Changes in Mitochondrial Dynamic Factors (mfn2 and drp1) Following High Intensity Interval Training and Moderate Intensity Continuous Training in Obese Male Rats

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Abstract

Objective: Mitochondrial content and function are important determinants of oxidative capacity and metabolic efficiency of skeletal muscle tissue. The aim of this study was to investigate the changes in mitochondrial dynamic factors (mfn2 and drp1) following high intensity interval training (HIIT) and moderate intensity continuous training (MICT) in obese male rats.

Materials and Methods: In this experimental study, 40 male wistar rats after inducing obesity with high fat diet (for 10 weeks), eight rats from the high-fat diet group (O) and eight rats of the standard dietary group (C) were sacrificed and other obese rats were randomly divided into three groups: obesity control (OC), MICT and HIIT groups. The HIIT protocol includes 10 bouts of 4-minute activity with intensity of 85-90% vo2max and 2-minute active rest periods and MICT protocol with intensity of 65-70% VO2max with covered distance was matched to that of HIT protocol for 12 weeks and 5 sessions per week. Protein levels of mfn2 and drp1 soleus muscle were measured by Western blot. For analyzing the data, One-way ANOVA and Tukey post hoc with SPSS–23 and the significance level was *P*-value≤ 0.05.

Results: Induction of obesity was associated with a significant decrease in soleus muscle mfn2 and drp1 (*P*-value= 0.001). The intervention of HIIT and MICT significantly increased of mfn2 and drp1 compared to control group (*P*-value= 0.001). Also, mfn2 and drp1 were significantly higher in HIIT compared to MICT group (*P*-value= 0.001).

Conclusion: It seems that HIIT and MICT increase the mitochondrial dynamic factors in skeletal muscle, and the effects of HIIT are significantly higher.

Keywords: High intensity interval training, Moderate intensity continuous training, Mitochondrial dynamic, Obesity

Introduction

Obesity is one of the most important health problems in the 21st century. Overweight and obesity is expected to affect about 3.3 billion people (about 58% of the world's adult population) by 2030 (1). Obesity risk factors are including genetic,

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environmental, stress and the high-fat diet (HFD). Obesity is associated with cardiovascular disease, type 2 diabetes mellitus and insulin resistance (2). Studies have shown that obesity is associated with skeletal muscle remodeling leading to impaired skeletal muscle function, including protein renewal, reduced glucose intake, decreased lipid metabolism, and mitochondrial dysfunction (3-5).

Mitochondria of skeletal muscle as dynamic organelles undergo fission, fusion, and mitophagy processes that are essential for their survival in growing cells, regulating cell death pathways, and removing damaged mitochondria (6).

However, the balance between fission and mitochondrial fusion can be broken by fat accumulation, causing mitochondrial disorders such as decreased mitochondrial membrane potential, decreased oxygen consumption, and increased Reactive oxygen species (ROS) production (6). Mitochondrial fusion is mediated by proteins called Mitofusin (Mfn), which are the dynamin-associated GTPases that are responsible for the fusion of mitochondrial outer membranes (7).

Mitochondrial fission in mammals is also regulated by Dynamin related protein 1 (Drp1) that is GTPase. DRP-1 is a cytosolic protein that can bind to the outer mitochondrial membrane, resulting in mitochondrial fragmentation and loss of some part of the membrane potential that separates damaged mitochondria from healthy cells. This process helps to the quality of mitochondria (8).

Some studies have shown that training reduces obesity-induced dysfunction in mitochondrial fusion and fission by increasing mitochondrial fission proteins and reducing or maintaining mitochondrial fusion protein levels (4). However, Axelrod et al. (2018) showed that 12 weeks of aerobic training (5 days a week, 85% HRMAX) had no significant effect on MFN expression of skeletal muscle in inactive adult biopsy specimens (9).

On the other hand, de las Heras et al. (2018) showed that eight weeks of aerobic training (treadmill running 5 days a week for 50 minutes per session) resulted in increased Drp1 levels and decreased MFN1 levels in brown adipose tissue of rats (10).

High-intensity interval training (HIIT) can have similar or even greater adaptations to skeletal muscle than Moderate intensity continuous training (MICT) (11). HIIT interventions increase lipid oxidation capacity and mitochondrial enzyme activity (12). Some researchers also support the idea that HIIT is more effective in weight loss in overweight and obese subjects than MICT (13-15).

Low oxidative capacity has been reported in obese individuals (16). Mitochondrial content and function are important determinants of oxidative capacity and metabolic efficiency of skeletal muscle tissue. Given the role of skeletal muscle in glucose metabolism, the role of dietary disorders in determining mitochondrial capacity is particularly important in the context of metabolic diseases such as obesity. Therefore, the present study aimed to investigate the changes in mitochondrial dynamic factors (mfn2 and drp1) following high intensity periodic training and moderate intensity continuous training in obese male rats.

Materials and Methods

This study is an experimental study. In this study, the ethical principles of working with laboratory animals, such as the availability of water and food, and appropriate keeping conditions were considered and the manner of killing rats was observed. In this study, 40 six-week-old male wistar rats' weight 120 ± 20 g based on the Cochrane formula were purchased from Pasteur Institute of Animal Research Center (Karaj, Iran). Animals were housed in quaternarycages under standard conditions (12 h dark cycle, 25 + 2 °C) after transfer to Guilan University School of Sport and Sport Sciences, with free access to water and food. After 2 weeks of adapting to the new environment and the standard diet, rats were first divided into two groups of standard diet (8 rats) and high fat diet (32 rats) for 10

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weeks. At the end of the first step (obesity induction), 8 rats from the standard diet group (C) and 8 obese rats from the high-fat diet (O) were killed to investigate the effect of obesity. The obese rats in the high fat diet group were randomly divided into 3 groups (each groups 8 rats), obese control (OC), moderate intensity continuous training (MICT) and high intensity interval training (HIIT) and then consume the standard diet. The standard diet consisted of 10% fat, 70% carbohydrate and 20% protein and high fat diet 60% fat, 20% carbohydrate and 20% protein (17).

Rats from the HIIT and MICT groups were trained for 12 weeks on training program. Also, the OC group did not receive any training program during these 12 weeks. It should be noted that during the two weeks of familiarity of all rat's had standard food, in 10 weeks Induction of obesity the obese group had high-fat diet and the healthy control group had standard food, and then during exercise, all three obese groups (OC, MICT and HIIT) had standard food freely, and access to water was free during the study period.

Training programs

High-intensity interval training (HIIT): After 10 weeks of high-fat diet, rats in both training groups (HIIT, MICT) performed a week of running adaptability on the treadmill before performing 12 weeks of training. The concurrent HIIT and MICT programs were performed for 12 weeks, 5 sessions per week with a 25-degree slope based on the modified training programs by Hafstad et al. (18). The HIIT program consisted of 10 four-minute activities with 90-85% VO2max intensity and 2-minute active rest periods with 45-50% VO2max intensity that progressively increased treadmill speed until the tenth week and the treadmill speed was maintained for the last two weeks (11th and 12th). Accordingly, the treadmill speed reached from 17 m/min in the first week to 26 m/min in the tenth week and maintained during the final two weeks.

Moderate intensity continuous training (MICT): The MICT program was at an intensity of 65-70 VO2max, which the distance matched with the HIIT program, so that the treadmill speed increased progressively until week 10 and was maintained for the final two weeks (18). Accordingly, the treadmill speed in the first week increased from 12 m/min to 16 m/min in the tenth week and the treadmill speed maintained for the final two weeks (eleventh and twelfth). Also, 10 minutes warm-up and 5 minutes low-intensity cooling were performed at the beginning and end of each training session (18) (Table 1).

Measurement of biochemical variables

C and O groups rats after 10 weeks of dietary intake and rats of HIIT, MICT, and OC groups after 12 weeks of training program using the combination of ketamine (75 mg / kg) and xylazine (10 mg / kg) anesthetized. After that, the soleus muscle was carefully removed and rinsed in physiological serum and immediately transferred to a microtube and placed in liquid nitrogen and transferred to a freezer at -80 ° C for subsequent assays.

Gel electrophoresis and western blot: Protein (20µg) of homogenized samples was separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS plate) using 5.5% and 10% solubilizing gel. Proteins separated by SDS plate were electrophoretically transferred to polyvinylidene Difluoride membrane and membrane was incubated with casein solution blocking buffer (SP-5020, Vector Laboratories, Burlingame, SANTA CRUZ) for one hour at room temperature or overnight at 4◦C.The membrane prepared for probe with

Table 1. HIIT and MICT programs

Exercise	VO2max	Exercise factors	The details
HIIT	90-85%	speed (m/min)	17 -26
		sessions per week	5
MICT	65-70 %	speed (m/min)	12 -16 m/min
		sessions per week	5

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primary antibodies (anti mfn2 and anti-drp1) was incubated again for 1 hour at room temperature for one night and after washing three times at room temperature with HRP conjugated secondary antibody. The bands on the membrane were determined by quantitative luminescence technique. At each time the membrane probe was stripped, the density of bands was determined using version 1.62 of the JImage densitometry software package, and beta-actin protein was used as control loading.

Statistical method

After ensuring that the distribution of weight data was normal, according to Shapiro-Wilk test, Levenes test was used to evaluates the Consensus of the variables. After identifying that the data distribution was normal, one-way ANOVA and Tukey's post hoc test was used to compare the variables of the research. The significance level was considered to be *P*-value≤ 0.05 in all cases. All statistical operations were performed with SPSS software version 23.

Ethical considerations

This study was approved by the ethics committee of Guilan University of Medical Sciences with registration number of IR.GUMS.REC.1397.081.

Results

Table 2 shows the mean and standard deviation of variables of study in different groups. The results of one-way ANOVA showed that there was a significant difference between the mean mfn2 of soleus muscle in different study groups (*P*-value= 0.000). Also, the results of one-way ANOVA showed that there was a significant difference (*P*-value= 0.000) between the groups in the values of drp1 of soleus muscle (*P*-value= 0.000) (Table 2). Based on the results of the Tukey post hoc test, both HIIT (*P*-value= 0.000) and MICT (*P*-value= 0.000) training interventions led to a significant increase in soleus mfn2 compared to the control group. On the other hand, there was a significant difference in mfn2 of soleus muscle between the HIIT and MICT groups. The mfn2 of soleus muscle was significantly higher in the HIIT group than in the MICT group (*P*-value= 0.028).

Also, based on the results of Tukey post hoc test, both HIIT (*P*-value= 0.000) and MICT (*P*-value= 0.009) training interventions significantly increased drp1 of soleus muscle compared to the control group. On the other hand, there was a significant difference in drp1 of soleus muscle between the HIIT and MICT groups. The drp1 of soleus muscle was significantly higher in the HIIT group than the MICT group (*P*-value= 0.001).

Discussion

The results of this study showed that both HIIT and MICT interventions led to a significant increase in soleus mfn2 and drp1 in obese male rats. Also, mfn2 and drp1 of soleus muscle were significantly higher in HIIT group than in MICT group.

Significant change in mitochondrial dynamic factors mfn2 and drp1 following high-intensity intermittent training, includes decreased Drp1 phosphorylation and increased MFN1 levels in the skeletal muscle of obese adult subjects (19) and moderate-intensity continuous training includes increased Drp1 levels and decreased MFN1 levels in brown adipose tissue (10). The mechanism of these different adaptations to training is not understood. Axelrod et al. (2018) exploring the effect of training on dynamic mitochondrial signaling in rats, suggested that endurance training affects all aspects of the mitochondrial life cycle (9).

It has been reported that the total content of Drp1protein increased in the skeletal muscle of healthy lean men 24 h after a period of high

Table 2. The mean and standard deviation of variables of study in different groups

Variable	Control	MICT	HIIT
mfn2	0.57 (± 0.09)	1.63 (± 0.09)	2.17 (± 0.38)
drp1	0.88 (± 0.14)	1.32 (± 0.15)	1.88 (± 0.31)

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intensity training and peaked 24 h after the third training session (20). Some studies have also shown that during the recovery period and 3 hours after training, Drp1 levels return to baseline phosphorylation status (21).

These findings indicate that post-training measurement is crucial because mitochondrial remodeling is a rapid and dynamic process. Inhibition of Mfn has been reported to be associated with decreased substrate oxidation, cell metabolism, and decreased membrane potential under obesity (22). In addition, Liu et al. (2014) reported that high dietary fat intake for 40 weeks reduced Mfn protein levels in the skeletal muscle by approximately 20% while Drp1 protein levels increased by approximately 50% (23).

Also, Jheng et al. (2012) Showed that mitochondrial fusion protein Mfn levels did not change while fission protein levels Drp1 increased in obese mice induced by high fat diet compared to lean mice, indicating an imbalance between fusion and fission in obesity (24). The consequences of mitochondrial fission and fusion in response to training in the skeletal muscle of obese subjects have not been well characterized. As mentioned, mitochondrial fission is predominant in cells that are metabolically active, leading to the development of mitochondrial metabolites, enzymes, and gene products throughout the mitochondrial reticulum. Mitochondrial fission promotes the membrane potential of oxygen-rich regions in mitochondria to low oxygen areas and ATP synthesis in these regions that would be beneficial in skeletal muscle for training due to high energy demand (6).

Interval aerobic training improves mitochondrial respiration as well as Mfn2, decreases DRP1 and increases PGC-1α, while disables ERK1/2-NK-P53 signaling pathways (25). It has been suggested that the expression of fission proteins and mitochondrial fusion in skeletal muscle changes immediately in response to energy demand (26). During severe muscle contraction, the need for ATP is strongly increased, which is supported by increased mitochondrial respiration by both substrates (NADH and FADH) and O2 consumption (27). As the intensity and duration of training increases, oxygen consumption and ATP production (oxidative phosphorylation) can affect two negative factors: (1) increased proton leakage which increases superoxide anion formation and (2) upregulation of amounts of unpaired protein. Second process, by decreasing the membrane gradient, proton reduces ROS production and increases heat production and disrupts mitochondrial oxidative phosphorylation.

In addition, both processes increase the net consumption of substrate and oxygen but decrease the efficiency of ATP production. Thus, mitochondrial evolutionary pressure acts to provide mechanisms to overcome these problems to ensure cell viability. Two potential mitochondrial strategies for maintaining oxidative phosphorylation efficiency and preventing oxidative damage are: (1) an increase in the inner membrane density and the number of mitochondria by biosynthesis, which have been shown in endurance training muscles (27), (2) under Morphological changes through mitochondrial fission and fusion, intense training indicate a state of depletion of high-energy phosphate substrate in skeletal muscle (28). Therefore, it is not surprising that this metabolic state affects the mitochondrial morphology and expression of mitochondrial fusion and fission proteins (29).

The first process leads to oxidative damage and damage to mitochondrial integrity and the The exact mechanism of mitochondrial fission and fusion is unclear. However, PGC-1α and ROS and NFkB have been identified as potential regulators (30). Upregulation of PGC-1α and mitochondrial biogenesis pathways have been postulated to be responsive to redox-sensitive training. Training by stimulating the beta-3 adrenergic receptor and activating the NO signaling pathway can also protect against insulin resistance. (31).

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Picard et al. (2013) observed that the mitochondrial morphology and the proteins involved in Mfn2 did not change in both training and control groups (32). According to in vitro data, energy deprivation can lead to mitochondrial fusion and elongation, whereas excess substrate availability leads to mitochondrial fragmentation (33). DNM1L is the Drp1 coding gene that was significantly upregulated after exercise intervention (19). Thus, increased expression of DNM1L leads to an increase in Drp1.Of course, since the present study does not measure DNM1L gene expression and is one of the limitations of the present study, we cannot conclusively comment on this case.

Thus, HIIT may have more effects than MICT on increased DNM1L gene expression and on mitochondrial oxidative enzymes in the HIIT group. The present study for the first time provided evidences that training can induce dynamic mitochondrial stimulation of skeletal muscle in obese rats; however, these adaptations appear to be dependent on the intensity of training. Drp1 in skeletal muscle may also undergo post-translational regulation. Post regulation of Drp1 translation is an important mechanism for regulating its function.

However, contrary to the results of the present study, no molecular alteration or reduction of mitophagy following training has been shown. Axelrod et al. (2018) showed that 12 weeks of aerobic training (5 days a week, 85% HRMAX) had no significant effect on MFN expression of skeletal muscle in inactive adult biopsy specimens (9). Acute training in mice also reduced MFN1 / 2 protein expression in skeletal muscle up to 24 h after exercise (34). Another study showed that Mfn protein levels decreased and DRP1 and ROS content in skeletal muscles of rats increased after 150 min of acute training (29). The difference between the results of the research done in this case can be attributed to the difference between the type of training protocols, methods and measurement time in the research. Mitochondrial fusion of damaged mitochondria can maintain mitochondrial function. Mitochondrial fusion plays an important role in the regulation of MFN mitophagy protein and is mainly regulated by the DRP1, which is often located in the cytoplasm (35).

Physical activity maintains healthy mitochondria under obesity (4). Therefore, as few studies have examined the relationship between mitochondrial dynamic change in obesity and physical activity, further studies on the positive or negative effects of training with varying intensity on molecular and cellular levels are needed. HIIT was one of the strengths of the present study; because this type of exercise can have different responses and adaptations than other training programs, despite the performance limitations. Limitations of this study include lack of measurement of DNM1L and mitochondrial oxidative conditions in response to training adaptation. Therefore, it is recommended to study different training protocols on mitochondrial dynamics along with determining mitochondrial oxidative conditions.

Conclusions

In summary, the results of the present study showed that altering energy balance through high intensity interval training and moderate intensity continuous training may increase Drp1 and MFN in skeletal muscle of obese subjects. These findings support the hypothesis that changes in mitochondrial dynamic factors (mfn2 and drp1) following high-intensity periodic training and moderate-intensity continuous training may improve mitochondrial function.

According to the results, it seems that HIIT and MICT increase the mitochondrial dynamic factors in skeletal muscle, and the effects of HIIT are significantly higher. Therefore, it is suggested that HIIT be considered in skeletal muscle in obese subjects for possible benefits.

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Conflict of Interest
There are no conflicts of interest

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