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Physical activity and apoptosis, a brief review of previous findings

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Abstract

Background: Physical activity affects the health of the body's organs through several processes. Apoptosis is one of the important cellular processes that play a role in maintaining the balance between cell death and tissue growth.

Aim: The aim of the present study was to examine the previous findings regarding the effect of physical activity and exercise on apoptosis in order to obtain a relatively comprehensive knowledge of this effect by summarizing and analyzing the data.

Materials and Methods: To collect the information of the articles, a search was made from PubMed, MEDLINE, SID, IranMedex, IranDoc, Magiran and Medlib databases. More than 80 scientific articles from 2000 to 2023 were reviewed. The keywords used were: physical activity, aerobic exercise, endurance exercise, apoptosis and cell suicide. After the review, finally 26 articles were selected. Then, the selected items were fully studied and finalized, and the items that were more complete than the others were selected as references.

Conclusion: Physical activity and exercise, especially aerobic exercise, as a safe, cheap and accessible method, can reduce apoptosis through several mechanisms. The breadth of studies in this field, and the overlapping of many data, allows us to confidently introduce exercise and aerobic activity as one of the best methods of regulating body homeostasis and reducing apoptosis.

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1. Introduction

One of the cellular processes that plays an important role in regulating the balance between cell death and tissue growth is apoptosis [1]. This process, which is one of the types of programmed death, generally affects cells from two external and internal routes [2]. In the external pathway, death messages such as -TNF α activate the death receptors of the cell membrane and cause the activation of caspases and thus start the apoptosis process. In the internal pathway, endoplasmic reticulum and mitochondria play the main role [2]. The most important death receptors are the tumor necrosis factor (TNF) family, including the tumor necrosis factor receptor-1 (TNFR-1) and the Fas ligand (FasL).

Cell death occurs after the binding of these receptors to their ligand, i.e. TNF-α, lymphotoxin, Fas ligand (FasL) and nuclear factor kappa light chain enhancer from inactivated lymphocyte (NF-κB) [3]. The process of apoptosis or programmed cell death is one of the main ways to maintain the homeostasis of body cells, which occurs under the control of various genes in the bodies of both multicellular and unicellular organisms. This process is carried out by many intracellular and extracellular factors that can be divided into four groups: injuries caused by various toxins and various radiations, the message of lack or lack of growth factors and hormones, activation of the ligand-receptor binding pathway and activation through immune system cells such as T lymphocytes. Any factor that can prevent the normal development of cells creates the ground for the occurrence of apoptosis [3].

Excessive apoptosis can lead to immunodeficiency syndrome (AIDS) and neurodegenerative diseases such as Alzheimer's and Parkinson's syndromes and ischemic injuries such as myocardial infarction and cancer [4]. One of the possible ways to combat the process of apoptosis is regular physical activity. The beneficial effects of physical activity in patients and healthy people have been well documented [5]. Exercises with appropriate intensity increase the level of the endogenous enzymatic antioxidant defense system [4].

A number of researches attributes the effectiveness of physical activity on the process of apoptosis to changes in the antioxidant capacity of the target tissue [6]. For example, Ahmadi et al. (2007) showed that physical activity by increasing the level of superoxide dismutase protein reduces cardiac apoptosis [7]. Since each study has only been conducted on a part of the apoptotic pathways and also only one or two tissues have been studied in each study, and none of the studies provide comprehensive data in this regard, the purpose of this study was to collect data from studies related to the effect of physical activity on apoptosis in order to gain a better understanding of the relationship between exercise and apoptosis.

2. Materials and Methods

This was a cross-sectional study in which we gathered information from various sources in both English and Persian language. English articles were collected from PubMed and MEDLINE databases, while Persian articles were sourced from databases such as SID scientific database, IranMedex database of medical science articles, IranDoc research center for information and scientific documents, as well as Magiran and Medlib publications. More than 80 scientific articles on physical exercises from 2000 to 2023 were reviewed. The keywords used were: physical activity,

aerobic exercise, endurance exercise, apoptosis and cell suicide. To select the used documents, first the titles found by the search engine were examined in terms of thematic relevance. After reviewing the title, the articles were evaluated in terms of the relevance of the abstract to the purpose. Finally, 26 articles were selected. Then, the selected items were fully studied and finalized, and the items that were more complete than the others were selected as references. This work has been done in several steps, including keywords, single finding, searching in sources, categorizing content, summarizing and sorting.

3. Discussion

Long-term aerobic exercise refers to continuous and rhythmic physical activity over an extended period of time that primarily relies on the aerobic energy system. In general, aerobic exercise is a type of exercise that increases the efficiency of aerobic pathways and increases cardio-respiratory endurance [8]. In this section, with the aim of understanding the possibility of improving the apoptotic pathway of tissues by exercise, we will review the research done in this direction. The results of some of these researches are summarized in Table 1.

Table 1. Summary of the results of some studies on the effect of physical activity on apoptosis

Row	Cause of apoptosis	Physical activity	Results	References
1	Diabetes	60 min of daily training, 5 days a week, for 10 weeks	Enhancement of BCL-2 and PI3K/AKT pathway	[18]
2	-	60 min at a speed of 18-23 m/min, 6 days a week, for 12 weeks	Increase Act	[21]
3	-	55 min at a speed of 10-24 m/min, 5 days a week, for 9 weeks	Reduction of BCL-2/BAX ratio, DNA fragmentation and mitochondrial permeability	[17]
4	H_2O_2	27-35 min with an intensity of 80-90% of max speed, 5 days a week, for 8 weeks	Decreased expression of α-TNF, NF-κB and Fas genes	[16]
5	-	60 min at a speed of 25 m/min, 12-24-36 weeks	Increasing SOD activity and decreasing apoptosis rate	[7]
6	Blood pressure	60 min with a speed of 25 m/min, 12-24-36 weeks	Decrease of TNF, FAS, cytochrome and increase of PI3	[19]
7	Ischemia	15 days at a speed of 30 m/min	Reduction of caspases and increase of antioxidants	[15]
8	-	60 min at a speed of 18-22 m/min, 6 days a week, for 12 weeks	Increase Akt	[21]
9	-	60 min at a speed of 12-27 m/min, for 20 days	Reduction of FADD, FAS, TNF and caspases	[2]
10	-	60 min at a speed of 30 m/min, for 5 days	Increased HSP70	[17]

It is reminded that mitochondria are a key organelle in the control of apoptosis and the depolarization of its membrane causes the release of pro-apoptotic agents [9]. In this regard, researchers believe that NO in physiological concentrations inhibits cytochrome oxidase in an inverse way in justifying the reduction of apoptosis due to endurance exercise with moderate intensity. This phenomenon leads to hyperpolarization of the mitochondrial membrane and thus prevents apoptosis [9]. Also, endurance activity increases mitochondrial biogenesis. Different intracellular anti-apoptotic proteins such as inducible nitric oxide synthase (iNOS),

myeloid cell leukemia or myeloid cell leukemia-1 (Mcl-1) (Glucose-regulated GRP) 78 Glucose (Grp78) and interleukin 8 increased during moderate intensity exercise and remained at high levels after non-exercise [10]. The levels of Mc1-1 decrease due to the depletion of the main downstream molecule of the NO signal, i.e. cyclic guanosine monophosphate (cGMP). As soon as the cGMP-NO signal is activated, some tissues of the body maintain the increased expression of Mc1-1 and slow down the process of apoptosis. Therefore, it is suggested that moderate intensity endurance training slows down the process of apoptosis through increasing the Mcl-1-cGMP-NO-iNOS pathway [10]. Also, research has shown that physical activity through the stimulation of multiple pathways and the activation of PGC-1α protein also causes changes in the state of mitochondria in cardiac and skeletal cells, which suppresses ROS production and increases mitochondrial resistance against permeability and apoptosis signaling [11].

Many researchers believe that physical exercise may increase cell survival proteins including manganese superoxide dismutase (MnSOD or SOD2), NF-κB, extracellular signal-regulated kinase (HSP), Akt pathway, and heat shock protein (HSP), promote heat in tissues (including heart tissue) [11]. There is evidence that HSP protein inhibits apoptosis by affecting mitochondria [12]. Li and his colleagues (2000) report that heat shock protein (HSP70) inhibits the process of apoptosis by reducing the release of cytochrome C and preventing the increase of caspase 3 [13]. Beere et al. (2000) states that HSP70 protein plays a role in reducing apoptosis by preventing the recruitment of procaspase 9 to the apoptosome [14]. Also, Franzoni and his colleagues (2017) have shown a significant relationship between HSP70 and BCL2 and believe that increasing the capacity of antioxidants and then reducing oxidative stress is one of the reasons for reducing apoptosis due to physical activity [6].

As a result, many researchers consider the effective role of physical activity as a result of improving the antioxidant status in the tissue [11]. Based on the research findings of Ebrahimnezhad et al. (2023), 8 weeks of high-intensity interval training led to a significant decrease in the apoptotic indices of the cerebral hippocampus tissue of desert rats, which indicates the protective effect of HIIT on the hippocampal tissue of rats through the optimal regulatory pathways of apoptotic indices [15]. Based on the findings of this research, the induction of hydrogen peroxide dose was associated with a significant increase in the expression of Fas, TNF-α, and NF-κB genes, and 8 weeks of training led to a significant decrease of these genes in the hippocampus tissue of rats [2].

Among the other mechanisms by which physical training reduces apoptosis is the increase in the expression of the SIRT1 protein gene due to physical activity. SIRT1 increases the ratio of oxidized nicotinamide adenine dinucleotide (NAD+) to reduced nicotinamide adenine dinucleotide (NADH), which can play the role of antioxidant in this situation [14]. In mammals, SIRT1 regulates FOXO transcription factors, which FOXO increases apoptosis by regulating essential genes of the cell death pathway. SIRT1 also regulates P53 [14]. Physical activity increases the antioxidant potential through the regulation of SIRT1 activity.

Radak and colleagues (2007) investigated the protective effect of endurance exercise on apoptosis. Research

results show that by reducing factors such as caspase 3 and increasing the level of antioxidants, myocardial tissue is protected [16]. By examining the effect of physical activity on apoptosis, Quindry et al. (2005) believes that many antioxidant enzymes in heart mitochondria are increased after exercise and most importantly, mitochondria show less sensitivity to apoptotic stimuli [17].

Kavazis (2009) reported an increase in BCL-2 protein expression, a decrease in the BCL/BAX-2 ratio, a decrease in BAX protein in mitochondria, a decrease in the accumulation of cytochrome C in the cytosol, and the amount of DNA fragmentation [18].

The results of the study of the effect of physical activity on apoptosis by Cheng Cheng and his colleagues (2013) have shown that exercise by strengthening the AKT/PI3k pathway and the BCL-2 family causes resistance to apoptosis caused by diabetes [19]. Huang et al. (2012) have expressed the protective effect of physical activity on apoptosis due to the reduction of TNF-α, Fas, TNFR-1 and FADD protein [20].

By examining the effect of exercise on apoptosis caused by blood pressure in the heart, they observed a decrease in protein, caspase 3, cytochrome C, BAX, FADD, TNFR-1, Fas, TNF-α, and also an increase in PI3k and Akt protein levels. In this regard, Lee and his colleagues (2013) showed that with a decrease in the level of TNF-α, Fas, FADD, caspase 3 and caspase 8, cardiac FasL receptors related to the apoptotic pathway were less activated in the training group. Also, apoptosis dependent on the mitochondrial pathway has decreased with an increase in BCL-2 protein level and a decrease in BAX protein level, caspase 9 and executive caspases [21].

Also, Santana et al. (2014) reported a significant decrease in gene expression of pro-apoptotic factors and a significant increase in the level of Akt and BCL-2 protein after aerobic training [22]. Hashemi and his colleagues (2009) also say that endurance swimming training is effective in reducing apoptotic changes [23]. In Jafari et al.'s study (2015), a decrease in BAX gene expression compared to BCL-2 was also found to decrease the apoptosis process [8]. Asgharpour-arshad and his colleagues (2017) also believe that aerobic exercise has a significant effect on the reduction of mitochondrial pre-apoptotic protein of the heart [24]. Along with the increase in the production of free radicals, adaptations will be made in the enzyme antioxidant system of the cell by performing aerobic activity, which may be able to neutralize the adverse effects of free radicals. At this time, SOD enzyme converts this radical into hydrogen peroxide radical (O_2H_2). The produced hydrogen peroxides will be regenerated by the glutathione peroxidase enzyme system, which includes glutathione and two other enzymes [25]. Also, as mentioned in this review article, physical activity through changes in different signaling pathways, including the increase of active protein NOS-i, HSP, SOD, SIRT1, NO-cGMP-Mcl-1 release, BAX, Fas, ROS reduction Cytochrome C, BCL-2, PI3K, PGC1-α, as well as changes in caspases activity slow down the process of apoptosis caused by various factors.

As a result, it can be expected that endurance activity reduces the apoptosis process. In contrast to these results, a group of researches identify physical activity as a factor in increasing the process of apoptosis. For example, Sandri and his colleagues (1995) believe that physical

activity increases the amount of DNA fragmentation and increases the process of apoptosis [26]. In line with this research, Qiguan et al. (1999) believe that aerobic exercise will decrease the level of BCL-2 and increase the Fas pathway in skeletal muscles. They also believe that activity reduces SOD levels. As a result, the resistance against free radicals also decreases [27]. Perhaps the logical reason for this conflict can be found in the different intensity of training, duration of training and type of physical training.

4. Conclusion

Physical activity and exercise, especially aerobic exercise, as a safe, cheap and accessible method, can reduce apoptosis through several mechanisms. The breadth of studies in this field, and the overlapping of many data, allows us to confidently introduce exercise and aerobic activity as one of the best methods of regulating body homeostasis and reducing apoptosis.

Consideration

The present study is the result of a class work in the specialized doctorate course of sports physiology in the Faculty of Sports Sciences of Shahid Chamran University, Ahvaz. We hereby express our appreciation and thanks to all the people who helped us in conducting this study.

Conflict of interest

The authors declared no conflicts of interest.

Authors' contributions

All authors contributed to the original idea, study design.

Ethical considerations

The authors have completely considered ethical issues, including informed consent, plagiarism, data fabrication, misconduct, and/or falsification, double publication and/or redundancy, submission, etc.

Data availability

The dataset generated and analyzed during the current study is available from the corresponding author on reasonable request.

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