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The Effect of Eight Weeks of Endurance Training with Royal Jelly Consumption on Oxidant-Antioxidant Markers of the Left Ventricle of Orectomized Rats with Diabetes

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ABSTRACT

Introduction: The simultaneous effect of endurance training (ET) and Royal Jelly (RJ) consumption on left ventricular oxidant-antioxidant markers as an important functional part of the heart is still not well known. Therefore, the aim of our study was to investigate the effect of eight weeks of ET and RJ on the levels of Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx) and Malondialdehyde (MDA) in the left ventricle of orectomized rats with diabetes (OVXD).

Methods: In this experimental study, 30 OVXD female rats aged 12-16 weeks and weighing 220-250 grams were divided into (1) OVXD control, (2) sham, (3) RJ, (4) ET and (5) ET+RJ groups. Also, 6 rats were included in the healthy control group (HC). Groups 4 and 5 trained five sessions a week with 55-75% of maximum running speed for eight weeks; Groups 3 and 5 received 100 mg/kg/day RJ by intraperitoneal injection.

Results: GPx and MDA values in RJ, ET and ET+RJ groups were significantly higher than OVXD group (P≤0.01). SOD levels in RJ groups were significantly higher than OVXD group (P≤0.01). Also, GPx values in RJ group were significantly higher than ET group (P≤0.01).

Conclusion: It seems that ET and RJ can reduce lipid peroxidation in the left ventricle of the heart in OVXD rats. RJ administration either alone or simultaneously with ET can have antioxidant effects, but the effect of exercise depended on the duration of the exercise period. Therefore, RJ consumption along with sports exercise can be recommended in menopause and diabetes.

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Introduction

Metabolic syndrome is a type of multifactorial disorder and is one of the most important reasons for reducing the quality of life in elderly men and women. So that in menopause, due to the malfunction of the estrogen hormone in women, with an increase in weight and visceral fat, fat metabolism disorders occur, and this factor itself leads to impaired insulin function, diabetes, increased blood pressure, and the occurrence of cardiovascular disorders. (1). Also, studies show that the malfunction of estrogen, the occurrence of disturbances in fat metabolism is caused by the mechanism of increasing inflammatory factors in mitochondrial function, which is caused by the increase of reactive oxygen species (ROS) and its markers such as Malondialdehyde (MDA). and Carbonyl Protein (PC) as well as a decrease in antioxidant system function with its markers such as Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx) and Total Antioxidant Capacity (TAC) in various organs such as brain, kidney and heart (2,3). Also, studies show that the malfunction of estrogen, the occurrence of disturbances in fat metabolism is caused by the mechanism of increasing inflammatory factors in mitochondrial function, which is caused by the increase of Reactive Oxygen Species (ROS) and its markers such as Malondialdehyde (MDA). and Carbonyl Protein (PC) as well as a decrease in antioxidant system function with its markers such as Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx) and Total Antioxidant Capacity (TAC) in various organs such as brain, kidney and heart (2,3). In this context, researchers in a study showed that oxidative stress markers in women with menopausal metabolic syndrome are

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morehealthier than menopausal women, and these people are more at risk of cardiovascular diseases (2).

Considering the increase in the age of the population in the world and the increase in the number of people susceptible to these diseases, as well as due to the lack of information and appropriate solutions to prevent the risks of menopause and diabetes, researchers have stated that regular exercise have favorable effects on improving the quality of life of elderly, menopausal and metabolic disease women (4); So that regular exercise leads to improvement of fat profile and sugar indices (5), reduction of inflammatory factors and improvement of mitochondrial biogenesis (6) in animal models with metabolic disorders. Also, exercise led to an increase in serum catalase and GPx levels in orectomized rats (7). On the other hand, considering the speed of progression of cardiovascular disorders in menopause and metabolic disorders, researchers have believed that, it is necessary to provide more complete solutions that can be more effective in a shorter period of time. Therefore, the use of natural antioxidants along with sports activities is recommended by researchers (8). Among these antioxidants, Royal Jelly (RJ), which is secreted from the submandibular glands of the worker bee, is known as an antioxidant that can be effective in reducing oxidative stress by increasing enzymatic and non-enzymatic antioxidants(9). In addition, researchers have shown that the use of Royal Jelly in different doses can improve liver metabolism and reduce oxidative stress in the liver tissue of orectomized rats (10). Also, in another study, researchers have shown that RJ consumption can lead to increased GPx, SOD and reduced cell damage by modulating Cyclooxygenase-2 (COX-2), improving cell metabolism, reducing ROS (11). However, studies have been conducted on the simultaneous effect of exercise and RJ consumption; For example, aerobic training with different doses of RJ led to a decrease in visceral fat weight, aerobic capacity and calorie consumption in rats with experimental autoimmune encephalomyelitis (12). Also, Endurance Exercise (ET) along with RJ consumption, increased the angiotensininhibitor converting enzyme-1 (ACE-1), nitric oxide, vascular endothelial growth factor (VEGF) in the heart tissue of rats with high blood pressure (13).

Despite the increasing interest of researchers in the use of antioxidants in addition to sports activities, it seems that there is still not enough information in this field, especially considering the importance of oxidative stress in the occurrence of cellular disorders in menopause and diabetes. It seems that obtaining more information on the simultaneous effect of ET and RJ on oxidant-antioxidant markers in left ventricular tissue is essential for researchers and patients. Therefore, the aim of this study was to investigate the effect of eight weeks of ET and RJ on MDA, SOD and GPx in the left ventricle of orectomized rats suffering from diabetes.

Methods

In this experimental study, 38 female Sprague-Dawley rats with an average age of 14 ± 0.2 weeks and a weight of 230 ± 20.00 grams were prepared and acclimatized for one week in the Sports Physiology Laboratory of Azad University. They were kept in unit of Marvdasht. In line with the ethical principles of working with laboratory animals throughout the research period, rats were kept under standard conditions according to the Helsinki Convention in terms of ambient temperature (22-24°C), light-dark cycle (12 to 12 hours), relative humidity (55 -60 percent) were kept in washable polycarbonate cages. In addition, special rat food was used for feeding. Also, during the period, access to water and food was free for the animals. It is worth noting that the ethical principles of working with animals were done. After seven days of compatibility with the environment, the rats underwent surgery in order to induce menopause the rats underwent surgery. For this purpose, rats were anesthetized with a solution of 50 mg/ml ketamine and 20 mg/ml xylazine. Then a gap of 3 cm was created on the white line in the middle of the abdomen. After observing the internal organs and tissues, the ovaries were separated with surgical scissors. Then, the corresponding gap was sewn with a single simple suture pattern with 3 zero vicryl thread and animal skin with 2 zero nylon surgical thread. OTC antiseptic solution was used to prevent infection at the surgical site. After the surgery, in order to ensure the lack of estrogen secretion and its effect on different tissues, the animals were kept under controlled conditions for three months. Next, to induce diabetes, the samples were subjected to a single peritoneal injection of Streptozotocin (STZ) 40 mg/kg, and

4 days after that, to ensure the induction of diabetes, blood glucose levels were measured and rats with sugar levels higher than mg/kg dl 250 were studied as ovarectomized rats with diabetes (OVXD) (14). In the process of conducting the present research, two rats died due to different effects of surgery and STZ, which reduced the total number of rats to 36. Then 30 OVXD rats were divided into (1) OVXD, (2) sham (Sh), (3) Royal Jelly (RJ), (4) endurance training (ET) and (5) ET+RJ. Also, in order to investigate the effect of orectomy and induction of diabetes, 6 healthy rats were included in the healthy control group (HC).

Endurance Training Protocol

"By using the treadmill to evaluate the maximum running speed, after 7 days of working with it (speed 8 m/min for 10 minutes a day), the rats were warmed up for 5 minutes at a speed of 5 m/min; Then, for each minute, 1 m/min was added to the speed. It was done until the rats were no longer able to run, so that the rat can hit the end of the treadmill three times in a row in less than one minute. Finally, based on this test, the speed and intensity of this test was designed." (15). Then the endurance training of rats for the first week at a speed of 20 m/min (55% of the maximum running speed) ran on the treadmill for 15 minutes, then in the second to fourth week, 10 minutes per week for the training time and the running speed was increased by 2 meters per minute until the time reached 45 minutes at a speed of 26 meters per minute in the fourth week. After that the training intensity did not change and only the training time was increased by 4 minutes per week until the training time in the eighth week should reach 60 minutes. In other words, the training intensity in the eighth week was equal to 55 to 75% of the maximum running speed. In the present research, the training was done for eight weeks, five sessions a week, and 5 minutes at the beginning and at the end of the training at an intensity of 50-55% of the maximum running speed was also considered as a cool-down and warm-up (15).

Royal Jelly Consumption

For RJ supplementation, 300 mg of RJ in every day was dissolved in 3.6 ml of normal saline for injection and 0.3 ml of RJ dissolved in normal saline was injected intraperitoneally to each mouse. The injection of this amount of solution was equivalent to 100 mg/kg in a day (13).

Sampling

48 hours after the completion of the protocol, the rats were anesthetized with Ketamine and Xylazine solution after 12 hours without food. After making sure of unconsciousness by foot pressure and slow abdominal shock reaction tests, the chest cavity of the rats was split and after discarding other tissues, the heart tissue was carefully extracted and after cutting the extra parts such as the right ventricles, right atrium, and left atrium, the remaining part, which was the left ventricle, was immersed in a nitrogen tank and then kept at -80 temperature until the variables were measured.

SOD, GPx and MDA Measurement Method

GPx values were measured using ELISA method with its dedicated diagnostic kit. This kit made by Navand Lab Kit (Version 0.8.1 Last updated 26 May 2019) made in Iran was measured with MU/ml scale. SOD values were measured using ELISA method with its specific diagnostic kit. This kit made by Navand Lab Kit company (Version 0.6 Last updated 15 February 2019) made in Iran was measured with U/ml scale.Also, MDA values were measured using a special MDA ELISA kit manufactured by ZellBio GmbH (Germany) with economic code ZB-MDA-96A and with μM scale.

Statistical Data Analysis Method

First, Shapiro-Wilk test was used to check the normality of data distribution.Considering the normality of the distribution of the findings, one-way analysis of variance was used to investigate the difference between groups, and Tukey's post hoc test was used to determine the location of the difference between groups.Data analysis was done using GraphPad Prism 8.3.3 software ($P \geq 0.05$).

Results

The results of the one-way analysis of variance test showed a significant difference in the values of SOD (P=0.001), GPx (P=0.001) and MDA (P=0.001) in the left ventricular tissue of rats in the groupson research.

The results of Tukey's post hoc test showed that SOD levels in the OVXD (P=0.001) and Sham (P=0.001) groups were significantly lower than the HC group;However, no significant difference was observed in the OVXD and Sham groups (P=0.99), however, it was significantly higher in

the RJ groups (P=0.007) than the OVXD group (Figure 1).

GPx values in OVXD (P=0.007) and Sham (P=0.03) groups were significantly lower than HC group; But no significant difference was observed in OVXD and Sham groups (P=0.98). However, in the RJ (P=0.001), ET (P=0.0013) and ET+RJ (P=0.007) groups, it was significantly higher than the OVXD group. In addition, GPx values in the RJ group were significantly higher than the ET group (P=0.007) (Figure 2).

MDA values in OVXD (P=0.001) and Sham (P=0.001) groups were significantly higher than HC group.No significant difference was observed in OVXD and Sham groups (P=0.99).But in the RJ (P=0.001), ET (P=0.001) and ET+RJ (P=0.001) groups, it was significantly higher than the OVXD group (Figure 3).

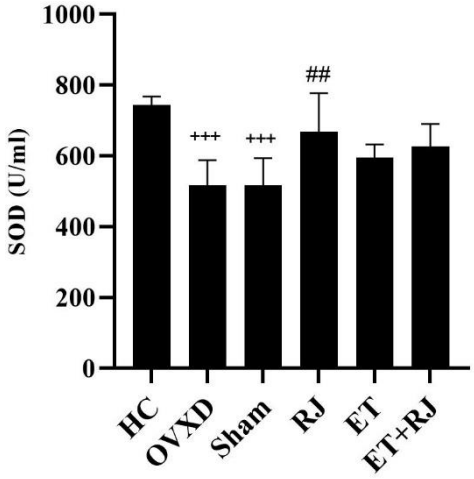

Figure 1. SOD levels in the left ventricle of orectomized diabetic rats
+++ (P≥0.001) significant decrease in OVXD and Sham groups compared to HC group
(P≥0.01) significant increase in RJ group compared to OVX and Sham groups

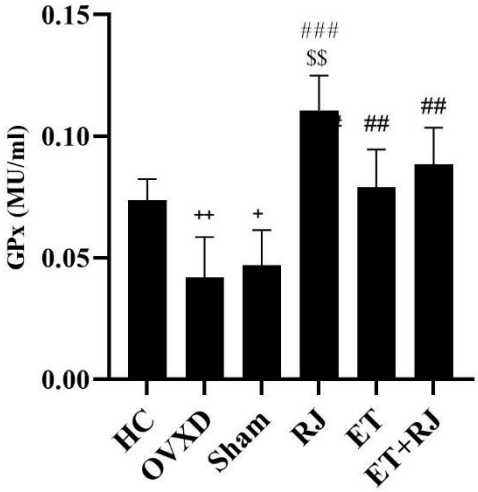

Figure 2. GPx values in the left ventricle of orectomized diabetic rats
++ (P≥0.01) and (P≥0.05) significant decrease in OVXD and Sham groups compared to HC group
(P≥0.001) and ## (P≥0.01) significant increase in RJ, ET and ET+RJ groups compared to OVX and Sham groups
$$ (P≥0.01) significant increase in RJ group compared to ET group

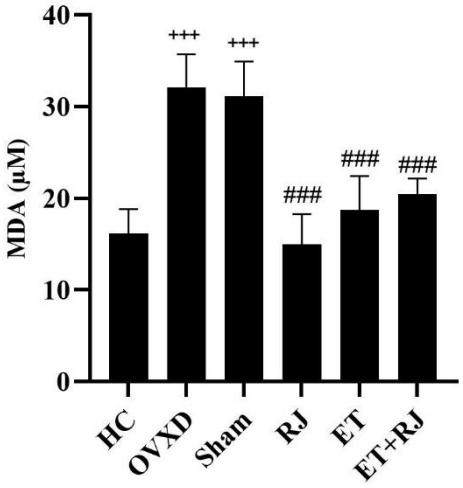

Figure 3. MDA values in the left ventricle of orectomized diabetic rats
+++ (P≥0.001) significant increase in OVXD and Sham groups compared to HC group
(P≥0.001) significant decrease in RJ, ET and ET+RJ groups compared to OVX and Sham groups

Discussion

The results of the present study showed that GPx values were significantly higher and MDA values were significantly lower in the left ventricular tissue of the ET group than the OVXD group. It is believed that regular and long-term exercises increase the metabolism of fats by increasing the efficiency of mitochondria; In addition, after exercise, the increase in catecholamines leads to an increase in annular adrenosine monophosphate (cAMP) and an increase in AMP-activated protein kinase, which leads to the phosphorylation of nuclear respiratory transcription factor 1 and 2 (NRF1/2) and The activation of this protein by binding to the DNA promoter leads to the transcription of catalase, SOD and GPx (16,17). In addition, the increase in oxidative resistance in the cell seems to occur faster than the activation of antioxidant transcriptional pathways (18). In confirmation of this, the researchers showed that the amount of reduced glutathione compared to hydrogen peroxide did not increase with aerobic exercise, and even after exercise, the ratio of GSH/GSSG decreased. Also, the high SOD values were not dependent on the exercise factor, so that no significant difference was observed in the training and non-training groups. Also, MDA values did not change significantly (18). Therefore, it seems that with long training sessions, more adjustments occur in the oxidant-antioxidant system. In line with the present study, the researchers showed that aerobic exercise on the treadmill increased GPx and decreased MDA in the left ventricle of rats after myocardial infarction, but the increase in catalase levels was not significant (19). Also, in another study, researchers showed that exercise training for 12 weeks increased GPx, SOD, and nitric oxide; In addition, in this research, the researchers observed physiological hypertrophy in the left ventricle, which occurred following exercise in the ventricle (17). In addition to the adaptations mentioned, the researchers believe that the oxidative stress caused by training sessions due to the increase in lipid peroxidation during exercise, the increase in ROS itself is known as a pathway to create long-term adaptations. So that the oxidative stress following exercise can lead to the activation of endothelial nitric oxide synthase (eNOS) to increase angiogenesis, mitochondrial biogenesis in blood vessels and ultimately increase antioxidant capacity (20). Therefore, in antioxidant adaptations in the cardiovascular system to sports training, more dimensions need to be investigated. In addition, sports exercises in our research have antioxidant effects and reduce oxidative stress with the mentioned mechanisms. The results of this research showed that SOD and GPx values were significantly

higher in RJ group and MDA values were significantly lower than OVXD group. RJ or its main ingredient called 10-hydroxy-2-decanoic acid, due to having high amounts of high-density lipoproteins, can reduce cholesterol and low-density lipoproteins, and this factor can improve the metabolism of fats and sugars leads to a decrease in MDA levels (21). In addition, these studies show that RJ by modulating the amount of hemoxygenase-1 (HO-1) leads to an increase in NRF2 in cardiomyocytes, and by increasing the expression of GPx, catalase and SOD, it leads to the decomposition of free radicals and ultimately to the reduction of MDA levels in the heart tissue (22). In this context, researchers showed that consumption of Royal Jelly increased the expression of NRF-2, HO-1, increased SOD, GPx and catalase, as well as decreased MDA in the heart tissue of rats fed a high-fat diet (22). In another study, researchers showed that 85 mg/kg dissolved in normal saline had favorable effects on increasing SOD, catalase, GPx, reducing MDA, C-reactive protein (CRP), and improving lipid profiles in the liver tissue of rats exposed to cadmium(9). In addition, 200 and 400 mg/kg/day led to an increase in SOD, catalase and GPx, as well as a decrease in apoptotic and inflammatory genes in rats with solid tumors (23). Therefore, it seems that RJ is effective in the oxidant-antioxidant balance of the cell through various non-enzymatic antioxidant pathways and the activation of gene expression pathways of antioxidant enzymes. Also, the results showed that in the ET+RJ group, GPx values were significantly higher and MDA values were significantly lower than in the OVXD group. In addition, GPx values in the RJ group were significantly higher than the ET group. Studies show that endurance training with the mechanism of increasing mitochondrial efficiency, improving fat metabolism, activating the cAMP/ampk/NRF2 pathway as well as activating the eNOS/VEGF/NRFs pathway leads to the transcription of catalase, SOD, GPx(16,17) increasing angiogenesis, mitochondrial biogenesis in vessels and ultimately reducing MDA (20). Also, RJ reduces cholesterol, low-density lipoproteins (21). Modulation of HO-1, increase of NRF2 lead to increased expression of GPx, catalase, SOD, decomposition of free radicals and ultimately decrease of MDA levels in heart tissue (21,22).In the context of the simultaneous effect of exercise and RJ on metabolic disorders, researchers have stated that ET and RJ simultaneously lead to an increase in NRF2, HO-1, SOD, GPx and catalase, as well as a decrease in MDA in cardiomyocytes of rats fed a high-fat diet(22). Also, visceral fat weight, aerobic capacity and caloric intake were improved following ET and RJ in an experimental autoimmune encephalomyelitis model (12). It was also mentioned in Omidi et al.'s study that aerobic exercise and RJ increased NO and ACE-I as markers of cardiovascular risk in rats exposed to high blood pressure (13). It seems that the transcriptional mechanisms of antioxidant enzymes (NRF-1/2) and cardiovascular risk markers such as angiotensin-2 and endothelin-1 are important for a better understanding of left ventricular function to detect the effectiveness of these two interventions. And in this research, not measuring them was one of our limitations. Therefore, it is suggested to investigate different aspects of the cellular molecular pathways of antioxidants in future studies. Also, not measuring the diameter of the left ventricular wall, not investigating the type of left ventricular hypertrophy in this study was one of our other limitations. Therefore, it is suggested to evaluate the level of cellular oxidation and anatomical changes of the heart tissue in future studies with pathological examinations.

Conclusion

It seems that endurance training and consumption of Royal Jelly have the effects of increasing antioxidants and reducing lipid peroxidation. However, considering the role of time in the adaptation caused by endurance training, it seems that Royal Jelly has stronger effects onIt has the expression of some antioxidants. In addition, exercise and RJ consumption simultaneously have favorable effects on the antioxidant system in the left ventricle of orectomized rats with diabetes. Therefore, according to the evidence and human and animal studies, it is recommended for this community to use an antioxidant such as Royal Jelly along with exercise.

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