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 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 caspase3-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).

| Variables                  | Healthy-control | Diabetic-control | Diabetic-exercise | intergroup p-value |
|----------------------------|-----------------|-----------------|------------------|-------------------|
|                           | (n=8)           | (n=8)           | (n=8)            |                   |
| Weight (gram)              |                 |                 |                  |                   |
| pretest                    | 291±21.18       | 277.65±18.59    | 262.38±12014     | 0.000             |
| posttest                   | 345.50±23.43    | 261.36±27.70    | 218.5±33.05      |                   |
| intergroup p-value         | 0.000*          | 0.000*          | 0.047*           |                   |
|                           | 0.63±0.02       | 0.002±0.061     | 0.001±0.061      | 0.011             |
| Body mass index (kg/m²)    |                 |                 |                  |                   |
| pretest                    | 0.001±0.058     | 0.003±0.46      | 0.003±0.57       |                   |
| posttest                   | 0.044           | 0.000*          | 0.137            |                   |
| intergroup p-value         | 0.000*          | 0.137           |                   |                   |
|                           | 20±32.86        | 20.25±2.65      | 20.14±1.95       | 0.000             |
| VO2max                    |                 |                 |                  |                   |
| pretest                    | 21.33±1.96      | 16.50±2.97      | 26.20±1.78       |                   |
| posttest                   | 0.286           | 0.000*          | 0.000*           |                   |
| intergroup p-value         | 0.286           | 0.000*          | 0.000*           |                   |
|                           | 100.33±18.80    | 524.62±8163     | 521.62±11        | 0.025             |
| Glucose (mg/dl)            |                 |                 |                  |                   |
| pretest                    | 99.5±5.21       | 626.87±19.76    | 527.20±66.62     |                   |
| posttest                   | 0.769           | 0.005*          | 0.781            |                   |
|                           | 7.64±3.25       | 3.84±1.55       | 9.76±2.84        | 0.002             |
| Bcl2 (ng/ml)(posttest)     | 2.26±0.89       | 2.38±0.73       | 1.72±0.91        | 0.453             |
|                           | 2.07±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 | 0.000 |

* Inter-group differences, β Inter-group differences
Figure 1. Changes of cardiac muscle BCL2 protein levels in healthy, control-diabetic, and diabetic-trained rats. β 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. β 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-α, 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.
REFERENCES

1. Chandrasagar G, Elanchezhiyan C, Ghosh K. Effects of Berberine chloride on the liver of streptozotocin-induced diabetes in albino Wistar rats. Biomedicine & Pharmacotherapy. 2018; 106: 227-236. [DOI:10.1016/j.biopharm.2018.01.007] [PubMed] [Google Scholar]

2. Chandrasagar G, Elanchezhiyan C, Ghosh K, Sethupathy S. Berberine chloride ameliorates oxidative stress, inflammation and apoptosis in the pancreas of streptozotocin induced diabetic rats. Biomedicine & Pharmacotherapy. 2017; 95: 175-185. [DOI:10.1016/j.biopharm.2017.08.040] [PubMed] [Google Scholar]

3. Hansen SS, Aasum E, Hafstad AD. The role of NADPH oxidases in diabetic cardiomyopathy. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2018; 1864(5): 1908-1913. [DOI:10.1016/j.bbadis.2017.07.022] [PubMed] [Google Scholar]

4. Sivasankar D, George M, Sriram DK. Novel approaches in the treatment of diabetic cardiomyopathy. Biomedicine & Pharmacotherapy. 2018; 106: 1039. [DOI:10.1016/j.biopharm.2018.07.051] [PubMed] [Google Scholar]

5. Chang W, Zhang M, Meng Z, Yu Y, Yao F, Hatch GM, et al. Berberine treatment prevents cardiac dysfunction and remodeling through activation of 5′-adenosine monophosphate-activated protein kinase in type 2 diabetic rats and in palmitate-induced hypertrophic H9c2 cells. Eur J Pharmacol. 2015; 769: 55-63. [DOI:10.1016/j.ejphar.2015.10.043] [PubMed] [Google Scholar]

6. Lew JKS, Pearson JT, Schwenke DO, Katare R. Exercise mediated protection of diabetic heart through modulation of microRNA mediated molecular pathways. Cardiovascular diabetology. 2017; 16(1): 10. [DOI:10.1186/s12933-016-0484-4] [PubMed] [Google Scholar]

7. Qiao Y, Zhao Y, Liu Y, Ma N, Wang Ch, Zou J, et al. miR-483-3p regulates hyperglycemia-induced cardiomyocyte apoptosis in transgenic mice. Biochemical and biophysical research communications. 2016; 477(4): 541-547. [DOI:10.1016/j.bbrc.2016.06.051] [PubMed] [Google Scholar]

8. Lee SD, Shyu WC, Cheng IS, Kuo CH, Chan YS, Lin YM, et al. Effects of exercise training on Cardiovascular apoptosis in obese rats. Nutrition, Metabolism and Cardiovascular Diseases. 2013; 23(6): 566-573. [DOI:10.1016/j.numecd.2013.11.002] [PubMed] [Google Scholar]

9. Williamson CL, Dabkowski ER, Baseler WA, Croston TL, Alway SE, Hollander JM. Enhanced apoptotic propensity in diabetic cardiac mitochondria: influence of subcellular spatial location. American Journal of Physiology-Heart and Circulatory Physiology. 2009; 298(2): H163-H1642. [DOI:10.1152/ajpheart.00688.2009] [PubMed] [Google Scholar]

10. Williamson CL, Dabkowski ER, Hollander JM. Enhanced apoptotic propensity in diabetic cardiac interstitial mitochondria: ed: Federation of American Societies for Experimental Biology, 2008.

11. Qi H, Jiang Y, Yin Z, Jiang K, Li L, Shuai J. Enhanced cytochrome c release and apoptosis in diabetic rats. British journal of pharmacology. 2016; 173(10): 1569-1579. [DOI:10.1111/bph.13466] [PubMed] [Google Scholar]

12. Geng FH, Li GH, Zhang X, Zhang P, Dong MQ, Zhao ZJ, et al. Berberine improves mesenteric artery insulin sensitivity through up-regulating insulin receptor-mediated signalling in diabetic rats. British journal of pharmacology. 2016; 173(10): 1569-1579. [DOI:10.1111/bph.13466] [PubMed] [Google Scholar]

13. Karstoft K, Clark MA, Jakobsen I, Müller IA, Pedersen BK, Solomon TPJ, et al. The effects of 2 weeks of interval vs continuous walking training on glycaemic control and whole-body oxidative stress in individuals with type 2 diabetes: a controlled, randomised, crossover trial. Diabetologia. 2017; 60(3): 508-517. [DOI:10.1007/s00125-016-4170-6] [PubMed] [Google Scholar]

14. Li LO, Greengood TJ, Paul DS, Ilkayeva O, Kovess TR, Pascual F, et al. Compartmentalized acyl-CoA metabolism in skeletal muscle regulates systemic glucose homeostasis. Diabetes. 2015; 64(1): 23-35. [DOI:10.2337/db13-1070] [PubMed] [Google Scholar]

15. Sjoberg KA, Frosug C, Kjobjsted R, Sylow L, Kleinert M, Betiket AC, et al. Exercise increases human skeletal muscle insulin sensitivity via coordinated increases in microvascular perfusion and molecular signaling. Diabetes. 2017; 66(6): 1501-1510. [DOI:10.2337/db16-1327] [PubMed] [Google Scholar]

16. Ma N, Liu HM, Xia T, Liu JD, Wang XZ. Chronic aerobic exercise training alleviates myocardial fibrosis in aged rats through restoring bioavailability of hydrogen sulfide. Canadian journal of physiology and pharmacology. 2018; 96(9): 902-908. [DOI:10.1139/cjpp-2018-0153] [PubMed] [Google Scholar]

17. Sun Y, Cui Di, Zhang Zhe, Zhang Tan, Shi Jun, Jin Haxiuj, et al. Attenuated oxidative stress following acute exhaustive swimming exercise was accompanied with modified gene expression profiles of apoptosis in the skeletal muscle of mice. Oxidative medicine and cellular longevity. 2016; 2016: 2016; 8381242. [DOI:10.1155/2016/8381242] [PubMed] [Google Scholar]

18. Zeigliniski MR, Davies JJ, Ghavami S, Rattan SG, Halayko AJ, Dixon JM. Chronic expression of Ski induces apoptosis and represses autophagy in cardiac myofibroblasts. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2016; 1863(6): 1261-1268. [DOI:10.1016/j.bbamcr.2016.03.027] [PubMed] [Google Scholar]

19. Dotzert MS, Murray MR, McDonald MW, Olver TD, Thomas J Velenosi, Anzel Hennop, et al. Metabolomic response of skeletal muscle to aerobic exercise training in insulin resistant type 1 diabetic rats. Scientific reports. 2016; 6: 26379. [DOI:10.1038/srep26379] [PubMed] [Google Scholar]

20. Verboven M, Ryckeghem LV, Belhoukouchia J, Dendale P, Eijnde BO, Hansen D, et al. Effect of exercise intervention on cardiac function in type 2 diabetes mellitus: a systematic review. Sports Medicine. 2019; 49(2): 255-268. [DOI:10.1007/s40279-018-0003-4] [PubMed] [Google Scholar]

21. Li S, Liang M, Gao D, Su Q, Laher I. Changes in Titin and Collagen Modulate Effects of Aerobic and Resistance Exercise on Diabetic Cardiac Function. Journal of cardiovascular translational research. 2019; 11-1. [PubMed] [Google Scholar]

22. Dai W, Lee D. Interfering with long chain noncoding RNA ANRIL expression reduces heart failure in rats with diabetes by inhibiting myocardial oxidative stress. Journal of cellular biochemistry. 2019; 120(10):18446-18456. [DOI:10.1002/jcb.29162] [PubMed] [Google Scholar]

23. Ramezani J, Azarbayjani MA, Peeri M. Simultaneous Effects of Aerobic Training and Berberine Chloride on Plasma Glucose, IL-6 and TNF-a in Type 1 Diabetic Male Wistar Rats. Nutrition and Food Sciences Research. 2019; 6(1): 9-16.. [DOI:10.29252/nfsr.6.1.9] [PubMed] [Google Scholar]

24. McDonald MW, Olver TD, Dotzert MS, Jurissen TJ, Noble EG, Padilla J, et al. Aerobic exercise training improves insulin-induced vasorelaxation in a vessel-specific manner in rats with insulin-treated experimental diabetes. Diabetes and Vascular Disease Research. 2019; 16(1): 77-86. [DOI:10.1177/1479584918815272] [PubMed] [Google Scholar]

25. Ferraro B, Donnaciou M, Solano I, Ferraraccio F, Maisto R, Gullotta E, et al. Addition of the Aldose Reductase Inhibitor Benzyloxyamine Derivative BF-5m to Prolonged and Moderate Exercise Training Enhanced Protection of the Rat Heart From Type-1 Diabetes. Frontiers in Pharmacology. 2019; 10:392. [DOI:10.3389/fphar.2019.00392] [PubMed] [Google Scholar]

26. Kanter M, Akus F, Takir M, Kostek O, Kanter B, Oymagil T, et al. Addition of the Aldose Reductase Inhibitor Benzyloxyamine Derivative BF-5m to Prolonged and Moderate Exercise Training Enhanced Protection of the Rat Heart From Type-1 Diabetes. Frontiers in Pharmacology. 2019; 10:392. [DOI:10.3389/fphar.2019.00392] [PubMed] [Google Scholar]
39/Sadighi and colleagues

27. Hadden C, Fahmi T, Cooper A, Savenka AV, Lupashin VV, Roberts DJ. Serotonin transporter protects the placental cells against apoptosis in caspase 3-independent pathway. J Cell Physiol. 2017; 232(12): 3520-3529. [DOI:10.1002/jcp.28512] [PubMed] [Google Scholar]

28. GB Singh, Raut SK, Khanma S, Kumar A., Sharma S, Prasad R, et al. MicroRNA-29bc modulates DUSP-1 expression in diabetes-induced cardiac hypertrophy. Molecular and cellular biochemistry. 2017; 424(1-2): 1-11. [DOI:10.1007/s11010-016-2858-3] [PubMed] [Google Scholar]

29. Raut SK, Singh GB, Rastogi B, Saikia UN, Mittal A, Dogra N, et al. mir-30c and mir-181a synergistically modulate p53-p21 pathway in diabetes induced cardiac hypertrophy. Molecular and cellular biochemistry. 2016; 417(1-2): 191-203. [DOI:10.1007/s11010-016-2729-7] [PubMed] [Google Scholar]

30. Russo I, Frangogiannis NG. Diabetes-associated cardiac fibrosis: cellular effectors, molecular mechanisms and therapeutic opportunities. Journal of molecular and cellular cardiology. 2016; 90: 84-93. [DOI:10.1016/j.yjmcc.2015.12.011] [PubMed] [Google Scholar]

31. Kayama Y, Raaz U, Jagger A, Adam M, Schellinger IN, Sakamoto M, et al. Diabetic cardiovascular disease induced by oxidative stress. International journal of molecular sciences. 2015; 16(10): 25234-25263. [DOI:10.3390/ijms161025234] [PubMed] [Google Scholar]

32. See H, Park CH, Choi S, Kim W, Jeon BD, Ryu S. Effects of voluntary exercise on apoptosis and cortisol after chronic restraint stress in mice. Journal of exercise nutrition & biochemistry. 2016; 20(3): 16. [DOI:10.20463/jenb.2016.09.20.3.3] [PubMed] [Google Scholar]

33. See H, Park CH, Choi S, Kim W, Jeon BD, Ryu S. Effects of voluntary exercise on apoptosis and cortisol after chronic restraint stress in mice. J Exerc Nutrition Biochem. 2016 Sep;20(3):16-23. [DOI:10.1016/j.jenb.2019.08.006] [PubMed] [Google Scholar]

34. Wu G, Tan J, Li J, Sun X, Du L, Tao S. miRNA-145-5p induces apoptosis after ischemia-reperfusion by targeting dual specificity phosphatase 6. J Cell Physiol. 2019 Mar 18; [DOI:10.1002/jcp.28291] [PubMed] [Google Scholar]

35. Ellison GM, Waring CD, Vicinanza C, Torella D. Physiological cardiac remodelling in response to endurance exercise training: cellular and molecular mechanisms. Heart. 2012 Jan;98(1):5-10. [DOI:10.1136/heartjnl-2011-300659] [PubMed] [Google Scholar]

36. Kwak HB, Song W, Llawer JM. Exercise training attenuates age-induced elevation in Bax/Bcl-2 ratio, apoptosis, and remodeling in the rat heart. FASEB J. 2006 Apr;20(6):791-3. [DOI:10.1096/fj.05-5161fje] [PubMed] [Google Scholar]

37. Ghajar H, Hosseini SA, Farsi S. The Effect of Endurance Training Along with Cadmium Consumption on Bcl-2 and Bax Gene Expressions in Heart Tissue of Rats. Annals of Military and Health Sciences Research. 2019; 17(1): e06795. [DOI:10.5812/ajmh.86705] [Google Scholar]

38. Ascensio A, Magalhães J, Soares JMC. Ferreira R, Neuparth MJ, Marques F, et al. Moderate endurance training prevents doxorubicin-induced in vivo mitochondriopathy and reduces the development of cardiac apoptosis. American Journal of Physiology-Heart and Circulatory Physiology. 2005; 289(2): H722-H731. [DOI:10.1152/ajpheart.01249.2004] [PubMed] [Google Scholar]

39. Siu PM, Bryner RW, Martyn JK, Alway SE. Apoptotic adaptations from exercise training in skeletal and cardiac muscles. FASEB J. 2004 Jul;18(10):1150-2. [DOI:10.1096/fj.03-1291fg] [PubMed] [Google Scholar]

40. Huang CC, Lin TJ, Chen CC, Lin WT. Endurance training accelerates exhaustive exercise-induced mitochondrial DNA deletion and apoptosis of left ventricle myocardium in rats. Eur J Appl Physiol. 2009 Dec;107(6):697-706. [DOI:10.1007/s00421-009-1177-8] [PubMed] [Google Scholar]

41. Madea B, Wagner R, Markwerth P, Doberenz E. Heat shock protein expression in cardiac tissue in amphetamine-related deaths. Romanian Journal of Legal Medicine. 2017; 25(1): 8-13. [DOI:10.4323/jrlm.2017.8] [Google Scholar]

42. ChenYP, Sivalingam K, Shibu MA, Peramaiyani R, Day CH, Shen CY, Lai CH, Chen RJ, Viswanadha VP, Chen YF, Huang CY. Protective effect of Fisetin against angiotensin II-induced apoptosis by activation of IGF-IR/Pi3K-Akt signaling in H9c2 cells and spontaneous hypertension rats. Phytomedicine. 2019 Apr;57:1-8. [DOI:10.1016/j.phymed.2018.09.179] [PubMed] [Google Scholar]

43. Liao Y, Li H, Pi Y, Li Z, Jin S. Cardioprotective effect of IGF-1 against myocardial ischaemia/reperfusion injury through activation of PI3K/Akt pathway in rats in vivo. J Int Med Res. 2019 Aug;47(8):3886-3897. [DOI:10.1177/0300060519857839] [PubMed] [Google Scholar]

44. Margaritelis NV, Theodorou AA, Paschalis V, Veskoukis AS, Dipia K, Zafeiridis A, Panayiotou G, Vrabas IS, Kyparos A, Nikolaidis MG. Adaptations to endurance training depend on exercise-induced oxidative stress: exploiting redox interindividual variability. Acta Physiol (Oxf). 2018 Feb;222(2): e12898. [DOI:10.1111/apha.12898] [PubMed] [Google Scholar]

45. Erekat NS, Rababah RA, Al-Jarrah MD. Overexpression of renal proapoptotic factors is attenuated subsequent to endurance exercise in Type I diabetes: An immunohistochemistry study. Journal of Natural Science, Biology and Medicine. 2019; 10(1): 24. [DOI:10.4103/jnsbm.JNSBM_60_18] [Google Scholar]

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