ORGINAL ARTICLE

The Aerobic Training and Berberine Chloride Intervention on Pancreatic Tissue Antioxidant Enzymes and Lipid Peroxidation in Type 1 Diabetic Rats

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Abstract

Objective: Aerobic training and berberine chloride include antioxidant characteristics. In this study, aerobic training and berberine chloride intervention on the activity of antioxidant enzymes and lipid peroxidation of pancreatic tissue were investigated in type 1 diabetic male wistar rats**.**

Materials and Methods: In the current study, 56 Wistar male rats were randomly assigned to seven different groups (n= 8), these groups include healthy control, diabetic control, Berberine-treated diabetes (15&30 mg/kg), aerobic training-treated diabetes, Diabetes treated with Berberine and aerobic training (15&30 mg/kg). The aerobic training schedule consisted of 6 weeks treadmills with a frequency of 5 sessions per week. The Berberine was also fed a specific dose every day and a half before training. The superoxide dismutase, glutathione peroxidase, catalase, and malondialdehyde were assessed using ELISA method.

Results: The results showed that aerobic training, as well as the intervention of Aerobic Training and Berberine chloride, had a significant effect on the increase of antioxidant enzymes SOD and CAT in the pancreatic tissue groups (*P*-value< 0.05), but did not significantly affect the GPX level (*P*-value> 0.05). There was a significant decrease in MDA level in all treatment groups (*P*-value< 0.05). In diabetic groups that received both treatments at the same time, the MDA level more decreased (*P*-value< 0.0005).

Conclusion: The aerobic training and berberine chloride concurrent intervention have a greater effect on the antioxidant enzymes in the pancreatic tissue of diabetic specimens. Therefore, it is recommended that aerobic training be done with berberine chloride.

Keywords: Type 1 diabetes, Aerobic training, Berberine chloride, Antioxidant enzymes

Introduction

Type 1 diabetes is an autoimmune disease that most often occurs in young people. In this disease, pancreatic beta cells, which produce insulin, are degraded and ultimately lead to lower insulin secretion(1).
Oxidative stress is associated with almost all pathological conditions, especially in the

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inflammatory process. (2). Oxidative stress is characterized by increasing the production of cellular oxidants (including superoxide, hydrogen peroxide and nitric oxide), or decreasing the concentration of antioxidants enzymes, including glutathione peroxidase (GPX), superoxide dismutase (SOD) and catalase (CAT). The fact that increased oxidative stress is an important factor in the development of diabetes is accepted (3,4). Usually, diabetes is associated with increased production of free radicals (4,5) or antioxidant deficiency (6,7). Reducing oxidative stress may protect cells from damage caused by oxidants, especially ROSs. The GPX enzyme is found in cells that metabolize peroxide to water (8). Any change in their levels makes the cells susceptible to oxidative stress and thus cell damage. CAT enzyme regulates H2O2 metabolism, which is a major cause of serious damage to fats, RNA, and DNA. The formation of H2O2 can suppress the metabolic activity of β-cells unless it is rapidly eliminated (9,10). CAT, converts H2O2 to water and oxygen and neutralizes it. In the case of catalase disorder, the pancreatic β-cell, which contains a large number of mitochondria, is caused by over-exposure to ROS under the influence of oxidative stress, which leads to dysfunction of β-cells and ultimately diabetes (11). The SOD enzyme is the first line of defense against ROSs that cause cell damage. This enzyme catalyzes superoxide into oxygen and peroxide. It can be argued that SOD also decomposes superoxide into other components that are less toxic (12).

Since ancient times, herbal medicines have been widely used to treat diabetes (13). Among these anti-diabetic herbal medicines, berberine chloride (BC) is an isoquinoline alkaloid, potentially potent anti-inflammatory and anti-oxidant (14) and hypoglycemic effects (15). It is found in many herbs such as berberis aquifolium, berberis vulgaris, and berberis aristata.

On the other, there is evidence that exercise inhibits progress in glucose tolerance (16) and may also reduce hyperglycemia in type 1 diabetic patients (17-19). In addition, evidence suggests that exercise can repair the mass of β-cells in type 1 diabetic rodents (20,21). The study also examined the effect of different Aerobic Training intensities on preventing damage to pancreatic β-cells in STZ-diabetic rats. Moderate intensity exercises had the best effect on the preservation of β-cells of the pancreas, which is one of the most important reasons for the anti-inflammatory and anti-oxidant effects of this intensity of exercise (21,22).

In this study, we sought to answer the question whether concurrent intervention of aerobic training with moderate intensity and berberine chloride has an effect on antioxidant enzymes and lipid peroxidation in Type 1 Diabetic Rats or not?

Materials and Methods

This was a laboratory trial on 56 adult male wistar rats from the Pasteur Institute of Iran, Tehran. The rats were taken to an animal room located on the International Campus of Shahid Sadoughi University of Medical Sciences in Yazd. All standard items including temperature conditions (24 ± 1 ° C), relative humidity (55 ± 3%), free access to water and a standard special diet of mice (made by Behparvar, Iran) as well as the dark/light cycle (12/12 hours). Also, the ethical guidelines for working with laboratory animals were met in accordance with the Helsinki Statement of 2008 (23). And before the study began, the code of ethics in the research was obtained with the identifier IR.PNU.REC.1397.033. Animals were placed in special cages of polycarbonate for two weeks to adapt to the new environment. In the course of two weeks, in order to get acquainted with the treadmill, the animals walked on a treadmill five days a week and each session for 5-10 minutes at a speed of 4-5 m/min.

The rats were randomly assigned into seven groups of eight. In the healthy control group, instead of STZ, a saline solution was injected. In other groups, diabetes was induced by intraperitoneal injection (IP) of fresh

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streptozotocin solution (Sigma, S0130) with pH=4.5 and at 60 mg/kg dissolved in 0.1 M citrate buffer(24). After the injection of STZ, a 5% glucose solution was used instead of water for 48 hours to reduce mortality in rats(25). After 72 hours of STZ injection, blood glucose concentrations were measured after 12 hours of fasting overnight, with a small lacrimal injury in the rat's tail area using Japan's glucocard-01 device. Rats with the blood glucose level above 300 mg/dl were included in the study as diabetic animals. Experimental groups included:

1. The healthy control group (Normal Ctr)
2. The diabetic control group (D)
3. Diabetic + Berberine chloride (D-BBr 15 mg/kg)
4. Diabetic + Berberine chloride (D-BBr 30 mg/kg)
5. Diabetic + Aerobic Training (D-AT)
6. Diabetic + Aerobic Training + Berberine chloride (D-AT-BBr 15 mg/kg)
7. Diabetic + Aerobic Training + Berberine chloride (D-AT-BBr 30 mg/kg)

The berberine used in this study was manufactured by Sigma Aldrich (with code number: 14050). The administration of berberine was done by gavage. In this study, doses of 15 and 30 mg/kg were used, and this dose was determined based on the EC50 berberine used in previous studies. The Berberine drug was given to specimens at all times and at a specific time. In groups that performed aerobic training, an hour before the start of the exercise. The drug was given to the specimens even on rest days and 48 hours after the last exercise session and after 12 hours of fasting, sampling was performed from control and treatment groups (27). To collect the specimens, animals were initially anesthetized by intraperitoneal injection (IP) with a combination of ketamine (30-50 mg/kg) and xylazine (3-5 mg/kg) based on rat weight(28). The chest of animals was then split and blood samples were taken directly from the heart of the rats. Blood was immediately poured into tubes containing ethylene diamine tetraacetic acid (EDTA). The samples were then centrifuged at a speed of 3000 rpm for 15 minutes, and their topical solution was stored inside labeled microtubules and kept until the test day at -80 °C. After the blood collection, the animals were sacrificed and the pancreatic tissue was carefully removed from the body of the rats and immediately labeled with microtube and transferred to tank containing liquid nitrogen to freeze, then transferred to a freezer -80. On the test day, place a small piece of pancreatic tissue at about 100 mg in 1 ml of PBS buffer (pH=7.4) and homogenizer (T10 Basic, IKA model, Germany) on ice for 5 minutes Completely solved. Then the solution was centrifuged for 20 minutes at 4 ° C with 6000 RPM. The supernatant was transferred to a 1 cc micro tube and finally concentrated on the Bradford method.

To measure the SOD enzyme in pancreatic tissue, a ZellBio Germany (Cat No: ZB-SOD-96A) kit with a sensitivity of 1 U/mL was used. To measure the GPX enzyme from a specific kit manufactured by ZellBio Germany (Cat No: ZB- GPX-96A) with a sensitivity of 5 U/mL. To measure the enzyme CAT from a specific kit manufactured by ZellBio Germany (Cat No: ZB-CAT-96A) kit with a sensitivity of 0.5 U / mL and to measure the MDA enzyme from the ZellBio proprietary kit Germany (Cat No: ZB-MDA-96A) was used by ELISA method. Glucoskeletan was also measured by Japan's glucocard-01 device.

The Kolmogorov-Smirnov test was used to determine the normality of the samples .We also used the two-way analysis of variance test and the Tukey's post hoc test to analyze the data. The results were presented as mean ± standard deviation and the significance level was considered as *P*-value< 0.05. Data were analyzed with SPSS software version 25.

Table 1. Aerobic Training program (26)

Practice variables	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Speed (m/min)	10	10	14-15	14-15	17-18	17-18
Duration (min)	10	20	20	30	30	40

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Ethical considerations

The study began, the code of ethics in the research was obtained with the identifier IR.PNU.REC.1397.033.

Results

The results of changes in body weight (BW), body mass index (BMI) and fast blood glucose (FBS) concentrations are presented in Table 2. FBS concentration were significantly decreased in the intervention groups (*P*-value= 0.015, 0.003), but no significant changes were observed in other treatment groups (*P*-value> 0.05).

The level of SOD in the diabetic control group was significantly lower than the healthy control group (*P*-value< 0.0002).

CAT levels in the D-AT group and D-BBr30mg/kg group showed a significant increase compared to the diabetic control group (*P*-value= 0.007, 0.030). There was no significant difference in other treatment groups compared to the diabetic control group.

The descriptive statistics of the variables in table 3. Data are presented as mean ± standard deviation.

The concentration of MDA enzyme was measured as a lipid peroxidation index in pancreatic tissue (Figure 1). The MDA level in the diabetic control group was significantly higher than the healthy control group (*P*-value= 0.0001). In all treatment groups, MDA had a significant reduction than the diabetic control group (*P*-value= 0.005, 0.001 and 0.003). Also, the levels of this enzyme in the D-AT, D-AT-BBr (15 mg/kg) and D-AT-BBr (30 mg/kg) groups were significantly lower than the D-BBr (15 mg/kg) group.

The correlation coefficient between variables is shown in Table 4. Between CAT with SOD and GPX, there is a significant and direct relationship (*P*-value= 0.003, 0.039). There is reverse and significant relationship between MDA with CAT and SOD (*P*-value= 0.004,

Table 2. Mean ± standard deviation of BW, BMI and Blood Glucose in the research groups. (BW): Bodyweight, (BMI): Body mass index, (FBS): Fast Blood Glucose.

Variable	week	Normal Ctr	D	Group D-BBr (15 mg)	D-BBr (30 mg)	D-AT	D-AT-BBr (15 mg)	D-AT-BBr (30 mg)
BW (gr)	1	283.63 (±18.20)	285.12 (±13.37)	283.81 (±21.84)	281.57 (±14.04)	281.78 ±3.01	283.63 (±5.79)	282.78 (±17.05)
	6	343.87 (±21.48)	198.57 (±4.47)	228.81 (±10.65)	283.88 (±10.05)*	205.36 (±11.59)	289.63 (±7.95)*	323.85 (±18.07)*
***P*-value**					0.032		0.021	0.001
BMI (g/cm2)	1	0.63 (±0.02)	0.61 (±0.02)	0.60 (±0.01)	0.62 (±0.03)	0.61 (±0.01)	0.60 (±0.01)	0.60 ±0.02
	6	0.64 (±0.0)	0.46 (±0.03)	0.45 (±0.03)	0.50 (±0.03)	0.48 (±0.06)	0.61 (±0.01)†	0.62 ±0.02†
***P*-value**							0.002	0.001
FBS (mg/dl)	6	96.25 (±2.76)	601.62 (±17.27)	584.75 (±23.87)	559.62 (±8.43)	583.87 (±10.58)	410.62 (±20.28)#	356.75 (±37.12)#
***P*-value**							0.015	0.003

Values include means ±SD assayed by two-way ANOVA and Tukey's post hoc test; signifi cant differences were seen between the experimental groups; (*, †) Indicate significantly increased compare to Diabetic control group. (#) Indicate significant decreased compare to the Diabetic control group. In a row *P*-value that nothing is written, the *P*-value is greater than 0.05.

Table 3. Mean (± standard deviation) of SOD, GPX, CAT and MDA in the research groups.

Variable	Normal Ctr	D	Group D-BBr (15 mg)	D-BBr (30 mg)	D-AT	D-AT-BBr (15 mg)	D-AT-BBr (30 mg)
SOD	4.29 (±0.20)	1.95 (±0.50)	3.05 (±0.11)	3.05 (±0.50)	3.92 (±0.23)*	4.59 (±0.86)*	3.87 (±0.41)*
***P*-value**					0.018	0.0001	0.001
GPX	21.13 (±1.63)	18.23 (±0.34)	19.00 (±2.64)	21.76 (±3.07)	24.60 (±11.54)	21.55 (±0.92)	19.29 (±2.12)
***P*-value**							
CAT	2.94 (±0.59)	1.63 (±0.28)	2.97 (±0.51)	2.50 (±0.54)	3.62 (±1.01)*	2.68 (±0.50)	3.77 (±0.91)*
***P*-value**					0.007		0.030
MDA	2.01 (±0.19)	8.57 (±1.52)	4.60 (±0.46)	3.57 (±1.19)	1.98 (±0.75)#	1.60 (±0.72)#	1.94 (±0.13)#
***P*-value**					0.0005	0.0001	0.0003

(*) Indicate significant difference compare to the diabetic control group. (#)Indicate significant decreased compare to the Diabetic control group. In a row p-value that nothing is written, the p-value is greater than 0.05.

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0.001). There was no significant relationship between other enzymes (table 4).

Discussion

In this study, we evaluated the effect of simultaneous Aerobic Training and supplementary Berberine chloride (15 and 30 mg/kg) on the activity of antioxidant and lipid peroxidation in pancreatic tissue of STZ-induced diabetic rats. Given that oxidative stress in diabetic individuals increases with free radical production, it can be suggested as one of the factors contributing to the progression of diabetes mellitus (29). It is believed that, in response to oxidative stress, antioxidant enzymes should protect cellular function in maintaining hemostasis (30).

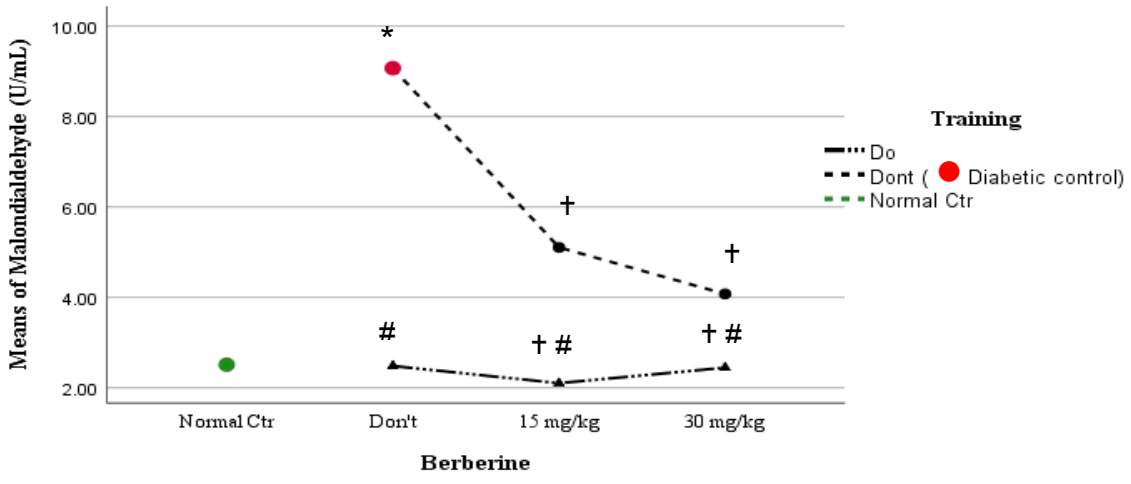
The high levels of MDA, which are lipid peroxidation products, represent the oxidative stress of diabetes. The results of this study showed that the Induction of diabetes increases the multifold of MDA. According to the results of this study, antioxidant defense of the pancreatic tissue has been reduced against the oxidative stress in STZ-induced diabetes in rats, which is accompanied by a significant increase in MDA in the diabetic control group. Aerobic Training, Berberine with doses of 15 and 30 mg/kg, all alone reduced MDA significantly in pancreatic tissue of diabetic specimens. The concurrent aerobic and

Table 4. Pearson correlation coefficient between the variables.

Variable	Variable	Pearson correlation	Significance
CAT	SOD	0.622	0.003 *
CAT	GPX	0.453	0.039 *
CAT	MDA	- 0.600	0.004 *
SOD	MDA	- 0.809	< 0.001 *
BW	MDA	- 0.581	0.006 *
FBS	MDA	0.508	0.019 *

(*) Indicates that there is a relationship between variables.

Berberine intervention resulted in a further reduction in MDA. According to the results, in groups with decreased MDA (especially interventional groups), BW and FBS levels were better than the diabetic control group and significant changes were observed. The relationship between MDA and BW was inversely and significant, and the relationship between MDA and FBS was direct and significant. G. Chandirasegaran et al. (2017) obtained similar results on diabetic rats (25). In this study, the lipid peroxidation of rats treated with Berberine (50 mg/kg) was significantly lower than the diabetic control group. In another study, it was shown that consumption of Berberine with doses of 150 and 300 mg/kg had a significant effect on MDA reduction in diabetic specimens (31). Berberine has reduced the amount of MDA in the pancreas of diabetic specimens, suggesting the protective effect of berberine in the pancreas due to its protective effect on lipid



(*) Indicate significantly increased compare to Normal control group. (†) Indicate significantly decreased compare to Diabetic control group. (#) Indicate significantly decreased compare to (D-Br15 mg/kg) group.

Figure 1. Malondialdehyde changes in the study groups.

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peroxidation damage.

During exercise, increased levels of oxidative stress promote antioxidant defense mechanisms in various tissues. This slight to moderate increase in radical oxygen species is part of the "hormesis" that triggers the optimal biological response to small amounts of toxins and stressors. (32). Also, this increase in exercise results in adaptations that include increased activity of antioxidant / oxidative-boosting enzymes, increased resistance to oxidative stress, and ultimately reduced oxidative damage. But overproduction of radical oxygen species is accompanied by harmful factors (22).

SOD catalyzes and removes superoxide radicals, converting them to water and oxygen molecules, thereby protecting tissues against free radicals. The reduction of SOD in diabetic specimens can be due to inactivation by H2O2 or glycation enzymes (33). In this study, SOD significantly increased in D-AT, D-AT-BBr (15, 30 mg/kg) groups compared to the diabetic control group. Therefore, Aerobic Training alone, as well as the intervention of Aerobic Training and Berberine chloride, may reduce the production of free radicals and also increase the activity of SOD antioxidant activity in pancreatic tissue, but Berberine chloride alone with selected doses (15 and 30 mg/kg) has no significant effect on SOD. In a study was shown that intake of Berberine chloride with a dose of 50 mg/kg in diabetic rats caused a significant increase in the SOD antioxidant enzyme (25). The results of another study showed that the consumption of Berberine with doses of 75, 150 and 300 mg/kg significantly increased the SOD enzyme (34). By comparing the results of this study with other studies, it can be concluded that Berberine with doses of less than 50 mg/kg cannot have a significant effect on the number of SOD enzymes. In a study, moderate-intensity exercise was shown to increase the activity of the SOD enzyme in mice (32).

Also, according to the results of this study, the level of CAT in the D-AT group and D-AT-BBr (30 mg/kg) group compared to the diabetic control group significantly increased. There were no significant changes in other treatment groups compared to the diabetic control group. In one study, CAT levels in the pancreas of diabetic rats treated with Berberine chloride increased significantly, which was probably prevented from forming hydroxyl radicals due to the antioxidant properties of Berberine chloride (25). The results of another study showed that physical exercise increases the amount of enzyme CAT in serum (35). H2O2 is one of the metabolic products that should be eliminated quickly, which is done by antioxidants such as CAT, otherwise, it can lead to dysfunction of β -cells and ultimately diabetes (11). Aerobic Training and Berberine chloride medications can prevent further damage to the pancreatic cells caused by oxidative stress, given their antioxidant properties.

GPX reduces its toxicity through the oxidation of glutathione (GSH) and the conversion of H2O2 to water (22). Decreased activity of GPx in tissues during diabetes may lead to harmful effects due to the accumulation of toxic products (36). In the present study, GPX increased in treatment groups, but this increase was not statistically significant. One study showed that treatment of diabetic rats with Berberine at a dose of 50 mg/kg significantly increased GPX activity in the pancreas(25). Therefore, the doses used in our research are likely to be less than those that have a significant effect on GPX. Also, the simultaneous intervention of Aerobic Training and Berberine chloride with selected doses did not have a significant effect on the GPX of pancreatic tissue.

Conclusions

Administration of Berberine chloride at doses of 15 and 30 mg/kg has no effect on the antioxidant enzymes of the pancreatic tissue of the rats, but simultaneous administration of Berberine chloride with Aerobic Training has a positive and significant effect on the antioxidant enzymes of the pancreatic tissue

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(SOD and CAT). Also, Berberine chloride alone with selected doses has a significant effect on MDA in the pancreatic tissue, but the simultaneous presentation of Berberine chloride and Aerobic Training has a more pronounced effect on MDA. Therefore, the simultaneous intervention of Aerobic Training and Berberine chloride can be used as an effective way to increase the antioxidant defense and decrease MDA in the pancreatic tissue of type 1 diabetes mellitus.

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