



Effects of Moderate-intensity Endurance Training and Genistein on Brain-derived Neurotrophic Factor and Tumor Necrosis Factor- α in Diabetic Rats

Omid Reza Salehi^{1*}, Seyed Ali Hosseini¹, Fatemeh Farkhaei¹, Parvin Farzanegi², Abdossaleh Zar³

1. Department of Sport Physiology, Marvdasht Branch, Islamic Azad University, Marvdasht, Iran

2. Department of Sport Physiology, Sari Branch, Islamic Azad University, Sari, Iran

3. Department of Sport Sciences, Faculty of Literature and Human Sciences, Persian Gulf University, Boushehr, Iran

ARTICLE INFO

Article type:
Research Paper

Article History:
Received: 28 Dec 2018
Accepted: 13 Mar 2019
Published: 24 Apr 2019

Keywords:
BDNF
Diabetes
Genistein
TNF- α
Training

ABSTRACT

Introduction: Diabetes is a metabolic disease that affects the neural and immune system, causing long-term health complications such as neuropathy and nephropathy. Considering that physical education and nutrition are foremost influential factors in the management of diabetes, the present study aimed to investigate the effects of moderate-intensity endurance training and genistein on the serum levels of brain-derived neurotrophic factor (BDNF) and tumor necrosis factor- α (TNF- α) in diabetic rats.

Methods: This experimental study was conducted on 40 diabetic rats, which were selected and divided into five groups of control, moderate-intensity endurance training, genistein consumption, moderate-intensity endurance training with genistein, and sham. The animals in groups two and four ran on a treadmill for eight weeks in three sessions per week (each session: 60 minutes) within the speed range of 10-17 m/min, and the rats in groups three and four received genistein with the daily dose of 30 mg/kg via intraperitoneal injection. Data analysis was performed using the Kolmogorov-Smirnov test, independent samples t-test, and two-way analysis of variance (ANOVA) at the significance level of ≤ 0.05 .

Results: Endurance training significantly increased the serum level of BDNF ($P=0.002$; effect size: 0.34), while it reduced serum TNF- α ($P=0.003$; effect size: 0.31). Similarly, genistein consumption significantly increased the serum level of BDNF ($P=0.01$; effect size: 0.24), while it decreased serum TNF- α ($P=0.001$; effect size: 0.37). Moreover, endurance training with genistein consumption had interactive effects on increasing serum BDNF ($P=0.04$; effect size: 0.15) and decreasing serum TNF- α ($P=0.019$; effect size: 0.20).

Conclusion: According to the results, moderate-intensity training and genistein consumption alone could improve the serum levels of BDNF and TNF- α in diabetic rats. However, the simultaneous consumption of genistein may enhance the effects of moderate-intensity training on BDNF and TNF- α in diabetic rats.

► Please cite this paper as:

Salehi OM, Hosseini SA, Farkhaei F, Farzanegi P, Zar A. Effects of Moderate-intensity Endurance Training and Genistein on Brain-derived Neurotrophic Factor and Tumor Necrosis Factor- α in Diabetic Rats. J Nutrition Fasting Health. 2019; 7(1): 44-51. DOI: 10.22038/jnfh.2019.37231.1163

Introduction

Diabetes is a metabolic disease defined as the high levels of blood glucose, which is caused by inadequate insulin production by pancreatic cells or the insufficient response to insulin by the cells (1). Diabetes is associated with long-term complications, such as neuropathy and

nephropathy (2), as well as the destruction of Schwann cells and myelinated neurons and reduction of neuronal populations (3).

The systemic inflammation in diabetes plays a pivotal role in the disease (4). As a result, the adipose tissue acts as an endocrine agent, which

* Corresponding author: Omid Reza Salehi, Department of Sport Physiology, Marvdasht Branch, Islamic Azad University, Marvdasht, Iran. Tel: 00987143112201; Email: omidreza.67salehi@gmail.com

© 2019 mums.ac.ir All rights reserved.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

secretes adipocytokines and cytokines and indirectly affects the level of interleukin-6 (IL-6). Furthermore, inflammatory factors (e.g., IL-6) have the potential to cross the blood barrier. Through specific mechanisms, these factors prevent the increased expression of the neurotrophin family (5), which play a key role in the regeneration and protection of neurons (3). The brain-derived neurotrophic factor (BDNF) is an important member of this family, and the excessive expression of the IL-6 and tumor necrosis factor- α (TNF α) that are induced by diabetic inflammation reduces the expression of BDNF (5).

Sports activities have been reported to be a non-pharmacological approach to the treatment of diabetes mellitus (6). Several studies have been focused on the effects of exercise on the serum levels of BDNF and TNF- α , reporting that three months (5), eight weeks (7), and six months of exercise (8) could significantly increase serum BDNF and decrease serum TNF- α in women and men with metabolic syndrome. On the other hand, the results of some studies have indicated that diet and exercise alone or together could reduce the progression of diabetes by up to 40% after six years (6). Over the past few years, extensive research has been focused on the effectiveness of the medicinal plants used in traditional medicine in the treatment of diabetic patients (9). Furthermore, research on the food supplements and herbs used in traditional medicine has suggested that the compounds in these supplements (e.g., dietary fibers, vitamins, flavonoids, sterols, and other antioxidant compounds) could decrease blood lipids, inhibit oxidation, release oxygen free radical, influence the immune system, and improve metabolic disorders in order to enhance the conditions of diabetic patients (10).

Genistein is a major isoflavone in soybean,

the protective role of which in arteries and heart has been confirmed. Recent studies have examined the effect of genistein in soybean on the lipid profile of diabetic patients (11). On the same note, researchers have claimed that the injection of 1 mg/kg of genistein in female, non-ovarian diabetic rats and diabetic rats could increase the synthesis and secretion of BDNF in the spinal cord. Moreover, the effect has been reported to be greater in diabetic rats compared to non-ovarian, diabetic rats (11).

According to the literature, genistein and daidzein could significantly reduce the incidence of adiponectin and lipid cells, as well as the activity of c-Jun N-terminal kinase and TNF- α (12). Although genistein has a significant effect on the treatment of diabetes during exercise in the patients with type II diabetes, it does not have a physiological response to increased blood glucose levels in those with type I diabetes during exercise (6).

Recent studies have indicated that the simultaneous combination of dietary supplements and exercise could positively influence several diseases, including diabetes (13, 14). However, no studies have addressed the combined effects of genistein and exercise on BDNF and TNF- α . The present study aimed to investigate the interactive effects of moderate-intensity endurance training and genistein on the serum levels of BDNF and TNF- α in diabetic rats. The main research hypothesis was to assess whether the consumption of genistein could accelerate the effects of moderate-intensity training, thereby increasing BDNF and decreasing TNF- α in diabetic rats.

Material and methods

This experimental study had a factorial design with five groups, as depicted below.

X1	Y
X2	Y
X1+X2	Y
~X	Y
(X)	Y
X1: training, X2: genistein, ~X: control, variable (X) :sham, y: dependent	

The sample population consisted of 40

adult male Sprague-Dawley rats with the mean

weight of 220.22 ± 25 grams, which were purchased from the animal breeding center of Marvdasht Islamic Azad University, Iran and transferred to the animal holding room of the physiology laboratory. During the study period, the animals were kept at the ambient temperature of $22 \pm 2^\circ\text{C}$ and controlled light (12-hour light/dark cycle) and maintained within an eight-day adaptation period. They also had free access to water and food during the research period (15).

Diabetes Induction

On day eight and after overnight fasting, 40 rats were subjected to the intraperitoneal injection of a single dose of streptozotocin (60 mg/kg) (Sigma-Aldrich, USA), which was dissolved in citrate buffer (16). Four days after the injection, the animals were examined using the punch method in order to measure the blood glucose level using a glucometer (15). In total, 40 rats with higher blood glucose levels than 300 mg/dl were enrolled in the study.

Animal Grouping

The training program and genistein consumption initiated one week after the induction of diabetes and maintenance of the animals. Diabetic rats were randomly assigned to five groups of eight, including 1) control, 2) moderate-intensity endurance training, 3) genistein consumption, 4) moderate-intensity endurance training with genistein consumption, and 5) sham. It is notable that the sham group received dimethyl sulfoxide, which is a genistein solvent. The genistein used in the present study was manufactured by Hangzhou Dingyan Cem Co., Ltd (batch No. 20151105).

Training Protocol and Genistein Consumption

The animals in groups two and four ran on a treadmill for eight weeks during three sessions per week (each session: 60 minutes) at the speed of 10-17 m/min (17). The animals in groups three and four received daily genistein via intraperitoneal injection (30 mg/kg) for eight weeks (18). Afterwards, blood samples were obtained from diabetic rats in order to measure the variables.

Before blood sample collection, the animals were kept fasting for 16 hours. The serum levels

of BDNF were measured using the Zellbio commercial kit (Germany) with the sensitivity of nanogram per milliliter (ng/ml), and the serum levels of TNF- α were measured using the Diaclone commercial kit (France) with the sensitivity of picogram per milliliter (pg/ml). The measurement of BDNF and TNF- α levels was performed using the ELISA assay.

Statistical Analysis

Data analysis was performed in SPSS version 21 using the Kolmogorov-Smirnov test to assess the normal distribution of the data, independent sample t-test, and two-way analysis of variance (ANOVA) at the significance level of 0.05. Since there were two factors (training and genistein) in the present study, two-way ANOVA was used. It is notable that all the ethical and legal aspects of this research were reviewed and approved by the Islamic Azad University of Marvdasht, Iran.

Results

Serum levels of BDNF and TNF- α in rats are depicted in Figures 1 and 2, respectively. To eliminate the effects of dimethyl sulfoxide injection on the variables of the study, independent sample t-test indicated no significant differences in the serum levels of BDNF ($t=1.22$; $P=0.24$) and TNF- α ($t=0.83$; $P=0.56$) between the control and sham groups.

The results of two-way ANOVA are presented in Table 1. According to the information in this table, endurance training ($F=12.35$; $P=0.002$; effect size: 0.34) and genistein consumption ($F=7.84$; $P=0.01$; effect size: 0.24) had significant effects on increasing the serum levels of BDNF in diabetic rats. In addition, endurance training combined with genistein consumption ($F=4.44$; $P=0.04$; effect size: 0.15) have an interactive effect on increasing the serum levels of BDNF in diabetic rats.

According to the results of two-way ANOVA, endurance training ($F=10.95$; $P=0.003$, effect size: 0.31) and genistein consumption ($F=14.62$; $P=0.001$; effect size: 0.37) had significant effects on reducing the serum levels of TNF- α in diabetic rats. Furthermore, endurance training combined with genistein consumption ($F=6.32$; $P=0.019$; effect size: 0.20) had interactive effects on reducing the serum levels of TNF- α in diabetic rats.

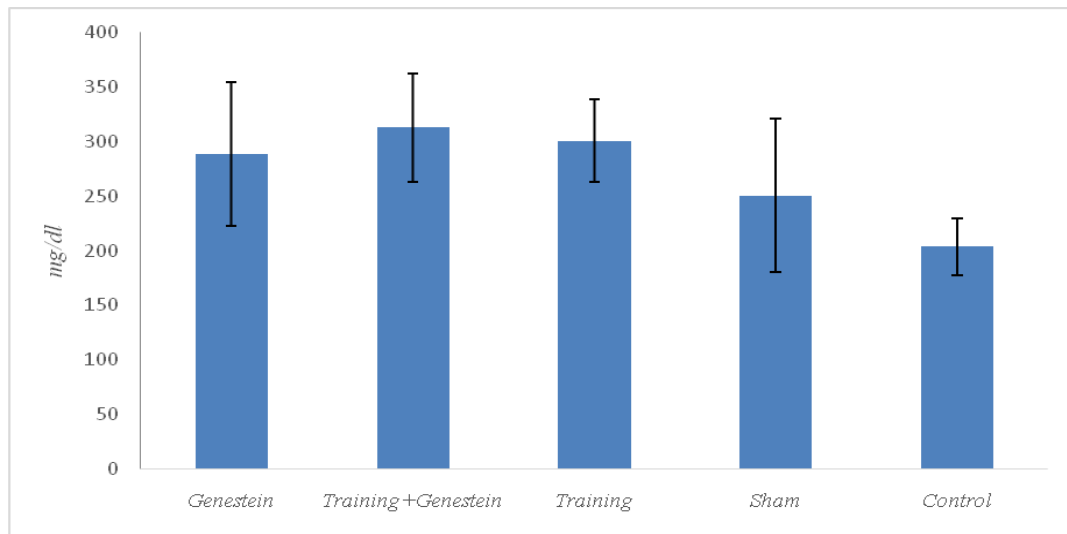


Figure 1. Serum Levels of Brain-derived Neurotrophic Factor in Five Research Groups of Rats

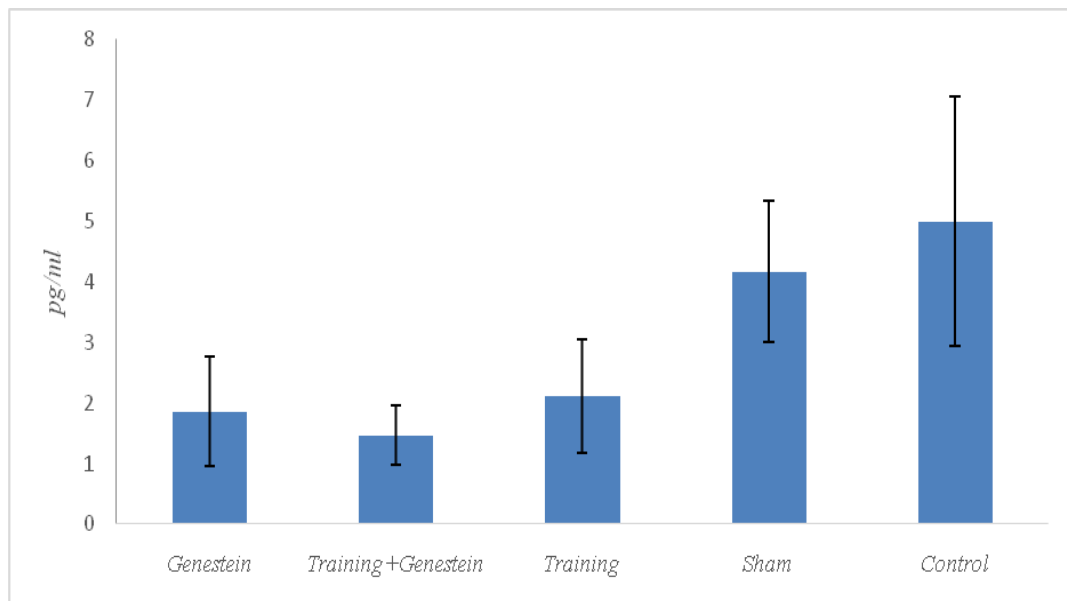


Figure 2. Serum Levels of Tumor Necrosis Factor- α in Five Research Groups of Rats

Table 1. Results of Two-way ANOVA to Determine Changes in Serum Levels of BDNF and TNF- α in Diabetic Rats

Variable	Factor	Mean	Standard Deviation	F	Significance Level	Effect Size
BDNF	Training	300.92	37.56	12.35	0.002	0.34
	Genestein	288.6	65.68	7.84	0.01	0.24
	Training with Genestein	312.9	49.87	4.44	0.04	0.15
TNF- α	Training	2.11	0.94	10.95	0.003	0.31
	Genestein	1.86	0.91	14.62	0.001	0.37
	Training with Genestein	1.46	0.49	6.32	0.019	0.20

BDNF: Brain-derived neurotrophic factor; TNF- α : tumor necrosis factor- α

Discussion

According to the results of the present study,

eight weeks of moderate-intensity endurance training had significant effects on increasing the

serum levels of BDNF and reducing the serum levels of TNF- α in diabetic rats. Diabetes is associated with increased inflammation, and the disease progression leads to the increased expression of proinflammatory agents (e.g., TNF- α) by macrophages in cells. Furthermore, mitogen-activated protein kinase and p38 with the cAMP receptor phosphorylation mechanism is a known agent for regulating the expression of the BDNF gene and activating exon IV (inhibitor of BDNF protein synthesis) (19). The mechanisms for the secretion of cytokines with exercise are highly complex and have not been well known yet. However, studies have indicated that regular exercise could stimulate the Th2 activity, thereby increasing the production of Th2 family cytokines and decreasing inflammation by increasing the production of anti-inflammatory cytokines (20).

Several studies have been focused on the effects of physical exercise on BDNF and TNF- α . In line with the present study, eight weeks of moderate- and high-intensity endurance training (2), 12 weeks of endurance training (21), six weeks of moderate-intensity endurance training (3), three months of endurance exercises (5), eight weeks of interval training (8), and six weeks of endurance training (22) in the men and women with metabolic syndrome and diabetes have been reported to significantly increase the levels of BDNF. One of the possible reasons for the consistency of these findings with the results of the present study is the long-term training period of the studies in this regard.

On the other hand, 12 weeks of endurance training were reported to have no significant effect on the reduction of TNF- α in the obese adolescents with type II diabetes (21), which is inconsistent with the results of the present study. This discrepancy could be due to the differences in the sample populations and duration of training. In another similar research, 12 weeks of moderate-intensity endurance training had no significant effect on the reduction of TNF- α in the plasma of the patients with type II diabetes (23). This incompatibility with the results of the present study could be due to the differences in the sample populations, duration of training, and measurement levels of the variables.

In another study, six weeks of high-intensity

training with the speed of 27 m/min and training combined with vitamin E consumption resulted in a significant increase in the levels of TNF- α and H₂O₂, while no significant changes were observed in the BDNF levels of rats (24). This inconsistency with the results of the present study could be due to the differences in the intensity of the training, sample populations, and baseline levels of BDNF and TNF- α in diabetic and healthy rats.

The anti-inflammatory effects of genistein on diabetes could be attributed to the onset of weight loss caused by the protein diet, which increases the mass of pancreatic beta cells and serum insulin levels, thereby facilitating the transfer of glucose to the pores of cells (25). Other studies in this regard have also denoted that the use of genistein may be associated with the reduced expression of NF- κ B and increased β -estradiol-17 (E₂) as a micronutrient of nerve cells, which in turn increases the expression of BDNF mRNA in nerve cells (11, 25).

Some studies in this regard have been focused on the effects of using genistein and soy isoflavones on inflammatory and neurotrophic factors, such as 1 mg/kg of genistein (11), 30 mg/kg of genistein (13), 20-2000 nanograms of genistein (26), the increased expression of BDNF mRNA (11, 26, 27), and improved lipid profile (13) in diabetic and ovariectomized rats. The findings of these studies are in congruence with the present study, and the consistency could be attributed to the long-term use of genistein in most of these studies.

Inconsistent with the current research, the eight-week consumption of 14 grams of soy protein per day had no significant effects on the changes in serum TNF- α in peritoneal dialysis patients (28). In addition, use of genistein (50 mg/kg of body weight/day) for two weeks has been reported to have no significant effect on the reduction of TNF- α in the rats with doxorubicin-induced nephropathy (29). This discrepancy could be attributed to the use of various doses and difference in the duration of the studies, which was eight weeks in the current research and two weeks in the mentioned study.

According to the results of the present study, eight weeks of moderate-intensity endurance training combined with genistein consumption had interactive effects on increasing the serum

levels of BDNF and decreasing the serum levels of TNF- α in diabetic rats. There have been limited studies regarding the interactive effects of physical exercise and genistein consumption. For instance, the research by Jourkesh et al. (2017) showed that six weeks of combined endurance and resistance training along with the consumption of soy extract had more significant effects on the improvement of endothelial nitric oxide synthesis and weight loss in the heart tissues of ovariectomized rats (30). Furthermore, resistance training and isoflavone consumption has been reported to exert significant effects on the improvement of the body composition in postmenopausal women (31), while aerobic exercise along with the consumption of soy isoflavones has been reported to have significant effects on the improvement of lipid profile in postmenopausal women (32).

Some studies have indicated that reduced levels of cholesterol and low-density lipoprotein could diminish oxidative stress, thereby resulting in the inhibition of pro-inflammatory factors. Therefore, the reduction of IL-6, IL-1 β , TNF, and IL-10 and increased superoxide dismutase following combined exercise and isoflavone consumption could be considered as a common mechanism in these interventions. In this regard, Giolo et al. (2018) stated that 10 weeks of combined aerobic and resistance training along with genistein use decreased pro-inflammatory factors in postmenopausal women (33). Moreover, aerobic exercises along with the consumption of soy seeds have been reported to exert significant effects on the improvement of parameters such as glucose, insulin, and low-density lipoprotein, while increasing superoxide dismutase in the muscle tissues of diabetic rats (34).

Inconsistent with the findings of the current research, 30 sessions of combined aerobic and resistance training along with the consumption of isoflavones (100 mg) per day had no interactive effects on the reduction of inflammatory factors (IL-6 and IL-8) in postmenopausal women (33). Considering the results of the present study regarding the interactive effects of genistein and moderate-intensity endurance training should be taken into account in further investigations.

Conclusion

According to the results, moderate-intensity endurance training along with genistein consumption could affect the improvement of diabetic disorders through increasing the serum levels of BDNF and reducing the serum levels of TNF- α in diabetic rats.

Acknowledgments

Hereby, we extend our gratitude to the Research Deputy of the Animal Sports Physiology Laboratory of Marvdasht Islamic Azad University, Iran, for assisting us in this research project.

Conflicts of interest

None declared.

Ethical Considerations

The animal experiments in the current research were performed in accordance with institutional guidelines and approved by the Ethics Committee of Laboratory Animals Care at Marvdasht Islamic Azad University in Marvdasht, Iran.

References

1. Lohrasebi M, Edalatmanesh MA, Hosseini SA, Farkhaie F, Salehi OM, Kazemi N, et al. Lipid lowering effects of coriandrum sativum extract and endurance training in streptozotocin induced diabetic rats. *Report of Health Care Journal*. 2016; 2(2): 25-34.
2. Salehi OR, Hosseini SA. The Effects of Endurance Trainings on Serum BDNF and Insulin Levels in Streptozotocin-Induced Diabetic Rats. *The Neuroscience Journal of Shefaye Khatam*. 2017; 5(2): 52-61. (Persian)
3. Eslami R, Sorkhkamanzadeh G, Kazemi AR, Gharakhanlou R, Banaifar AA. Effect of 6-Week Endurance Training on BDNF Expression in Motor Root of Spinal Cord in Rats with Diabetic Neuropathy. *Journal of Mazandaran University of Medical Sciences*. 2015; 25(124): 94-106. (Persian)
4. Banitalebi E, Razavi T, Norian M, Bagheri L. The effect of combined aerobic exercise training and green tea extract on serum TNF- α and IL-6 levels in obese women with type 2 diabetes. *Daneshvar Medicine Journal*. 2016; 23(123): 11-20.
5. Osali A, Eskandari M. The Effect of three months aerobic exercise with moderate intensity on serum BDNF and TNF- α in women with metabolic syndrome. *Medical Journal of Mashhad University of Medical Sciences*. 2016; 59(4): 242-51.
6. Hosseini S, Azarbayjani M. The effect of aqua extract of saffron with resistance training on glycemic

- indexes of streptozotocin induced diabetic rats. *Armaghane Danesh*. 2013; 18(4): 284-94.
7. Salimi Avansar M. The Effects of Eight Weeks Interval Training and Curcumin Consumption on TNF- α and BDNF Levels in Men with Metabolic Syndrome. *Journal of Ardabil University of Medical Sciences*. 2017; 17(3): 299-310. (Persian)
8. Osali A, Mostafavi H. The effect of six months aerobic exercise with moderate intensity on BDNF, IL-6, and short-term memory in 50-65 years old women with syndrome metabolic. *Yafte*. 2017; 19(4): 88-101. (Persian)
9. Farkhaie F, Hosseini S, Edalat Manesh M. The effect of endurance training with Niglla Sativa extract on lipid profile of diabetic rats. *Jahesh Journal*. 2013; 14: 11-8.
10. Fallah Huseini H, Fakhrzadeh H, Dastpak A, Azarabadi M, Mohtashami Tokabny R. Review of antihyperlipedemic herbal medicine. *Journal of Medicinal Plants*. 2005; 3(15): 9-20. (Persian)
11. Azizpour M, Hoveida R, Ahmadyasl N. Evaluating the effect of genistein on the amount of BDNF protein in the spinal cord of diabetic ovariectomized rats. *International Journal of Medical Research & Health Sciences*. 2016; 5(4): 228-31.
12. Yanagisawa M, Sugiya M, Iijima H, Nakagome I, Hirono S, Tsuda T. Genistein and daidzein, typical soy isoflavones, inhibit TNF- α -mediated downregulation of adiponectin expression via different mechanisms in 3 T 3-L 1 adipocytes. *Mol Nutr Food Res*. 2012; 56(12): 1783-93.
13. Hashemi HS, Hosseini SA. The effect of moderate intensity endurance training and lipid lowering genistein in Streptozotocin induced diabetic rats. *Journal of Shahrekord University of Medical Sciences*. 2017; 19(1): 10-23. (Persian)
14. Hosseini SA, Ahmadi M, Sharifi A, Shadmehri S, Zar A. The effect of resistance training and genistein on leptin and lipid profile of streptozotocin-induced diabetic rats. *Feyz, Journal of Kashan University of Medical Sciences*. 2018; 22(3): 248-57. (Persian)
15. Hosseini SA, Shojae T, SA. H. The Effect of Cinnamon on Glycemic Index and Insulin Resistance of Streptozotocin Induced Diabetic Rats. *Lorestan University of Medical Sciences Journal*. 2005; 16(4): 70-8.
16. Shojae T, Hosseini S. Reviwe the effect of endurance training on glycemic indexes of streptozotocin induced diabetic rats. *Jahesh Journal*. 2013; 15: 39-46.
17. Rahmati M, Khazani A, Gharakhanlou R, Movaheddin M, Manaheji H. Chronic effects of moderate intensity endurance training on neuropathic pain symptoms in diabetic rats. *Physiology and Pharmacology*. 2013; 16(4): 435-45. (Persian)
18. Šošić-Jurjević B, Filipović B, Ajdžanović V, Brkić D, Ristić N, Stojanowski MM, et al. A Brife cmmunication: subcutaneously administrated genistein and daidzein decrease serum cholesterol and increase triglyceride levels in male middle- aged rats. *Ex Biol Med*. 2007; 232(9): 1222-7.
19. Bałkowiec-Iskra E, Vermehren-Schmaedick A, Balkowiec A. Tumor necrosis factor- α increases brain-derived neurotrophic factor expression in trigeminal ganglion neurons in an activity-dependent manner. *Neuroscience*. 2011; 180: 322-33.
20. Farzanegi P, MohammadZadeh M, Azarbayjani MA. Interactive effect of exercise training with ω -3 supplementation on resting levels of TNF- α and IL-10 in Karat Men. *Journal of Hormozgan University of Medical Sciences*. 2014; 18(1): 26-34.
21. Lee SS, Yoo JH, Kang S, Woo JH, Shin KO, Kim KB, et al. The effects of 12 weeks regular aerobic exercise on brain-derived neurotrophic factor and inflammatory factors in juvenile obesity and type 2 diabetes mellitus. *J Phys Ther Sci*. 2014; 26(8): 1199-204.
22. Taheri Chadorneshin H, Afzalpour ME, Abtahi H, Foadoddini M. Effect of Intense Exercise Training on Hydrogen Peroxide, Tumor Necrosis Factor-Alpha and the Selected Neurotrophins in Rat's Brain. *Quarterly of the Horizon of Medical Sciences*. 2015; 20(4): 231-6.
23. Arslan M, Ipekci SH, Kebapcilar L, Dogan Dede N, Kurban S, Erbay E, et al. Effect of aerobic exercise training on MDA and TNF- α levels in patients with type 2 diabetes mellitus. *Int Sch Res Notices*. 2014; 2014: 820387.
24. Foadoddini M, Afzalpour ME, TaheriChadorneshin H, Abtahi-Eivary SH. Effect of Intensive Exercise Training and Vitamin E Supplementation on the Content of Rat Brain Neurotrophic Factors. *Iran Red Crescent Med J*. 2018; 20(2): e57298.
25. Yousefi H, Alihemmati A, Karimi P, Alipour MR, Habibi P, Ahmadiasl N. Effect of genistein on expression of pancreatic SIRT1, inflammatory cytokines and histological changes in ovariectomized diabetic rat. *Iran J Basic Med Sci*. 2017; 20(4): 423-9.
26. Pan M, Han H, Zhong C, Geng Q. Effects of genistein and daidzein on hippocampus neuronal cell proliferation and BDNF expression in H19-7 neural cell line. *J Nutr Health Aging*. 2012; 16(4): 389-94.
27. Habibi P, Babri S, Ahmadiasl N, Yousefi H. Effects of genistein and swimming exercise on spatial memory and expression of microRNA 132, BDNF, and IGF-1 genes in the hippocampus of ovariectomized rats. *Iran J Basic Med Sci*. 2017; 20(8): 856-62.
28. Imani H, Tabibi H, Atabak SH, Rahmani L, Hedayati M, Neyestani T, et al. Effects of soy consumption on serum lipid and apoprotein levels in peritoneal dialysis patients. *Iranian Journal of Nutrition Sciences & Food Technology*. 2007; 2(3): 33-44.
29. Yousefinejad A, Siassi F, Javanbakht MH, Mohammadi H, Ghaedi E, Zarei M, et al. Effect of Genistein and L-carnitine and Their Combination on

Lipid Profile and Inflammatory Cytokines in Experimental Nephrotic Syndrome. *Rep Biochem Mol Biol.* 2018; 7(1): 1-8.

30. Jourkesh M, Choobineh S, Soori R, Ravasi AA. Effect of combined endurance-resistance training and soy extract supplementation on expression of eNOS gene in ovariectomized rats. *Arch Med Sci Atheroscler Dis.* 2017; 2: e76-e81

31. Orsatti FL, Nahas EAP, Nahas-Neto J, Maesta N, Orsatti CL, Fernandes CE. Effects of resistance training and soy isoflavone on body composition in postmenopausal women. *Obstet Gynecol Int.* 2010; 2010: 156037.

32. Chilibeck PD, Vatanparast H, Pierson R, Case A, Olatunbosun O, Whiting SJ, et al. Effect of exercise

training combined with isoflavone supplementation on bone and lipids in postmenopausal women: a randomized clinical trial. *J Bone Miner Res.* 2013; 28(4): 780-93.

33. Giolo JS, Costa JG, da Cunha-Junior JP, Pajuaba AC, Taketomi EA, de Souza AV, et al. The Effects of Isoflavone Supplementation Plus Combined Exercise on Lipid Levels, and Inflammatory and Oxidative Stress Markers in Postmenopausal Women. *Nutrients.* 2018; 10(4): 424.

34. Bhattamisra SK, Mohapatra L, Panda BP, Parida S. Effect of isoflavone rich soya seed extract on glucose utilization and endurance capacity in diabetic rat. *Diabetol Croat.* 2013; 42(2): 42-52.