. The animals were tested once a week and the training intensity was determined according to the new values of the test.

High intensity interval training protocol

According to the mentioned cases, the animals will get acquainted with the way of implementing the protocol and running on the treadmill. Considering the familiarity of the animals with treadmill exercises, the first week of interval training at a speed of 38 meters per minute at high intensity for two minutes and at a speed of 16 meters per minute at low intensity for two minutes in two sets It started. In the second, third and fourth weeks, the speed of the treadmill at high intensity increased by 1 meter per minute every week, and the number of sets also increased by 1 set every week. Before and after each training session, the animals walked on a treadmill for 5 minutes at a speed of 10 meters per minute in order to warm up and cool down (Khalafi et al., 2020).

Table 1. High intensity interval training protocol.

week	1	2	3	4
Speed (M/min)	38-16	39-16	40-16	41-16
Duration (min)	2-2	2-2	2-2	2-2
Interval (set)	2	3	4	5
Session in week	5	5	5	5

Sampling and biochemical analyses

After completing the training protocol in order to eliminate the short-term effect of exercise, 48 hours after the last training session, the rats were anesthetized by intraperitoneal injection of xylazine solution (10 mg/kg) and ketamine (70 mg/kg) and the muscle (EDL) and soleus muscle (SOL) were extracted and after washing with physiological serum and separating blood and waste materials, they were immediately placed in a liquid nitrogen tank for quick freezing and 24 hours after sampling, the weight of the tissue samples Muscle mass was calculated using a Sartorious CPA224S scale with an accuracy of 0.0001 mg, and 250 mg was separated from each muscle and transferred to a -80°C freezer. Tissue preparation and preparation: after re-equalizing the weight of all the extracted tissues, first the samples were homogenized by buffer (Tris+ HCL, pH=8, EDTA 0.003 g, NaCl 0.08 g, NaCl 0.025 Sodium deoxycholate, 0.01 gram SDS, 1.2 tablets (Protease inhibitor cocktail) were analyzed to evaluate protein amounts. To homogenize the tissue, 3 to 4 times (based on slow and fast twitch muscle tissue) the weight of the sample. The lysing buffer was poured and with a tomy 2 microsmash homogenizer, at a speed of 4000 rpm and for 8 times of 20 seconds with a time interval of 3 minutes between times to prevent heating and opening of protein bonds (denature), It was homogenized. Then the homogenized tissue was centrifuged for 12 minutes at a temperature of +4 degrees Celsius and at a speed of 3600 rpm. The soluble supernatant was separated and stored in a freezer at -80 degrees. The Bradford method was used to determine the protein concentration and The protein concentration of the samples was calculated by the standard curve.

Western blotting

To perform the western blot test, equal amounts of proteins were analyzed by 18% polyacrylamide SDS PAGE gel for sarcolipin protein (due to the low molecular weight (6 kDa) of sarcolipin protein) and 12% gel for FNDC5 proteins. and PGC1α, were used. After the electrophoresis step, the gel proteins were transferred to the PVDF paper and the paper was placed in the blocking solution for 90 minutes. Then the paper was placed in the primary antibody (ANTI-SARCOLIPIN, Merck, Germany) for 18 hours (OVERNIGHT) at a temperature of 4 degrees Celsius, and on the second day, it was washed 3 times with TBST solution, and the PVDF paper was kept for 18 hours. It was incubated with secondary antibody for 90 minutes. After this step, the blots were covered with ECL kit and exposed using radiology film. Then, the blots were washed in STREAPING buffer and the primary antibody (ANTI-FNDC5, made by Abcam, England) and for PGC1α protein, antibody (ANTI-PGC1α, Santa Cruz, made in the United States) was used, which was finally re-incubated it was done and the desired proteins appeared in the radiology film. Finally, the blots were washed again in the stripping buffer, the beta-actin antibody was placed on the paper, and the secondary antibody was incubated again. For the final evaluation, Image G software was used for densitometry of the proteins identified on the blots.

Statistical analysis

In the present study, after confirming the normality of data distribution with the Shapiro-Wilk test, Student's T (T-test) was used for independent samples to investigate the effect of the independent variable on the dependent variable. All the statistical operations of the research were done using SPSS software version 23 and the significance level was considered as $\alpha < 0.05$, and Excel 2016 software was also used to draw graphs and tables.

Results

The weight changes of the animals decreased in the experimental group compared to the control group according to the training time during 4 weeks, but these changes did not have a significant difference in the results of the statistical analysis (T-test) between the groups (P=0.058). that these changes are shown (Figure 1).

The results of the statistical test (T-test) showed that there was a significant difference between the protein levels of SLN, PGC1α and FNDC5 in the SOL muscle in the high-intensity interval training group and the control group, respectively (P=0.028), (P=0.013) and (P=0.036), (Figure 2). and Western blotting images associated with protein changes in the soleus muscle (Figure 3).

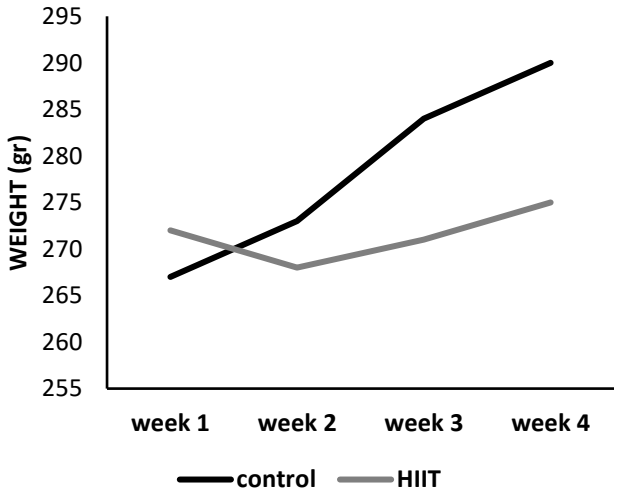

Figure 1. Average weight changes of animals during the training period in HIIT and control groups.

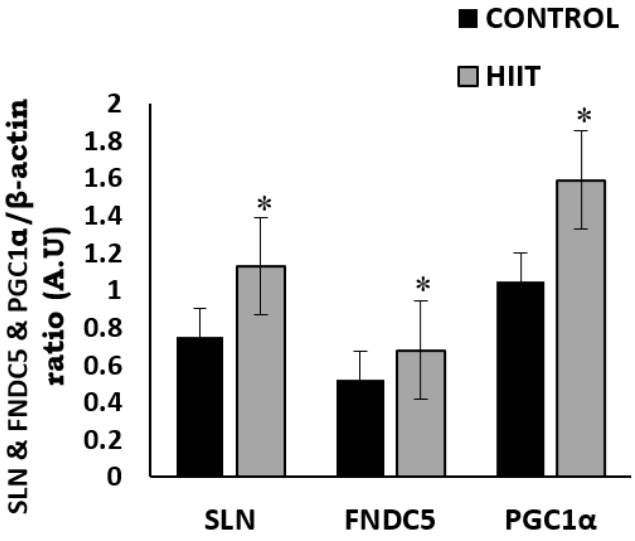

Figure 2. Changes of SLN, FNDC5 and PGC1α proteins compared to β-actin protein in HIIT and control groups in slow twitch muscle (SOL). * p<0.05.

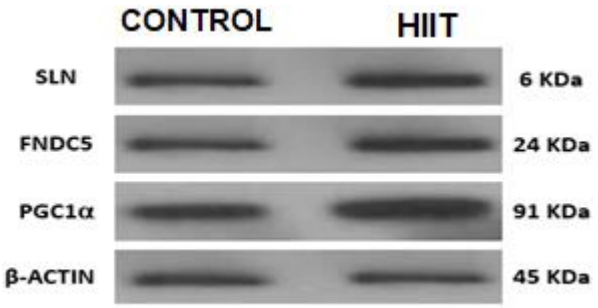

Figure 3. Changes in the expression of the research proteins in the blots measured by western blotting in the HIIT and the control group in the soleus muscle.

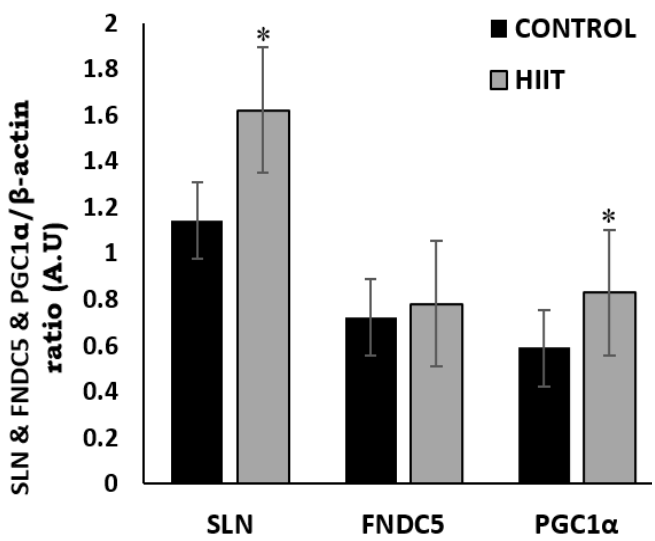

Figure 4. Changes in the expression of the research proteins in the blots measured by western blotting in the HIIT and the control group in the extensor digitorum longus (EDL) muscle. * p<0.05.

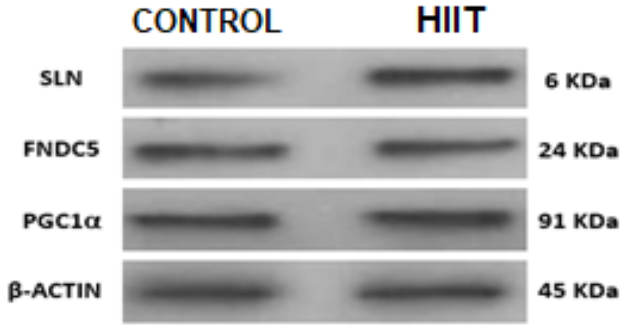

Figure 5. Changes in the expression of the research proteins in the blots measured by western blotting in the HIIT and the control group in the extensor digitorum longus (EDL) muscle.

Also, a significant increase was observed in the expression levels of SLN and PGC1α proteins in the EDL muscle (P=0.02) and (P=0.034) respectively, but in the levels of FNDC5 protein in the EDL muscle among the research groups, no significant changes were observed (P=0.14), (Figure 4). Figure 5 is related to the changes in the expression of research proteins in the blots measured by western blotting in SOL and EDL muscles.

Discussion

According to the investigations and statistical analysis carried out in the present study, it was found that performing high-intensity interval training due to the metabolic and mechanical stress on fast-twitch muscles at high intensities and slow-twitch muscles at low intensities, cause changes in the amounts of regulatory proteins in the process of metabolism and energy production in the organs effective in muscle contractions. Thus, in this study, high-intensity interval training increased the amount of sarcolipin protein (SLN) as a regulator of calcium exchange through the SRCCA pump, which is associated with significant energy consumption, in both types of ST and FT fibers. These changes were observed along with the increase of the effective factor in mitochondrial biogenesis (PGC1α) in both types of muscle, as well as the effective factor in fat tissue metabolism (FNDC5) in SOL muscle. On the other hand, it can be considered that these changes will increase the calories consumed during and after exercises, which can ultimately be related to the increase in basic metabolism and control of weight management.

In this regard, studies have shown that an important part of the increase in basal metabolism by exercise is related to the calcium cycle in the process of muscle contraction in the conditions of activity and rest, which requires energy expenditure (Periasamy et al., 2017). Therefore, it has been reported in a study that the amount of energy consumption in the conditions of physical activity considering that the percentage of FT and ST fibers in the

SOL muscle is 30% and 70% for each type of fiber, respectively, and in the EDL muscle fiber is 90%. The percentage of FT and 10% of ST are equal to 50% of the total energy expenditure, and it is also generally reported that between 17 and 22% of the total basal metabolic energy is dedicated to the calcium cycle That in this research have investigated the energy contribution of the SERCA pump and the calcium ion cycle in resting metabolism conditions in fast and slow twitch muscles. This research was conducted on 93 adult male mice in a 12-hour sleep-wake cycle with available food. The results of this research showed that the difference in oxygen consumption of muscles related to the level of ATP energy charge by SERCA pump and mitochondrial activity was different in different phenotypes of muscle fibers. At the end, the results of this study supported the 50% contribution of SERCA pump ATP consumption in resting metabolism in both SOL and EDL muscles. These results emphasize the importance of the role of skeletal muscles in the energy contribution of the whole body and suggest that the SERCA pump can be an important element for regulating energy balance and metabolic changes to deal with obesity and other metabolic disorders (Norris et al., 2010).

In the research conducted in the field of calcium exchanges by SERCA pump and its connection with the energy generation process, methods such as inhibitors and enhancers of the activity of regulatory proteins are used, in this regard, have reported in a study that the inhibition of sarcolipin protein caused a decrease in basal metabolism by reducing the process of non-shivering thermogenesis (NST) and reducing the conversion of white adipose tissue to brown by reducing the UCP1 protein, and in addition, inhibiting sarcolipin through Decreased activation of the calmodulin kinase pathway caused decreased changes in the levels of mitochondrial regulatory proteins (Bal et al., 2020). On the other hand, another study has showed the changes in sarcolipin protein levels are not dependent on the amount of mitochondrial biogenesis due to exercise and diets (Gamu et al., 2017) and also, a study has investigated the effect of four weeks of incremental endurance training on sarcolipin, FNDC5 and PGC1α proteins in Soleus and extensor digitorum longus of male Wistar rats, and the results of this research showed that moderate intensity training caused SLN and pgc1α increased in SOL and EDL muscle that due to the intensity of training these changes were higher in SOL muscle (Fasihiyan et al., 2021). In order to determine the effect of sarcolipin protein changes, Ball et al. SLN/SERCA increase the signaling of proteins related to calcium exchanges, mitochondrial biogenesis and oxidative metabolism, which will ultimately increase energy consumption by muscles (Bal et al., 2021). In this regard, it has been determined that exercise is one of the important factors for increasing the expression of SLN protein, and finally, after adapting to physical training, part of the increased effect of meta-bolism due to training can be attributed to the sarcolipin protein (Martinez et al., 2021). Moreover, another study has shown that following exercise training in fast and slow twitch muscles in the group where SLN levels were increased, glycolytic enzymes in EDL muscle and oxidative enzymes as well as mitochondrial biogenesis in muscle SOL had a significant increase, and in addition, in the group where SLN protein was increased, the resistance to fatigue during physical activity increased strongly (Sopariwala et al., 2015).

Moreover, in accordance with the findings of the present study, it has been reported that the overexpression of sarcolipin caused an increase in the mitochondrial mass in fast-twitch muscles, and in addition, an increase in CaMK and CaN aligned with an increase in PGC-1α, which the results of this study show By itself, sarcolipin can control oxidative capacity through calcium-dependent signaling pathways and the ratio of ATP to ADP, and the increase in sarcolipin levels can affect mitochondrial content through AMPK and CaMK signaling pathways. and the activation of PGC-1α (Maurya et al., 2015). In addition, it has been reported in a review study that there is a direct relationship between PGC1α and FNDC5 changes as a result of exercise, in this regard, reported in a review study that as a result of interventions such as being in Exposed to cold, consumption of high-fat food (HFD), illness and exercise, the amount of proteins related to thermogenesis will increase, among which SLN, PGC1α proteins and also proteins effective in converting white adipose tissue to brown adipose tissue. such as UCP1 and FNDC5 are also increased, and finally these changes will increase the basic metabolism (Maurya et al., 2018).

In general, effective interventions on thermogenesis, such as exercise training, due to different metabolic and mechanical pressures, cause unique physiological changes in the amounts and expression of regulatory proteins, which will require many studies to understand these factors. The limitations of the research in the current study were the evaluation of the gene expression of the proteins in the study, as well as the use of the method of inhibitors and enhancers of sarcolipin protein activity, as well as the lack of measurement of fat phenotype changes. Finally, according to the results of this research, it is suggested that in a similar research, the effect of inhibitors and stimulators of SLN protein gene expression and metabolic proteins such as UCP1 should also be investigated in long-term periods of time.

Conclusions

According to the results of the present research, high-intensity interval training due to high metabolic stress can increase the amount of proteins affecting the body's energy expenditure and basic metabolism, such as sarcolipin, FNDC5 and PGC1α proteins, in different phenotypes of fibers, increase the muscle

mass, which can increase the burning of fat and reduce the disorders related to obesity by increasing the basic metabolism. Therefore, by examining and understanding the physiological factors, in terms of cellular-molecular changes, it can be concluded that high-intensity interval training, through the adjustments of the calcium cycle (SLN), the process of converting white adipose tissue to brown (FNDC5) and mitochondrial biogenesis (PGC1α), can increase basal metabolism and be used as a non-invasive agent in the prevention and treatment of obesity-related diseases.

What is already known on this subject?

Physical exercises with high intensity can increase the metabolism in the resting situation, which increases the energy consumption in the form of heat generation through the increase of the regulatory proteins in the muscles.

What this study adds?

HIIT method increases calcium pump regulatory proteins, which subsequently consume more energy in the sarcoplasmic reticulum to regulate the calcium cycle by increasing the sarcolipin protein, which increases mitochondrial biogenesis and ultimately produces and consumes more ATP.

Organ Cross-Talk Tips:

- Cross-talk between organelles of muscle cells such as sarcoplasmic reticulum and mitochondria in fast and slow fibers through intracellular signaling cause thermogenesis and increase metabolism, which will ultimately increase lipolysis.
- Cross-talk between types of muscle and regulatory proteins according to the intensity of the exercises that cause changes in body fat mass.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study has been approved by the Ethics Committee of the Research Institute of Physical Education and Sports Sciences with code IR.SBU.REC.1401.039.

Informed consent Animal study.

Author contributions

Conceptualization: M.F., A.J., M.N; Methodology: M.F., M.T.; Software: A.J.; Validation: M.F., M.T.; Formal analysis: M.N., M.F.; Investigation: M.T.; Resources: M.F.; Data curation: M.F., M.T.; Writing - original draft: M.N., M.F.; Writing - review & editing: M.F., M.N.; Visualization: A.J.; Supervision: M.N.; Project administration: A.J., M.N.; Funding acquisition: M.N.

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