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Research Article

The effect of eight weeks of aerobic training on some apoptotic factors of elderly men

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Abstract

Background: Considering the significant increase in apoptosis in the elderly, which is related to cardiovascular diseases, cancer, etc. The purpose of this research was to investigate the effect of eight weeks of aerobic exercise on some factors of apoptosis in elderly men was investigated.

Materials and Methods: This research was conducted using a semi-experimental method with 30 healthy elderly men aged 60 to 75 years. who voluntarily participated in this research project and were randomly divided into two experimental (15 people) and control (15 people) groups. The experimental group participated in aerobic exercises for 8 weeks (three sessions of 1 hour per week) based on the special recommendations of the American College of Sports Medicine (ACSM) for the elderly. The control group did not have any physical activity during this period. Serum caspase-8, P53 and IGF-1 were measured by ELISA method. Dependent t-test and independent t-test were used to check the intra-group and inter-group differences of variables. Data analysis was done using SPSS version 20 software and the significance level was considered $p \leq 0.05$ in all steps.

Results: The results showed that eight weeks of aerobic exercise increased the serum levels of caspase 8(P=0.0001) and decreased the serum levels of P53(P=0.0001) and IGF-1(insulin-like growth factor) (P=0.0001).

Conclusion: According to the findings of the present research, it seems that eight weeks of aerobic exercise significantly increases the serum levels of caspase 8 and decreases the serum levels of P53 and IGF-1 in elderly men. According to these results, more research is needed in this field.

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1. Introduction

Aging is a natural process that includes all living beings, including humans, and aging is accompanied by physiological and psychological changes (1). Demographers consider the age of 60 to 65 as the beginning of old age (2). In the year 2019, for the first time in human history, the number of elderly people in the world exceeded children (under five years old). It is also expected that by 2050, the number of elderly people aged 60 and over will double and the number of people aged 80 and over will increase three times (3). In Iran, although currently less than %10 of the population is made up of elderly people aged 60 and over(4), but this ratio is expected to increase rapidly from 2030 and reach about %30 of Iran's population in 2050(5). Scientists have tried for a long time to express the basics of the evolution of aging specifically, one of the main hypotheses that was later proven by microscopic studies in tissue sections is the acceleration of the aging process with an increase in programmed cell death or apoptosis(6). Apoptosis is a regular program of cell death that is very important in terms of physiology and occurs from two pathways inside (mitochondria) and outside the cell (death receptor) with morphological changes such as cell wrinkling, chromatin condensation and DNA fragmentation (7). In the extracellular pathway, the binding of important ligands such as IL-1β (Interleukin 1 beta), TNFα (Tumor necrosis factor alpha) and Fas to death-inducing membrane receptors causes the activation of caspase-8 (Cysteine-dependent aspartate-directed protease 8). Activated caspase 8 can directly activate executive caspases, and executive caspases such as caspase 3 are activated in the next steps by initiator caspases and start the caspase cascade, while in the intracellular pathway (to title of the most important path in causing apoptosis) mitochondria and endoplasmic reticulum are at the center of the process and under the influence of stress factors (glucocorticoids, cytokines, nitric oxide and oxygen reactive species) they induce apoptosis by activating caspases (8). Caspases are part of the family of cysteine proteases and play a central role in the initiation and execution phase of apoptosis. Therefore, the evaluation of caspase activity as a biochemical marker of apoptosis is relevant. Other important factors are also involved in the control of apoptosis, which either prevent its creation, such as IGF-1 (insulin-like growth factor), Bcl-2 (B-cell leukemia 2), or accelerate the process of apoptosis, such as Bax and p53 (9). IGF-1 is a peptide hormone of 70 amino acids that is secreted by the liver. This hormone plays a major role in preventing apoptosis and controlling aging. According to research results, IGF-1 can reduce apoptosis in several ways. Sports activity increases IGF-1 hormone in the body, IGF-1 also leads to inhibition of apoptosis in two ways. The first pathway is the activation of PI-3K and then Akt. The second path is the activation of HSPs (8, 10). On the other hand, P53 is also the most reliable serum marker for inducing cell apoptosis (11). This protein is considered a cell protection factor in a low or physiological state, but if the damage has passed the threshold, it will be a pre-apoptotic factor and, in that case, it will cause changes and start the transcription of apoptosis-helping factors.

Also, p53 induces apoptosis through the non-caspase pathway by increasing Bax protein and releasing cytochrome c from mitochondria and extends apoptosis by decreasing Bcl-2 (12). As it has been mentioned, the amount of apoptosis increases during old age, so it is expected that the process of apoptosis will be strongly affected by the change in mitochondrial integrity caused by increasing age (13). Also, studies have shown that exercise as a method non-medicinal treatment can change cell apoptosis by changing and modulating different factors. But some researchers stated that high-intensity exercise can accelerate the process of apoptosis(14, 15), while unlike intense sports activity, performing moderate and continuous exercises probably reduces apoptosis.(16-18) However, in conflicting studies, intense activity has been associated with a decrease in apoptosis and moderate activity has been associated with an increase in it. For example, Jokar et al (2022) showed that 4 weeks of high-intensity interval training leads to a significant decrease in P53 protein in diabetic rats(19). In Kazemi et al.'s study (2018), a period of aerobic exercise was associated with a significant increase in caspase 3 (20), in another study, eight weeks of aerobic exercise did not have a significant effect on the level of caspase 3 (21). Due to the conflicting results of sports training in young and sick samples, there has been less comprehensive study on the effect of aerobic training on the amount of apoptosis indicators in elderly samples. Therefore, the purpose of this research is to investigate the effect of eight weeks of aerobic training on some apoptotic factors in elderly men.

2. Materials and Methods

The current research was semi-experimental and of an applied type, which was carried out in the form of a pre-test, post-test design with a control group on the elderly of Borujerd city who met the conditions to enter the study. The criteria for entering the samples into the study were as follows. Age of people should be from 60 to 75 years, Have the ability to exercise, Do not have any physical disease or history of any special disease, Be interested in participating in the sports program, Do not participate in sports programs inside or outside the retirement center.Then, through the questionnaire of sports medical records and practical test, subjects who had a history of taking any supplements or drugs in the past month or had a specific disease or disorder were excluded from the research. The demographic characteristics of the subjects were measured and recorded, and after the examination by the doctor and the explanation of the research objectives, written consent was obtained from the participants. The purpose of obtaining this consent was to confirm their willingness to participate in the study and to inform them that they can withdraw at any time if they do not wish to participate in the study. The research samples were randomly divided into two groups of 15 people, control and experimental.

Selected aerobic exercise protocol

The subjects performed the selected exercise program 3 times a week for 8 weeks. It is worth noting that this exercise program was implemented based on the specific recommendations of the American College of Sports Medicine (ACSM) for the elderly and based on the principles of exercise science adapted from the recommendation of Dekker et al (2014) (22). A treadmill was used to implement the walking program.

The duration of each training session was 15 to 30 minutes. The subjects' heart rate while working on the treadmill was continuously adjusted using the heart rate monitor of the control device and to maintain the intensity of the exercise within the designated range. At the beginning of the activity, due to the possibility of low physical fitness, the duration and intensity of the activity was gradually increased, so that at the beginning of the activity, the duration of the training session was considered 15 minutes, and after two weeks of the activity, the subjects did 20 minutes, and in the following weeks with They worked for 30 minutes. During this interval, the intensity of the activity also increased gradually from 60% of the maximum heart rate at the beginning and up to 75% of the maximum heart rate (23).

Blood sampling and biochemical evaluation

Blood was taken from the subjects fasting in two stages 24 hours before the start of the training protocol and then 24 hours after the end of the last session of the training protocol from the antecubital vein while sitting. To determine the serum levels of caspase-8 (with a sensitivity of 0.051 ng/ml) and protein p53 (with a sensitivity of 5.59 ng/l) by the ELISA method and based on the instructions of the manufacturer of the kits of Technology Bioassay Laboratory (intra-test coefficient of variation less than 8 and 10 percent) were done. Also, IGF-1 values were measured by ELISA method with the kit of Mediagnost, Germany (with a sensitivity of 0.09 ng/ml with intra-assay coefficient of variation less than 6.8 and 6.7%).

Statistical analysis

The homogeneity of the variables in the research groups was determined using Levin's test, and the normality of the data was determined using the Kolmograph Smirnov test. Dependent t-test was used to examine intra-group differences in variable values, and independent t-test was used to examine inter-group differences. Data analysis was done using SPSS version 20 software and the significance level was considered as $p \leq 0.05$ in all steps.

3. Results

The characteristics of the research subjects are presented in Table 1.

Table 1: Mean and standard deviation related to the age, height and weight of the subjects

Group / Variable	Experimental	Control
Age	63±6.8	60.4±2.7
Weight(kg)	81.8±7.8	79.7±6.02
Height(cm)	164.8±7.8	169.5±4.6

Figure.1- shows the serum content of caspase-8 in the study groups before and after the intervention. The value of this index increased in the experimental group after a period of aerobic exercise, so that in the experimental group, the average of caspase-8 before The intervention was 8.82, which reached 10.58 after eight weeks of aerobic exercise. Also, in the control group, the average value of caspase-8 was 8.55, which reached 8.56 after eight weeks. The level of significance obtained from the paired t-test indicates that the intra-group changes of caspase-8 are statistically significant only in the experimental group. (P=0.0001) In contrast, no significant changes were observed in the control group (P=0.67). Also, the examination of inter-group changes in caspase-8 values using independent t-test shows that the changes between control and experimental groups are significant (P=0.0001).

Figure.2- shows the serum content of P53 in the studied groups before and after the intervention. The value of this index decreased in the experimental group after a period of aerobic exercise, so that in the experimental group, the average P53 before the intervention was equal to 573.5, which reached 537.4 after eight weeks of aerobic training. Also, in the control group, the average value of P53 was 552.3, which reached 551.7 after eight weeks. The significance level obtained from the paired t-test indicates that the intra-group changes of P53 are statistically significant only in the experimental group. (P=0.0001) In contrast, no significant changes were observed in the control group (P=0.45). Also, the examination of inter-group changes in P53 values using independent t-test shows that the changes between control and experimental groups are significant (P=0.0001).

Figure.3- It shows the serum content of IGF-1 in the studied groups before and after the intervention. The value of this index decreased in the exercise group after a period of aerobic exercise, so that in the experimental group, the average of IGF-1 before the intervention It was equal to 66.55, which reached 63.4 after eight weeks of aerobic training. Also, in the control group, the average value of IGF-1 was 65.85, which reached 65.75 after eight weeks. The level of significance obtained from the paired t-test indicates that the intra-group changes of IGF-1 are statistically significant only in the experimental group. (P=0.0001) In contrast, no significant changes were observed in the control group (P=0.45). Also, examining the inter-group changes in IGF-1 values using the independent t test shows that the changes between the control and experimental groups are significant (P=0.0001).

4. Discussion

the present study was conducted to investigate the effect of eight weeks of aerobic exercise on some apoptosis factors in elderly men. The findings of the present study showed that eight weeks of aerobic training causes a significant increase in the serum levels of caspase 8. In this regard, Khan Souz et al. (2020) showed an increase in caspase-8 after eight weeks of endurance training in infarcted rats.(24) In another study, eight weeks of resistance training increased caspase-8 in diabetic rats (25). Contrary to the findings of the present study, it was shown that exercise training is associated with a decrease in caspase-8 activity levels in the heart tissue of obese rats.(26) In another non-equivalent study by Kim and colleagues (2010), they showed that eight weeks of training decreases the amount of caspase-8 (27). The reason for the discrepancy is probably the age difference of the subjects. Considering that the study subjects of Kim et al were young, but the samples of the present study were elderly, the increase of caspase-8 could be due to the rapid development of apoptotic factors in old age (28). Another finding of the present study was a significant decrease in P53 after eight weeks of aerobic exercise. In line with the findings of the present study, Sharifi et al. (2012) reported a decrease in p53 protein levels in trained men(29), in the same vein, a significant decrease in p53 levels in rats after eight weeks of resistance training (climbing the fence with carrying closed load to the tail of rats) was reported.(30) in another parallel study, Bahman Baglo and colleagues (2021) also showed that endurance training decreases p53 protein levels in diabetic rats(31) and also Hooshmand Moghadam et al (2021). They investigated the effect of twelve weeks of resistance training on some markers of apoptosis in elderly men and reported a significant decrease in p53 levels.(32)

Contrary to the present finding, it was shown that short-term compound training is accompanied by a significant increase in p53 protein.(33) In this regard, Ghorban Alizadeh and his colleagues (2020) investigated the effect of 12 weeks of aerobic training on the expression of the P53 gene. The results showed that 12 weeks of training Aerobic exercise is associated with an increase in the expression of the P53 gene.(34) One of the important factors in the conflict is the difference in the age of the research subjects. In the current research, elderly rats have been used, and considering that it has been proven that the amount of AMPK protein in elderly rats decreases in comparison with young rats(35) and on the other hand, AMPK protein will lead to the activation of p53 protein. Therefore, the reduction of AMPK protein in elderly rats is associated with the reduction of P53 protein.(36) In general, in relation to key proteins such as P53, exercise training can show contradictory results; Because factors such as duration, intensity, recovery time and other factors are very important in the results on this protein (31) Recent studies show an important function of p53 protein in regulating the IGF-1/AKT/mTOR pathway to regulate energy metabolism. IGF-1 was another variable investigated in this study. The presented results show that eight weeks of aerobic training causes a significant decrease in the amount of this protein. In line with the present research, Kordi et al (2019) showed a significant decrease in IGF-1 levels after eight weeks of aerobic and combined exercise in elderly men (37).

Bagheri et al (2015) investigated the effect of eight weeks of combined exercise on GH and IGF-1 in the serum of elderly women and showed that eight weeks of combined training is associated with a decrease in IGF-1, which is consistent with the findings of the current research (38), but Shabani et al (2017) in a non-aligned study showed that resistance training increased IGF-1 The elderly are associated (39) In addition, Tisai et al (2015) showed that 12 months of resistance training in elderly men increases the level of IGF-1 (40). The contradiction of the existing reports is probably due to the difference in the type of training, the training used In Shabani et al.'s research, it was resistance, but in this research, aerobic exercises were used. Considering that the source of energy in aerobic exercises is mainly provided by the breakdown of fat tissue, and then free fatty acid (FFA) and glycerol increase, and the increase in free fatty acid by affecting the hypothalamus causes an increase in somatostatin and further inhibition of GH (41) and because growth hormone stimulates the synthesis of IGF-1 in the liver, inhibition of GH is associated with a decrease in IGF-1 synthesis(42, 43) Among the limitations of the present study, we can mention the lifestyle, individual differences and hereditary factors of the subjects.

Conclusion

According to the findings of the present research, it seems that eight weeks of aerobic exercise significantly increases the serum levels of caspase 8 and decreases the serum levels of P53 and insulin-like growth factor (IGF-1). However, due to the increase of caspase-8, more investigation is needed in this field.

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Compliance with ethical standards

Conflict of interest None declared.

Ethical approval the research was conducted with regard to the ethical principles.

Informed consent Informed consent was obtained from all participants.

Author contributions

Conceptualization: S.H.M., B.A., M.KH.; Methodology: S.H.M., B.A., M.KH.; Software: S.H.M., B.A., M.KH.; Validation: S.H.M., B.A., M.KH.; Formal analysis: S.H.M., B.A., M.KH.; Investigation: S.H.M., B.A., M.KH.; Resources: S.H.M., B.A., M.KH.; Data curation: S.H.M., B.A., M.KH.; Writing - original draft: S.H.M., B.A., M.KH.; Writing - review & editing: S.H.M., B.A., M.KH.; Visualization: S.H.M., B.A., M.KH.; Supervision: S.H.M., B.A., M.KH.; Project administration: S.H.M., B.A., M.KH.; Funding acquisition: S.H.M., B.A., M.KH.

References

1. Kaldi AR. A study on physical, social and mental problems of the elderly in district 13 of Tehran. Age Ageing. 2004 May;33(3):322. doi: 10.1093/ageing/afh097. PMID: 15082448.

2. Mellor D, Russo S, McCabe MP, Davison TE, George K. Depression training program for caregivers of elderly care recipients: implementation and qualitative evaluation. J Gerontol Nurs. 2008 Sep;34(9):8-15; quiz 16-7. doi: 10.3928/00989134-20080901-09. PMID: 18795560.

3. Farrell K, Westlund H. China's rapid urban ascent: an examination into the components of urban growth. Asian Geogr. 2018;35(1):85-106. https://doi.org/10.1080/10225706.2018.1476256

4. Ghasemi S, Zanjari N, Sharifi F, Fakhrzadeh H, Alizadeh M. The indicators of comparison of healthy elderly people 65-69 and 60-64 in two age groups in Tehran. Iranian Journal of Diabetes and Metabolism 2003;13(1):50-6. URL: http://ijdld.tums.ac.ir/article-1-5261-en.html

5. Sadeghi R ZH, ZAhedian A, Norollahi T. . ; 2013. Trends in Iran's population, past, present and future. Tehran: Statistical Center of Iran. 2013;14:70-9.

6. Rajaei F, Abedpour N, Salehnia M, Jahanihashemi H. The effect of vitrification on mouse oocyte apoptosis by cryotop method. Iran Biomed J. 2013;17(4):200-5. doi: 10.6091/ibj.1184.2013. PMID: 23999716; PMCID: PMC3882923.

7. Dabrowska C, Li M, Fan Y. Apoptotic Caspases in Promoting Cancer: Implications from Their Roles in Development and Tissue Homeostasis. Adv Exp Med Biol. 2016;930:89-112. doi: 10.1007/978-3-319-39406-0_4. PMID: 27558818.

8. Kwak HB. Effects of aging and exercise training on apoptosis in the heart. J Exerc Rehabil. 2013 Apr;9(2):212-9. doi: 10.12965/jer.130002. Epub 2013 Apr 25. Erratum in: J Exerc Rehabil. 2013 Dec;9(6):549. PMID: 24278863; PMCID: PMC3836520.

9. Riyahi Malayeri, S., Mirakhorli, M. The Effect of 8 Weeks of Moderate Intensity Interval Training on Omentin Levels and Insulin Resistance Index in Obese Adolescent Girls. Sport Physiology & Management Investigations, 2018; 10(2): 59-68. http://www.sportrc.ir/article_67070.html?lang=en.

10. Starnes JW, Taylor RP, Park Y. Exercise improves postischemic function in aging hearts. Am J Physiol Heart Circ Physiol. 2003 Jul;285(1):H347-51. doi: 10.1152/ajpheart.00952.2002. Epub 2003 Mar 20. PMID: 12649077.

11. Attardi LD. The role of p53-mediated apoptosis as a crucial anti-tumor response to genomic instability: lessons from mouse models. Mutat Res. 2005 Jan 6;569(1-2):145-57. doi: 10.1016/j.mrfmmm.2004.04.019. PMID: 15603759.

12. Dincer Y, Himmetoglu S, Bozcali E, Vural VA, Akcay T. Circulating p53 and cytochrome c levels in acute myocardial infarction patients. J Thromb Thrombolysis. 2010 Jan;29(1):41-5. doi: 10.1007/s11239-009-0328-0. Epub 2009 Jun 24. PMID: 19551350.

13. Ashkenazi A, Dixit VM. Death receptors: signaling and modulation. Science. 1998 Aug 28;281(5381):1305-8. doi: 10.1126/science.281.5381.1305. PMID: 9721089.

14. Quadrilatero J, Bombardier E, Norris SM, Talanian JL, Palmer MS, Logan HM, Tupling AR, Heigenhauser GJ, Spriet LL. Prolonged moderate-intensity aerobic exercise does not alter apoptotic signaling and DNA fragmentation in human skeletal muscle. Am J Physiol Endocrinol Metab. 2010 Mar;298(3):E534-47. doi: 10.1152/ajpendo.00678.2009. Epub 2009 Dec 8. PMID: 19996388.

15. Peterson JM, Bryner RW, Sindler A, Frisbee JC, Alway SE. Mitochondrial apoptotic signaling is elevated in cardiac but not skeletal muscle in the obese Zucker rat and is reduced with aerobic exercise. J Appl Physiol (1985). 2008 Dec;105(6):1934-43. doi: 10.1152/japplphysiol.00037.2008. Epub 2008 Oct 2. PMID: 18832755; PMCID: PMC2612474.

16. Mohammadi, S., Rostamkhani, F., Riyahi Malayeri, S. et al. High-intensity interval training with probiotic supplementation decreases gene expression of NF-κβ and CXCL2 in small intestine of rats with steatosis. Sport Sci Health 18, 491–497 (2022). https://doi.org/10.1007/s11332-021-00829-5.

17. Serviente C, Burnside A, Witkowski S. Moderate-intensity exercise reduces activated and apoptotic endothelial microparticles in healthy midlife women. J Appl Physiol (1985). 2019 Jan 1;126(1):102-110. doi: 10.1152/japplphysiol.00420.2018. Epub 2018 Sep 20. PMID: 30236051; PMCID: PMC6383638.

18. McMillan EM, Graham DA, Rush JW, Quadrilatero J. Decreased DNA fragmentation and apoptotic signaling in soleus muscle of hypertensive rats following 6 weeks of treadmill training. J Appl Physiol (1985). 2012 Oct;113(7):1048-57. doi: 10.1152/japplphysiol.00290.2012. Epub 2012 Aug 2. PMID: 22858629.

19. Jokar M, Sherafati Moghadam M. Effect of 4 weeks of High-Intensity Interval Training on P53 and Caspase-3 Proteins Content in the Heart Muscle Tissue of Rats with Type 1 Diabetes. JSSU 2022; 29 (11) :4255-4267.URL: http://jssu.ssu.ac.ir/article-1-4947-fa.html.

20. Kazemi A, Mirza-zade E. The Effect of Endurance Training on Tumor Tissue Levels of Caspase-3 and Caspase-9 in Mice with Breast Cancer. ijbd 2018; 11 (3) :32-43.URL: http://ijbd.ir/article-1-691-en.html.

21. Seo 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: 10.20463/jenb.2016.09.20.3.3. Epub 2016 Sep 30. PMID: 27757383; PMCID: PMC5067423.

22. J D. Exercise and Physical Functioning in Osteoarthritis Medical, Neuromuscular and Behavioral Perspectives. New York Heidelberg Dordrecht London Springer. 2014:132-8. https://link.springer.com/book/10.1007/978-1-4614-7215-5.

23. King AC, Oman RF, Brassington GS, Bliwise DL, Haskell WL. Moderate-intensity exercise and self-rated quality of sleep in older adults. A randomized controlled trial. JAMA. 1997 Jan 1;277(1):32-7. PMID: 8980207.

24. Khansooz, M., Abedi, B., Palizvan, M. R., Saremi, A. Evaluation of Apoptotic Regulator Markers after a Period of Increased Endurance Training in Serum of Wistar Rats with MI. Journal of Sport Biosciences, 2020; 12(1): 109-126. doi: 10.22059/jsb.2020.287398.1357.

25. montazery taleghani, H., shakeri, N., ebrahim, K., soori, R., Gholami, M. The effect of 8 weeks resistance exercise on cardaic apoptosis biomarkers in diabetic rats. Metabolism and Exercise, 2019; 9(2): 149-161. doi: 10.22124/jme.2020.15392.177.

26. Lee SD, Shyu WC, Cheng IS, Kuo CH, Chan YS, Lin YM, Tasi CY, Tsai CH, Ho TJ, Huang CY. Effects of exercise training on cardiac apoptosis in obese rats. Nutr Metab Cardiovasc Dis. 2013 Jun;23(6):566-73. doi: 10.1016/j.numecd.2011.11.002. Epub 2012 Mar 7. PMID: 22402061.

27. Kim KB KY, Park JJ, Effects of 8-week Exercise on Bcl-2, Bax, Caspase-8, Caspase-3 and HSP70 in Mouse Gastrocnemius Muscle. Journal of Life Science 2010;20(9):1409-14. DOI:10.5352/JLS.2010.20.9.1409.

28. Norouzi Kamareh MH ZM, Ghaderi Pakdel F, tolouei azar j Effect of 12 weeks aerobic training and oral green tea extract on cardiac caspase-3 expression in aged male rats. Iran Journal of Sport Sciences biosciences. 2018;10(2):221-35. https://doi.org/10.22059/jsb.2018.245693.1220.

29. Sharafi H, Rahimi R. The effect of resistance exercise on p53, caspase-9, and caspase-3 in trained and untrained men. J Strength Cond Res. 2012 Apr;26(4):1142-8. doi: 10.1519/JSC.0b013e31822e58e5. PMID: 22446679.

30. Askari B BN, Rashid Lamir A. Effects of 8 Weeks of Resistance Training and IGF-1 Injection on Biochemical Markers of Cancer and Colorectal Structures in Rats. mljgoums. 2017;11(6):23-29. URL:http://mlj.goums.ac.ir/article-1-1020-en.html.

31. Neda Aghaei Bahmanbeglou MSM, Mousa Amirahmadi. The Effect of Ampk and P53 Proteins On Tor Pathway Following Endurance Training In The Left Ventricle Of The Heart Of Diabetic Rats By Streptozotocin And Nicotinamide. Iranian Journal of Diabetes and Metabolism. 2002;21(1):13-23. URL: http://ijdld.tums.ac.ir/article-1-6016-en.html.

32. . Hooshmand Moghadam B GA, Eskandari M, Parseh S, Hojjati Marvast M. Twelve weeks of resistance training intervention on serum levels of some apoptosis markers in elderly men. Journal of Torbat Heydariyeh University of Medical Sciences. 2021;8(4):10-9. URL: http://jms.thums.ac.ir/article-1-887-en.html.

33. Asghari Rakabardkolaee M BA, Abdi A, Hasrak K. The review of short-term concurrent training on expression of P53 and P21 tumor suppressor genes in men with prostate cancer. Journalof Knowledge & Health 2018;13(1):46-54.

34. Ghorbanalizadeh M, Bashiri J, Gholami F. [Effect of 12-week aerobic training on cardiac p53 and AIF gene expression in male rats]. Med J Tabriz Uni Med Sciences Health Services. 2020 August-September; 42(3):310-318. doi: 10.34172/mj.2020.050.

35. Bartlett JD, Hwa Joo C, Jeong TS, Louhelainen J, Cochran AJ, Gibala MJ, Gregson W, Close GL, Drust B, Morton JP. Matched work high-intensity interval and continuous running induce similar increases in PGC-1α mRNA, AMPK, p38, and p53 phosphorylation in human skeletal muscle. J Appl Physiol (1985). 2012 Apr;112(7):1135-43. doi: 10.1152/japplphysiol.01040.2011. Epub 2012 Jan 19. PMID: 22267390.

36. Sanchis-Gomar F. Sestrins: novel antioxidant and AMPK-modulating functions regulated by exercise? J Cell Physiol. 2013 Aug;228(8):1647-50. doi: 10.1002/jcp.24338. PMID: 23359071.

37. Kordi N, Pakzad Hasanlu F, Arab Taheri Z. Effect of eight-week aerobic and periodic exercises on IGF-1 and lipid profile in elderly men. cjhaa 2018; 3 (2) :7-13

URL: http://cjhaa.mubabol.ac.ir/article-1-76-en.htmlin.

38. Bagheri L FM. The Effect of 8 Weeks Combined Training on The Ratio of Growth hormone to Insulin-like growth factor1 of Elderly Women. Physiology of Sport and Physical Activity. 2015;8(2):1249-56.

39. Shabani F EA, Salman Z. Effectiveness of Different Severities of Exercise Exercise on Work Memory in the Elderly. Aging psychology. 2017;3(1):55-67.

40. Tsai CL, Wang CH, Pan CY, Chen FC. The effects of long-term resistance exercise on the relationship between neurocognitive performance and GH, IGF-1, and homocysteine levels in the elderly. Front Behav Neurosci. 2015 Feb 10;9:23. doi: 10.3389/fnbeh.2015.00023. PMID: 25713518; PMCID: PMC4322723.

41. Seo DI, Jun TW, Park KS, Chang H, So WY, Song W. 12 weeks of combined exercise is better than aerobic exercise for increasing growth hormone in middle-aged women. Int J Sport Nutr Exerc Metab. 2010 Feb;20(1):21-6. doi: 10.1123/ijsnem.20.1.21. PMID: 20190348.

42. McCall GE, Byrnes WC, Fleck SJ, Dickinson A, Kraemer WJ. Acute and chronic hormonal responses to resistance training designed to promote muscle hypertrophy. Can J Appl Physiol. 1999 Feb;24(1):96-107. doi: 10.1139/h99-009. PMID: 9916184.

43. Eliakim A, Nemet D. The endocrine response to exercise and training in young athletes. Pediatr Exerc Sci. 2013 Nov;25(4):605-15. doi: 10.1123/pes.25.4.605. PMID: 24214442.