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Original Article

The Effect of Interval Training With Resveratrol on Some Apoptotic Indices of the Heart Tissue of Rats With Diabetes Caused by Streptozotocin

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Abstract

Background: Today, diabetes is considered one of the main causes of death so that the aim of this study was to investigate the effect of interval training with resveratrol on some apoptotic indices of the hepatocyte tissue in diabetic male rats.

Materials and Methods: In this experimental trial, 42 male rats were randomly divided into 6 groups, including diabetic saline, diabetic, healthy, supplement, interval exercise, and resveratrol supplementation + interval exercise (7 mice in each group). The program of interval training groups and resveratrol supplementation + interval training on the treadmill included 3 sessions per week, and each session was 10 sets of 1-minute activity that started with 14 meters per minute and reached 28 meters per minute in the eighth week. BCL2, BAX, and CASPASE-3 levels were determined by enzyme-linked immunosorbent assay kits (Zelbio, Germany, Catalog: RK03522, RK03549).

Results: CASPASE and BAX -3 levels were higher in diabetic-saline and diabetic groups compared to the other groups ($P=0.001$). Bcl-2 levels were lower in diabetic-saline and diabetic groups in comparison to other groups ($P=0.001$). The mean BAX/BCL2 ratio was higher in diabetic-saline and diabetic groups ($P=0.001$). Interval exercise and resveratrol administration alone or especially resveratrol intervention combined with interval exercise caused a significant decrease in mean CASPASE-3 and BAX concentrations ($P=0.001$), BAX/BCL2 ratio ($P=0.001$), while a significant increase in the BCL-2 concentration ($P=0.001$) in the myocyte tissue.

Conclusion: The results demonstrated that exercise could increase BAX and BCL-2. This improvement was greater when combined with resveratrol.

Keywords: Interval training, Resveratrol, Apoptosis, Diabetes

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Introduction

Changes in glucose, fat, and protein metabolism have been identified in patients with diabetes. These metabolic disorders lead to a wide range of long-term effects called "complications caused by diabetes on the body". Several studies have shown the negative effect of diabetes mellitus directly on the heart muscle, namely, the myocardium (1). Cardiovascular diseases are the main cause of death in patients with diabetes, not only because of high blood pressure and coronary artery disease but also owing to the side effects of diabetes, directly affecting the heart and independent of other pathological factors (2). It has been reported that apoptosis plays an important role in the process of heart disease (3). The induction of apoptosis as one of the damages of diabetes on the myocardium has been demonstrated by the activation of the components of the apoptosis pathway and caspase activity, and the death of myocardial cells is known as an essential event in the development of heart damage caused by diabetes (3). In fact, various studies indicated that diabetes significantly increases the rate of apoptosis in heart cells (4). As a control point between the cell surface and internal signals for the formation of apoptosis and the activation of the caspase cascade, the proteins of the Bcl-2 family play an important role and are divided into anti-apoptotic proteins/inhibitors (e.g., 2-Bcl, Bcl-W, Bcl-XL, Bfl-1-2, and MCL-1) and pro-apoptotic proteins/promoters (e.g., Bim, Bik, Bid, Bad, Bcl-Xs, Bak, Bax, and Hrk) (5). The Bcl-2 protein can exert a role in causing or preventing apoptosis. The cooperation of MCL-1, Bcl-2, and Bcl-XL has an anti-apoptotic effect by preventing the release of cytochrome C from mitochondria, while other proteins such as Bim Bik, Bid, and Bad play an effective role in causing apoptosis by releasing cytochrome from mitochondria C (6). It is known that Bcl-2 itself does not perform antioxidant activity, but it may have an indirect

effect on increasing antioxidant activity. Therefore, the increase of the Bcl-2 protein allows the cells to better deal with free radicals, and this is achieved as a result of increasing the activity of antioxidant defense enzymes (7).

Considering the role of free radicals in inducing apoptosis and creating oxidative stress (OS) conditions, compounds that can inhibit free radicals in cells are of great importance. Resveratrol, whose chemical formula is trans (3, 5, and 4-trihydroxyacetylene), belongs to the group of polyphenols and is a phytoalexin that protects plants against fungi in nature. This substance is found in abundance in many plant species, including grape skin, peanut berries, rhubarb root, and other plants in small amounts (8). It has been found that this substance has many pharmacological and biological characteristics, including anti-atherosclerosis, anti-blood pressure, antioxidant and reduced OS, anti-apoptotic, and anti-inflammatory properties. On the other hand, it improves plasma markers related to type 2 diabetes (8).

In this regard, Seya et al showed the positive effect of resveratrol administration on reducing the apoptosis of cardiomyocyte cells (9). On the other hand, researchers have always emphasized the role of exercise in the prevention and treatment of obesity and type 2 diabetes in their research; they have further confirmed that exercise is one of the effective strategies to reduce the development of heart damage and the incidence of cardiovascular complications and mortality during diabetes (10). Exercise exercises protect the heart from the complications of diabetes by reducing OS and apoptosis in cardiac cells (11). Tofighi et al have also found that the combined use of resveratrol and exercise protects the heart against the production of OS after ischemia through the activation of antioxidant defense (12). However, no research has so far investigated the effects of intermittent exercise with resveratrol supplementation on apoptotic indices in the heart tissue of diabetic male rats, or no clear results have been reported in this regard. Therefore, the present study sought to evaluate the long-term effect of intermittent exercise on the regulatory markers of the internal pathways of apoptosis, including BAX, Bcl-2, the ratio of BAX to BCL-2, and CASPASE-3 as the most active factor from the family of caspases in the heart tissue of diabetic male rats treated with streptozotocin (STZ).

Materials and Methods

In this realization, the samples of the current research included laboratory rats. Considering that the subjects were under control in terms of many variables in the laboratory, the current research is of an experimental type. This research was conducted in 2022.

The statistical sample of the research project was male Wistar rats about 2 years old with an average weight of 250-300 g. After being selected in the laboratory animal breeding and maintenance center of Islamic Azad University, Sari branch and being familiarized with the exercise protocol, these animals were divided into 6 groups (7 heads in each group), including healthy control groups, diabetic, saline diabetic, resveratrol supplement, and exercise groups. intermittent, and resveratrol supplement + intermittent exercise. All rats were kept in the same food and water conditions.

After transferring the animals to the laboratory, they were placed in polycarbonate cages with the humidity of 55 ± 5%, temperature of 22 ± 2°C, and a 12:12 light-dark cycle with proper ventilation. In all stages of the research, the water needed by the animals was freely available to them in a 500 mL special bottle for laboratory animals. In this project, diabetes was induced by injecting a single dose of STZ 50 mL/kg intraperitoneally, and blood sugar above 250 mg/dL 48 hours after the injection was regarded as induced diabetes (13).

The interval training consisted of eight weeks, three sessions per week, and each session included 10 sets of 1-minute activity with 50% intensity and 2 minutes rest between sets, which started with 14 meters per minute in the first week. The speed was increased by 2 meters per minute every week until it reached 28 meters per minute in the eighth week (14,15).

The resveratrol (Reha Pharmaceutical Company, Iran) supplement was prepared based on previous studies. For each administration of resveratrol, 100 µL of 7% ethanol or 10% DMSO with water was prepared for each rat, and resveratrol was suspended in it and prescribed to reduce the percentage of errors for all subjects. It was prepared in one place. In the groups of resveratrol supplement and resveratrol supplement + intermittent exercise, they were injected intraperitoneally with a dose of 20 mg/kg body weight. This process was continued for 8 weeks (16).

After performing the research, all animals with completely similar conditions and following 12-14 hours of fasting and 48 hours after the last training session and injections, were unconscious with a ratio of 5-2 with the intraperitoneal injection of ketamine (60 mg of base per kg) and xylazine (5 mg of base per kg) kg weight). Next, the heart tissue was separated and kept at -80°C and then sent to the laboratory. BCL2 and BAX levels were determined by the enzyme-linked immunosorbent assay method using special commercial kits (Zelbio, Germany, Catalog: RK03522) with a sensitivity of less than 0.078 ng/mL and 15.6 pg/mL, respectively. Moreover, the activity measurement kit manufactured by Zelbio, Germany was used to quantify the activity of CASPASE-3 (Catalog: RK03549).

The results were presented as the mean ± standard deviations. Data were analyzed using a one-way analysis of variance and, if necessary, Tukey's post hoc test. The considered significance level was 0.05, and all statistical operations were performed using SPSS software, version 20.

Results

The average amount of BAX and CASPASE-3 in diabetic patient groups (equal to 20.314 ± 3.18 ng/mg protein and 2.35 ± 0.364 ng/mL, respectively) and diabetic-saline (equal to 21.871 ± 3.723 ng/mg protein and 0.325 ± 2.291 ng/mL protein, respectively) significantly higher ($P = 0.001$) compared to other groups (Figures 1 and 2).

The comparison of the BCL-2 value among different groups also showed a significant difference ($P = 0.001$). The amount of BCL-2 in diabetic patient groups (2.321 ± 0.383 ng/mL of protein) and diabetic saline (2.428 ± 0.479 ng/mL of protein) was significantly lower in comparison to the other groups ($P = 0.001$, Figure 3). Additionally, a significant difference was observed in

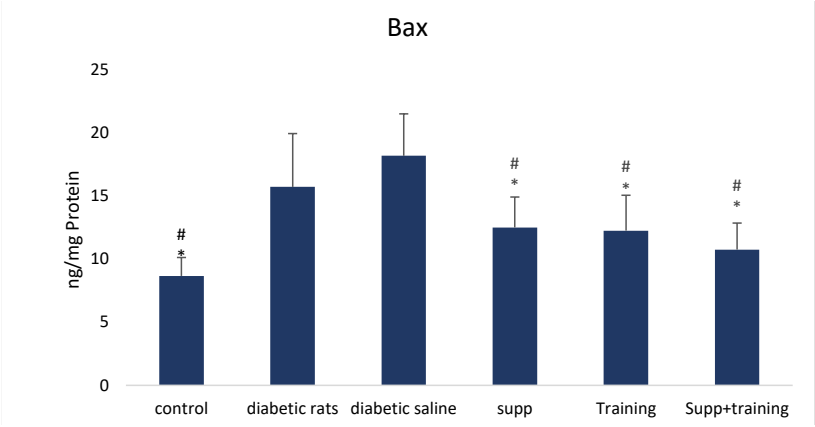

Figure 1. BAX in Different Groups. *Note*. * Significant compared to the patient group; # Significant in comparison to the saline group

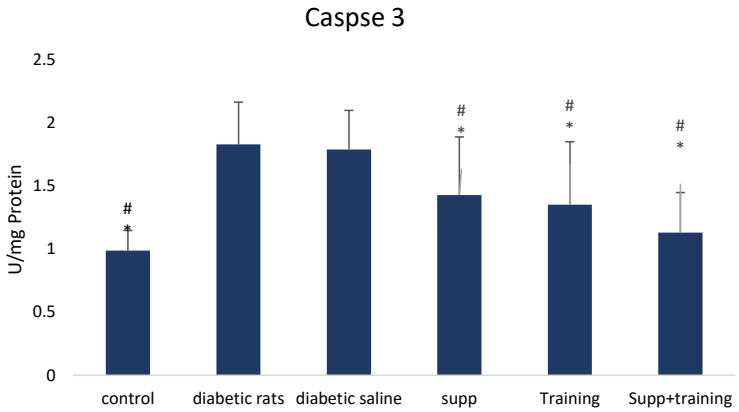

Figure 2. Caspase-3 In Different Groups. *Note*. *Significant in comparison to the patient group; #Significant compared to the saline group

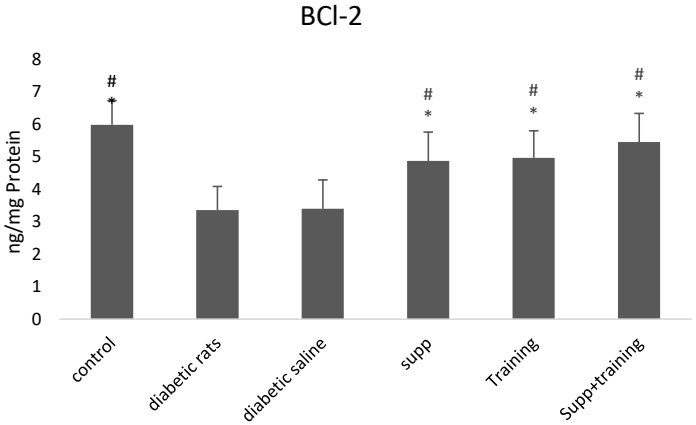

Figure 3. BCL-2 in Different Groups. *Note*. *Significant compared to the patient group; #Significant in comparison to the saline group

the BAX/BCL2 ratio between the groups ($P=0.03$). The BAX/BCL2 ratio was significantly higher in the diabetic (2.011 ± 8.968 ng/mg protein) and saline (9.330 ± 2.550 ng/mg protein) patient groups compared to the other groups ($P=0.001$, Figure 4).

The effect of interval exercise and the administration of resveratrol alone or especially with interval exercise could significantly decrease the amount of BAX and CASPASE-3 (Figures 1 and 2, $P=0.001$). A significant increase in the amount of BCL-2 ($P=0.001$) and a significant decrease in the average ratio of BAX/BCL2 (Figure 1, $P=0.001$) were observed in male rats with diabetes compared to diabetic and saline diabetic groups.

Discussion

The findings of the present study demonstrated a significant decrease in the cardiac levels of BAX, CASPASE-3, and BAX/BCL-2 ratio, while a significant increase in BCL-2 following eight weeks of interval training and resveratrol consumption in diabetic rats, which is in line with previous findings, indicating the significant effect of exercise on apoptotic indices (17-19). In this respect, Siu et al investigated the effect of eight weeks of regular low-intensity exercise on the cardiac and skeletal muscles of rats. The results showed a significant increase in Bax levels and a significant change in caspase 3 (19). In a study, old female Wistar rats performed high-intensity interval training on a treadmill for 8 weeks. The research results represented a significant increase in BCL-2 brain levels whereas a significant decrease in Bax levels (18). In another study, Salehi et al reported a significant increase in the amount of BCL-2, while a significant decrease in the cardiac levels of BAX with the effect of various periodic and continuous exercises on some indices of cardiac tissue apoptosis in diabetic rats (20).

The main factors in causing apoptosis are proteases called caspases, with their activation, nuclear proteins, and cellular skeleton proteins; in addition, proteins involved in message transmission are targeted, ultimately leading to cell death (21). The activation of caspases occurs in two ways, including the extrinsic (dependent on death receptors) and intrinsic (dependent on mitochondria) pathways (22). In the internal pathway, with the relative change of anti-apoptotic (BCL-2) and pro-apoptotic (Bax), the permeability of the mitochondrial membrane to cytochrome C increases, and with its release, the apoptosome is formed and causes the activation of caspase 9 and 3. In the external pathway, the increase in the amount of serum tumour necrosis factor α (TNF-α) and its binding to the TNF receptor, which is a type of death receptor, causes its trimerization and ultimately the activation of caspase 8 and 3 (22). Further, hyperglycemia with an increase in hydroxyl free radicals causes high expression of Bax protein, and the translocation of Bax to mitochondria leads to the release of cytochrome C, and as a result, the activation of caspase 3, which leads to apoptosis. By reducing the level of hydroxyl radicals, insulin reduces the release of cytochrome C to the cytosol and causes a significant decrease in caspase 3 activity becomes(23).

Researchers believe that in addition to the beneficial effects of exercise on type 2 diabetes in terms of improving glucose metabolism and delaying and preventing diabetes, it also plays a protective role against the complications of diabetes through reducing apoptosis and OS (24). Therefore, it has been shown that exercise reduces the ratio between pro-apoptotic proteins such as BAX and anti-apoptotic proteins such as BCL-2 and decreases the signaling activation of CASPASE-3, the final caspase of the apoptotic pathway (17). One of the possible mechanisms in the field of the protective ability of exercise training can be the capacity to prevent the formation of free radicals. *Reactive oxygen species* (ROS) are produced in the mitochondrial electron transport chain of the cell, but when the level of ROS exceeds the antioxidant capacity, it can lead to apoptosis. ROS is closely related to diabetes and can cause apoptosis through different pathways (25).

Furthermore, nowadays, it is recommended that medicinal plants should be used with different biological

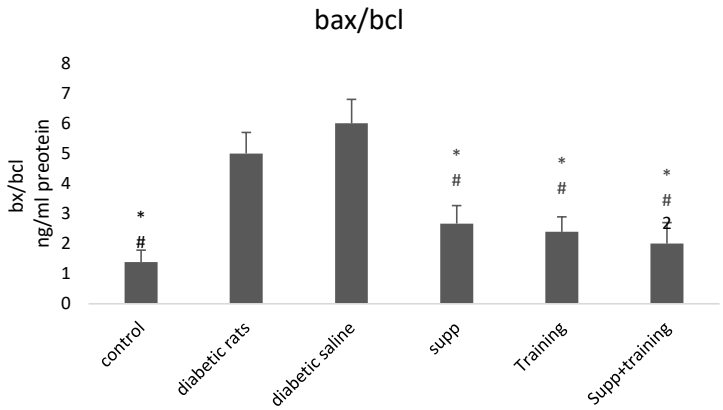

Figure 4. Bax/bcl2 Ratio in Different Groups. *Note*. *Significant in comparison to the patient group; #Significant compared to the saline group

properties in line with sports exercises due to less side effects and reduced treatment costs. Resveratrol supplement is a plant compound belonging to the group of polyphenols and exerts a part of its anti-apoptotic effects through antioxidant properties and apoptosis regulatory factors in the hepatocyte tissue of diabetic rats (26). The results of the current research revealed that a combination of exercise and consumption of resveratrol causes a significant decrease in the cardiac levels of BAX, CASPASE-3, and BAX/BCL-2 ratio, while a significant increase in BCL-2.

Consistent with the results of Mehri et al (27), Negarestani et al (28) and Hajighasem et al (29) also reported similar results about the combined effect of exercise and resveratrol. Regarding the mechanism of the combined effect of exercise and resveratrol, Jamali et al concluded that the combined use of resveratrol and exercise protects the heart from the production of OS after ischemia through the activation of antioxidant defenses (25). It seems that exercise and resveratrol together increase the mitochondrial level of an important antioxidant enzyme such as superoxide dismutase 2 (12). Exercise and resveratrol can reduce OS caused by apoptosis in special tissues, the effect of which is more prominent in the heart muscle. The displacement and placement of the Bax protein in the outer membrane of mitochondria simultaneously increase with the increase of OS (30). This discussion can partly depend on the activation of cytosolic c-Jun N-terminal kinase (JNK); thus, JNK inhibits the Bcl-2 protein by being phosphorylated by cellular stress stimuli. Inside the mitochondria, JNK increases the permeability of the mitochondrial membrane and therefore causes the release of pro-apoptotic factors such as apoptosis-inducing factor and cytochrome C, thereby triggering the caspase cascade (30). Another way to inhibit apoptosis and increase cell lifespan is the relationship between exercise and resveratrol, as well as Silent Information Regulator 1 proteins, which increase during exercise. These proteins cause the activation of downstream proteins such as PGC-1α, which subsequently improves mitochondrial function and prevents apoptosis (30). Moreover, exercise training and resveratrol can increase the expression of mitochondrial *adenosine triphosphate*-sensitive potassium channels, along with other mitochondrial proteins that can help protect the heart (31). On the other hand, inflammatory factors are also important. TNF-α can cause the spread of apoptosis through the increase of caspase (22). However, the anti-inflammatory effects of exercise and resveratrol on reducing TNF-α have been reported in some studies (32,33). Therefore, exercise and resveratrol together can reduce apoptosis by reducing TNF-α. In this research, the amount of inflammatory cytokines was not measured, which is one of the limitations of the research.

Conclusion

In general, the findings of the present study demonstrated that the administration of resveratrol alone and especially in combination with exercise caused a significant decrease in the amount of the Bax protein in the heart tissue in rats with diabetes, while the combined administration of resveratrol and exercise caused a significant increase in the Bcl-2 level. Eventually, the administration of resveratrol and intermittent exercise alone decreased the ratio of BAX to Bcl-2, but the combined administration of resveratrol with intermittent exercise represented a stronger effect.

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Authors' Contribution

Investigation: Masome Nobaha, Hamidreza Negarestani, Fatemeh Ahmadi.
Methodology: Masome Nobahar, Fatemeh Ahmadi.
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Supervision: Masome Nobahar.
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Writing–review & editing: Masome Nobahar.

Competing Interests

The authors have no conflict of interests.

Ethical Approval

All the experiments conducted in this research were performed in accordance with the customary policy of Iranians for the protection of vertebrate animals and for experimental scientific purposes, and the study was approved by the Ethics Committee of Payam Noor University, Sari Branch with the ethics code ID IR.PNU.REC.1400.060.

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