

## Response of Some Apoptotic Indices to Six Weeks of Aerobic Training in Streptozotocin-Induced Diabetic Rats

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### ABSTRACT

**Background and objectives:** Cardiac apoptosis is one of the most important cardiovascular complications of diabetes. We aimed to investigate the changes of Bax, Bcl2 and caspase 3 in cardiac tissue of diabetic rats after six weeks aerobic exercise.

**Methods:** Thirty two male Wistar rats were randomly divided into healthy control, diabetes control and diabetes + exercise groups. Diabetes was induced by intraperitoneal injection of streptozotocin solution (55 mg/kg). Two weeks after the injection, fasting blood glucose levels were measured to confirm induction of diabetes. The exercise program was performed five days a week for six weeks. Variables were evaluated by ELISA and western blot analysis. All statistical analyses were performed in SPSS (version 22) using ANOVA and at significance of 0.05.

**Results:** The induction of diabetes in the control groups resulted in a significant increase in Bax, Bax/Bcl2 ratio and a significant decrease in Bcl2 levels ( $P=0.024$ ). The six-week training exercise in diabetic groups significantly decreased Bax and Bax/Bcl2 ratio and significantly increased Bcl2 ( $P=0.018$ ).

**Conclusion:** Our finding showed that diabetes could increase apoptosis in cardiac tissue. In addition, the six-week aerobic exercise can be used as a non-pharmacological strategy to reduce diabetes-related apoptosis in cardiomyocytes.

**Keywords:** apoptosis, aerobic exercise, diabetes

## INTRODUCTION

Diabetes mellitus is a disease caused by long-term hyperglycemia due to impaired insulin production or function. Diabetes can lead to various microvascular and macrovascular complications. The number of people with diabetes worldwide increased from 108 million in 1980 to 422 million in 2014 (1-4). Cardiac hypertrophy is believed to be a major pathological process in the development of diabetic heart injury and is characterized by alteration of the ventricular cavity, which involves cardiac muscle hypertrophy and ultimately cardiac fibrosis (5). In fact, hyperglycemia, hypertension and impaired fat metabolism in diabetic patients initiate many myocardial, structural, molecular and early pathological disorders. Cardiac muscle apoptosis is thought to be a consequence of the inflammatory responses and oxidative stress associated with hyperglycemia in the cardiac tissue (6). Cardiac muscle apoptosis has been documented as an important cause of progressive fibrosis, myocardial remodeling and ultimately cardiac dysfunction in animal and human models (7). It is thought that apoptosis is responsible for heart failure and can be considered as a predictor of adverse outcomes in heart disease or heart failure (8).

The Fas receptor-dependent (type 1) apoptosis pathway is initiated by binding of the Fas ligand with the Fas receptor leading to formation the initiator caspase of the death receptor signaling pathway. Activated caspase dissociates procaspase 3 to form active caspase 3 (9, 10). Caspase 3 and activated caspase 8 can cleave the Bcl2-like domain 3 (BID), which is an agonist involved in the death domain. This isolated BID relative to the 3 T-domains eventually releases mitochondrial cytochrome C (9) that may ultimately lead to formation of apoptosome. Exercise is part of the primary care for diabetic patients (11). Evidence suggests that exercise slows progression of glucose intolerance and may decrease hyperglycemia in both type 1 and type 2 diabetes patients (12). The hypoglycemic effect of exercise has been traditionally linked to increased muscle glucose uptake and increased insulin sensitivity (12). It has been shown that exercise training can exert cardioprotective

effects by reducing oxidative stress and apoptosis in cardiomyocytes (13). However, some studies have reported that a session of exercise for up to 48 hours can increase the rate of apoptosis (14), while some studies have shown that continuous moderate exercise training may reduce apoptosis in different tissues (15-17). Zeglinski et al. showed that four weeks of regular aerobic exercise can reduce cardiomyocytes apoptosis in diabetic rats (18). Dotzert et al. stated that endurance training prevents abnormal cardiac contraction in diabetic rats (19). It has been demonstrated that exercise not only increases myocardial contractile performance but also can prevent diabetic complications by reducing oxidative stress and apoptosis in cardiomyocytes (20-22).

The impact of aerobic exercise with various intensities on cardiac tissue has always been controversial. Given the high prevalence of diabetes and its impact on the cardiovascular system, finding effective non-pharmacological therapies for the prevention and treatment of cardiovascular disease in diabetic patients seems essential. Therefore, the present study investigated the effect of six weeks of aerobic exercise on some regulatory factors in diabetic rats.

## MATERIALS AND METHODS

Thirty six male Wistar rats (4–6 weeks old) were purchased from the experimental animal center of Pastor Institute of Iran (Karaj, Iran). The rats were housed in standard acrylic glass cages in groups of four, in a room maintained at constant temperature and humidity with a 12-hour light: dark cycle. The rats were fed standard chow diet with water *ad libitum*. The experimental protocol was approved by the Institutional Animal Care and Use Committee of the National Centre for Cell Science. This study was approved by the ethics committee of biomedical research of Payame Noor University (code: PNU. REC. 1397.033).

Diabetes was induced in 24 rats by intraperitoneal injection of 55 mg/kg streptozotocin (STZ) dissolved in 0.1 M citrate buffer (pH 4.5) (23). The remaining rats were treated with vehicle and were considered as the control group. Three days after the STZ injection, blood glucose level was measured using a glucometer (Glucocard 01, Japan). A blood glucose level of >200 mg/dl indicated

diabetes (24, 25). After four days of familiarity with laboratory environment, the subjects were randomly divided into three groups: healthy control, diabetic and diabetic + aerobic exercise.

#### Exercise protocol

Prior to the exercise protocol, all animals were subjected to treadmill activity for one week. The introductory program consisted of five sessions of walking and running at a speed of 5 to 8 m/s at zero slope for 8 to 10 minutes. The speed and time increased gradually to 10 m/min for 10 minutes in the first week, 10 m/min for 20 minutes in the second week, 14-15 m/min for 20 minutes in the third week, 14-15 m/min for 30 minutes in the fourth week, 17 m/min for 30 minutes in the fifth week, and 17-18 m/min for 40 minutes in the sixth week. Physical activity was performed five days a week for six weeks. Each session started with three minutes of warmup and finished with cool down at intensity of 4-5 m/min. During the treadmill running, electric shock was not used minimize stress during exercise (26).

After anesthesia and spinal cord transection, the thoracic region was cleaved and the heart was carefully separated from the body and immediately immersed in a saline solution. The hearts were later transferred to tubes and stored at -80 °C.

Tissue levels of Bcl2 and Bax were measured using a commercial ELISA kit (ZellBio, Germany) according to the manufacturer's instructions. The sensitivity of the kit for Bcl2 and Bax was 0.3 and 0.1 ng/ml, respectively. Caspase 3 enzyme activity assay was performed using an Abcam kit according to the manufacturer's instructions. In this method,

by affecting the substrate available in the kit, caspase 3 produces a highly fluorescence product that is excited at 485 nm and emits light at 535 nm (27). Samples were removed from the freezer and placed on ice. Then, 200 µl of RIPA buffer was added to each sample. The samples were crushed three times in one hour using a homogenizer (T 10 Basic Model, IKA Germany). The RIPA buffer was mixed with phenylmethylsulfonyl fluoride at a ratio of 1/250. The suspension was then centrifuged at 12,000 rpm for 20 minutes at 4 °C. The supernatant was transferred to a microtube.

Data were expressed as mean ± standard error of the sample. Data were analyzed in SPSS (version 22, SPSS Inc., Chicago, USA) using one-way ANOVA and Tukey's test. A p-value of less than 0.05 was considered statistically significant.

#### RESULTS

Changes in Bax, Bcl2, Bax/Bcl2 and caspase-3 ratios in the study groups are presented in table 1. Data analysis showed that there was a significant difference in the Bcl2 level, Bax/Bcl2 ratio and relative density of caspase-3/beta-actin in cardiomyocytes of subjects in the study groups (Figures 1-4). However, there was no significant difference between the groups in terms of Bax expression.

Based on the results, the caspase3/beta actin ratio was significantly higher in diabetics compared with healthy controls ( $P<0.05$ ). After the training intervention, the caspase3/beta actin ration reduced significantly compared to diabetic individuals ( $P<0.05$ ).

Table 1. Results of intra-group and inter-group analysis of research variables between in the study groups

Variables		Healthy-control (n=8)	Diabetic-control n=8)	Diabetic-exercise n=8)	intergroup p- value
Weight (gram)	pretest	291±21.18	277.65±18.59	262.38±120.14	<sup>β</sup> 0.000
	posttest	345.50±23.43	261.36±27.70	218.58±330.05	
	intergroup p-value	0.000*	0.000*	0.047*	
Body mass *index (kg/m <sup>2</sup> )	pretest	0.63±0.02	0.002±0.061	0.001±0.61	<sup>β</sup> 0.011
	posttest	0.001±0.058	0.003±0.46	0.003±0.57	
	intergroup p-value	0.044 *	0.000*	0.137	
VO <sub>2max</sub>	pretest	20±32.86	20.25±2.65	20.14±1.95	<sup>β</sup> 0.000
	posttest	21.33±1.96	16.50±2.97	26.20±1.78	
	intergroup p-value	0.286	0.000*	0.000*	
Glucose (mg/dl)	pretest	100.33±13.80	524.62±8163	521.62±11	<sup>β</sup> 0.025
	posttest	99±5.21	626.87±19.76	527.20±66.62	
	intergroup p-value	0.769	0.005*	0.781	
Bcl2 (ng/ml) (posttest)		10.84±3.25	3.84±1.55	9.76±2.84	<sup>β</sup> 0.002
Bax (ng/ml) (posttest)		2.26±0.89	2.38±0.73	1.72±0.91	0.453
Bax/Bcl2 (posttest)		0.207±0.0049	0.754±0.47	0.180±0.110	0.011
Relative density of caspase3/beta actin		1±346	5.392±0.76	3.335±0.82	<sup>β</sup> 0.000

\* Inter-group differences, <sup>β</sup> Inter-group differences

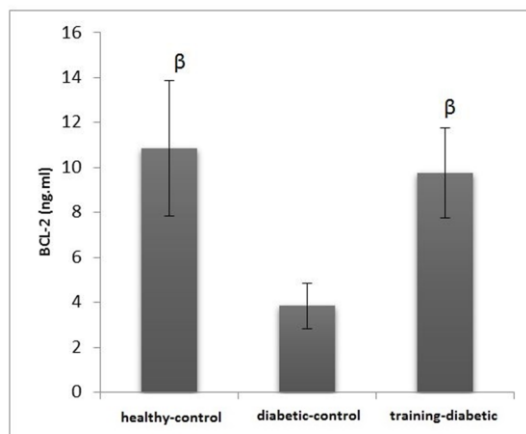


Figure 1. Changes of cardiac muscle BCL2 protein levels in healthy, control-diabetic, and diabetic-trained rats.  $\beta$  indicates difference with the diabetic control group

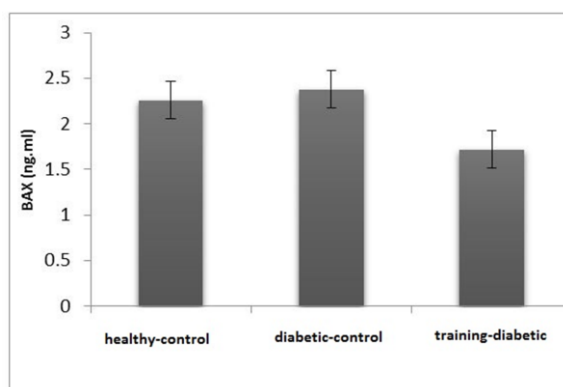


Figure 2. Changes in cardiac muscle BAX protein levels in normal, control-diabetic and diabetic-trained rats. \* indicates difference with the control group

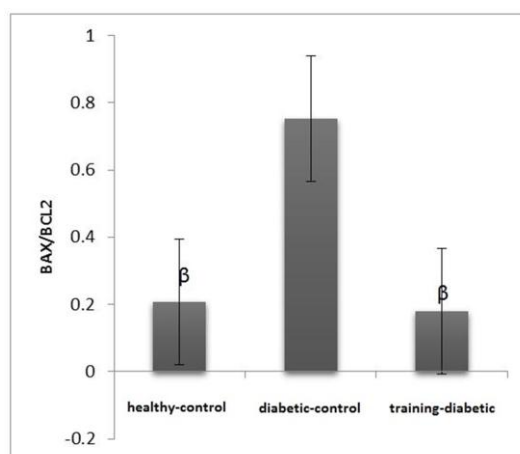


Figure 3. Changes in the levels of BAX/BCL2 in cardiomyocytes in the healthy control, control-diabetic and diabetic-trained rats.  $\beta$  indicates difference with the diabetic control group.

## DISCUSSION

The aim of this study was to determine the effect of a six-week aerobic training program with progressive intensity on Bax, Bcl2 and caspase-3 levels in cardiomyocytes of STZ-induced diabetic rats. The results showed that induction of diabetes by intraperitoneal injection of STZ (55 mg/kg) increased the levels of Bax and Bax/Bcl2 ratio and decreased Bcl2 level in cardiomyocytes. Diabetes is associated with a high incidence of cardiovascular disease, which is the leading cause of morbidity and mortality. Diabetes is an important risk factor for the progression of cardiac hypertrophy, cavity enlargement and heart failure (28-31). The distinctive features of chronic heart failure are left ventricular dysfunction, apoptosis and necrosis of the heart cells (32). Exercise is a non-pharmacological method used for reducing symptoms and improve quality of life in patients with chronic heart failure. Research has shown that exercise training is a safe method for reversing molecular and functional abnormalities in people with heart failure (6, 8, 10).

The mitochondrial-dependent apoptosis pathway is closely controlled by the Bcl2 family of proteins. The balance between pro- and anti-apoptotic Bcl2 family members can strongly affect cell fate (33, 34). In the present study, induction of diabetes significantly increased Bax and Bax/Bcl2 ratio and significantly decreased Bcl2. In the non-diabetic groups, six weeks of aerobic training significantly reduced Bax and Bax/Bcl2 ratio and significantly increased Bcl2 and caspase-3 levels. The training intervention also caused a significant decrease in Bax and Bax/Bcl2 ratio as well as a significant increase in Bcl2 values. Exercise training has been shown to decrease the pro-apoptotic signaling of the Bcl2 family by reducing caspase-3 and Bax and increasing Bcl2 level, thereby reducing the Bax/Bcl2 ratio in the heart of older individuals (35, 36). It has been reported that exercise training increased Bcl2 and decreased Bax mRNA expression in non-diabetic subjects (31). In addition, exercise has been shown to reduce the level of Bax and Bax/Bcl2 ratio in the cardiomyocytes of obese mice (37). Chang et al. showed that 10 weeks of moderate-intensity aerobic training reduced the number of TUNEL-positive cardiomyocytes in diabetic

rats (5). The cardioprotective effects of aerobic exercise can be also attributed to the activity of heat shock proteins (38-40). In this regard, Madea et al. showed that aerobic exercise may limit diabetes-related heart disease (41).

Similar to previous studies, we showed that exercise intervention can significantly reduce diabetes-induced apoptosis and slow down progression of heart failure in diabetic rats. A previous study reported that six weeks of aerobic training could increase phosphorylation of AKT in young mice (42, 43). Exercise reduces some lipoproteins and inflammatory factors such as TNF- $\alpha$ , IL-6, as well as some antioxidants and growth factors, which can in turn influence cellular homeostasis mediators such as caspases, thereby decreasing cardiac apoptosis. However, some studies have shown that long-term aerobic exercise and endurance training, although does not provide the basis for cardiac hypertrophy, can increase myocardial apoptosis by increasing oxidative stress (44, 45).

## CONCLUSION

Our findings suggest that six weeks of aerobic exercise may significantly affect some indices of apoptosis in cardiomyocytes of diabetic rats. However further studies should be performed on the effects of endurance training with different intensities to draw a definite conclusion. In the present study, we did not evaluate morphological changes and expression of other proteins involved in the external pathway of apoptosis, which are limitations of the present study. Therefore, it is recommended to conduct future studies on the effects of different exercise trainings on other cardiac apoptosis indices.

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## CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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