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The Effect of Aerobic Exercise and Berberine Chloride on Mitochondrial Biogenesis Indices of Visceral Adipose Tissue of Diabetic Rats

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ABSTRACT

Background and Objective: Oxidative stress contributes to insulin resistance, beta-cell dysfunction, and hyperglycemia-induced cellular damage, leading to diabetes mellitus. The purpose of this study is to explain the effect of aerobic exercise and berberine chloride on the expression of UCP-1 and PPARγ genes in the visceral fat tissue of diabetic rats.

Methods: In this laboratory study, 32 adult male Wistar rats weighing about 240-280 were randomly divided into four groups (n=8): diabetes (DM), diabetes-berberine (DMB), diabetes-aerobic exercise (DMT), diabetes-aerobic exercise-berberine (DMTB). The rats became diabetic by injecting 60 mg/kg STZ. The rats whose blood sugar was higher than 300 mg/dl were included in the present study as diabetic animals. The exercise groups then performed an incremental aerobic exercise program (10-18 m/min, 10-40 min/day, five days/week) on a treadmill for six weeks. The supplement group also received berberine chloride (30 mg/kg/day) orally by gavage once a day.

Findings: Data analysis showed that there is a significant difference in the expression of UCP-1 (p=0.000) and PPARγ (p=0.002) genes between the groups. Furthermore, the results showed that the expression of UCP-1 gene in the diabetes-exercise group (2.96±1.85 and p=0.015), diabetes-berberine chloride (2.88±1.16 and p=0.02) and diabetes-exercise-berberine chloride (4.7±0.97 and p=0.000) showed a significant increase compared to the diabetes group. Also, PPARγ gene expression in the diabetes-exercise-berberine chloride group (1.6±0.36 and p=0.002) showed a significant increase compared to the diabetes group.

Conclusion: According to the results of this study, aerobic exercise and berberine chloride is one of the possible ways to prevent inflammation and damage caused by diabetes.

Keywords: *Aerobic Exercise, Berberine Chloride, Diabetes, UCP-1, PPARγ.*

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Introduction

Diabetes is considered as a life-threatening disease and has various complications such as retinopathy, nephropathy, neuropathy and infertility as well as cardiovascular diseases that should be considered in the treatment of diabetes (1). In this regard, one of the solutions is the identification and role of effective enzymes and hormones in diabetes (2). UCPs are able to sequester oxidized substrates and dissipate potential energy in the inner membrane as heat to reduce the overproduction of ROS (Reactive Oxygen Species) from mitochondria (3). Overproduced ROS can increase proton conductance by UCP1-3, leading to the scavenging of superoxide radicals through the mitochondrial respiratory chain reaction (4). Elevated glucose levels have been shown to up-regulate UCP1 expression and protect cells against glucose-induced ROS damage (5). UCP-1 is one of the important proteins in regulating the thermogenesis of brown fat and has the ability to convert white fat into brown fat (6).

One of the important complications of obesity is heart disease, which occurs especially in the walls of coronary arteries due to the accumulation of cholesterol. In reverse cholesterol transport, cholesterol is de-precipitated from the vessel wall and delivered to HDL (High-Density Lipoprotein) to be transported to the liver and excreted through the intestine. Various proteins are involved, including the liver X protein and sterol-27-hydroxylase, which are stimulated by the peroxisome proliferator (PPARγ). Therefore, gene expression and the increase of these factors can be one of the desirable mechanisms in the elimination of excess cholesterol through the liver and intestine (7).

Berberine is an active ingredient of traditional Chinese medicine that has various medicinal effects. Mitochondria is one of the important targets of berberine for exerting its medicinal effects, but its specific mechanism needs further study (8). The offspring of a study by Fang et al. showed that the regulation of mitochondrial activity is related to various pharmacological actions of berberine, such as regulating blood sugar and lipids and inhibiting tumor progression (9). The use of berberine is suggested for patients who have recently been diagnosed with type 2 diabetes with obesity and dyslipidemia (10).

On the other hand, regular exercise has an effective therapeutic role in improving the health of people with diabetes. In this regard, it was shown that regular and moderate exercise will reduce oxidative stress and diabetes complications by increasing antioxidant defense (11). In a study by Boström et al., it was found that three weeks of swimming training led to a 65-fold increase in UCP-1 mRNA expression in abdominal fat tissue (6). Woodhead et al., in a study investigating mitochondrial-derived peptides and activity, showed that acute exercise, especially aerobic exercise, increases the energy demand of skeletal muscle, causing mitochondrial stress and mitochondrial-related adaptations that are the characteristics of exercise training (12). Nourshahi et al. showed in a study that eight weeks of continuous and high-intensity interval training increases UCP1 in visceral and subcutaneous adipose tissue (13).

Also, the results of a study by Jafari et al. showed that regular exercise training was associated with an increase in the expression of PPARβ and PPARγ genes, which can be effective in reducing the risk of heart attack (14).

Despite the fact that a few studies have been conducted on the effect of various exercise programs with different durations and intensities on mitochondrial biogenesis indicators, no study was found on the effect of endurance exercise training with berberine chloride on the expression of UCP-1 and PPARγ genes in visceral fat tissue. On the other hand, discovering a safe method to minimize the negative effects of diabetes has always been of interest to researchers. Therefore, it seems that addressing the role of physical activity and herbal supplements is of considerable importance, which shows the necessity of further addressing this issue. Therefore, this study was conducted with the aim of investigating the effect of aerobic exercise and berberine chloride on mitochondrial biogenesis indices of visceral adipose tissue of diabetic rats.

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Methods

This experimental study has been approved according to the policies related to animal protection and with the approval of the Research Ethics Committee of the Islamic Azad University, Sari Branch with the code IR.IAU.SARI.REC.1401.222. To conduct the present laboratory research, all the standard conditions including temperature conditions (24±1°C), relative humidity (55±3%), free access to water and standard rat food (manufactured by Behparvar Company, Iran) and Dark:light cycle (12 hours) were observed, and 32 adult male Wistar rats weighing about 240-280 grams were purchased from the Pasteur Institute and transferred to the animal room. Then the rats were randomly divided into four groups (n=8): diabetes (DM), diabetes-berberine (DMB), diabetes-aerobic exercise (DMT) and diabetes-aerobic exercise-berberine (DMTB) in transparent polycarbonate cages with dimensions of 30×15×15 cm made by Razi Rad Company, and were matched according to body weight. First, in order to get familiar with the treadmill, the animals walked on the treadmill five days a week and each session for 5-10 minutes at a speed of 4-5 meters per minute. Then, 16 rats became diabetic. Diabetes was induced by intraperitoneal injection of a single dose of 60 mg/kg streptozotocin (manufactured by Sigma with code: S0130) dissolved in citrate buffer. To diagnose whether the rats were diabetic, 72 hours after the injection, a small wound was made by a lancet in the animal's tail, a drop of blood was placed on a glucometer strip (mini-01, made in Japan) and the amount of blood sugar was measured. Blood sugar of 300 mg/dL indicated that the rats became diabetic (15). After STZ injection, 5% glucose solution was used instead of water for 48 hours in order to reduce the mortality of rats.

The supplement used was berberine chloride hydrate powder (manufactured by Sigma company with code: 14050) taken from the barberry plant with a purity of 90%. This powder was dissolved in normal saline solution as needed in each session. Then, the prepared solution with a dose of 30 mg per kilogram of body weight was given orally (gavage) to the target groups on all days of the week for six weeks (16).

Then, the rats in the training groups were subjected to an exercise program with moderate intensity and physiologically efficient treadmill exercise (50-55% of maximum oxygen consumption) for 6 weeks and five days a week (manufactured by Borj Sanat Azma, model T.S 8000), performed at a frequency of three days of training and one day of rest (Table 1). In each training session, 5 minutes were given for warming up and 5 minutes for cooling down at a speed of 4-5 m/min, which was added to the main training time. The speed and duration of training were gradually increased according to Table 1. No type of electric shock was used during the exercise program, and if necessary, the animals were forced to continue the exercise by using their hands or creating a sound stimulus on the cover of the treadmill (17).

Table 1. Endurance training program

Exercise variables	The first week	The second week	The third week	The forth week	The fifth week	The sixth week
Speed (m/min)	10	10	14-15	14-15	17-18	17-18
duration (minutes)	10	20	20	30	30	40

All animals were anesthetized under identical conditions (48 h after the last training session and 12 h of fasting) by intraperitoneal injection of a combination of ketamine (60 mg/kg) and xylazine (5 mg/kg). Visceral fat tissue was transferred to liquid nitrogen immediately after separation and purification from blood and then stored in a refrigerator at -80°C until the time of measurement.

To investigate the expression of UCP1 and PPARγ genes, Real time PCR technique was used by Rotor Gene 6000 machine (Corbett Research, Australia) with 40 cycles. For PCR, 2x master mix buffer, forward

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and reverse primer combination, cDNA and injection water were used. The resulting mixture was prepared in an amount of 10 microliters in a special vial of the Corbett machine and then it was placed in the router of the machine. The level of mRNAs of each gene was calculated relatively compared to the level of mRNAs of GAPDH gene (Table 2).

Quantitative description of data was done using central dispersion indices such as mean and standard deviation, and Kolmogorov Smirnov test was used to determine the normality of data distribution and Levine's test was used to check homogeneity of variances. One-way analysis of variance and Tukey's post hoc test were used for statistical analysis, and $p \leq 0.05$ was considered significant.

Table 2. Sequence characteristics of primers related to each of the genes

Gene	Primer sequence
UCP1	
Forward	5'- TTCTTTTCTGCGACTCGGAT -3'
Reverse	5'- GCCCAATGGTGTTTAGCATC -3'
PPARγ	
Forward	5'- GGACGCTGAAGAAGAGACCTG -3'
Reverse	5'- CCGGGTCCTGTCTGAGTATG -3'

Results

Data analysis showed that there is a significant difference in UCP-1 gene expression between the groups (p=0.000, F=12.619). Furthermore, the results showed that the expression of UCP-1 gene in the diabetes-exercise group (2.96±1.85 and p=0.015), diabetes-berberine chloride (2.88±1.16 and p=0.02) and diabetes-exercise-berberine chloride (4.7±0.97 and p=0.000) had a significant increase compared to the diabetes group. Moreover, the expression of UCP-1 gene in the diabetes-exercise-berberine chloride group increased significantly compared to the diabetes-exercise group (2.96±1.85 and p=0.035) and the diabetes-berberine chloride group (2.88±1.16 and p=0.026) (Figure 1).

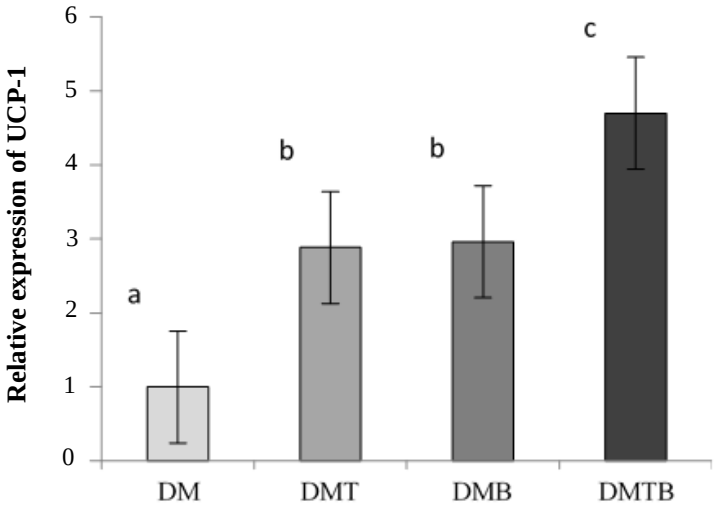


Figure 1. Changes in the relative expression of UCP-1 in different groups by one-way analysis of variance (p<0.05 level). DM: diabetes, DMT: diabetes-exercise, DMB: diabetes-berberine chloride, DMTB: diabetes-exercise-berberine chloride

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Data analysis showed that there is a significant difference in PPARγ gene expression between groups (p=0.002, F=6.416). Furthermore, the results showed that PPARγ gene expression in the diabetes-exercise-berberine chloride group significantly increased compared to the diabetes group (1.08±0.33 and p=0.002) and the diabetes-berberine chloride group (p=0.03 and 1.17±0.19) (Figure 2).

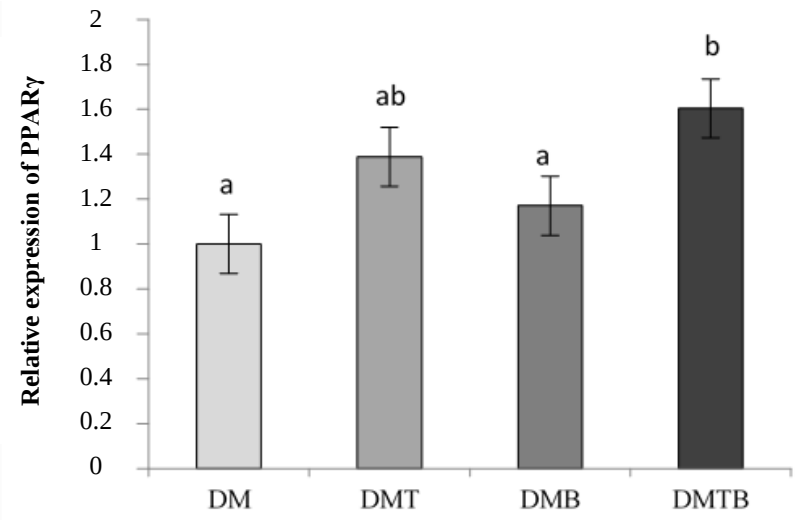


Figure 2. Changes in the relative expression of PPARγ in different groups by one-way analysis of variance (at p<0.05 level). DM: diabetes, DMT: diabetes-exercise, DMB: diabetes-berberine chloride, DMTB: diabetes-exercise-berberine chloride

Discussion

The results of the present study showed that aerobic exercise and berberine chloride significantly increased the levels of UCP1 and PPARγ in the experimental groups compared to the diabetic control group. In confirmation of these results, Kim et al. showed decreased the expression of PGC-1α and UCP-1 in subcutaneous adipose tissue (18) and Senese et al. showed decreased expression of UCP-1 in adipose tissue (19) of HFD mice. Decrease in UCP-1 may be caused by increased expression of myostatin in skeletal muscles, which causes phosphorylation and activation of SMAD3 in obese individuals (20). However, in the present study, aerobic exercise could compensate the negative effect of diabetes on the expression of PPARγ and UCP-1. In line with this research, Ziegler et al. showed in a research that both types of aerobic and resistance training increase the expression of PGC-1α and UCP-1 in visceral adipose tissue in rats (21). Also, Khaledi et al. showed that aerobic exercise and vitamin D supplementation increased PGC-1α and UCP1 gene expression in diabetic rats (22). In a study, Ranjbari et al. showed that the simultaneous consumption of nettle extract and swimming exercise reduces blood glucose and also activates the expression of PGC-1α and UCP-1 genes, which play a role in the browning of adipose tissue (23). Aerobic activity reduces the intracellular energy charge, followed by the activation of AMPK and the activation of PGC-1α in the nucleus to affect the increase in the expression of genes involved in mitochondrial biogenesis and even the increase of PGC-1α. In the present study, the possible increase of PGC-1α following aerobic exercise in HFD rats was associated with the increase of UCP-1 expression. In the study of Kianmehr et al., an increase in the expression of UCP-1 was observed after exercise on treadmill (24).

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In the current research, PPARγ gene expression levels in the combined experimental group (diabetes-berberine chloride-exercise) showed a significant increase compared to the diabetes group and the diabetes-berberine chloride group. PPARγ is able to reduce oxidative stress and inflammation by suppressing the transcription of NF-kB gene as well as increasing the expression and release of NO (25). Few researches regarding the investigation of sports training have focused on the expression of PPARγ gene. However, Haczeyni et al. showed in a study that PPARγ levels increased significantly in weeks 10 and 14 (26), which is in line with the results of the present study. In general, it has been shown that exercise can regulate PPARγ protein. In another study by Turgut et al., the results indicated an increase in PPARγ protein gene expression in the training group compared to the control group (27). Wu et al. showed that aerobic exercise intervention improved lipid metabolism in obese rats, and this mechanism may be related to the regulation of the LncSRA/p38/JNK/PPARγ signaling pathway (28).

Several hypotheses have been proposed for the molecular mechanisms of browning of white adipose tissue through PPARγ protein. For example, since exercise training is known to increase sympathetic innervation in subcutaneous fat tissue, increasing sympathetic innervation can help the browning of subcutaneous fat tissue. The possible cellular and molecular mechanism of this pathway is that the sympathetic nervous system controls adaptive thermogenesis in brown fat by activating beta-adrenergic receptors. PPARγ is the main enhancer of UCP1 gene (29). Also, PPARγ is a therapeutic target for obesity, high fat and diabetes (30). Zhang et al. showed that exercise activity causes upregulation of hepatic PPARγ gene in obese rats (31). It has been shown that the increase of PPARγ caused by long-term aerobic exercise regulates the expression of CPT-1 and its target gene MCAD (Medium-Chain Acyl-Coa Dehydrogenase) and subsequently reduces insulin resistance through increasing the oxidation of fatty acids (31). The mechanisms underlying the increase in PPARγ induced by exercise are unknown. In a study, Kawanishi et al. showed that exercise training caused the upregulation of hepatic PPARγ by reducing the expression of CD36 in liver macrophages. It was also stated that low-intensity exercise increases serum levels of oxLDL and subsequently increases the expression of PPARγ and LXRα (32).

In the present study, it seems that berberine chloride and aerobic exercise with their synergistic effects improved the expression of the above factors in fat tissue. The possible anti-hyperglycemic mechanisms of berberine are that it can stimulate glycolysis, suppress hepatic gluconeogenesis, adipogenesis, and mitochondrial function, and increase insulin secretion by activating adenosine 5-monophosphate kinase (AMPK) (33). As a result, berberine will probably reduce the blood glucose level through the mentioned mechanisms.

The results of the present study showed that aerobic exercise and berberine chloride is one of the possible ways to prevent the damage caused by diabetes. This treatment method can be a suitable alternative to drug therapy in dealing with diabetes and its complications. Also, aerobic exercise and consumption of berberine chloride can be a good way to reduce oxidative stress caused by diabetes.

Conflict of interest: There is no conflict of interest between the authors.

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