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Aerobic Exercise Improves Cardiac Biomarkers in an Obese Rat Model Induced by High-Fat and Fructose Diet Via Nuclear Factor Erythroid 2/ Protein P21/Oxidation Resistance Protein Pathway

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ABSTRACT

Background: Obesity is considered as a major risk factor for chronic diseases such as cardiovascular dysfunction. The aim of the present study was to investigate the effect of aerobic training on the Nuclear Factor Erythroid 2 (NRF2)/ Protein P21 (P21)/Oxidation Resistance Protein (OXR1) pathway in the experimental model of obesity induced by high-fat and fructose diet.

Materials and methods: Twenty-Four male Wistar rats were randomly divided into three groups including standard diet, high-fat/fructose diet and high-fat/fructose diet+ Aerobic exercise group. At the end of study, the anthropometrics parameters, lipid profile and antioxidant gene expression (OXR1, P21, NRF2) were measured in all groups.

Results: A high-fat diet containing fructose increased serum total cholesterol, body mass index, and Li index in male rats. The expression level of OXR1, Nrf2 and P21 genes in the cardiac tissue of obese rats was changes compare to the control group. However, 8 weeks exercise caused to improves the cardiac damage parameters and antioxidant genes in obese rats.

Conclusion: It seems that aerobic exercise could modulate the antioxidant defense system and improve fat metabolism in cardiac tissue. It is suggested that aerobic exercise can be considered as useful treatment in obese patients with cardiovascular dysfunction.

Keywords:
Exercise, Cardiac Biomarkers, Obesity, NRF2, P21, OXR1.

INTRODUCTION

Obesity is a public health crisis in advanced and international societies, the prevalence of which is increasing, especially in industrialized countries. Although there are many definitions and classifications for obesity, the most important acceptable classification of the World Health Organization for defining obesity is based on body mass index (1). Obesity is considered as a major risk factor for chronic diseases such as cardiovascular diseases, type 2 diabetes (T2D), blood pressure, non-alcoholic fatty liver disease (NAFLD) and some types of cancer. Its prevalence is increasing with 400 million obese and 1.6 billion overweight worldwide. Although genetics play a role in regulating body weight, body size and composition, and the metabolic response to nutrition in humans (1), the global increase in obesity in the short term cannot be explained. genetic, although there are individual differences in genetic predisposition to environmental factors such as diet (2). Obesity is associated with oxidative stress, adipokine imbalance, and decreased antioxidant defenses that lead to dyslipidemia, vascular disease, and hepatic steatosis, or NAFLD (3). In fact, reactive oxygen species are naturally produced during cell aerobic processes (4). The effect of reactive oxygen species is regulated by the action of enzymatic and non-enzymatic antioxidants. The imbalance between the activity and intracellular levels of these antioxidants and oxidants as a result of increasing oxidant factors and decreasing antioxidant factors in the living system is called oxidative stress, which leads to various cell disorders and damages (5). Oxidative stress is the basis for the development of

1 there are many definitions and classifications for obesity, the most important acceptable classification of the World Health Organization for defining obesity is based on body mass index

cardiovascular diseases, cancer, chronic liver diseases (especially fatty liver) and type 2 diabetes and complications of diabetes, and in this regard, various studies have shown that these diseases increase the production of reactive oxygen species (ROS) and the reduction of antioxidant defense mechanisms is accompanied (6).

The transcription factor sensitive to redox conditions, called nuclear factor erythroid type 2 (Nrf2), is the "main regulator" of redox homeostasis and cell survival through the induction of antioxidant defense enzymes, in order to prevent oxidative damage by ROS. The Nrf2 transcription factor is a leucine zipper base transcription factor that induces transcription of ARE-containing genes including antioxidant enzymes, electrophile-conjugating enzymes, ubiquitin/proteasomes, and chaperones and heat shock proteins in response to cellular stresses including ROS (7). Nrf2 is widely expressed in tissues and under non-stress conditions, it is retained in the cytosol by Kelch-like ECH-associated protein 1 (Keap1), which causes proteasomal degradation of Nrf2. After recognizing the messages imposed by oxidative and electrophilic molecules including ROS, heavy metals and some pathogenic processes, Nrf2 is separated from Keap1 and its proteasomal degradation is stopped and enters the nucleus. This transcription factor, by connecting AREs in target genes, it induces their expression (8).

On the other hand, oxidation resistance factor 1 (OXR1) acts as an essential sensor of cellular oxidative stress, which exists in many eukaryotic organisms, including humans. OXR1 modulation is believed to be involved in the regulation of genes related to the antioxidant defense system required for the detoxification of reactive oxygen species (9). In this context, a study has identified that OXR1 as a novel gene can suppress oxidative stress by regulating P21 and Nrf2, and significantly interferes with mammalian antioxidant and inflammatory systems. It has been suggested that the OXR1-P21-Nrf2 antioxidant defense system functions to reduce various pathological changes caused by oxidative stress (10). Also, the protective molecular mechanism of P21 against reactive oxygen species-induced cellular damage through upregulation of Nrf2-dependent antioxidant response has been documented in a previous study (11). Each of these three genes has been investigated separately in the cardiac system, which suggested that p21 controls LPS-induced cardiac dysfunction by modulating inflammatory and oxidative stress (12).

Aerobic physical activity is an activity (such as walking, cycling, tai chi, and yoga) that increases the heart rate and breathing volume to supply the oxygen needed by the active muscles. It is recommended that adults over 18 years of age do at least 150 minutes per week of moderate intensity or 75 minutes per week of high intensity aerobic physical activity with participation in strengthening activities at least twice a week (13). The main cardiovascular response to dynamic aerobic exercise is an increase in oxygen intake (Vo2), cardiac output, and heart rate, which is parallel to the intensity of the activity, as well as an initial increase and then a plateau in stroke volume. Progressive increase in systolic blood pressure, with maintenance or slight decrease in diastolic blood pressure, as a result of continuity of pulsation pressure and a moderate increase in mean pressure, with a decrease in peripheral vascular resistance. Blood is diverted from metabolically less active skeletal muscles and viscera to active skeletal muscles. Therefore, dynamic aerobic exercise initially imposes a large load (volume load) on the cardiovascular system, including the myocardium (14). It has been shown that a high-fat diet can affect aging markers in the heart cells of obese rat, while aerobic exercise can lead to a reduction in the aging of heart cells in obese rat through the effect of be on P21, P53 and P16 factors (15).

Therefore, the aim of the present study was to investigate the OXR1, P21, NRF2 signaling transduction changes in the cardiac tissue in response to aerobic exercise in obese rats induced by high-fat and fructose diet.

MATERIAL AND METHODS

Animals

Male Wistar rats were purchased from Ahvaz Jundishapur University of Medical Sciences. After two weeks of adapting to the new environment of the laboratory and feeding on a standard diet (20% of calories from fat, 20% of protein and 60% of carbohydrates, which had 1.3 kcal/gr of energy), accordingly, first the rats were randomly divided into two groups. One group was fed a standard diet (8 rats) for 8 weeks (2 months) and another group was fed a high-fat diet containing fructose (16 rats) for 8 weeks (2 months) (16). After the end of eight weeks, when the studied rats were subjected to a high-calorie

diet (60% fat and 25% fructose), they were randomly divided into two obese groups (the entire research period, 60% fat food containing 25% fructose consumed) and the obese group + aerobic exercise (the entire research period, they consumed 60% fat food containing 25% fructose, in addition to doing aerobic exercise from the eighth week to the end of the research period). All stages of the research coincided with ethical principles of working with animals, according to the ethical guidelines of the national institutes for the care and use of laboratory animals (Helsinki protocol 2006) approved by the Islamic Azad University of Ahvaz branch (Ethics code: IR, IAU, AHVZ.REC1402/020).

High fat diet

This feed is produced to induce obesity. According to the constituents of normal rodent food, a 60% high-fat diet (60% HFD) contained 60% of its energy using fat that had 2.5 kcal/gr of energy (90% from processed animal fat) and 10% soybean oil) which was added to the standard rodent feed, which was prepared by Isfahan Royan biotech company. To make 100 kg of 60% high-fat pellets, 45 kg of standard pellet powder, 30 kg of animal fat (resulting from melting cow tail and soybean oil) were molded into standard pellets. This formula was suitable in terms of the number of calories and energy needed to induce obesity. For control diet the ingredients were including, casein, corn starch, sucrose, mixture of vegetable and animal fats, maltodextrin, soybean oil, calcium carbonate, monocalcium phosphate, corn gluten, corn, wheat bran, mineral premix and various vitamins.

High fructose diet

To prepare a 25% solution by volume of fructose, the relationship (100 x solution volume (ml) / soluble volume (ml) = volume percentage) was used, so that we dissolved 250 ml of fructose liquid in 750 ml of water to make a 25% solution. A volume of fructose is obtained. 25% fructose solution by volume was prepared daily and provided freely in 500 ml bottles specially for rats.

Aerobic exercise protocol

The forced exercise protocol was performed for 8 weeks. In the current study, the endurance training protocol of moderate to intense training intensity, with progressive intensity and duration and respecting the principle of gradual overload, was used based on the study of Chang Huan et al. (2011) (17); Thus, the obese group + exercise was exposed to the treadmill exercise (model no. Exer-3/6 Treadmill; Columbus Instruments, Columbus, OH), 5 sessions a week for 6 weeks. All the training sessions were held at the end of the animals' sleep cycle and between 16:00 and 18:00 in the evening. The speed and duration of the treadmill exercise gradually increased from 10 meters per minute for 10 minutes in the first week, 10 meters per minute for 20 minutes in the second week, 14 to 15 m per min, 20 min in the third week, 14 to 15 m per min for 30 min in the fourth week, it increased to 17-18 m per min for 30 min in the fifth and sixth weeks. In order to achieve the obtained adaptations to a uniform state, all training variables were kept constant in the final week (sixth week).

MEASUREMENT OF ANTHROPOMETRIC INDICATORS

Weight measurement

To check the weight changes of the subjects, every week on a specific day, all the animals in all the groups were weighed, so that the weight chart of each group can be checked during the research period. Also, rats were weighed immediately after anesthetizing the animal and before dissection.

Abdominal circumference measurement (AC)

Abdominal circumference was measured in centimeters immediately in front of the rear leg in the largest part of the abdomen.

Measurement of chest circumference (TC)

The back of the front hand was measured in centimeters for the chest circumference. Then, to measure the ratio of abdominal circumference to chest circumference (AC/TC), the size of the abdomen was divided by the size of the chest and its ratio was obtained.

Body length measurement

Body length was measured in centimeters from the tip of the nose to the anus.

Body mass index (BMI)

Body weight in grams divided by body length from nose to anus to the power of two in centimeters was calculated as body mass index.

$$BMI = \frac{W(g)}{L^2(cm)}$$

Lee index measurement

Lee's index as an index of body composition in rodents using the formula; The cube root of body weight in grams divided by body length from

nose to anus in centimeters was calculated.

Measurement of nutritional parameters

The amount of food and water consumed by rats in all groups was measured and recorded on a daily basis during the entire research period. The average amount of food and water intake of each group was determined and based on that, the following nutritional parameters were calculated.

Measurement of cardiac parameters

At the end of the experiment, all animals in all groups were anesthetized and blood sample was collected from the heart. the collected samples were centrifuged at 3000 rpm for 15 min and the serum was separated. Then, the amount of lipid profile markers in plasma samples were measured using the assay kits and according to the instructions (Zelbio Co. made in Germany).

Measurement of oxidative stress indexes

At the end of the study duration, the rats were anesthetized and blood samples were collected, centrifuged and the supernatant samples were applied to measured malondialdehyde (MDA) and total antioxidant capacity (TAC) via the special assay kits and using spectrophotometry method (Zelbio Co. made in Germany).

Real Time-PCR Gene expression

At the end of the six-week training program, the rats were anesthetized by intraperitoneal injection of ketamine (90 mg/kg) and xylazine (10 mg/kg). the cardiac tissue samples were collected. Then, in order to evaluate the expression of NRF2-P21-OXR1, the RNA in the cardiac tissue was extracted using RNeasy Plus Mini Kit. Then, the cDNA synthesis step was done using the Quantitect Reverse Transcriptase kit. finally, 1 microliter of cDNA and a proportional amount of each of the reverse primers and 10 microliters of Master Mix Real-Time plus a proportional volume of RNase free water were prepared in a mixture and Real-time PCR reaction was performed and the amount of the expression of each of the above genes was measured in comparison with the glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as a control gene using Real-Time RT-PCR method.

Statistical Methods

The SPSS software was used for data analysis. ANOVA statistical test and the post hoc test were used to compare between groups. Finally, the data were calculated as Mean±SEM and $P<0.05$ was considered significant.

RESULTS

Anthropometric indicators

As shown in Table 1, the initial weight of the groups did not differ significantly ($P<0.05$), but in the final months of the research, the average weight changes of the rat in the group The high-fat diet weight was significantly higher than the control group ($P<0.05$). On the other hand, aerobic exercise caused weight loss caused by a high-fat diet, and the average weight changes of the high-fat diet and aerobic exercise group in the final months were lower than the high-fat diet group, and it was statistically significant ($P<0.05$).

Table 1: Body weight in rats from different groups.

Month 8	Month 7	Month 6	Month 5	Month 4	Month 3	Month 2	Month 1	Initiate Weight	Groups	Variants
0/401±4/7	5/387±1/7	1/349±1/8	3/302±3/9	5/296±4/10	1/257±1/10	0/228±2/10	4/216±1/13	4/198±7/13	HFFD (n = 8)	WEIGHT (g)
4/294±7/10	6/315±8/12	5/362±3/11	9/325±3/12	6/291±1/12	4/268±8/11	1/243±2/12	6/219±5/11	0/194±4/10	Train (n = 8)	
5/297±8/9	8/279±3/9	8/268±1/8	9/255±9/8	3/230±1/9	4/222±1/10	6/214±1/11	8/206±4/11	3/196±3/10	Normal (n = 8)	

Also, the results of statistical analysis showed that the average weight changes of the high-fat diet and aerobic exercise group were not significant compared to the control group ($P<0.05$). moreover, table 2 and figure 2 shows the descriptive data of the research including the mean and standard error of mean of the changes in anthropometric indices of rats in different experimental groups (3 groups) in the first, sixth and eighth months.

Biochemical parameters

Table 3 shows the descriptive data of the research, including the mean and standard deviation of the biochemical variables of the serum levels of rats in the high-fat diet group and the control group after consuming fatty food with fructose in order to confirm the induction of obesity.

MDA and TAC assessment

As shown in figure 3, the analysis of oxidative stress indexes shows that the MDA concentration level in HFFD group significantly increases in compare to the control group. Although in trained rats the MDA level significantly lower compares to the HFFD rats. Moreover, TAC as an index of antioxidant defense system demonstrated the significantly decreases in HFFD rats compared to the controls. eight weeks exercise caused to increases of total antioxidant capacity level compared to the HFFD group.

Table 2: Mean and standard deviation of anthropometric indices in rats of different groups.

Groups									Variants
Normal			Train			HFFD			
Month 8	Month 7	Month 6	Month 5	Month 4	Month 3	Month 2	Month 1	Initiate Month	
94/20±58/0	72/20±18/0	58/18±86/0	95/21±12/0	89/23±12/0	93/18±15/0	62/23±71/0	46/22±83/0	13/19±63/0	Abdominal Circumference (cm)
74/15±46/0	63/14±57/0	97/13±38/0	36/15±67/0	81/16±57/0	67/14±03/0	29/17±91/0	12/16±54/0	21/14±21/0	Chest Circumference (cm)
33/1±72/0	42/1±34/0	32/1±21/0	43/1±23/0	42/1±63/0	29/1±3/0	36/1±31/0	40/1±14/0	35/1±06/0	Abdominal/Chest Circumference
98/25±12/0	19/25±75/0	77/21±34/0	83/25±72/0	46/25±38/0	89/21±15/0	54/24±69/0	19/24±35/0	5/22±43/0	Bod Length (cm)
44/0±69/0	42/0±36/0	41/0±2/0	44/0±28/0	56/0±98/0	40/0±62/0	67/0±65/0	66/0±42/0	39/0±21/0	Body mass index
26/0±81/0	26/0±16/0	27/0±9/0	26/0±68/0	28/0±26/0	26/0±59/0	30/0±43/0	30/0±3/0	26/0±46/0	Lee Index

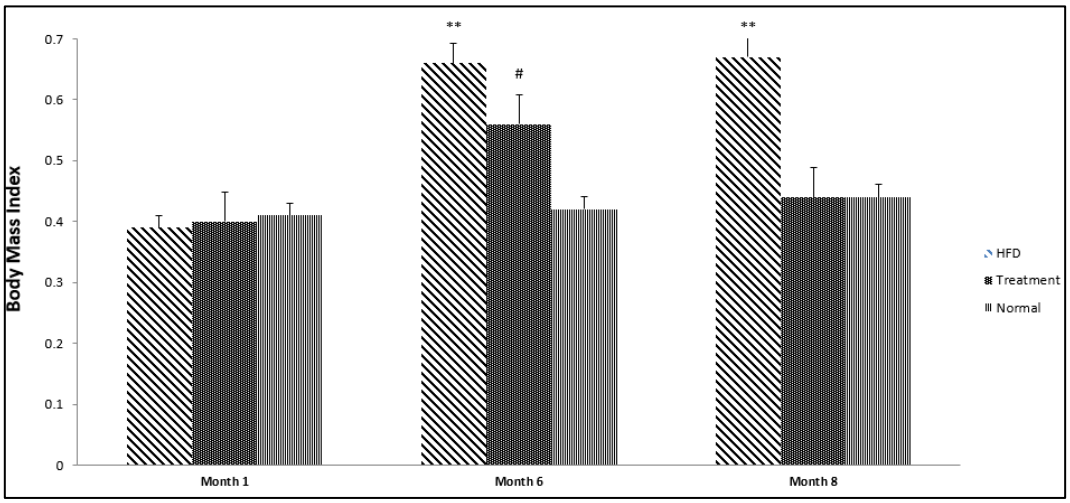
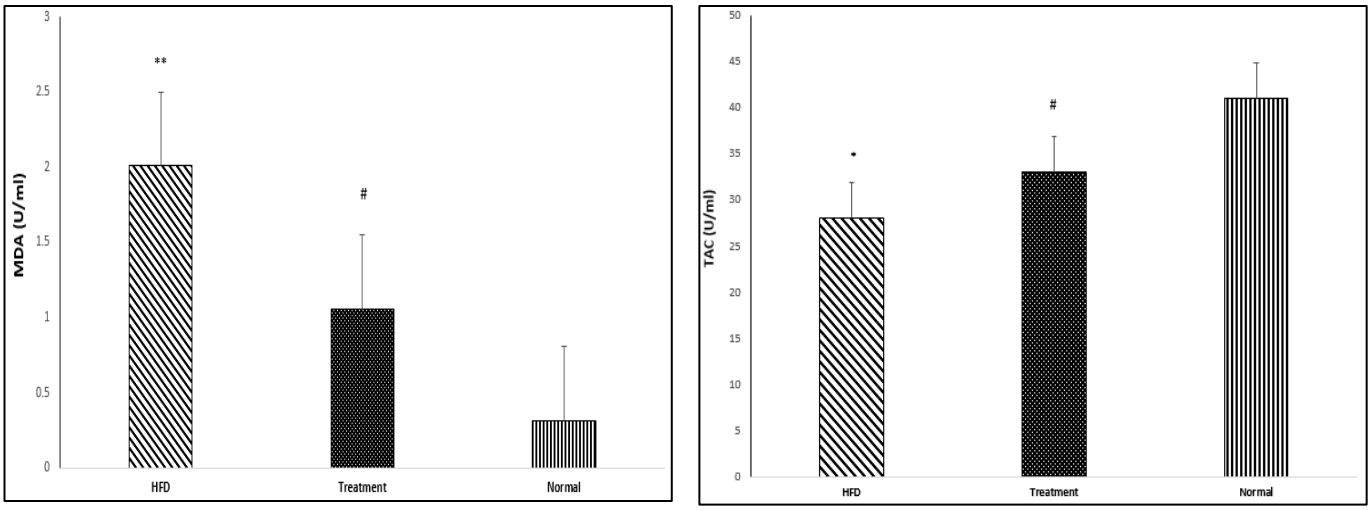


Figure 1: BMI values between high-fat and fructose diet (HFFD), high-fat and fructose diet and aerobic exercise (Train) and control group (Normal).

Table 3: Serum biochemical parameters in all groups.

Groups			Variants
Normal	HFFD	Train	
0/66±0/11	*0/134±1/15	2.2±87.2#	Chol (mg/dL)
33/75±05/13	*3/185±06/11	10.1±112.3#	Tg (mg/dL)
37/6±42/1	*17/2±7/0	0.5±4.1#	HDL (mg/dL)
5/37±05/4	*73/86±71/4	4.1±53#	LDL (mg/dL)
26/11±76/0	*7/15±53/0	4±12.6#	INSULIN (mU/L)



(A) (B)

Figure 2: Measurement of concentration level of MDA (A) and TAC (B) in different groups: The comparison of groups has been done by One-Way ANOVA, and HSD. * vs Normal group and # vs HFD group.

Oxidative stress gene expression

As shows in figure 4, the data analysis of real time PCR shows that the level of OXR1 gene expression in the high-fat and high-fructose diet group (HFFD) was significantly higher than the control group (Normal) ($P<0.05$). Also, a significant difference in the expression levels of the above gene was observed between the high-fat and fructose diet (HFFD) group compared to the high-fat and fructose diet (HFFD) and aerobic exercise (Train) group ($P<0.05$) on the other hand, the expression level OXR1 gene was higher in the high-fat and fructose diet group (HFFD) and aerobic exercise (Train) than the control group (Normal). Also, the statistical analysis showed a significant decreases in OXR1 gene expression compare to the HFD group ($P<0.05$). the level of P21 gene expression in the high-fat and high-fructose diet group (HFFD) was significantly higher than the control group (Normal) ($P<0.05$). Also, a significant difference in the expression levels of the above gene was observed between the high-fat and fructose diet (HFFD) group compared to the high-fat and fructose diet (HFFD) and aerobic exercise (Train) group ($P<0.05$). on the other hand, the expression level P21 gene was higher in the high-fat and fructose diet group (HFFD). Although, the level of Nrf2 gene expression significantly decreases and exercise caused to significant increases in compare to the HFFD group.

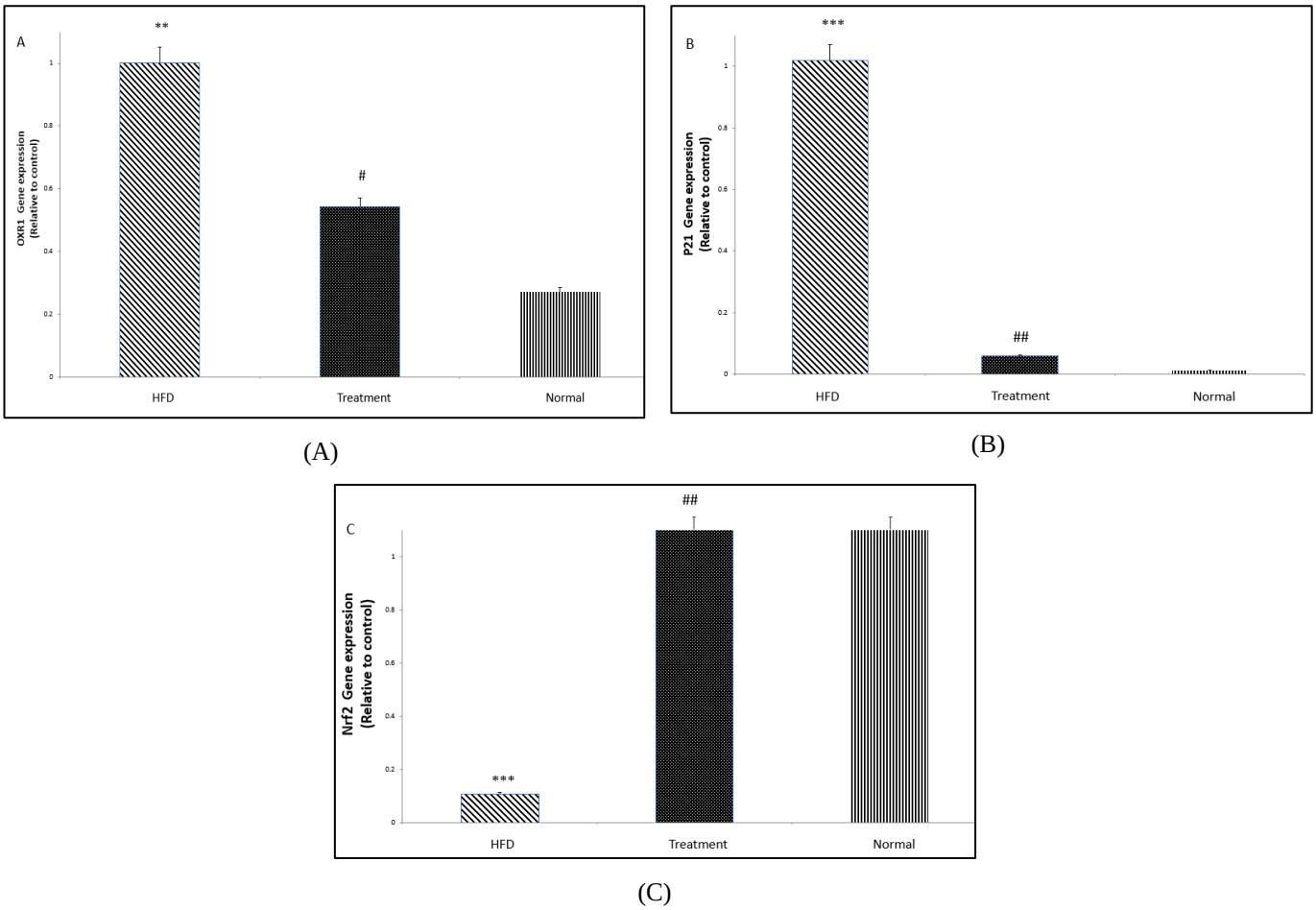


Figure 3. Comparison of gene expression level of OXR1 (A), P21 (B) and Nrf2 (C) in different groups: The comparison of groups has been done by One-Way ANOVA, T-Test and HSD. * vs Normal group and # vs HFD group.

DISCUSSION

In the current study documented the effect of high-fat and fructose-containing diet on the induction of obesity in the cardiac tissue and the results of the present study showed the protective role of exercise on anthropometric factors and the lipid profile indexes in rats.

Obesity-inducing high-fat, high-carbohydrate (HFCD) models have several advantages. Elevated triglyceride levels are mainly observed in high-fructose-fed rat, while obesity is mainly achieved through a high-fat diet (18). One of the advantages of using HFCD is that cardiac tissue is damaged relatively quickly, which allows for detailed study of morphological, biochemical and functional features of the pathogenesis of cardiovascular changes, in addition to metabolic changes (19).

Considering the above, in the present study, a high-fat and fructose diet was used to induce obesity in rats. Depending on the amount of fat consumed, diets are divided into different types. Low-fat diets with a fat content of 10% (LFD), high-fat diets with a fat content of 30-50% (HFD), very high-fat diets with a fat content of more than 50% (VHFD). With HFD and VHFD, the effect of diet on body mass depends on the total amount of fat consumed (20). The type of fats eaten also affects body mass and metabolism. In an experiment with Wistar rats fed with 40% HFD containing different fats (fish liver, palm and soybean oil), the highest body mass was obtained in the group receiving soybean oil (21). Other studies show that experimental animals fed cod oil did not increase their body mass and also had higher insulin sensitivity (22).

On the other hand, the results of the present study showed that inducing obesity in rats with high-fat food containing fructose increases the expression of OXR1 and P21 genes, while it had no significant effect on the expression of Nrf2 gene. Inactivity and overweight are the two main factors in justifying the relationship between obesity and the possibility of cardiovascular diseases, so that for every one unit increase in body mass index (BMI), the risk of cardiovascular diseases increases by 8%. (23).

Also, according to studies, for every 5 unit increase in BMI, the risk of hypertension increases by 10% (24).

Obesity is considered as an independent risk factor and direct cause of cardiovascular diseases. Severe obesity causes hemodynamic changes, structural and functional changes in the heart, and long-term severe obesity eventually leads to heart failure (25). In fact, the increase in blood pressure over time plays an important role in vascular changes. Destruction and replacement of elastin in response to blood pressure leads to more deposition of collagen and calcium and as a result, the stiffness of blood vessels. In addition, inflammatory cytokines and oxidative metabolites produced in obesity cause endothelium dysfunction and participate in the mentioned pathophysiology. These vascular changes cause serious damage to the heart. In young people, obesity and hypertension cause eccentric ventricular hypertrophy due to increased vascular volume (26).

Studies have also shown that the amount of fat accumulation in the heart is directly related to the increase in BMI. The heart finds remodeling in order to cope with these changes, which causes the situation to deteriorate further. Also, atrial fibrillation, which is caused by the disorder of the electrical activity of the atrium of the heart, increases in obesity. This increase in prevalence can be caused by higher blood pressure, heart failure, cardiovascular disease, and increased size and dysfunction of atria in obese people (27).

On the other hand, increasing evidence shows a strong relationship between oxidative stress and obesity, and it has been found that body mass index (BMI) is positively correlated with biomarkers of oxidative stress. Obesity can induce systemic oxidative stress through several molecular signaling pathways, such as superoxide generation from NADPH oxidases (NOX), oxidative phosphorylation, glyceraldehyde autooxidation, protein kinase C (PKC) activation, and polyol and hexosamine pathways (28). Oxidative stress can cause obesity by activating adipocyte differentiation, preadipocyte proliferation, and increasing the size of mature adipocytes (29). In addition, oxidative stress can alter food intake by affecting hypothalamic neurons that control satiety and hunger behaviors (30).

OXR1 acts as an essential sensor of cellular oxidative stress present in many eukaryotic organisms, including humans (31), and was first identified during a study in 2000 as a gene capable of Coping with oxidative stress caused by Escherichia coli was identified (Volkert et al., 2000). It is believed that the modulation of OXR1 is involved in the regulation of genes related to the antioxidant defense system required for the detoxification of reactive oxygen species and also modulates the cell cycle and the process of apoptosis (32). The obtained results of the current study showed that High fat and fructose diet caused to increases OXR1 gene expression in cardiac tissue which suggested the oxidative stress effect of this model. Although exercise leads to alleviates the oxidative damages which demonstrated by decreases level of OXR1 gene expression.

It is well documented that Nrf2 controls the expression of key components of the antioxidant enzymes system. the results of the present study, showed that establishment of the obesity model using high fat and fructose diet caused to down regulation of Nrf2 gene which decrease the antioxidant defense system and 8 weeks exercise leads to improve the Nrf2 expression in cardiac tissue. However, contrary to the results of the present study, Faraj Tabar et al., in a study in 2021, investigated the effect of aerobic exercise on ethanol consumption model focused the Nrf2 gene expression changes in cardiac tissue. Their results showed a significant decrease in Nrf2 gene expression (33). The difference in the results observed in the present study with other studies on Nrf2 may be related to the diet used in the present study and the type and duration of aerobic exercise. However, more studies are needed in this regard to determine the clear future of the effect of aerobic exercise on the pathway of oxidative stress in the cardiac system in obese rats.

CONCLUSION

In summary, the findings of the present research showed that inducing obesity in rats with high-fat and fructose diet modulated the OXR1, P21, Nrf2 signal transduction. Also, aerobic exercise alleviates oxidative stress by improves expression of antioxidant genes in the cardiac tissue which associated by improves in lipid profile indexes and anthropometrics factors. These results suggested the protect cardiovascular

effect of exercise in obesity.

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There is no found.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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