Endurance Training and MitoQ Supplementation Increase PERM1 and SMYD1 Gene Expression and Improve Hemodynamic Function in the Cardiac Muscle of Male Wistar Rats

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Abstract

Background: Histone methyltransferase (SMYD1) and the muscle-specific protein PERM1 play an important role in maintaining cardiac energetics and function. The present study aimed to examine the effect of two types of endurance training (running and swimming) plus MitoQ supplementation on PERM1 and SMYD1 gene expression and the hemodynamic function of the cardiac muscle of male Wistar rats.

Methods: The animals underwent MitoQ supplementation alone, endurance training alone, or endurance training + MitoQ supplementation for eight weeks. The gene expression of PERM1 and SMYD1, which was measured by real-time polymerase chain reaction (PCR) and quantified by 2⁻ΔΔCT method, and hemodynamic function were compared between groups using two-way multivariate analysis of variance.

Results: Cardiac gene expression of PERM1 and SMYD1 increased significantly through running (PERM1, P < 0.05; SMYD1, P < 0.01), swimming (PERM1, P < 0.05; SMYD1, P < 0.05) and MitoQ supplementation (PERM1, P < 0.001). The effects of MitoQ supplementation on the cardiac gene expression of PERM1 were additive to the effects of both running and swimming (PERM1, P < 0.001; SMYD1, P < 0.05). Swimming-induced enhancement in cardiac expression of PERM1 and SMYD1 was associated with a significant increase in ±dP/dt max (P < 0.05).

Conclusion: The expression of genes involved in cardiac metabolism can be affected by endurance training and this effect could be improved through MitoQ supplementation.

Keywords: Endurance training, PERM1, SMYD1, Hemodynamic function, Energy production

Introduction

The cardiac muscle is an organ with high dependence on energy. Energy homeostasis via mitochondrial oxidative phosphorylation, is indispensable for sustained cardiac contractile function, which is why the number of mitochondria is high in the heart (1). The contractile capacity of cardiomyocytes is improved by specialized energy transmission systems (2). Transduction pathways and transcriptional regulators of energy metabolism, including members of the peroxisome proliferator-activated receptor gamma coactivator 1 (PGC1) family, one of the most important metabolic molecules in mitochondrial biogenesis and oxidative metabolism (3), and estrogen-related receptors (ERRs) in particular play a key role in energy metabolism, transcriptional regulation of energy homeostasis, biogenesis, and mitochondrial function and dynamics (4,5).

Energy production is essential to maintaining cardiac function. Recent studies have shown that PERM1 and SMYD1 play an essential role in maintaining energy homeostasis and cardiac function (6-8). Peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1α) and PPARGC1 and ESRR-induced regulator muscle 1 (PERM1) are specifically expressed in skeletal and cardiac muscles and regulate cardiac energy metabolism (7). PERM1 is induced by PGC-1α and ERR, the master regulators of cardiac energy metabolism and mitochondrial biogenesis, which interact with various transcriptional factors involved in the tricarboxylic acid (TCA) cycle, OXPHOS, and mitochondrial substrate...
metabolism. Additionally, with the help of supporting lipid and amino acid homeostasis, it plays an important role in regulating energy metabolism (9,10).

The SET and MYND domain-containing proteins (MYND) consist of five members in humans and mice (i.e., SMYD1, SMYD2, SMYD3, SMYD4, and SMYD5). These proteins have methyltransferase activity on histone and non-histone substrates (11). SMYD1 is a striated muscle-specific histone methyltransferase epigenetic factor (12). SMYD1 interacts with various transcription factors and leads to metabolic reactions. It is an upstream regulator of PGC-1α, which is the master regulator of cardiac metabolism (6,8,13). PERM1 regulates a subset of PGC-1s/ERRs target genes as part of the SMYD1 metabolic network (6,8). PGC-1α is highly inducible in response to physiological conditions, such as endurance training, to send signals to boost myocardial ATP production (14).

Endurance training improves aerobic fitness and cardiac function and has a positive effect on hypertrophy and angiogenesis of cardiac muscle (15,16). In animals, running on a treadmill and swimming, as two common endurance training models, it enhances energy demands and leads to improvement of cardiac contractility, relaxation, and systolic capacity (17). Meanwhile, endurance training increases oxidative phosphorylation capacity and capillary density in the cardiac muscle (18,19). PERM1, as an exercise-induced gene, affects the response of oxidative metabolism in muscles (20). Additionally, a recent study has reported that resistance training after myocardial infarction leads to enhanced SMYD1 expression (21). Nevertheless, the impact of different types of training on PERM1 and SMYD1 expression in cardiac muscles is still not fully understood.

Antioxidant supplements are commonly consumed by endurance athletes to accelerate training-induced oxidative stress recovery and improve performance. MitoQ is a mitochondria-targeted antioxidant supplement which eliminates reactive oxygen species (ROS), and reduces mitochondrial oxidative damage (22). MitoQ improves cardiomyocyte damage (23), cardiac hypertrophic remodeling (24), and training-induced mitochondrial DNA damage (25). Xi et al indicated that MitoQ alleviated mitochondrial damage by increasing PGC-1α, which plays an important role in mediating mitochondrial biogenesis (26). However, the effect of MitoQ on PERM1 and SMYD1 gene expression in the cardiac muscle has not been investigated.

Although recent studies have shown that PERM1 and SMYD1 play a crucial role in maintaining energy homeostasis and cardiac function and it is well established that endurance training enhances mitochondrial content and function, no study has investigated the effectiveness of dietary and training interventions on PERM1 and SMYD1 gene expression in the cardiac muscle. Due to the importance of mitochondria in cardiac energy production, the current study investigated the possible beneficial effects of the simultaneous use of MitoQ supplementation, as a targeted mitochondrial antioxidant, and endurance training, as the most effective stimulator of cardiac energy metabolism.

Materials and Methods

Animals
Forty-two male Wistar rats (180–220 g) were obtained from Kerman University of Medical Sciences. The rats were kept under standard conditions (12 hours/12 hours light/dark cycle) with controlled temperature (22–23 °C) and free access to regular water and food. These rats were randomly divided into six groups (n = 7): (1) control group which received normal rat nutrition and was not subjected to any training intervention or supplementation (C), (2) Supplementation group, which received MitoQ supplement (MQ), (3) Endurance training group, which had a treadmill training protocol 5 days a week for 8 weeks (RT), (4) Treadmill endurance training + supplement group, which received supplement in addition to the treadmill training protocol (RT-MQ); (5) Swimming endurance training group, which performed a swimming training protocol 5 days a week for 8 weeks (ST), and (6) rats that received supplement in addition to the swimming training protocol (ST-MQ). The experimental protocol was approved by the Ethics Committee of the Faculty of Veterinary Medicine at Shahid Bahonar University of Kerman (license number: IR.UK.VETMED.REC.1400.010).

Endurance training protocol
The endurance trainings in this study involved running on a treadmill, 5 days/week for 8 weeks and swimming. The intensity and duration of trainings gradually increased. The training protocols consisted of running on a treadmill (intensity between 15 m/min and 26 m/min for 20–60 minutes) and swimming (load between 0 and 3% of body mass for 30–60 minutes). For the latter protocol, three rats were put into a swimming pool (60 cm depth and 140 cm diameter). Table 1 reports the training protocols.

Table 1. Continuous swimming and running in treadmill training protocols.
<table>
<thead>
<tr>
<th>Week</th>
<th>Continuous swimming training</th>
<th>Treadmill running training speed</th>
</tr>
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<tbody>
<tr>
<td>1st</td>
<td>0%</td>
<td>30 min</td>
</tr>
<tr>
<td>2nd</td>
<td>0%</td>
<td>40 min</td>
</tr>
<tr>
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<td>1%</td>
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</tr>
<tr>
<td>6th</td>
<td>2%</td>
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</tr>
<tr>
<td>7th</td>
<td>3%</td>
<td>50 min</td>
</tr>
<tr>
<td>8th</td>
<td>3%</td>
<td>60 min</td>
</tr>
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training protocols used during this study (27,28).

**MitoQ supplementation**
The MitoQ group rats were given an oral administration of MitoQ (250 μM MitoQ, MitoQ Company, New Zealand) daily through drinking water for a period of 8 weeks. Based on previous findings of effective doses and durations of treatment with MitoQ, the dose of 250 μM was found to be safe. MitoQ was prepared fresh and administered in light-protected water bottles that were changed every 3 days (29,30).

**Hemodynamic measurements**
Forty-eight hours following the last training session, all animals were weighed and then anesthetized with intraperitoneal injection of sodium thiopental (50 mg/kg). To evaluate the left ventricular performance, a polyethylene catheter (PE-50) filled with heparin saline (15 units/mL) was inserted into the right carotid artery and advanced into the left ventricle (LV) through the aortic valve (31). The left ventricular systolic pressure (LVSP), end diastolic pressure (LVEDP), maximal positive changes in left ventricular pressure (+dP/dt max, a contractility index), maximum rate of reduction in left ventricular pressure (-dP/dt max, a relaxation velocity index), contractility index [ + max dP/dt divided by pressure (P) at the time of maximum change with the dimension of 1/s], and Tau (left ventricular relaxation time constant as a relaxation index of the cardiac muscle) indices were measured and calculated. After 15 minutes of recording, the inferior vena cava was closed, and the lungs were washed by injecting 10 ml normal saline into the RV for 1 minute. Then we separated the cardiac muscles and weighed them. Left ventricular hypertrophy index was estimated using the following formula: Left ventricular weight (mg)/body weight (g). During the experiment, body temperature was maintained at 37 °C by a thermostat attached to a metal plate placed in the center of the operating table. The heart and left ventricle muscles and weighed them. Left ventricular hypertrophy index was estimated using the following formula: Left ventricular weight (mg)/body weight (g). During the experiment, body temperature was maintained at 37 °C by a thermostat attached to a metal plate placed in the center of the operating table. The heart and left ventricle muscles and weighed them. Left ventricular hypertrophy index was estimated using the following formula: Left ventricular weight (mg)/body weight (g). During the experiment, body temperature was maintained at 37 °C by a thermostat attached to a metal plate placed in the center of the operating table. The heart and left ventricle muscles and weighed them. Left ventricular hypertrophy index was estimated using the following formula: Left ventricular weight (mg)/body weight (g).

**Real-time PCR**
Total RNA was extracted by total RNA extraction kit (Bio Basic, CANADA), according to the RNA isolation protocol of the manufacturer’s instruction. The cardiac tissues (15–30 mg) were homogenized to a fine powder in liquid nitrogen. After this step, 350 μL of buffer lysis-DR buffer was added to the powdered tissue. It was then incubated for 5 minutes at room temperature. The resulting mixture was then centrifuged for 1 minute at 9000 g at room temperature. Ethanol (250 μL) was added to it and mixed thoroughly. The material was transferred to the EZ-10 RNA column and then centrifuged at ambient temperature at 9000 g for 1 minute. After that, 500 μL of GT solution was added and after resting at room temperature for 1 minute, it was centrifuged at 9000 g for 1 minute at room temperature. The flow-through was discarded. Then, 500 μL of NT solution was added and after resting at room temperature for 1 minute, it was centrifuged at 9000 g for 1 minute at room temperature. Following the protocol, we centrifuged the mixture at 9000 g for 2 minutes and opened the lid until the ethanol completely evaporated.

Next, 30–50 μL RNase-free water was added. The mixture was kept at room temperature for 2 minutes and then centrifuged at 9000 g for 2 minutes. After determining the concentration and purity of the total RNA by a NanoDrop spectrometer (HELA, USA), the cDNA was synthesized by using a cDNA Synthesis kit according to the manufacturer’s protocol (Parstous, Iran). Real-time PCR was performed on an ABI StepOne Plus instrument. The thermal reaction was as follows: Stage 1: Denaturation, 95 °C for 10 minutes, Stage 2: 40 cycles at 95 °C for 20 seconds, and 60 °C for 30 seconds, and finally, melt curve analysis was performed, which started from 60 °C and increased by 0.3°C. 18S was used as a housekeeping gene and the expression of target genes was quantified by the 2^(-DeltaCt) method. The sequences of primers are listed in Table 2.

**Statistical analysis**
All data were shown as mean ± SEM. Statistical analyses were performed using Prism 7 (GraphPad Software, Inc.) and SPSS software version 28 (SPSS Inc., Chicago, IL, USA). The MANOVA test (two-way) was used for comparison. P<0.05 was considered statistically significant.

**Results**
*The effect of endurance trainings and MitoQ supplementation on heart and left ventricular muscle weight*
A significant main effect of swimming training was found in relation to heart weight-to-rat weight ratio (HW/RW) [F (1, 23) = 7.357, 26%, P<0.05] and left ventricular weight-to-rat weight ratio (LVW/RW) [F

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**Table 2. Quantitative real-time polymerase chain reaction primers**

<table>
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<tr>
<th>Primers</th>
<th>Forward primer (5'-3')</th>
<th>Reverse primer (5'-3')</th>
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<tr>
<td>SMYD 1</td>
<td>CACATCTTGGTGATGATG GCC</td>
<td>CTCATCGCCGACGACTTGG</td>
</tr>
<tr>
<td>PERM 1</td>
<td>GAAAAACAGTCCTGCTCG GCC</td>
<td>CTTGCACCTGGGTTCGCTT</td>
</tr>
<tr>
<td>18S</td>
<td>ACCACAGGATCGAAACAA ACC</td>
<td>GACAAATGCTTTTGTTCGATTG</td>
</tr>
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(1, 23) = 5.071, 20%, P < 0.05] in the swimming training group (Figure 1a, b). The animals from the swimming training group had higher HW/RW (P < 0.05) and LVW/RW (P < 0.05).

**The effect of endurance training and MitoQ supplementation on hemodynamic functions**

Swimming training caused a significant increase in the values of heart rate, +dP/dt max, and -dP/dt max indices [max +dP/dt F (1, 23) = 15.207, 40%, P = 0.001; -dP/dt F (1, 23) = 15.316, 40%, P = 0.001; cardiac rate F (1, 23) = 13.114, 37%, P = 0.001] (Figure 2a, b).

MitoQ supplementation illustrated a significant impact on the +dP/dt max index [swimming +dP/dt F (1, 23) = 5.680, 20%, P = 0.026; running +dP/dt F (1, 24) = 7.472, 24%, P = 0.012] (Figure 2c).

The +dP/dt max, -dP/dt max, and heart rate (P < 0.01) indices were significantly greater in swimming training. Eight weeks of consumption of MitoQ supplement significantly increased +dP/dt max (P < 0.05) in the swimming and running training.

**The effect of swimming training and MitoQ supplementation on PERM1 and SMYD1 gene expression**

PERM1 and SMYD1 gene expression data displayed significant training effect [PERM1 F (1, 23) = 6.478, 22%, P = 0.018; SMYD1 F (1, 23) = 6.394, 22%, P = 0.017] (Figure 3a), supplement effect [PERM1 F (1, 23) = 116.457, 83%, P = 0.000; SMYD1 F (1, 23) = 12.816, 36%, P = 0.002] (Figure 3b), and interaction effect between the effect of swimming training and supplement [PERM1 F (1, 23) = 37.682, 62%, P = 0.000 (Figure 3c, e); SMYD1 F (1, 23) = 4.388, 16%, P = 0.047 (Figure 3d, f)].

PERM1 (P < 0.05) and SMYD1 (P < 0.05) gene expression significantly increased in the training group. Eight weeks of consumption of MitoQ supplement significantly increased PERM1 (P < 0.001) and SMYD1 (P < 0.01) gene expression in the animals receiving MitoQ supplementation.

**The effect of running training and MitoQ supplementation on PERM1 and SMYD1 gene expression**

PERM1 and SMYD1 gene expression data revealed significant training effect [PERM1 F (1, 22) = 7.556, 26%, P = 0.012 (Figure 4 a); SMYD1 F (1, 22) = 8.440, 39%, P = 0.001 (Figure 4 a)], supplement effect [PERM1 F (1, 22) = 14.511, 84%, P = 0.000 (Figure 4 b); SMYD1 F (1, 22) = 0.167, 8%, P = 0.686 (Figure 4 b)], and interaction effect running training + supplement [SMYD1 F (1, 22) = 42.370, 66%, P = 0.000 (Figure 4 c, e); PERM1 F (1, 22) = 34.388, 61%, P = 0.000 (Figure 4 d, f)].

The expression of PERM1 (P < 0.05) and SMYD1...
Effect of endurance training and MitoQ on cardiac muscle

* * *

(P<0.01) was significantly higher in the trained group, but it had no significant change in the control group. Eight weeks of consumption of MitoQ supplement significantly enhanced PERM1 (P<0.001) gene expression compared to the control group.

The effect of endurance trainings and MitoQ supplementation on PERM1 and SMYD1 gene expression

SMYD1 and PERM1 gene expression data demonstrated the significant effect of training [PERM1 F(2, 23) = 12.451, 43%, P = 0.000 (Figure 5a); SMYD1 F(2, 23) = 5.999, 27%, P = 0.006] (Figure 5a), supplement effect [PERM1 F (1, 33) = 105.507, 76%, P = 0.000 (Figure 5a); SMYD1 F (1, 33) = 0.828, 2%, P = 0.396 (Figure 5b)], and the interaction effect of endurance training + supplement [SMYD1 F (2, 33) = 15.366, 48%, P = 0.000 (Figure 5c, d); PERM1 F (2, 33) = 22.992, 58%, P = 0.000 (Figure 5c, e)].

Training groups experienced a significant increase in PERM1 (P<0.001) and SMYD1 (P<0.01) gene expression. Eight-week MitoQ consumption indicated a greater effect on PERM1 (P<0.001).

Discussion

The present study aimed to investigate the effect of two different types of endurance training in addition to MitoQ supplementation as the mitochondria-targeted

![Figure 3. The effect of swimming training (a) and supplement (b) on changes in PERM1 gene expression compared to the 18S and SMYD1 genes; interaction effect between swimming training and supplement of SMYD1 (c, e) and PERM1 (d, f), ST-MQ (n=7), swimming training (ST) (n=6). The results are presented as mean ± SEM. * P<0.05; ** P<0.01; *** P<0.001.](image-url)
antioxidant on the expression of PERM1 and SMYD1 genes in the cardiac muscle of male Wistar rats. The results indicated swimming training increased cardiac hypertrophy and improved the contractility index as well as relaxation of the heart. Both types of endurance training enhanced the expression of the SMYD1 and PERM1 genes. Furthermore, the interaction of the two types of training + supplement synergistically augmented the expression of SMYD1 and PERM1 genes compared with training or supplementation alone. In addition, MitoQ supplementation greatly increased PERM1 gene expression.

Endurance training is widely assumed to improve cardiovascular and metabolic adaptations (32-34). It can induce physiological cardiac hypertrophy with improved contractile function (34,35). Our findings indicated that swimming training promotes the heart and left ventricular hypertrophy and improves ventricular contraction (+ dP/dt), contractility velocity index, relaxation index (-dP/dt), contractility, and Tau relaxation index. This positive effect was more prominent in the cardiac contractility and + dP/dt indices, which were enhanced in the swimming training group.

Swimming is a form of high-stress training which has several advantages compared to other types of training. The concentrations of stress hormones, such as catecholamine, are more stable compared with running on a treadmill (36). Higher norepinephrine and adrenaline levels than training on a treadmill lead to activation of the sympathetic nervous system (37). The water’s hydrostatic pressure exerted on the blood vessels leads to vasoconstriction and forces the cardiac wall to
produce stronger contractions to overcome this increased resistance, leading to hypertrophy (38). The heart has to keep contracting to provide the body with the oxygen and nutrients it needs.

The changes caused by the hypertrophy of the heart and left ventricle and its effect on hemodynamic parameters in swimming training can be attributed to the heart’s physiological adaptations induced by the training. The effects of MitoQ supplementation together with swimming or running endurance training were also examined on heart weight, left ventricular weight, heart weight to body weight ratio, and left ventricular weight to body weight ratio.

SMYD1 plays a crucial role in heart development, where it appears to be downstream of the binding factor GATA 6 (GATA6) and upstream of the heart- and neural crest derivatives-expressed protein 2 (HAND2) (13). It has been reported that SMYD1 overexpression is sufficient to improve the cardiac hypertrophy phenotype (39) and enhance mitochondrial respiration capacity (6).

In the present study, running and swimming training enhanced the expression of SMYD1 gene by 39 and 23%, respectively. The findings of Liang et al indicated four weeks of interval training ameliorated cardiac function in rats after myocardial infarction, leading to increased expression of SMYD1, cardiac troponin I (cTnI), and α-actinin among other changes in gene expression (21).

The regulation of SMYD1 in metabolism is through transcriptional control of PGC-1α (6). PGC-1α is abundant in the heart after training. Treadmill running (40,41) and swimming (42,43), separately and combined, increase PGC-1α expression in the rat myocardium. Many studies have shown that the limited capacity of cardiac cells to regenerate increases with endurance training such as running and swimming (44,45). Additionally, Oka et al reported that SMYD1 interacts with PERM1 promoter in cardiomyocytes and activates its expression (8).

Endurance training reduces the level of ATP and elevates intracellular calcium, which activates two pathways, AMP-activated protein kinase (AMPK) and

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Figure 5 The effect of endurance training and supplementation on changes in SMYD1 gene expression compared to 18S (a) and PERM1 genes (b); The effect of supplementation on changes in SMYD1 gene expression compared to 18S (a) and PERM1 genes (c); interaction effect between endurance training and supplementation of SMYD1 (d) and PERM1 (e). The results are presented as mean ± SEM (n = 7; *P<0.05; ***P<0.001)
calcium calmodulin/dependent protein kinase (CaMK); PERM1 is important for CaMKII activation and PGC-1α induction (20). In addition, PERM1 regulates homeostasis of lipid and amino acid metabolites in mitochondria, where PERM1 ablation alters the levels of various lipids, amino acids, and acyl carnitine species, promoting mitochondrial biogenesis of the heart and protecting against hypoxic damage (9). In our study, running on a treadmill and swimming training affected the expression of the PERM1 gene, by 26% and 23%, respectively. Thus, the expression of the SMYD1 and PERM1 genes in the cardiac tissue may have been enhanced under the influence of endurance activity. The high fluctuations in the energy requirement of cardiac and skeletal muscles might also explain why PERM1 is only detected in these tissues. Gioscia-Ryan et al (30) and Rossman et al (46) have reported that MitoQ provides antioxidant effects. In addition, the molecular structure of MitoQ contains CoQ10 and TPP cations, which makes it several hundred-fold more potent than an untargeted antioxidant in terms of preventing mitochondrial oxidative damage (47). PGC-1α is a transcriptional coactivator which plays an important role in mediating mitochondrial biogenesis. Xi et al indicated that MitoQ treatment increases PGC-1α expression in a dose- and time-dependent manner (26). Swimming therapy upregulates PGC1α and GLUT4 mRNA expression in the heart and reduces the activity of the antioxidant enzymes (42). Our findings revealed MitoQ supplementation was effective in PERM1 gene expression and it is possible that a certain level of oxidative stress may stimulate its increase.

Investigation of the trainability of the smyd1 gene, has focused on the expression of this gene in high oxidative stress and pathological conditions, and there is a lack of studies on the physiology and exercise conditions in the cardiac tissue. We chose two different types of moderate-intensity endurance training. Although one type of exercise was sufficient, we wanted to have a better understanding of the effect of different swimming and running training protocols on the expression of this gene and examine whether it can be taught.

According to several reports, the use of antioxidant supplements and training for reducing oxidative stress can be an effective health strategy to maintain an optimal antioxidant status (48,49). The benefits of antioxidant supplements may be related to improving cellular redox status and lowering oxidative changes in DNA, lipids, and proteins (50). A recent study has shown that MitoQ protects against training-induced increases in mitochondrial DNA damage (25). Broome et al indicated MitoQ would improve 8 km cycling time trial performance compared to placebo (51). Consequently, it is plausible to hypothesize that strategic supplementation may be a good approach to mitigate the training-induced oxidative stress and improve its recovery following endurance training. We observed that endurance training with MitoQ supplementation further enhanced PERM1 and SMYD1 gene expression. Swimming training + supplementation and running training + supplementation affected PERM1 gene expression by 62% and 61%, respectively. Also, the interaction effect of running training + supplement and swimming training + supplement affected the SMYD1 gene expression by 66% and 16%, respectively. Given that the effect of swimming + supplement training had the least effect, further investigation on this finding is necessary.

Our findings showed that regardless of type, endurance training affected PERM1 and SMYD1 gene expression by 27% and 43%, respectively. We also observed that the combined use of endurance training and MitoQ supplementation favorably affected PERM1 and SMYD1 gene expression by 58% and 48%, respectively.

Conclusion
Both types of endurance training had beneficial effects on PERM1 and SMYD1 gene expression. A synergistic effect was also observed between endurance training and MitoQ supplementation on PERM1 and SMYD1 gene expression.

Authors’ Contribution
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Formal analysis: Soheil Aminizadeh, Mahboube Salajeghe Tezergi.
Funding acquisition: Mahboube Salajeghe Tezergi.
Investigation: Rohollah Nikooie.
Methodology: Mahboube Salajeghe Tezergi.
Project administration: Rohollah Nikooie.
Resources: Daruosh Moflehi.
Software: Mahboube Salajeghe Tezergi.
Supervision: Rohollah Nikooie.
Validation: Daruosh Moflehi.
Visualization: Soheil Aminizadeh.
Writing-original draft: Rohollah Nikooie, Soheil Aminizadeh.
Writing-review & editing: Rohollah Nikooie, Soheil Aminizadeh.

Competing Interests
No conflict of interest, financial or otherwise, is declared by the authors.

Ethical Approval
All procedures in the present study were approved by the Ethics Committee of the Faculty of Veterinary Medicine of Shahid Bahonar University of Kerman, Kerman, Iran (license number: IR.UK.VETMED.REC.1400.010).

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