ORGINAL ARTICLE

The Effect of Aerobic Exercise & L-Carnitine Consumption on Diabetes-Induced Apoptosis & Oxidative Stress Factors in Rat

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Abstract

Objective: The use of non-enzymatic antioxidants in the form of dietary supplements has a positive effect on reducing oxidative stress, and preventing apoptosis as they interrupt free radicals. The aim of this study was to investigate the aerobic exercise and L-carnitine consumption impacts on diabetes induced apoptosis, oxidative stress factors, and mitochondrial enzymes in rats.

Materials and Methods: In this Clinical trial study, 45 male Wistar rats (200-300 g) were divided into six groups including sham, healthy control, diabetic control, diabetic & L-carnitine, diabetic & aerobic exercise, diabetic receiving L-carnitine & aerobic exercise . The rats attained a diabetic state with a single dose of STZ intraperitoneal injection (55 mg/kg body weight) and receiving L-carnitine 100 mg per day. The aerobic exercise protocol including five sessions per week was administered. The heart tissues of the dependent variables were measured by ELISA 24 hours after the last session of the exercise program. One-way ANOVA and Tukey's post hoc test at *P*-value< 0.05 were used to analyze the data.

Results: result show that aerobic exercise and L-carnitine consumption have a significant effect on BAX (*P*-value= 0.001), Bcl-2 (*P*-value= 0.001), and SOD (*P*-value= 0.001) in diabetic rats.

Conclusion: The results of the present study confirm the role of aerobic exercise and L-carnitine in improving the indices of apoptosis and oxidative stress in type 2 diabetic rats.

Keywords: Aerobic exercise, L-carnitine, Diabetes, SOD, BAX, Bcl-2.

Introduction

Diabetes is a metabolic disorder which can cause hyperglycemic state. This disease can be due to defects of insulin secretion, the resistance to insulin action, or both of them. Serious long-term complications of diabetes include microvascular and microvascular diseases (1). Diabetes can also cause tissue damage and cell death or apoptosis, which plays a vital role in the growth and development of organs, homeostasis and destruction of damaged cells

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(1). The studies show that any defects in this pathway can cause accumulation of mutated cells and ultimately leads to the death of the patient. Moreover, the increased prevalence of apoptosis in the hearts of the streptozotocin-induced diabetic rats was shown in the animal model (2).

The oxidative stress caused by diabetes may have an important role in occurring apoptosis in hyperglycemic condition. Oxidative stress reflects an imbalance between the production of reactive oxygen species (ROS) and the antioxidant agents eliminating ROS. In a diabetic's heart, accumulation of ROS can be enhanced by mitochondrial deficits, spontaneous glucose oxidation and increased xanthine oxidase activity (3). Regardless of its origin, active forms of oxygen can cause cell death through mechanisms such as lipid peroxidation, cellular protein changes, and various ways of creating stress messages. Also, an increase in the levels of free radicals and the simultaneous reduction of defense mechanisms against it can provoke cellular and enzymes damage, increase lipid peroxidation, and develop insulin resistance (4).

Oxidative stress is one of the known mechanisms of apoptosis induction. While compulsory exercises increase the levels of antioxidants (5). Therefore, the impact of exercise on the induction or inhibition of apoptosis has not been proved yet.

Regarding the production of free radicals by diabetes and exercise and finally the development of apoptosis, one of the issues that have attracted researchers' attention is finding ways to reduce the negative consequences of diabetes and the production of free radicals. The use of antioxidant agents, in this regard, can be very helpful as they featuring various mechanisms decrease the intensity of oxidative stress reactions and their molecular effects on macromolecules such as lipids, proteins, DNA, and reduce the cellular effects and finally minimize their clinical problems (3).

One of the substances featuring anti-oxidant properties is L-carnitine. (6). L-carnitine facilitates the β-oxidation of long chain fatty acids, contributes in the metabolism of branched-chain amino acids, and protects cellular membrane (7). The previous studies have revealed that L-carnitine protects antioxidant enzymes against oxidative damage (8). Various researches yielding contradictory results have been conducted on the effect of L-carnitine on antioxidant enzymes and apoptotic factors (9,10).

Given that oxidative stress is one of the causes of apoptosis and considering the importance of apoptosis in diabetes, reducing the negative effects of diabetes has always been the focus of studies. The aim of this study was to investigate the aerobic exercise and L-carnitine consumption impacts on diabetes induced apoptosis, oxidative stress factors, and mitochondrial enzymes in rats.

Materials and Methods

This is a clinical trial study in which the ethics of working with laboratory animals including the availability of water and food and the appropriate maintenance conditions were considered. The way the rats were killed was also observed. In the present study, 45 rats weighing 250-300 g were provided from Razi vaccine & serum research institute and moved to the research center. After one- week familiarity with the new environment, the rats were randomly divided into six groups including sham group (5 rats), healthy control group (8 rats), diabetic control group (8 rats), diabetic group receiving L-carnitine (8 rats), diabetic group receiving aerobic exercise (8 rats), diabetic group receiving L-carnitine and aerobic exercise (8 rats). During the research period, the animals were kept in transparent 15 × 15 × 30 cm polycarbonate cages manufactured by Razi Rad company at 20-22°C and 55-65% moisture and 12:12 light cycles; the animals were also fed with pellet-form food provided from livestock feed production centers. Thirty two rats attained a diabetic state with a single dose of nicotine

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amide and STZ injection. First, nicotine amide (95 mg / kg of body weight) was intraperitoneally injected into the rats. After 15 minutes, STZ (55 mg / kg of body weight) prepared in sodium citrate buffer with pH = 7.4 was intraperitoneally injected. Rats of control groups received the same amount of buffer. Five days after the injection, a drop of blood was drawn from the tail of the rats and then placed on glucometer strips. The rats with serum glucose level higher than 300 mg/dL were considered diabetic. The rats receiving L-carnitine received 100 mg per day (11,12). The aerobic exercise group received aerobic exercise on treadmill for six weeks, five days a week from 9 AM to 11 AM (13). The protocol started with the speed of 10 m for 10 min at a grade of zero percent in the first week and gradually reached the speed of 20 m for 40 min at the grade of 5 in the sixth week taking into account the principle of overload.

In the references of the study, the exercise intensity of the diabetic rats is the equivalent of intensity at the threshold of lactate (13,14). It is also equivalent of about 75% of maximum oxygen consumption which is a relatively high intensity for the diabetic rats (15). An acoustic stimulant (hitting the treadmill) was used to stimulate the rats to run. In order to familiarize the rats of the control group with the treadmill, they walked on it once a week for 5 min, with the speed of 10 m and at a grade of zero percent. After 6 weeks, all the rats were anesthetized with chlorophyram through the respiratory tract and a surgical biopsy was performed.

Finally, BAX and Bcl-2 concentration were measured using Bradford method, and SOD (superoxide dismutase) activity was measured via Winterbourne method. Indicators of central tendency and Shapiro-Wilk Test were respectively used to describe the data and analyze normality of data distribution. As for the inferential analysis of data, one-way ANOVA and Tukey's post hoc test were used via SPSS/21. In order to verify the research hypotheses, the significance level $\alpha \leq 0/05$. Needless to say, Excel was used for drawing diagrams.

Ethical considerations

The ethical code of this research is IR.SSRI.REC.1397.337. This code was taken from the Sports Sciences Research Institute of the Ministry of Science and Research and Technology of Iran.

Results

The results of the study (table 1) showed that aerobic exercise and L- carnitine consumption have a significant effect on heart Bcl-2 in rats (*P*-value= 0.001). It was also revealed that the healthy control group has no significant difference with the sham groups (*P*-value= 0.208), aerobic exercise, and L-carnitine supplements. However, a significant difference was observed between the other groups. Regarding to BAX result show that aerobic exercise and L- carnitine consumption have a significant effect on BAX in the rat heart (*P*-value= 0.001). Finally Regarding SOD, it was revealed that aerobic exercise and L- carnitine consumption have a significant effect on SOD in the rat heart (*P*-value= 0.001). It was also demonstrated that the healthy control group has no significant difference with the aerobic exercise group (*P*-value= 0.103) and aerobic exercise and L-carnitine supplement group (*P*-value=0.941). Furthermore, there is no significant difference between the sham group and the diabetic control group (*P*-value= 0.995), but there is a significant difference between the other groups.

It should be noted that the results of the post hoc and pairwise comparisons for each variable are presented separately in the form of graphs. (Figure 1-3)

Discussion

Table 1. results of one-way ANOVA test

Variable	F	*P*-value
BAX	77.36	0.001
Bcl-2	63.05	0.001
SOD	38.172	0.001

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The findings of the study have revealed that an intervened combination of aerobic exercise and L-carnitine supplement increased the Bcl2 of heart tissue in the diabetic rats, which is in line with the findings of the studies conducted by Habibi et al (2016), Cai et al (2015), (2005), (16,17). Although the exact mechanism of apoptosis is still unknown, it may be different regarding the cell and type of stimuli. It was also revealed that doing exercise leads to apoptosis induction which is a natural procedure for destroying damaged cells without any significant inflammatory reactions. This procedure ensures the normal functioning of the body (3). The protective mechanisms against apoptosis, due to inhibition process, may be affected by NF-kB, which prevents sensitivity to apoptosis and improves the incremental regulation of Bcl-2 anti-apoptotic cells (18). Anti-apoptotic Bcl-2 overexpression leads to reducing heart tissue damage and improving cardiac function.

The previous related studies have confirmed that doing exercise can prevent Caspase 9 activation in cardiovascular patients through reducing pro-apoptotic BAX protein and increasing anti-apoptotic Bcl-2 protein, and consequently inhibiting cytochrome c release. Caspase 9 can also positively regulate apoptosis process by activating Caspase 3.

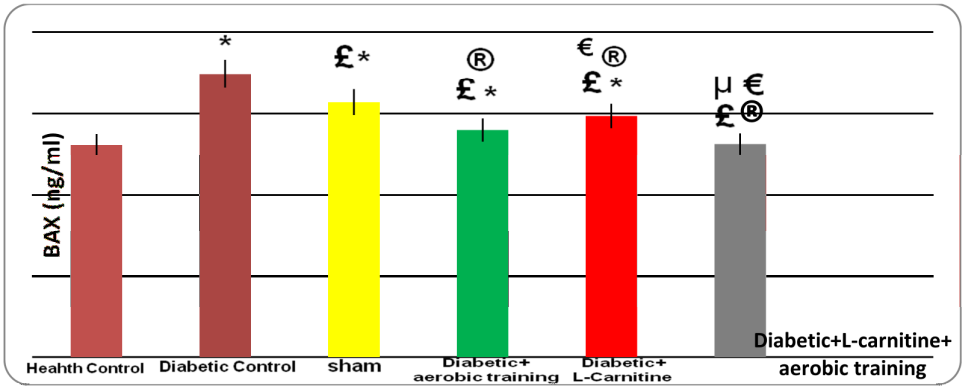

Figure 1. BAX Tukey post hoc test results.

*:Significant difference compared to healthy control group. **£**: Significant difference compared to Diabetic group. **®**: Significant difference compared to Sham group. **€**: Significant difference compared to Diabetic aerobic exercise group **µ**: Significant difference compared to Diabetic L-carnitine group.

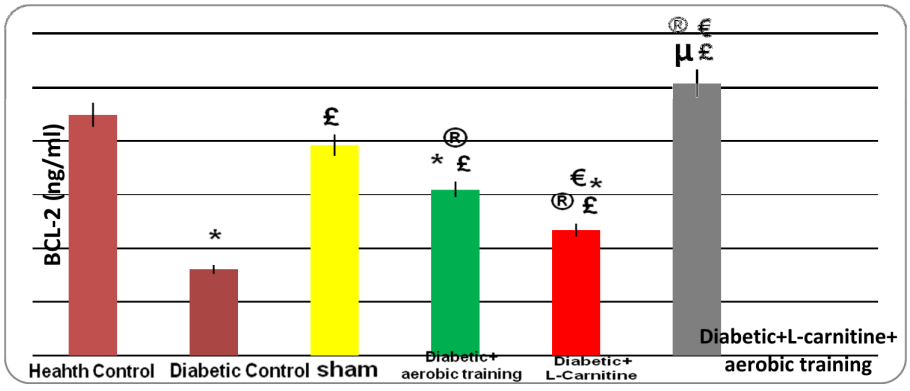

Figure 2. BCL-2 Tukey post hoc test results.

*:Significant difference compared to healthy control group. £: Significant difference compared to Diabetic group. ®: Significant difference compared to Sham group. €: Significant difference compared to Diabetic aerobic exercise group µ: Significant difference compared to Diabetic L-carnitine group.

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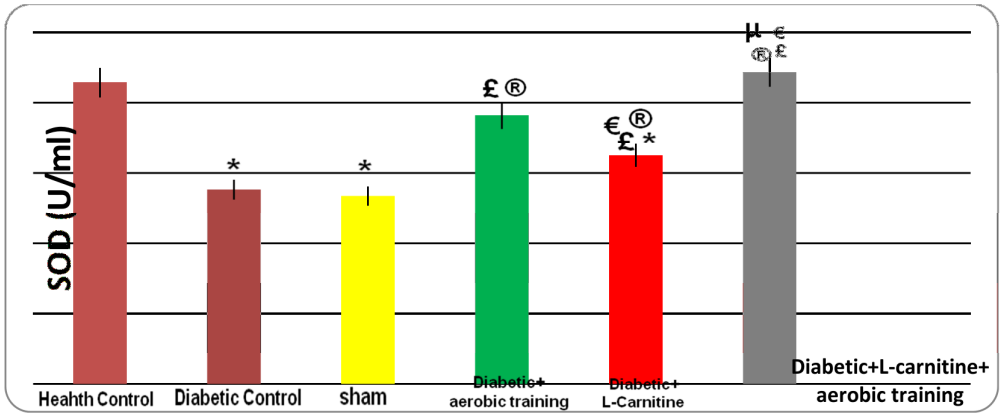

Figure 3. SOD Tukey post hoc test results.

*:Significant difference compared to healthy control group. £: Significant difference compared to Diabetic group. ®: Significant difference compared to Sham group. €: Significant difference compared to Diabetic aerobic exercise group µ: Significant difference compared to Diabetic L-carnitine group.

The levels of Caspase 3 and 9 were not determined in the present study, which can be regarded as limitations of this research. However, the other studies have shown that decreasing the activities of initiator Caspase 9 and executive Caspase 3, exercise can prevent apoptosis and DNA fragmentation from both internal and external pathways. (19).

Generally, this is an important point of view that highlights the importance of sport therapy for improving antioxidant signaling as a means of preventing apoptosis. Increasing Bcl-2 by consolidating the mitochondrial wall, inhibiting cytochrome c release, regulating calcium released from sarcoplasmic, reducing the effect of exercise-induced ROS enhances cellular immunity and prevents stress-induced apoptosis. Bcl-2 is an anti-apoptotic protein that plays a role in the internal pathway of apoptosis and prevents Caspase-3 activity. Bcl-2 is an anti-apoptotic protein that plays a role in the internal pathway of apoptosis and prevents Caspase-3 activity. Given that a six-week protocol was used in this study, it is likely that exercise-induced adaptations activate anti-apoptotic pathways.

On the other hand, L-carnitine reduces the obesity caused by high fat diet and excess carnitine inhibits triglyceride and total lipid uptake (20). The main function of L-carnitine is to facilitate fat oxidation by transporting long-chain fatty acids to mitochondria in which beta-oxidation is performed. Therefore, most dietary lipids using carnitine can be regarded as an energy source (20). L-carnitine has protective properties against drugs that induce mitochondrial damage. Therefore, it is likely that the amount of L-carnitine dose along with an increased amount of Bcl2 improve cardiac function. Furthermore, the intervened combination of aerobic exercise and L-carnitine supplement increases the heart tissue Bcl2 in diabetic rats. It was confirmed that the alpha-tumor necrosis factor (TNF-α) increases apoptosis by expressing inducible nitric oxide synthase (iNOS) and nitric oxide (NO) (20). However, the levels of alpha-tumor necrosis factor were not measured, which is one of the limitations of the present study. Anyway, the heart tissue Bcl-2 increased. Therefore, an increase in anti-apoptotic Bcl-2 of the heart tissue through exercise and L-carnitine may be related to the interactive anti-oxidant and lipid-lowering effects of L-carnitine and exercise.

However, this finding of the present study does not expand upon the results of the studies carried out by Jafari et al (2015), Li et al (2016), and Sun et al (2016) indicating no changes in Bcl-2 after doing exercise (21, 22, 23). In this line, Seo et al (2016) investigated the effect of optional activity (rotary wheel) on the factors involved in apoptosis and reducing stress (24). They came to the conclusion that

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there is no significant difference in Bcl-2 liver expression level. The controversy of the present study with the above findings is probably the location of the tissue, the type of subjects, the subjects' conditions, the type of exercise protocol, or the abnormal levels of apoptosis regulating factors. The reason of the controversy between the findings of this study and the above-mentioned findings may be attributed to measurement location tissue, the types of the subjects, the subjects' conditions, the type of exercise protocol, or the abnormal levels of apoptosis regulating factors.

The results of the present study have revealed that the intervened combination of aerobic exercise and L-carnitine supplement significantly reduces the amount of heart tissue BAX in diabetic rats, which is in line with the findings of the study conducted by Cai et al (2015), (17). However, it is not consistent with the findings of the studies carried out by Li et al, (22), Cai et al confirmed that high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) both lead to a decrease in BAX gene expression in comparison with the control group (17). The previous studies have shown that aerobic exercises significantly reduce the amount of visceral fat and improve insulin resistance (25). As it was revealed in the present study, after the training period, the BAX levels of heart tissue in diabetic rats decreased. Also, regular aerobic exercises enhance the body's antioxidant capacity, which may reduce cellular damage in heart tissue.

The results of the present study have demonstrated that a six-week intervened combination of aerobic exercise and L-carnitine supplement leads to a significant increase in SOD factors in the heart tissue of diabetic rats. This finding is consistent with Alipour et al (2012), and Hung et al (2009), (26,27). Disruption of oxidative balance in favor of oxidative stress plays an important role in diabetes. In endothelial cells, mitochondrial ROS production increases in response to increased blood glucose levels. An increase in ROS production leads to its transfer from renal tubular epithelial cells to mesangial cells, resulting in fibrosis of the interstitial matter and tissue damage (28). It was revealed that Superoxide dismutase as the first line defense antioxidants against ROS is produced during exhaustive exercises (27).

It has been reported that interval training exercises improve the antioxidant status of diabetes in comparison to the other training programs. Generally, there is a close relationship between the production of reactive oxygen species and the intensity of exercise (29). It was also revealed that low-intensity exercises are associated with high SOD activity; and high-intensity exercises are related to glutathione peroxidase activity. Exercise intensity can produce free radicals that stimulate the metabolic pathways of antioxidants by themselves. At the beginning of each sport activity that starts at a low intensity, i.e. the amount of free radical production is much low, the first line defense antioxidant that is activated is the SOD. However, an increase in the intensity of exercise activates glutathione peroxidase and neutralizes H2O2. Therefore, high glutathione peroxidase activity will be accompanied by a lower increase in SOD. The studies yielded different results due to the differences in the type, intensity, and duration of exercise (30).

Excessive production of active oxidative species in exercise may have a deleterious effect on cells, tissues, lipid peroxidation and proteins. Some studies recommend taking more antioxidants or antioxidant supplements during or after exercise (31). The mechanism of the effect of L-carnitine on the oxidative indices has not been accurately specified. L-carnitine carbonyl group can stabilize free radicals formed on alpha-carbon with conjugation, and it can protect the components of the plasma against toxic effects of active oxygen species and nitrogen. It has been argued that L-carnitine exerts its antioxidant effects through increasing glutathione levels by inducing transcription of genes involved in glutathione biosynthesis, increasing bioavailability, producing and maintaining it

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(30). In the present study, L-carnitine can possibly contribute the improvement of the oxidative conditions of the heart tissue in diabetic subjects.

Conclusions

In summary, the results of the present study showed that six weeks of aerobic training with concomitant administration of L-carnitine had an effect on Bcl-2, BAX and SOD in the heart tissue of diabetic rats. It was also found that aerobic exercise and consumption of L-carnitine had more influence on research variables than exercise and L-carnitine consumption. Therefore, aerobic exercise can be safely recommended to reduce the adverse effects of diabetes, but supplementation should be consulted with a physician.

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Conflict of Interest

There was no conflict of interest in conducting this study.

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