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Research Paper

Modulating Effects of Aerobic Exercise on Apoptosis Markers in Cardiac Cells of Diabetic Rats With Morphine Deprivation Syndrome

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ABSTRACT

Background: Diabetes and morphine play are critical in causing cardiac apoptosis.

Objective: This study investigates the effect of eight weeks of aerobic training on apoptosis indices in the heart tissue of diabetic rats with morphine withdrawal syndrome.

Methods: In this study, 32 male Wistar rats were randomly assigned into four groups, including diabetic control, diabetic control+morphine withdrawal syndrome, diabetic+aerobic exercise, and diabetic+morphine withdrawal syndrome+aerobic exercise. Subsequently, the induction of diabetes and morphine was done. The training groups participated in an increasing treadmill running program for 8 weeks (3 sessions per week). Then, 24 h after the last training session, the heart tissue was sampled. The levels of Bax and Bcl-2 proteins in the tissue of the left ventricle of the rat heart were measured by the ELISA method. At the significance level of $P<0.05$, the data was analyzed using the one-way analysis of variance and the Tukey post hoc test.

Findings: The amount of Bax was significantly higher in the groups of diabetic control+morphine withdrawal syndrome ($P=0.002$) and diabetic+morphine withdrawal syndrome+aerobic exercise ($P=0.008$) compared to the diabetic control group. Also, the level of Bcl-2 protein in the diabetic control group was significantly lower than in the diabetic+aerobic exercise ($P=0.004$) and diabetes+morphine withdrawal syndrome+aerobic exercise ($P=0.04$) groups. In addition, the Bax/Bcl-2 ratio was lower in the diabetic+aerobic exercise ($P=0.001$) and diabetes+morphine withdrawal syndrome+aerobic exercise ($P=0.045$) groups compared to the diabetic control group.

Conclusion: The results suggest that aerobic exercise can be an effective non-pharmacological way to reduce the effects of apoptosis on heart tissue cells in diabetic and diabetic rats with morphine withdrawal syndrome.

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Journal of
Inflammatory Diseases
(Previous Title: The Journal of Qazvin University of Medical Sciences)

Introduction

A disease characterized by elevated blood sugar due to defects in insulin action, insulin secretion, or both, diabetes mellitus is a leading cause of death worldwide. Inactivity and technological advances, which are characteristic of developed and developing countries, have increased the prevalence of various diseases, including diabetes [1]. Studies show that diabetes causes blood sugar metabolism disorder and chronic complications in the structure and function of blood vessels in different tissues of the body. Cardiomyopathy is a type of heart disease that causes inflammation and weakness of the heart muscles, such as atherosclerosis and high blood pressure in diabetics [2]. One of the causes of cardiomyopathy in diabetic patients is the increased production of free radicals, followed by increased apoptosis in cardiomyocytes due to hyperglycemia [3]. Apoptosis is a biochemical process that causes programmed cell death. According to recent studies, apoptosis plays a major role in the process of cardiovascular diseases [4]. As a result, the inhibition of apoptosis in the myocardium is a critical strategy in the treatment of cardiovascular diseases and its complications in patients with type 2 diabetes [5]. The process of cell apoptosis occurs in two internal and external pathways, the most important of which is the internal pathway of apoptosis [3]. Growing evidence suggests that apoptotic processes regulate several pivotal proteins, including Bax and Bcl-2, both of which play essential roles in the activation of apoptotic signaling pathways. Bcl-2 family proteins are among the key proteins that play a vital role in the regulation of apoptosis. The Bcl-2 family is classified into anti-apoptotic proteins, Bcl-XL Bcl-2, and pro-apoptotic Bax proteins [6]. The Bcl-2 protein binds to Apaf-1 and prevents the activation of caspase-9 by maintaining the cellular integrity of the mitochondrial membrane and removing H+ ions [7]. However, the Bax protein can neutralize the action of Bcl-2. For this reason, in most studies, both of these factors are evaluated to measure apoptosis. By reducing the stability of the mitochondrial outer membrane, Bax protein causes the release of cytochrome C, the activation of the caspase cascade, and finally apoptosis [8]. In hyperglycemic conditions, the expression and function of pro-apoptotic proteins (Bax) increase, and the activity and expression of anti-apoptotic proteins (Bcl-2) decrease, ultimately leading to an increase in apoptosis [5].

The use of exercise training (resistance or endurance) as a non-pharmacological intervention has an effective role in reducing oxidative stress and then controlling the complications caused by diabetes [9]. Many studies have been conducted to determine the influence of varying levels of exercise intensity on the apoptosis of skeletal and cardiac muscle cells; however, there are still uncertainties in this field [10]. Exercise protects the heart against the complications of diabetes by reducing oxidative stress and apoptosis in cardiac cells. Considering that apoptosis can cause cardiomyopathy, many studies have shown that exercise can be a protective factor for the heart of these patients [11]. However, the kind of exercise and kind of protocol is a question that researchers are trying to discover. Endurance training develops antioxidant capacity, induces autophagy, inhibits unnecessary apoptosis, and provides a suitable environment for liver cell activity [12]. On the other hand, research shows that moderate-intensity aerobic exercise lowers blood glucose, increases insulin sensitivity, directly alters the expression of apoptosis-related proteins, and increases antioxidant activity in the myocardium [10]. Kashani et al. (2022) observed that high-intensity interval training does not affect Bax protein; however, training with a curcumin supplement increased the expression of Bcl-2 protein and neutralized the effect of Bax [13]. In their research, Liang et al. (2022) investigated the effect of treadmill training on apoptotic pathways in rats and observed that treadmill training decreased Bax and Bcl-2 in the heart tissue of rats [14].

Morphine is the main ingredient of opium latex. Its excessive consumption has adverse effects, such as depression, respiratory destruction, addiction, coma, and death. After a period of dependence on opioid substances and following a sudden withdrawal, the body and central nervous system respond to the absence of the substance with a set of symptoms known as withdrawal syndrome [15]. Long-term use of morphine can induce neuronal apoptosis in the brain by increasing the expression of Fas and caspase-3 as apoptotic proteins and decreasing the expression of Bcl-2, an anti-apoptotic protein. Therefore, a large number of apoptotic neurons were observed in the hippocampus of addicted rats [16].

Evidence shows that exercise reduces the symptoms of addiction in addicted animals by releasing endogenous opioids, the possible mechanism of which is the down-regulation and reduction of the sensitivity of opioid receptors [17]. Exercise affects at least some of the same neural pathways and brain mechanisms that are activated by morphine or other opioids. As a result, it relatively reduces the desire to consume morphine and other addictive compounds [18]. However, the kind of exercise and method is unclear. Given that so far there has not been enough study on the effect of exercise training on the complications of heart damage and apoptosis caused by diabetes

and suffering from morphine withdrawal syndrome, in this research, for the first time, the effects of endurance training on the levels of apoptotic proteins Bax and Bcl-2 and the ratio of Bax/Bcl-2 in the heart tissue of diabetic male rats with morphine withdrawal syndrome.

Materials and Methods

This was an experimental/laboratory study in the form of a pretest/posttest with a control group. It was conducted on 32 male Wistar rats (in the age range of 8-10 weeks, weighing 230±30 g) from Baqiyatullah University, Iran. After purchase, the samples were kept in polycarbonate cages (manufactured by Razi Company) and in standard laboratory conditions (temperature=22±2°C, humidity=40%-50%, and light/dark cycles=12:12 h) during the research period. The samples were fed with standard pellets for laboratory rats (provided by Pars Livestock Company) and used food and water freely. All the steps of the research were approved and carried out following the ethical principles of working with laboratory animals (in line with the Helsinki protocol). After weighing the mice (using a Sartreus TE151502S digital laboratory scale with an accuracy of 100 g, made in Germany), the rats were randomly divided into 4 groups as follows: 1) Diabetic control; 2) Diabetic+morphine withdrawal syndrome; 3) Diabetic+aerobic exercise; and 4) Diabetic+morphine withdrawal syndrome+aerobic exercise.

Diabetes induction protocol

After a 12-h fast, an intraperitoneal injection of the STZ solution (Sigma, St. Louis, MO; 50 mg/kg dissolved in fresh citrate buffer 0.5 mol/L, pH 4.5) was used to induce diabetes. Non-diabetic rats were also given an equal volume of citrate buffer. A drop of blood was deposited on a glucometer strip 48 h after injection by making a small wound on the tail vein with a lancet, and the strip was measured by a glucometer device (Roche, Germany)—the rats whose blood sugar levels above 300 mg/dL were labeled as diabetic. The blood sugar of the rats was measured to ensure that it did not return at the end of the training period.

Morphine withdrawal syndrome protocol

To induce addiction in rats in the morphine withdrawal syndrome groups, morphine solution (Tamad Company) and 3% sucrose were used to reduce the bitterness caused by morphine. The dissolved percentage of morphine was prescribed with doses of 0.1, 0.2, 0.3, and 0.4 mg/mL each for 48 h and a dose of 0.4 mg/mL for the following days until the 21st day. At the end of the 21st day, naloxone (Sigma Company, USA) at a rate of 2 mg/kg of body weight was injected intraperitoneally into the samples. The withdrawal symptoms, such as jumping, climbing, scratching, grinding teeth, redness around the eyes, diarrhea, tremors, eyelid drooping, erection, and standing on two legs for 30 min were examined [19, 20].

Aerobic exercise protocol

Treadmill familiarization was done 48 h after the induction of acute morphine withdrawal syndrome for one week. The familiarization program included 5 sessions of walking and running at a speed of 5 to 8 m/min and a 0% slope for 8 to 10 min. Subsequently, an aerobic training program, including 8 weeks of running on a treadmill, on 3 non-consecutive days for 20 min and at a speed of 12 m/min was started. In the continuation of training, 5 min were added to the training time every week until it reached 50 min. Also, the speed of the treadmill was increased by 1 m/min every week until it finally reached 18 m/min. This was a zero-incline exercise program with a 3-min warm-up and cool-down at a speed of 7 m/min [21]. Table 1 shows the details of the endurance training program of the present study.

Tissue sampling and measurement of research variables

Following an overnight fast, the rats were sedated with intraperitoneal injections of ketamine (75 mg/kg) and xylazine (10 mg/kg) 24 h following the previous training session. Then, the chests of the animals were split open, and the cardiac tissue was separated under sterile conditions and immediately frozen in liquid nitrogen and stored for further analysis. At different stages, while respecting ethical issues, we attempted to avoid any physical abuse or unnecessary methods. The tissues were kept at -80°C and then sent to the laboratory for research. To measure the desired indicators, first, the heart tissue was powdered using liquid nitrogen, and then 0.1 g of the powder was homogenized with 1 mL of buffer (phosphate-buffered saline), and the extracted solution was centrifuged for 15 min at a speed of 5000 rpm, and its supernatant was used to measure the desired indicators. Using the ELISA method and kits of the CUSIBIO company (USA), the protein levels of Bax (Kit number: CSB-EL002573RA and with a sensitivity of <15.6 pg/mL) and BCI2 (Kit number: CSB-E08854r EL002573RA and with a sensitivity of <0.078 pg/mL) were evaluated.

Journal of
Inflammatory Diseases
(Previous Title: The Journal of Qazvin University of Medical Sciences)

Table 1. Details of the training protocol

Exercise Sessions	Exercise Components	Week							
		1st	2nd	3rd	4th	5th	6th	7th	8th
1st	Speed (m/min)	12	13	14	15	16	17	18	18
	Duration (min)	20	25	30	35	40	45	50	50
2nd	Speed (m/min)	12	13	14	15	16	17	18	18
	Duration (min)	20	25	30	35	40	45	50	50
3rd	Speed (m/min)	12	13	14	15	16	17	18	18
	Duration (min)	20	25	30	35	40	45	50	50

Journal of
Inflammatory Diseases

Statistical method

Statistical analyses were performed using the SPSS software, version 18 for Windows (SPSS Inc., Chicago, USA). The data were reported as Mean±SEM. After confirming that all continuous variables were normally distributed using the Shapiro–Wilk test, the statistical differences between the groups were obtained by the one-way analysis of variance followed by the Tukey post hoc test. All tests were two-sided and the significance level was considered P<0.05.

Results

The values of apoptosis regulatory indices in the studied groups are given in Figure 1, 2, and 3. The results of the one-way analysis of variance showed a significant difference between the studied groups in terms of the Bax variable (P=0.003, F=171.4 with df=3). The results of the Tukey test showed that the Bax level in the diabetic+aerobic exercise group is lower than the diabetic control (P=0.049) and the diabetic+morphine withdrawal syndrome (P=0.002) groups. Also, a significant difference exists between the diabetic control+morphine withdrawal syndrome and the diabetic+morphine withdrawal syndrome+aerobic exercise (P=0.008) groups. However, no significant difference was observed in the Bax variable between the groups of diabetic+morphine withdrawal syndrome+aerobic exercise and the diabetic control group (P=0.35) (Figure 1).

In addition, the analysis of variance test results revealed a significant difference between the studied groups regarding the Bcl-2 variable (P=0.045, F=6.67 with df=3). The results of the Tukey test showed that Bcl-2 levels in the diabetic+aerobic exercise group were significantly higher than individuals in the diabetic+morphine withdrawal syndrome and diabetic control groups (P=0.004 and P=0.001, respectively). Also, the level of Bcl-2 in the diabetic+morphine withdrawal syndrome group was significantly lower than the groups of diabetic+morphine withdrawal syndrome+aerobic exercise and diabetic+aerobic exercise (P=0.001 and P=0.03, respectively). However, no difference was observed between the diabetic+morphine withdrawal syndrome+aerobic exercise and diabetic control groups (P=0.70) (Figure 2). Meanwhile, the results of the one-way analysis of variance test showed a significant difference between the studied groups in terms of the Bax/Bcl-2 ratio (P=0.001, F=5.57 with df=3). The results of the Tukey test showed that the ratio of Bax/Bcl-2 in the diabetic+morphine withdrawal syndrome group is significantly higher than in other groups (P<0.05). There was no significant difference in Bax/Bcl-2 between the other groups (P>0.05) (Figure 3).

Discussion

The results showed a significant difference between the protein levels of Bax and Bcl-2 and the ratio of protein Bax to Bcl-2 in the heart tissue of rats in the two groups. Based on the findings, the amount of Bax and the ratio Bax/Bcl-2 decreased while the amount of Bcl-2 increased in the groups of diabetic+aerobic exercise and diabetes+morphine withdrawal syndrome+aerobic exercise. According to the findings of Montazeri Taleghani et al. (2022), individuals with diabetes can avoid tissue fibrosis in their hearts due to collagen deposition by engaging in high-intensity strength training and moderate-intensity endurance training. Therefore, they suggested that exercise training can be employed as an effective non-pharmacological method to alleviate the consequences of diabetes-induced apoptosis and fibrosis in

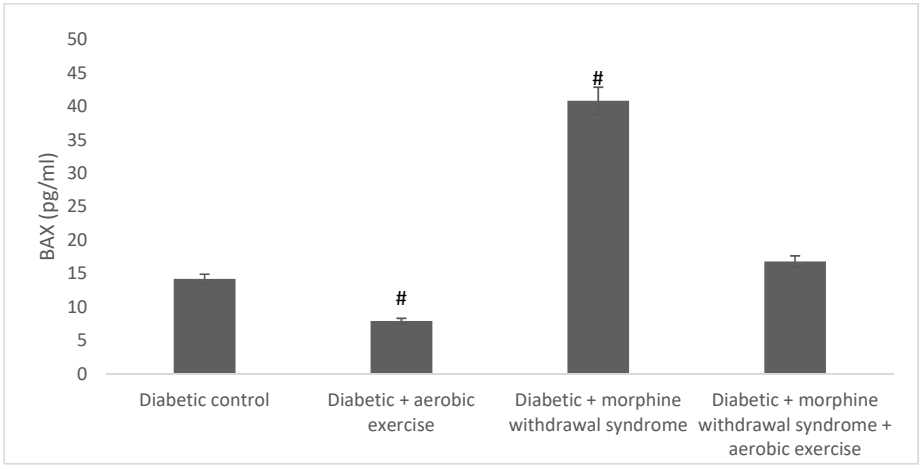

Figure 1. Bax difference in the studied groups

#Significant difference (P<0.05) with the diabetic control group.

Journal of
Inflammatory Diseases

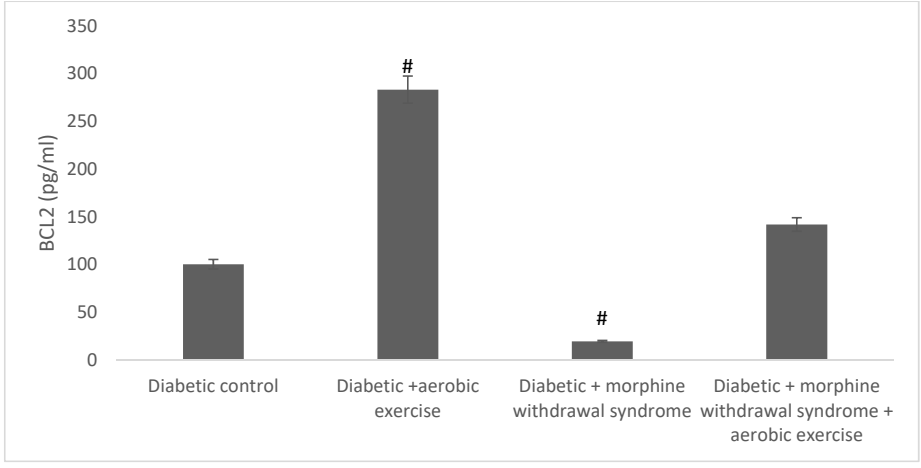

Figure 2. Bcl-2 difference in the studied groups

#Significant difference (P<0.05) with the diabetic control group.

Journal of
Inflammatory Diseases

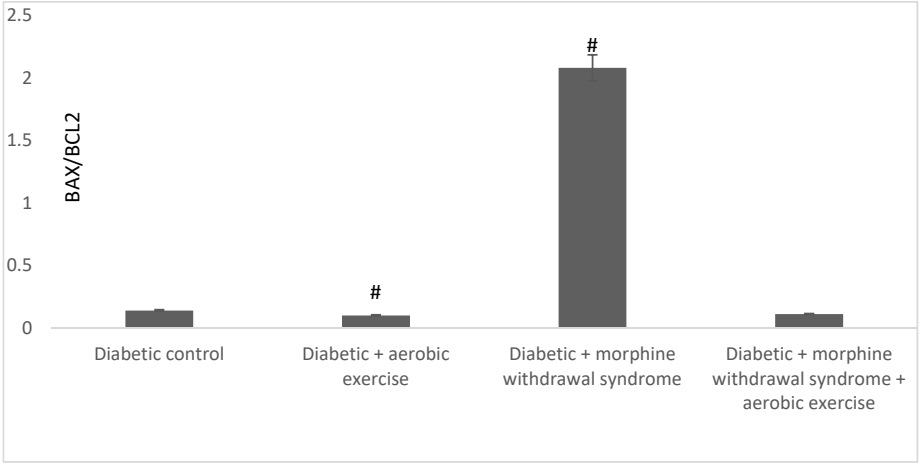

Figure 3. Bax/Bcl-2 difference in the studied groups

#Significant difference (P<0.05) with the diabetic control group.

Journal of
Inflammatory Diseases

Journal of
Inflammatory Diseases
(Previous Title: The Journal of Qazvin University of Medical Sciences)

heart tissue [22]. Wang et al. [23] reported that 12 weeks of aerobic training increased the level of caspase-3 and also decreased the amount of Bax and Bcl-2 in the hearts of type 2 diabetic rats. In the study by Azimnejad et al. [24], endurance training decreased the expression of *caspase-3* and *Bax* genes. It increased *Bcl-2* gene expression in diabetic heart tissue, which indicates the effectiveness of endurance training in improving apoptosis in type 2 diabetics. In contrast, Yoo et al. (2019) observed that exercise training does not affect the apoptosis pathway or the levels of Bax, Bcl-2, cytochrome, and caspase-3 in rat heart and skeletal muscle [25]. Jafari et al. (2015) also showed that after 12 weeks of endurance training with moderate to severe intensity, the level of Bcl-2 protein was not significantly different between the training group and the control group in the heart of Wistar rats [26]. Most of these contradictions are related to the differences in the training protocol, apoptosis indices, age and gender of the subjects, and the measured tissue, which makes the generalization difficult.

On the other hand, the increase in oxidative stress following diabetes causes an increase in the amount of reactive oxygen species and a decrease in the capacity of antioxidant defense. As a result, programmed death of cardiac cells or apoptosis pattern occurs [1]. Research has reported that the cause of apoptosis in cardiac cells due to diabetes is the occurrence of an inflammatory process in addition to increasing oxidative stress [8]. The resulting oxygen free radicals, the deactivation of the ERK1/2 kinase enzyme, and the activation of another kinase enzyme called c-JUN/AP-1 can indicate the occurrence of apoptosis following oxidative stress [5]. The increase in blood sugar causes the apoptotic process to be imbalanced by the production and increase in the function of Bax protein and the decrease in production and function of the anti-apoptotic protein Bcl-2 [6]. An increase in the production or activity of the anti-apoptotic protein Bcl-2 due to long-term exercise prevents the release of cytochrome C and the destruction of the mitochondrial membrane, which ultimately leads to maintaining the integrity of the cell membrane. Physical activity reduces the release of cytochrome C, which blocks the transmission of downstream apoptotic messages [27]. Also, exercise can increase lymphokine B, affect pro-apoptotic cells, and play an anti-apoptotic role. Since diabetes is associated with increased oxidative stress, long-term exercise can reduce the activity of free radicals by reducing nicotinamide adenine dinucleotide phosphate. Bax protein activation increases mitochondrial membrane permeability [28]. In this research, mitochondrial function is improved by increasing Bcl-2, the most important inhibitor of apoptosis. The main role of mitochondria in apoptosis is the release of cytochrome C into the cytosol, which ultimately increases the mitochondrial membrane potential. This issue is necessary for energy production and maintaining homeostasis [3]. Altogether, three important factors are involved in the induction of apoptosis: An increase in glycosylated hemoglobin, oxidative stress, and excessive accumulation of glycogen in muscle cells [4]. Researchers agree that exercise, by reducing oxidative stress, is one of the most important factors in reducing the process of induced damage in diabetes [9]. Among other things, following exercise activities, the level of IGF-I expression in muscle and heart tissue increases. Since this factor has a protective role in the cells of the body and is effective in improving hypoglycemia and increasing insulin sensitivity of muscle tissue [27], a part of the positive effects of regular exercise in reducing the complications of diabetes are applied in this way.

Several studies have shown that morphine induces apoptosis in neurons. Long-term morphine treatment induces apoptosis in the brains of laboratory rats by increasing Fas factor (pro-apoptotic) and decreasing Bcl-2 protein (anti-apoptotic) [16]. Also, long-term use of morphine leads to the induction of apoptosis in different areas of the heart. The increase of apoptotic factors due to morphine can be caused by the activation of opioid receptors. However, increasing the antioxidant capacity protects cells against the toxic effects of morphine [15]. Morphine may cause tissue apoptosis through changes in the expression of Fas, Bcl-2, and caspase-3. The findings provide evidence for the underlying mechanism and pathophysiology of tissue damage caused by long-term opioid use [16, 20]. Hasani et al. [29] stated that continuous and intermittent exercises and zinc sulfate reduce the level of oxidative stress in rats dependent on morphine in deprivation syndrome. The mechanism involved may be activating the endogenous opioid system by treadmill running [17]. Parvareh et al. [30] found that nine weeks of strength training increased the pain threshold of addicted mice with withdrawal syndrome. Zarinkalam et al. [31] concluded that endurance training may have cardio-protective effects for morphine-dependent rats by increasing serum apelin levels. Therefore, they advised morphine-dependent patients to perform such physical activities to prevent heart disorders. Mokhtari Zaer et al. [32] reported in a study that 10 days of voluntary exercise on a spinning wheel decreases the expression of Bax protein and increases the expression of Bcl-2 protein in the hippocampus of rats addicted to morphine. In addition, exercise prevents disorders related to cognitive function in these subjects. Exercise affects some of the same neural pathways and brain mechanisms that are activated by morphine or other opiates, and as a result, the

desire for external morphine decreases [17]. Also, exercise training with decreasing regulation and decreasing the sensitivity of opioid receptors has led to the release of endogenous opioids, which reduces the symptoms of addiction. Exercise significantly increases the production of natural morphine of beta-endorphin origin in the brain, which produces the same pleasant effect and euphoria following the consumption of morphine or other opiates by affecting brain receptors [18]. Studies believe that exercise, due to its positive effect on antioxidant defense, oxidative stress, and chronic inflammation, is probably associated with a decrease in apoptosis in different tissues of the body under different conditions, including in the state of morphine addiction [7, 12]. These findings support the hypothesis that exercise can probably be an effective intervention in the prevention of abuse of drugs and their treatment programs.

Conclusion

According to the findings of this research, aerobic exercise can be effective in reducing complications caused by diabetes and morphine addiction in the cardiomyocytes of rats. In addition, the results of this study showed that aerobic exercise can reduce physical and psychological dependence on morphine in rats, hence, exercise is one of the most effective and low-cost methods of addiction treatment.

Some of the drawbacks of this study include the failure to measure factors that impact antioxidant defense, the quantity of Bcl-2, Bax, and HOMA-IR proteins, and other factors that affect the apoptotic pathway, such as caspase-3. The reason is the high financial costs. Maybe by measuring these factors, we would get a better understanding of apoptotic signaling pathways.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Islamic Azad University, Boroujerd Branch (Code: IR.IAU.B.REC.1401.029).

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Authors' contributions

Supervision, funding acquisition, investigation and visualization: Abbas Saremi; Methodology, formal analysis software, and validation: Mojtaba Khansooz; Conceptualization and writing the original draft: Maryam Sadegh jhola; Review and editing: Abbas Saremi; Data curation: All authors.

Conflict of interest

The authors declared no conflict of interest.

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Journal of
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