Original Article

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The Effect of High Intensity Interval Training on Muscular Biomarkers of Mitochondrial Biogenesis in Male Rats

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ABSTRACT

BACKGROUND AND OBJECTIVE: PGC1α increases expression and coactivation of transcription factors for increases in mitochondria biogenesis-related genes. The purpose of the current study was to determine the effect of high intensity interval training on muscular biomarkers of mitochondrial biogenesis in male rats.

METHODS: Type of research design in the current study was semi-experimental. In the current study 18 Wistar rats were separated into HIIT and control groups. HIIT protocol was done 60 min in each session for four sessions in each week. HIIT group was carried out 15×4 min bouts of HIIT with 85 to 90% of VO_{2max} that sustained with three min recovery (between each bout of HIIT) with 70% of VO_{2max}. PGC1α and Tfam and their gene translations were evaluated by commercial kits and Real-Time PCR method, respectively.

FINDINGS: Outcomes indicated that serum levels of PGC1α (CI=8.5±1.02, 6.3 to 10.6) and Tfam (CI= 7.9±1.16, 5.42 to 10.33) were significantly increased. Also, PGC1α and Tfam gene expression in both fast- (1.14±0.13) and slow (1.1±0.16 muscles were significantly increased (p=0.003 and p=0.0001, respectively).

CONCLUSION: It appears that, present HIIT protocol has capability to significant increase in both muscular and serum levels of biomarkers of mitochondrial biogenesis (PGC1α and Tfam) in male rats. Likewise, there is a possibility that HIIT essence is an inducer factor for further expression of this biomarkers in slow-twitch than fast-twitch muscles.

KEY WORDS: *Gene Expression, Skeletal Muscles, Mitochondrial Transcription Factor A.*

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Introduction

Recognizing the cellular and molecular mechanisms of fitness with sports exercises (especially endurance) has expanded in the last decade. Many messenger pathways and mechanisms of genetic transcription have been identified in skeletal muscle in compatibility with sport exercises including calcineurin, calcium/calcineurin-dependent kinase proteins (CaMK), mitogen activating protein kinase P-38 (MAPK), prodidin kinase activated by AMP (AMPK) and PGC1α (1). It seems that the most effective and powerful upstream activator and mechanism is PGC1α (1).

One of these factors in mitochondrial transcription that acts in conjunction with PGC1α is the mitochondrial transcription A or Tfam. It is believed that the correct start of transcription of heavy chain propulsion is exclusively dependent on the mitochondrial Tfam RNA polymerase. But TFB1m and TFB2m are two distinct mitochondrial isoforms that have been identified recently and play an important role in the onset of transcription. Also, studies have shown that Tfam expression in skeletal muscle is increased following endurance training in humans. Therefore, the increase in Tfam expression during exercise is primarily attributed to mitochondrial biogenesis in skeletal muscle (2). Exercise improves muscles' mitochondria as a result of resistance training, and especially endurance performance (3).

Few studies have focused on mitochondrial responses to exercises in the muscles. The results of study of Krichner et al. indicated a significant increase in mitochondrial enzymes in both groups of exercise and treadmill exercises compared to the control group. However, treadmill training increased the content of mitochondrial enzymes more than rotary (optional)(4). The results of Steiner et al. showed that 8 weeks of treadmill training for 1 hour per day, 6 sessions per week and 25 m/min are associated with increased expression of PGC1α, SIRT1 and mitochondrial DNA (3). Regarding studies on the effect of intense periodic exercises (HIIT) on mitochondrial biogenesis, few studies have investigated this effect.

HIIT can be defined as short-term, medium-term (30 to 5 minute) with intensive courses. The basic principle of HIIT is to create continuous pressure on the physiological components in order to create consistency. In a meta-analysis it was shown that a 4-12 weeks HIIT is associated with more training achievements than other training forms (5). Also, researchers have shown that only six sessions of HIIT in 2 weeks can improve muscle oxidative capacity and endurance function and change metabolic control (6). In this regard, several studies have shown that exercise activity can play an important role in accelerating mitochondrial biogenesis in skeletal muscle (7-9).

In a study by Wright et al., was found that expression of proteins indicative of a biogenesis increases earlier than the increase in PGC1α (9). Hoshino et al. performed an HIIT study on mitochondrial enzymes changes in red and white muscles, 10 minutes, with a 2 minute rest for 4 weeks and 5 days a week at an intensity of 55-30 m/min. Their results indicated a greater increase in PGC1α after exercise, especially in the red muscle (22%), relative to the white muscle (16%) (10).

As stated, there is only little evidence of the effect of exercise on the development of mitochondrial biogenesis in the muscles. Also, according to searches in scientific databases, (possibly) there is no study regarding the effect of intense periodic exercise (HIIT) on mitochondrial biogenesis biomarkers such as PGC1α and Tfam in the muscle and in particular in both slow and fast muscles of rats. Therefore, the aim of this study was to investigate the intense periodic exercise training on mitochondrial biomarkers in fast and slow muscle contraction muscles in male rats.

Methods

In this experimental study, 20 male Wistar rats (3 months and weights 300-270 gr) were selected. The rats were in the animal laboratory and in a room of 5×10 meters in controlled conditions in terms of free access to standard water and food, lighting (12 hour cycle), temperature (degrees of temperature 22 to 26 ° C) and humidity (Range from 50 to 60%). Rats were randomly divided into two groups of ten for HIIT and control group. Two rats from the HIIT group were excluded from the process (n=8) due to intolerance to exercise. All laws and procedures for treating animals (introduction, practice, anesthesia and animal killing) are based on AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care International)(11) and were approved with Code of Ethics in Research (IR.ut.Rec.139500). For better control of the keeping conditions, the body weight of the rats was evaluated periodically every three days. This research was approved by the Ethics Committee with a specific research code.

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Practice protocol: The rats became familiar with the living conditions of the animal house and how to run on the treadmill for 5 days (12). In order to reduce anxiety in rats, in addition to observing these factors, during the study period, rats were evaluated by a person, practiced and examined (13). Maximum oxygen consumed (VO2max) of rats was evaluated using a sloping treadmill (four lines, TSE systems company, Germany) with a maximum positive and negative slope of +30 to -15°C. VO2max was evaluated using the ramp protocol according to study of Hoydal et al. After warm up at a speed of 0.2 m/s, the speed was increased by an increase of 0.03 m/sec every 2 minutes, until the rats were able to continue the test (inability to run on the treadmill and going to the treadmill space (13). Recommended gradient 25+ degrees have the best use and result for measuring both VO2max and exercise sessions (13). HIIT was performed for 60 minutes at a meeting and for four sessions per week for three consecutive weeks. After warming up to 10-15 minutes with 60-50% VO2max, the HIIT 15 group performed a 4-minute period with 90-85% VO2max with three minutes of 70 VO2max recovery between HIITs. Also, VO2max was evaluated at the end of each week (four times in total). The control group was free in the cages until the end of the training weeks and did not do any training. The weight of the rats during the training sessions was significantly increased compared to the control group, indicating no excessive exercise pressure.

Preparation of tissues and blood sampling: In this study, after completion of training weeks and 48 hours after the last training session, rats were anesthetized using sevoflurane (5-4%). Then, the PBS fluid (150 ml, pH=7.4) was injected into the left ventricle of the rats and immediately replaced by formaldehyde (200 ml, 4%). Then, soleus muscle (as slow contraction muscle) and long fistulae muscle (or EDL as a sharp contraction muscle) were sampled from about 45 to 60 minutes after completion of injections of PBS and formaldehyde from rats. Then, the slices were stored in a mixture of sucrose (30%) and PBS (70%) for 12 hours.

They were then quickly freezed using N2 liquid and kept at -70 °C. After completion of the above steps and receiving the desired kits and materials, soleus muscles and opening muscles of long fingers of rats were sampled in the desired slices and, after washing with PBS, in the microvessels containing RNAlaterTM (RNA) Stabilization reagent 50 mL (20%) was immersed for gene expression experiments. A blood sample was taken from the tail of the animal and was centrifuged at 3000 rpm for 7 minutes at 5 °C (Model 5810, Opendorf, Germany) and for measuring the serum levels of PGC1α and Tfam (for two the stage before the HIIT protocol was executed and 48 hours after the last training session) until the completion of the post-test phase were stored at -70 ° C (14). Serum PGC1α was measured by sandwich ELISA using the cloud-clone commercial code (SEH337Ra, USA).

Internal accuracy (CV) and external accuracy of PGC1α kit were less than 10 and 12%, respectively, and the sensitivity of measurement was 127.12 ng/ml. Also, Tfam was measured by sandwich ELISA and using the commercial kit of Cusabio Co. (code: CSB-EL023413RA, Japan). Internal accuracy (CV) and external accuracy of the Tfam kit were less than 8 and 10%, and the sensitivity was 5.8 µg/ml, respectively. Also, the extraction of PGC1α RNA and Tfam RNA under gene codes of 83516 and 83474 genes was carried out using the superscript kit (Qiagen Inc., Germany) (15). Then, RNA extraction was done by Real Time-PCR using the 6000 rotor system. The melting curve analysis was performed to determine the validity of the PCR product. After the PCR stage, to study the properties of primers, temperatures of 50° to 99°C were used to prepare the melting curve. Beta-actin (β-actin) was used to compare and determine the expression of PGC1α and Tfam gene according to primers sequence. Finally, for the quantification of mRNA expression, the ΔΔCT method was used to compare the β-actin control gene.The sequence of forward primers for PGC1α and Tfam were respectively TTCCACCAAGAGCAAGTAT and GAAGGGAATGGGAAAGGTAGA and sequence of reverse primers for PGC1α and Tfam were respectively CGCTGTCCCATGAGGTATT and AACAGGACATGGAAAGCAGAT (15). In addition, sequence of forward and reverse primers for β-actin were respectively TGTCACCAACTGGGACGATA and AACACAGCCTGGATGGCTAC.

Statistical analysis: After collecting data, using statistical software Stata version 12 and determining the labels for dependent variables were analyzed. So that the values of central tendency and dispersion (mean and standard deviation) as well as graph plot were used to estimate the descriptive statistics of the research. Then independent and independent t-test was used to estimate intergroup and intra-group differences. The repeated measures test (and Bonferron's post hoc test) were also used to determine the intra-group differences in weight variables and VO2max (over four time intervals) and $p < 0.05$ was considered significant.

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Results

The results indicated that there was no significant difference between HIIT and control groups (Fig 1). The findings also showed a significant increase in the VO2max values of the HIIT group in the first week (47.6±4.84), the second week (53±8.08), and the post-test (60.8±7.44) in comparison with the pre-test values (60233±4.86) (p=0.0001, p=0.0001, p=0.002). Significant increase in the VO2max values of the HIIT group was observed in the post-test (60.8±7.44) compared to the values of the first week (33.02±4.86) (p=0.04, Fig 2).

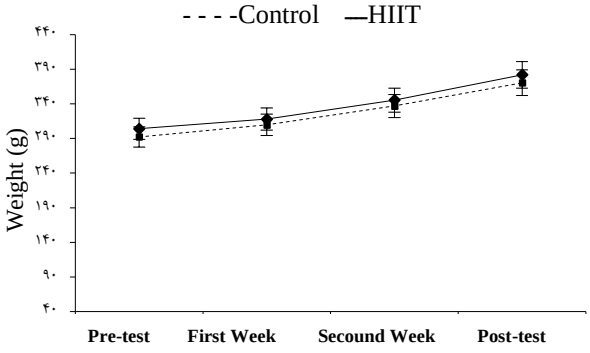


Figure 1. Changes in body weight (g) of HIIT rats and control group with separation of the different stages

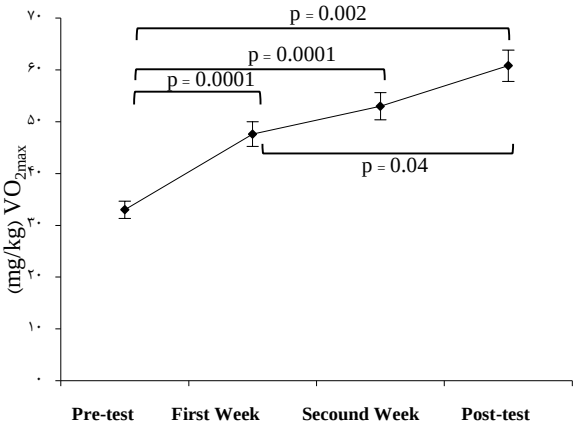


Figure 2. Intragroup variations of VO2max (ml/kg 0.75/min) of HIIT group by separation of different stages

Also, the findings showed that serum levels of PGC1α in rats in the HIIT group were significantly increased compared with control group (10.6 to 6.3, CI=8.5±1.02; Table 1). In addition, the findings indicated that serum Tfam levels in HIIT rats were significantly increased in comparison to the control group (10.33 to 42.5, CI=7.9±1.16), (table 1).

Table 1. Serum levels of PGC1α and Tfam in rats of HIIT group (8 rats) and control group (10 rats) after 3 weeks of HIIT intervention

Indicator*	group	pretest mean±SD	Post-test Mean±SD	Intragroup t values	P-value	Interagroup t values	P-value
PGC1α (ng/ml)	HIIT	2.13±0.83	10.94±3.19	-7.43	0.0001*	8.3	0.0001*
	conrol	2.1±0.73	2.45±0.59	-1.25	0.242		
Tfam (ng/ml)	HIIT	13.61±2.34	21.47±3.22	-4.41	0.003*	6.8	0.0001*
	conrol	13.17±1.51	13.59±1.6	-1.32	0.218		

* The significance level accepted in p<0.05, M: Mean and SD: The standard deviation.

Significant increase was observed in the expression of PGC1α gene in rats in the HIIT group (1.0±0.16) in comparison to the control group (0.84±0.41) (p=0.003) (Fig 3a). In addition, the expression of PGC1α gene in EDL muscle of rats in the HIIT group (1.14±1.13) was significantly increased in comparison with the control group (0.73±0.19) (p=0.0001; Fig 3b). Also, the expression values of Tfam gene expression in the soleus muscle in rats of the HIIT group (1.07±0.19), as compared to the control group (0. 68±0.22), also significantly increased (0.0001) P) (Fig. 3c). In addition, the expression levels of Tfam gene of EDL muscle in rats of HIIT group (1.02±0.4) were significantly increased in comparison with the control group (0.64±0.27) (P=0.008); Fig. 3d).

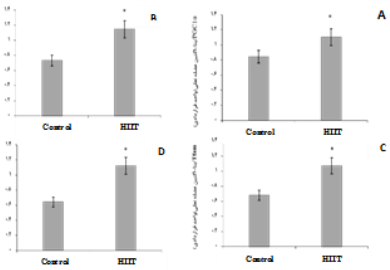


Figure 3. A) The effect of HIIT on the expression of soleus muscle PGC1α gene in HIIT group and control group. The values of t between the groups were 3.55 and

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the significance level was 0.003. B) The effect of HIIT on the expression of EDG muscle PGC1α gene in HIIT group and control group. The t values between the groups were 5.17 and the significance level was 0.0001. C) The effect of HIIT intervention on Tfam gene expression of soleus muscle in HIIT group and control group. The t values between the groups were 4.14 and the significant level was 0.0001. D) The effect of HIIT intervention on Tfam gene expression of EDL muscle in HIIT group and control group. The t values between the groups were 3.039 and the significance level was 0.008. * Indicates the significance level accepted in $p<0.05$.

Discussion

The results of the study on serum levels of PGC1α and Tfam showed an increase of 5 folds and 57.75% in the HIIT group, respectively. Additionally, incremental changes were observed in expression levels of PGC1α and Tfam in the soleus muscles and EDL muscles. This means that after the third week of HIIT, PGC1α values in soleus and EDL muscles increased 31.05 and 56.65%, respectively, and in Tfam values of soleus muscles and EDL, respectively, were 57.07 and 74.98, respectively, compared to control group. Generally, the observed increases in both PGC1α and Tfam biomarkers in EDL muscle were greater than the muscle in male rats (EDL muscle> soleus muscle). Also, there was a significant increase in VO2MAX values after three weeks of HIIT.

Regarding the effects of exercise on mitochondrial biogenesis in the few results available and in agreement with the findings of the present study, Derbre et al. evaluated the effect of exercise training at 75% Maximum oxygen consumption on PGC1α response and mitochondrial biogenesis in male rats. The practice protocol included 3 weeks training and 5 days a week, each session 25 (first sessions)-60 minutes (last sessions) at a speed of 26.86 m/min (first sessions) to 30 m/min (last sessions) on treadmill exercise with a gradient of 15 percent. The results indicated an increase in expression of PGC1α, NRF-1 and cytochrome C after exercise with a 75% VO2max intensity (16). Results of the study of Geng and colleagues represents a significant increase of PGC1α and mitochondrial enzymes (Cytochrome oxidase-4 and cytochrome C) in compliance with the voluntary exercise in skeletal muscle (1).

Koltai et al. evaluated the effect of 6 weeks of treadmill on 12 male rats. During the first two weeks, the exercises were performed on a daily basis with a 60% initial VO2max duration of 30 minutes, three days a week and the second week afterwards. Continued to 22 m/min and tilt of 10%. Their results indicate an increase in muscle mitochondrial mass (succinate dehydrogenase, citrate synthase, cytochrome C, mitochondrial DNA), increased activity of PGC1α, SIRT1, AMPK protein-degrading and composition of mitochondria (fishen-1 and mitofusion-1) (17). Wright et al. also found that expression of mitochondrial biogenesis proteins (NRF-1, cytochrome C, NRF-2, and cytochrome oxidase type 4 propellant) increased sooner than the increase in PGC1α, possibly activating PGC1α induces the initial phase of the adoption/adaptation increase by exercise activity in muscle mitochondria, and the subsequent increase in PGC1α improves the proteins involved in increasing mitochondrial biogenesis (9). In addition, Ramos-Filho et al. evaluated the effect of HIIT on respiratory changes and mitochondrial chains in rat muscle. Their training lasted 6 weeks and 3 sessions per week, including 20 second swimming sessions with 10 seconds of rest. The initial applied load was 9% of body weight, which increased 1% by weight each week (a total of 14% by the end of the exercise program). Their results indicated increased mitochondrial breathing (OXPHOS enzyme) in the anterior and lower limb muscles and decreased respiration in soleus muscle. Also, the production of H2O2 in the anterior and lower limb muscles increased and decreased in soleus muscle. In addition, electron leakage was higher in the anterior gastrocnemius (glycerol 3 phosphate) and diclofenacid (glycerol phosphate, succinat), and not in soleus muscle after HIIT (18).

The results of Steiner et al., evaluated the effect of treadmill training on mitochondrial biogenesis in male rats, indicated that 8 weeks of treadmill training for 1 hour per day, 6 sessions per week, with a 25 m / min intensity increased expression of PGC1α, SIRT1, and mitochondrial DNA (3). As seen in the above studies, although the results of the findings regarding the incremental changes in PGC1α were consistent with the use of intense periodic exercises, none of them investigated Tfam values in rats. Regarding the effect of HIIT exercises on mitochondrial biogenesis, Hoshino et al. reviewed the effect of these exercises on mitochondrial enzyme changes in the red and white muscles of rats. They performed ten stages of 1 minute with 2 minutes of rest for 4 weeks and 5 days a week at an intensity of 30-55 m/min. Their results indicated a greater increase in PGC1α after exercise, especially in the red muscle (22%), compared with the white muscle (16%). In addition, mitochondrial enzymes (citrate

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synthase, type 4 cytochrome oxidase and beta-hydroxyl-cobalt dehydrogenase) increased in both red and white muscle after HIIT). Also, palmitate oxidation ratios in mitochondria after training, especially in red muscle (37% in under sarcolemma mitochondria and 19% in mitochondria between myofibrilia) were comparable to white muscle (36% in under sarcolemma mitochondria and 12% in mitochondria between myofibrilia (10). However, in this study, the effect of HIIT on rat Tfam values was not evaluated. Also, in the study of Hoshino et al., the 25% gradient for treadmill and the relative severity of exercise for rats were not used. Therefore, the findings of this study should be cautious with their results and other studies. One of the research limitations is the lack of evaluation of the protein content of both mitochondrial biomarkers (PGC1α and Tfam) by western blotting and the lack of evaluation of the gene expression of the muscles of both sides of the body due to financial research constraints. Therefore, it seems that the use of the HIIT protocol on the treadmill (with intensity and duration) in male rats is capable of significantly improving the serum and muscle levels of both biomarkers of mitochondrial biogenesis (PGC1α and Tfam) in rats. The results of this study showed that the increase of PGC1α values was higher in serum, EDL muscles and then in soleus muscles (serum> EDL> soleus).

Also, the increase in Tfam values was greater in EDL muscles, serum and then in soleus muscles (EDL> serum>soleus), respectively. It seems that the nature of HIIT training (short-term and high-intensity cases) is the cause of further increase of these biomarkers in fast contraction muscles relative to slow contraction muscles (soleus).

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