Golestan University of Medical Sciences

Jorjani Biomedicine Journal

Online ISSN: 2645-3509

Interactive Effects of Resistance Training and Genistein Consumption on the Levels of VCAM, ICAM and CRP in Diabetic Rats with Streptozotocin

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Article Type:

Original Article

Article History:

Received: 10Oct 2020
Revised: 16 Oct 2020
Accepted: 1 Nov 2020

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DOI: 10.29252/jorjanibiomedj.8.4.54

Abstract

***Background and Objective*:** Reports indicate that over 60% of people with diabetes die from cardiovascular diseases. The present study was conducted to investigate the interactive effects of resistance training and genistein consumption on the serum levels of vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1) and C-Reactive Protein (CRP) in diabetic rats with streptozotocin.

Material And Methods: In this experimental study, 40 diabetic rats were selected and divided into 5 groups of 8 subjects, including: (1) control, (2) sham (dimethyl sulfoxide), (3) resistance training (4), genistein consumption, and (5) resistance training and genistein consumption. Rats in groups 3 and 5 received 8 weeks of resistance training, 3 sessions per week, with 30 to 100% body weight, and rats in groups 4 and 5 received 30 mg/kg of peritoneal genistein per day. Data were analyzed using independent sample t-test and two-way ANOVA in SPSS software ($p \leq 0.05$).

Results: Genistein consumption has a significant effect on reduced serum levels of VCAM and ICAM in diabetic rats ($p \leq 0.05$). Eight weeks of resistance training has a significant effect on reduced serum levels of ICAM and CRP in diabetic rats ($p \leq 0.05$). Resistance training and genistein consumption have interactive effects on reduced serum levels of VCAM and CRP in diabetic rats ($p \leq 0.05$).

Conclusion: Resistance training and genistein consumption simultaneously appear to reduce the risk of atherosclerosis in diabetic rats.

Keywords: Resistance training, Genistein, VCAM-1, ICAM-1, CRP

Introduction

Diabetes is a metabolic disorder characterized by chronic hyperglycemia and a disorder of carbohydrate, fat and protein metabolism due to defective insulin secretion, or both (1, 2). The number of people with diabetes in the world is expected to increase to 22% from 1995 to 2025 (3, 4). Diabetes causes major changes in most of the body's systems, causing immediate or delayed complications. The disease leads to complications such as cardiovascular complications, nephropathy, and so on. Reports indicate that over 60% of people with diabetes die of cardiovascular disease (2, 4). Pathogenesis pathways and diabetes-induced heart damage can separately activate nuclear factor kappa B (NF-KB) as a very important factor in the oxidation system. In previous studies, researchers have pointed out that NF-KB plays an important role in regulating genes involved in cellular responses such as inflammation, cellular immunity, cell growth and cell death (5). Also, C-reactive protein (CRP), as the most important factor, indicates insulin inflammation and glucose metabolism directly or indirectly. Hence, high levels of CRP increase in people with high levels of fat, which reduces insulin sensitivity (6).

Studies have shown that cardiovascular diseases have inflammatory backgrounds. As a result of the onset of vascular inflammation and subsequent activation of endothelial cells and the synthesis of pro-inflammatory proteins such as chemokines, and as a result of an increase in gene expression and the appearance of intercellular adhesion molecules, the atherosclerosis process begins. Hence, one of the most sensitive cell markers in identifying the process of formation of atherosclerotic plaques in the vascular endothelial wall, are intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) (7). Increased adhesion molecules can cause monocytes to enter the endothelium. With the migration of smooth muscle cells in the vascular walls, the fibrous deposition of the fibrous tissue in that area increases, causing extension of the atheromatous plaque. The importance and necessity of preventing cardiovascular diseases to maintain health, has led many researchers to focus on the prevention of these diseases by interventions such as physical activities (8).

Researchers believe that regular physical activity can have a major role in reducing the complications of diabetes, including obesity, hypertension, hyperlipidemia and hyperinsulinaemia, and increased insulin sensitivity (9). Researchers have pointed out in their studies that anti-inflammatory effects of sports activities are likely to be applied by varying the amount of adhesion molecules. Although short-term and unstable sports activities may increase the amount of adhesion molecules, regular rehearsal of these exercises in long term may lead to a reduction in in systemic inflammation. However, there is still insufficient information about the effect of the type of exercise on these factors. Many studies have been conducted on the effect of exercise on fat profile, adhesion molecules and CRP. For example, 10 weeks, three sessions a week, endurance training and resistance training improved lipid profiles and decreased levels of sICAM-1 in obese inactive women (10). Eight weeks, five sessions per week of resistance training had a significant effect on the improvement of lipid profile of diabetic rats with streptozotocin (1). However, 10 weeks, three sessions per week of resistance training and endurance exercises had no significant effect on VCAM-1 and the fat profile of overweight women (8). 12

weeks of resistance training resulted in a significant decrease in the levels of Receptor Advanced Glycation End (RAGE) Products, but did not have a significant effect on gene expression levels of ICAM and VCAM in diabetic rats with Streptozotocin (5). Over the past few years, extensive research has been conducted on the effectiveness of medicinal plants used in traditional medicine in diabetic patients (7). Research on food supplements and herbs used in traditional medicine suggests that the compounds contained in them, including dietary fibers, vitamins, flavonoids, sterols and other antioxidant compounds, can, in addition to lowering blood lipids, inhibit oxidation and remove oxygen-free radicals, and may be effective in improving the immune system and improving metabolic disorders in the body (11).

Genistein is a major isoflavone in soybean herb, whose protective role in the arteries and heart has been proven. Recent studies have looked at the genistein of soybean in the lipid profile of diabetic individuals (12). For example, 10 and 30 mg of genistein had a significant effect on decreasing leptin and improving the fat profile of diabetic rats with streptozotocin (1); genistein and daidzein significantly reduced TNF-α by reducing adiponectin and fat cells and JNK activity (13). Daily consumption of 30 mg/kg body weight of genistein for eight weeks had a significant effect on the improvement of fat profile in diabetic rats with streptozotocin (14). Also, regarding the concurrent use of genistein and sports exercises in animal samples, the positive effects of these two factors on lipid profiles and leptin levels have been reported (1, 14).

Review of literature shows that although exercise and genistein consumption have beneficial effects on diabetes, due to the differences in adaptation between resistance training and endurance training, it seems that the present study can provide researchers with more information about the interactive effect of resistance training and genistein consumption.

Considering the importance of research on atherosclerosis markers and inflammatory factors to reduce the complications of diabetes as well as the lack of sufficient information on the interactive effectives of soy substances such as genistein and resistance training, the aim of this study was to investigate the interactive effects of resistance training and genistein consumption on level of VCAM, ICAM, and CRP in diabetic rats with streptozotocin.

Materials and Methods

Subjects

In this experimental study, 48 adult Sprague Dawley male rats from the Animal Breeding Center located at the House of Animals at the Islamic Azad University of Marvdasht Branch were purshased and took a part as the study animals in this study. All rats were transferred to the animal storage room at the physical exercise laboratory (ambient temperature of 22 ± 2 ºC, controlled light (12-hour cycle of light and dark), and went through eight-day adaptation period. During the course, the animal's access to water and food was free. On day 8, after an overnight fasting, rats were anaesthetized with chloroform and subjected to intraperitoneal injection of 60 mg/kg streptozotocin (manufactured by the Sigma Company) dissolved in a citrate buffer with pH 7.4. Four days after injection, blood samples were collected from animals' tail by punching, using a glucometer. Rats with blood glucose greater than 300 mg/dl were entered as subjects (15). The onset of a training program was conducted one week after induction of diabetes and maintenance of

the rats. Based on blood glucose, diabetic rats were randomly assigned into 5 equal groups of 8 subjects, including (1) Diabetic control, (2) sham (dimethyl sulfoxide), (3) resistance training, (4) genistein, and (5) resistance training with genistein consumption.

Also, in order to investigate the effects of diabetes induction on the research variables, 8 rats were placed in the healthy control group.

It's worth mentioning that genistein was manufactured by Hangzhou Dingyan Cem Co., Ltd. with Batch No 20151105. Groups 4 and 5 received 30 mg/kg peritoneal genistein daily for eight weeks (16). It is also worth noting that all ethical and legal aspects of this research were reviewed and approved at Islamic Azad University, Marvdasht Branch (IR.MIAU. REC.1396.123).

Resistance training protocol

To familiarize the rats with resistance training and how to climb the ladder, each one was placed on the lowest ladder staircase and trained to climb the ladder without connecting the weights and by placing their hind legs on the stairs.To force the rats to move on the ladder while standing on a ladder staircase and stopping by touching the tail and creating sound simultaneously, they were conditioned and continued to move. An initiation program was performed by climbing the ladder for one week and every other day, and each session, three to four repetitions without weight connection were performed. The resistance training protocol consisted of eight weeks of climbing a ladder to a height of one meter, the distance between each of the steps of four centimeters and the vertical slope. Before the start of the training program in each session, the rats went up three repetitions without weight and without rest between the repetitions to warm up the ladder. The weight selected at the beginning of the training was 30% of the body weight of the rats and increased to 100% in the last week. The training protocol was that the weights were examined by a leukoplast adhesive before the rats' tail sensitivity to this type of adhesive; and for training, the weight were connected to the rats' beginning of the tail.

The rats performed two repetitions with each attached weight. Then a new weight was added to their tail. The training load consisted of 50, 75, 90 and 100 percent of the highest weight that the rats managed to raise from the ladder. At the last session of each week of training, after the training program of the relevant session and rest of the rats, the maximum weight that rats were able to raise was marked. So that as the weight of the last repetition was added, it continued until the rats were not able to lift the weights anymore (17).

Measure the VCAM, ICAM and CRP

The measurement of the amount of VCAM, ICAM and CRP was done using the Zellbio trade company's kit manufactured in Germany by the ELISA method.

Statistical analysis

The Shapiro-Wilk test was used to investigate the normal distribution of the data. Inferential analysis of data was done using One-way ANOVA and two-way ANOVA, at significant level of 0.05 and using SPSS software.

Result

The mean and standard deviation of the serum levels of the variables of the research are presented in Fig 1-3. Independent sample t-test was used to investigate the effects of genistein solvent on the variables of the study.

The results of Tukey's post hoc test showed that serum levels of VCAM (P = 0.001),

ICAM (P = 0.001) and CRP (P = 0.001) in the control diabetic and sham groups were significantly higher than the healthy control group. There was also no significant difference in the serum levels of VCAM (p = 0.73) and CRP (p = 0.11) in the control diabetic and sham groups.

However, serum levels of ICAM (p = 0.006) in the sham group were significantly lower than the Diabetic control group.

To investigate the interactive effects of resistance training and genistein on the research variables, the results of two-way analysis of variance (ANOVA) showed that genistein consumption had a significant effect on the reduction of serum levels of VCAM in diabetic rats (P = 0.005, and F = 9.19, effect size =0.24), but eight weeks of resistance training did not have a significant effect on serum levels of VCAM in diabetic rats (p = 0.24, F = 1.38, and effect size = 0.04), however, resistance training and genistein consumption had interactive effects on the reduction of serum VCAM in diabetic rats (p = 0.001, F = 13.67, and effect size= 0.32) (Fig 1).

Genistein consumption (p = 0.04, F = 4.18, and effect size =0.12), and resistance training (p = 0.001, F = 19.52, and effect size = 0.40) had a significant effect on serum levels of ICAM in diabetic rats, but eight weeks of resistance training and genistein consumption had no interactive effect on decreasing ICAM serum levels in diabetic rats (P = 0.27, F = 1.25, and effect size = 0.04) (Fig 2).

Genistein consumption had no significant effect on serum levels of CRP in diabetic rats (p = 0.058, F = 3.18, and effect size = 0.11); however, eight weeks of resistance training had a significant effect on the reduction of serum levels of CRP in diabetic rats (p = 0.001, F = 33.85, and effect size =0.53). Also, eight weeks of resistance training and genistein consumption had interactive effects in reducing serum levels of CRP in diabetic rats (p = 0.04, F = 4.29, and effect size= 0.12) (Fig 3).

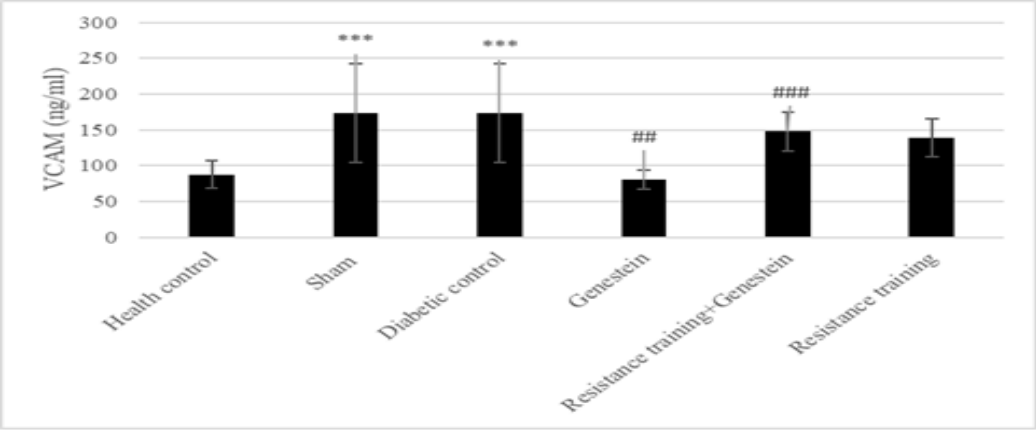

Figure 1: The result of One and Two-way analysis of variance (ANOVA) to investigate the interactive effects of resistance training and genistein on serum levels of VCAM
*** (p≤0.001) Increases serum levels of VCAM Sham and Diabetic control compared to Health control group
(p≤0.001), ## (p≤0.01) Reduction serum levels of VCAM in genistein and Resistance training + genistein groups compared to Diabetic control group

It can be concluded that resistance training modulated the effect of genistein in reducing serum levels of VCAM

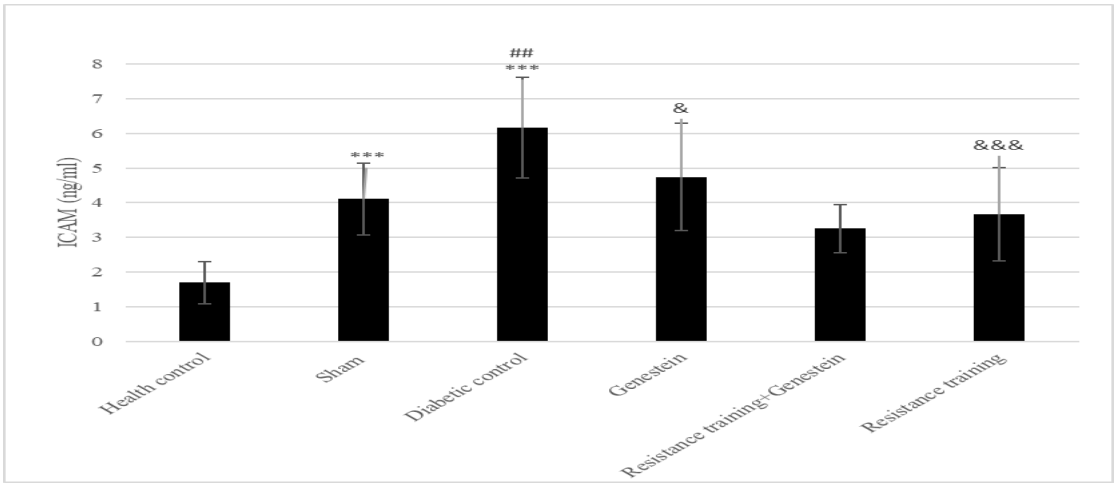

Figure 2: The result of One and Two-way analysis of variance (ANOVA) to investigate the interactive effects of resistance training and genistein on serum levels of ICAM
*** (p≤0.001) Increases serum levels of ICAM Sham and Diabetic control compared to Health control group
##(p≤0.01) Increases serum levels of ICAM in c Diabetic control group compared to Sham group.
& (p≤0.05), &&& (p≤0.001) Reduction serum levels of ICAM in genistein groups and Resistance training groups compared to Control group.

It can be concluded that resistance training and genistein consumption do not have an interactive effect on reducing serum levels of ICAM.

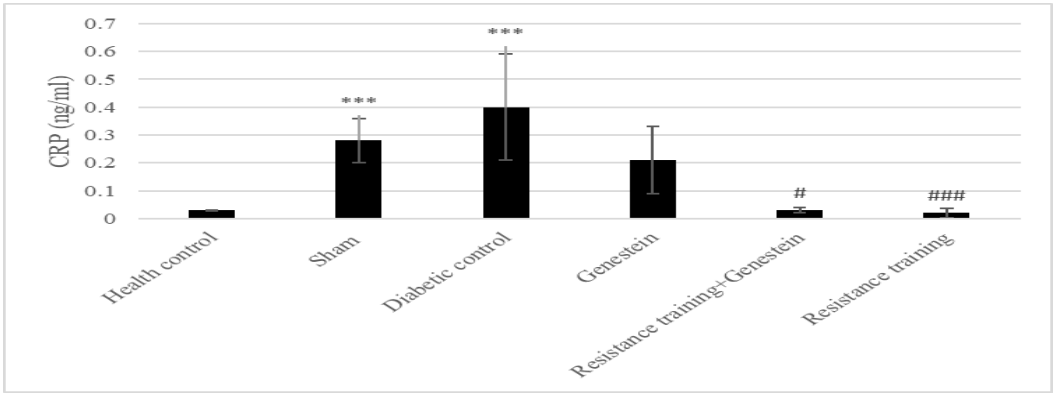

Figure 3: The result of One and Two-way analysis of variance (ANOVA) to investigate the interactive effects of resistance training and genistein on serum levels of CRP
*** (p≤0.001) Increases serum levels of ICAM Sham and Diabetic control compared to Health control group
# (P≤0.05), ### (p≤0.001) Reduction serum levels of CRP in Resistance training groups and Resistance training + genistein group compared to Diabetic control group.

Based on the results of two-way analysis of variance, it can be concluded that genistein consumption has modified the effect of resistance training, however, resistance training and genistein consumption interactively reduce serum levels of CRP.

Discussion

The results of this study showed that genistein consumption has a significant effect on the reduction of serum levels of VCAM and ICAM in diabetic rats, but does not have a significant effect on serum levels of CRP in diabetic rats with streptozotocin. Researchers believe that diabetic patients face problems such as cardiovascular risk factors, including

hypertension and impaired fat profile, which a total of these risk factors is known as metabolic syndrome (18). Inflammation is known to be a potential risk in the onset of atherosclerosis, and sudden death due to heart attacks and diabetes (19). Evidence suggests the effect of cellular and vascular adhesion molecules on the evolution of atherosclerosis. The connection of blood cells to the arterial surface is one of the first events in the diagnosis of atherosclerosis (20). Increased blood glucose levels in diabetic patients have been reported to increase serum levels of ICAM-1, VCAM-1 and CRP (6). Cell damage in diabetes and the development of insulin resistance are closely related to the presence of oxidative stress in the cell. Oxidative stress is likely to increase the risk of diabetes directly by reducing insulin sensitivity and destruction of insulin producing cells and degradation of pancreatic cells. Also, oxidative stress can be incrementally and actively involved in the production of systemic inflammation and increased levels of pro-inflammatory cytokines (21). Most researchers believe that elevated cholesterol, neutrophil accumulation and hypoxia in the cell will result in the production of inactive IL-1β formulation, and inactive IL-1β with caspase-1 interfering into an active form of IL-1β results in IL- 6 as well as CRP (22). Nevertheless, genistein isoflavone via cAMP /PKA increases the production of NOS and NO from non-genomic pathways. The c-AMP central molecule has many messaging pathways and plays an important role in maintaining the vascular function. The pathway activity of cAMP/PKA causes endothelial nitric oxide phosphorylation, which results in its activity and thus the production of NO. In addition, the activation of the pathway of cAMP/PKA inhibits vascular inflammation by suppressing the adhesion of leukocytes to endothelial cells and thus decreasing ICAM-1 and VCAM-1 (23, 24). Genestein also reduces weight, through a protein-based diet, increases the mass of pancreatic beta cells and increases serum insulin levels in diabetic disease, and subsequently facilitates the transfer of glucose to the cell wall; following the reduction in weight and reduced fat mass, the reduction of pro-inflammatory factors from the Nf-kB signaling pathway can be pointed. Genistein results in reducing the production of CRP via inhibiting the inhibitory protein of IκBα (Inhibitor of NF-κB alpha), increasing the phosphorylation of IKK (an enzyme which inhibits the protein IκB), and the phosphorylation of IL-1β receptors (25, 26). In confirmation of the findings of the present study, eight weeks of taking one mg / kg of body weight of genistein had a significant effect on the reduction of Nf-kB and IL-1β in ovariectomized rats and overariectomized and diabetic rats with full food fatty regime and STZ (25). Daily consumption of 30 mg per kg of body weight of genistein for eight weeks had a significant effect on the improvement of fat profile in STZ-diabetic rats, thus reducing low density lipoproteins and low density lipoprotein and cholesterol can reduce inflammation (14). Also, in line with the current study, the researchers showed that the use of genistein reduced the expression of ICAM-1 and VCAM-1 levels in endothelial cells of humans (27, 28); six months of genistein consumption at an amount of 30-54 mg / dl per day showed no significant effect on the reduction of CRP levels in women with menopause (29). On the other hand, studies have shown that consumption of soy and its products to improve inflammatory factors is dosage-dependent. Regarding the relationship of inflammation and its role in the adhesion of leukocyte cells in endothelial cells,

controversial results were reported on the dosage (23, 24).

The results showed that eight weeks of resistance training had a significant effect on the reduction of serum ICAM and CRP levels and a non-significant decrease in VCAM in diabetic rats; inflammation is known as an indirect risk factor in increasing arteriosclerosis and sudden death due to heart attacks and diabetes (18). However, sports activities seem to be inhibiting inflammatory mediators from adipose tissue by increasing anti-inflammatory cytokines; in fact, sports activities enhance antioxidant defense and reduce free radicals, and hence can lead to a reduction in the inflammatory indices (6, 8). Also, sports activities can reduce the levels of VCAM, ICAM and CRP in the bloodstream by reducing the production of cytokines in adipose tissue, muscle and mononuclear cells, and indirectly by increasing insulin sensitivity and improving endothelial function. Studies have shown that increased caloric intake can lead to a reduction in CRP in several ways, including weight loss (30). Physical activity may be effective in modulating vascular inflammation by modulating effective mechanisms for regulation of adhesion molecules such as renin angiotensin system and reducing the release of chemical intermediates and pro-inflammatory copies such as Nf-kB. Inhibitory NF-KB is present in the cytoplasm in inactive mode, and mediates the onset of endothelial activity by intermediaries and the translation of ICAM-1 (31). In addition, angiotensin-2 by stimulating NADPH oxidase, increases the incidence of ICAM-1 (32). Each of the above-mentioned mechanisms can partly justify the changes in the concentration of adhesion molecules. Also, sports activity, on the one hand, improves antioxidant defense of the endothelial and blood, and inhibits nitric oxide destruction by active oxygen particles; and on the other hand, by increasing the production of nitric oxide by endothelial cells, and as a result of vessel tuning, platelet aggregation is controlled, and the level of adhesion of the mediators to the vascular wall is controlled, thereby modifying endothelial activity and general inflammation (33). However, the mechanism of resistance training to reduce inflammation is not well defined. In line with the current study, the researchers stated that resistance training with different intensities reduced the levels of CRP and HS-CRP in young men (34), and diabetic and non-diabetic rats (35); eight weeks of moderate and high intensity endurance training reduced serum levels of ICAM-1 and insignificantly decreased the serum levels of VCAM and CRP in diabetic rats (6). Eight weeks of endurance training and high intensity interval training also reduced the serum levels of ICAM-1 and VCAM-1 in obese men, while in normal weight group only VCAM-1 was significantly reduced after endurance training (36); eight weeks of resistance training significantly decreased the serum levels of ICAM-1 and CRP. However, eight weeks of resistance training did not significantly reduce serum levels of VCAM-1 in diabetic rats (37). In addition, resistance and endurance training significantly decreased ICAM-1, VCAM-1 and CRP levels in old obese women (38, 39). On the other hand, inconsistent with the current study, aerobic exercise and weight loss had no significant effect on ICAM-1 and VCAM-1 changes in obese women (40). The reasons for the inconsistency of this study with the current study can be seen in the differences in the population and the statistical sample, as well as the differences in the initial levels of research variables. Eight weeks, three sessions and 40 minutes of endurance training

for each session with an intensity of 75% of maximum heart rate did not have a significant effect on the levels of VCAM-1 in middle-aged women (41). Among the reasons of inconsistency of this study with the present study can be the difference in the type, intensity and training in two studies. Also, 12 weeks of resistance training did not have any significant effect on ICAM-1 and VCAM-1 changes in type 2 diabetic rats (5). The reasons for the inconsistency of this study with the present study are the differences in the intensity of training and the differences in animal modeling.

Also, the results of the present study showed that resistance training and genistein consumption had interactive effects on the reduction of serum levels of VCAM and CRP in diabetic rats. However, the interaction of resistance training and the consumption of genistein in reducing serum levels of ICAM was not significant. Regarding the interactive effects of genistein consumption and exercise training on adhesion molecules, no study was found, however, many researchers have investigated the interactive effect of training and the consumption of genistein. For example, eight weeks of resistance training and concurrent consumption of 10 and 30 mg / kg of genistein had interactive effects on reducing leptin and improving the lipid profile of diabetic rats with streptozotocin (1); also, endurance training and consumption of 30 mg/kg of body weight of genistein had a significant effect on the improvement of lipid profile (14) and decreased serum levels of VCAM, CRP, brain-derived neurotrophic factor (BDNF) and tumor necrosis factor-α (TNF-α) in diabetic rats with streptozotocin (6, 24, 42). Studies show that resistance training and genistein consumption in the present study have been able to inhibit vascular inflammation by suppressing the adhesion of leukocytes to endothelial cells and thus reduce ICAM-1 and VCAM-1 via cAMP/PKA (23, 24) signaling pathway activation, decreasing Nf-kB (32, 35), Due to the influence of inflammatory factors such as Nf-Kb on the increase of adhesion cells, it seems that failure to measure this factor is considered as one of the limitations of the present study. Therefore, it is suggested that in future studies, for further information on the interactive effects of exercise and genistein, this factor should also be measured alongside the adhesion cells. Regarding the use of different drugs such as insulin and metformin in diabetic patients, it seems that the lack of control of drug interventions is another limitation of this study. Therefore, in future studies, it is suggested that groups should be considered to control other factors affecting physiological factors in diabetic patients in order to make such research more practical. Also, due to the effect of genistein solvent on VCAM levels, it seems that one of the limitations of the research is the effect of dimethyl sulfoxide on the variables of the research. Therefore, it is recommended in future studies to investigate the effect of this solvent on the standard amount of adhesion molecules in rats.

Conclusion

Resistance training and genistein consumption simultaneously appear to reduce the risk of cardiovascular disease and atherosclerosis in diabetic rats. However, further studies in this area are necessary. It is also recommended to conduct such studies in human samples with seamless cautiousness.

Acknowledgments

The author would like to express her heartiest thanks and gratitude to all individuals who cooperated with conducting the current research study.

Conflict of interest

There are no conflicts of interest for the authors.

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How to cite:

Pouranfar S, Azarbaijani M.A, Abedi B. Interactive Effects of Resistance Training and Genistein Consumption on the Levels of VCAM, ICAM and CRP in Diabetic Rats with Streptozotocin. Jorjani Biomedicine Journal. 2020; 8(4): 54-66.