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Aerobic Exercise Relieves Cardiac Inflammation by Modulating AP1/JNK Genes in Diet-Induced Obesity Rat Model

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ABSTRACT

The obesity has increased the risk of cardiovascular diseases. The purpose of this research is to investigate the effect of aerobic exercise in cardiac inflammation in the experimental model of obesity induced by high-fat and fructose diet. Twenty-four Wistar rats were randomly divided into three groups including, Control, OB: high fat/fructose diet (60% fat and 25% fructose) group and OB+EX: obesity+aerobics exercise group. At the end of the study, concentration level of CRP, amyloid A, fibrinogen, pro/anti-inflammatory cytokines, and also the expression level of AP1 and JNK genes were assessed in all groups. High-fat/fructose diet increased the serum level of inflammatory biomarkers compared to the control group. The concentration level of TNF-a and IL-6 significantly increases in compared to the control rats. Conversely, the level of IL-10 significantly decreases compared to the control group. These results were in line with increases the genes expression of AP1 and JNK compared to the control rats. although, aerobic exercise showed the significant efficacy with prevent inflammatory process in cardiac system which demonstrated by down regulation of inflammatory genes and increases of anti-inflammatory cytokines. According to the obtained data, it seems that aerobic exercise could modulate the inflammatory cascade in cardiac system with suppress the expression of AP1 and JNK genes and improve inflammatory biomarkers in cardiac tissue.

Keywords: Aerobic Exercise, Obesity, Inflammation, AP1, JNK.

INTRODUCTION

Obesity increases the risk of chronic diseases, including diabetes and cardiovascular disease (i). Obesity increases the level of free fatty acids in the plasma, which leads to increased insulin resistance and atherosclerosis (ii). free fatty acids enhancement causes to increases in the level of cytokines and free fatty acids. On the other hand, high-fat diets could activate Mitogen Activated Protein (MAP) kinase pathway, which lead to c-Jun N-terminal kinases (JNK) activation (iii). JNK is considered as one of the key factors related to the cytokines enhancement in cardiovascular system. several studies have shown that cytokines can activate the metabolic pathway of JNK signaling which in the long term leads to apoptosis and abnormal chronic inflammation diseases specially in cardiovascular diseases such as cardiac hypertrophy and endothelial dysfunction. JNK can be activated by various stimulations such as cytokines, ultraviolet radiation exposure, reactive oxygen species (ROS) and free fatty acids exacerbation (iv). The activation of JNK leads to the activation of downstream proteins such as various enzymes, cytoplasmic substrates, and various transcription factors that lead to a destructive inflammatory process (v). Macrophages are responsible for the production of inflammatory cytokines such as TNF-α and IL-6, which

can lead to impaired insulin signaling and insulin resistance and cardiovascular disease ([vi]). Under these conditions, JNK stimulates the production of cytokines through the transcription of the activator protein-1 (AP-1) proteins. AP-1 is involved in a number of cellular pathways including differentiation, proliferation and apoptosis ([vii]). JNK activation leads to the phosphorylation of the c-Jun part in the AP-1 protein, which stimulate inflammatory metabolic pathways and cell death ([viii]). This evidence suggests that the agents which targeting the JNK gene can reduce inflammation and reduce the progression of cardiovascular disease.

Regular aerobic physical activity has various health benefits, especially in people with obesity. Aerobic exercises can lead to weight loss and body fat loss. However, regardless of weight and fat changes, aerobic activity can reduce many of the complications of obesity, such as the risk of cardiovascular disease ([ix]). several studies have shown that aerobic exercise is associated with a reduction in inflammatory markers, lipid profile, and cardiac disease in obesity ([x]). Aerobic exercise can also lead to improved cardiovascular system performance ([xi]). Some studies have shown that aerobic exercises have potency to modulate the MAP3K pathway in the cardiovascular system ([xii]).

Considering the above literature, the aim of the current study was to investigate the effect of aerobic exercise on cardiac inflammation through modulating the genes expression AP-1/JNK in obesity model induced by high fat/fructose diet.

MATERIAL AND METHODS

Animals

Twenty-four male Wistar rats at the age of 8 weeks with weight range of 210±15.4gr were obtained from the Laboratory Animal Breeding Center of Jundishapur University of Medical Sciences, Ahvaz, Iran. After two weeks of adapting to the new laboratory environment and feeding with standard diet (20% of calories from fat, 20% of protein and 60% of carbohydrates, which had 1.3 kcal per gram of energy), the rats randomly divided into two groups. One group was fed a standard diet (number of 8 rats) for 8 weeks and another group was fed a high-fat diet containing fructose (number of 16 rats) for 8 weeks. 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 rats consumed food with 60% fat and 25% fructose) and the obese group + aerobic exercise (the rats consumed 60% fat food containing 25% fructose throughout the research period, in addition to doing aerobic exercise from the eighth week to the end of the research period) were categorized. 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.REC1402/022).

Treadmill Exercise Protocol

The rodent treadmill used in the current experiment consists of five compartments, and at the end of each compartment, there is a row of wire transversely that can apply an electric shock of 1 milliampere to stimulate the rats to run. The bottom of the opening is a rubber belt that rotates at an adjustable speed. The rats must run forward regularly. In order to control the speed of the treadmill, first the length of the belt was measured with a tape measure and then a mark was placed on the belt with a marker. Then the time of one belt rotation was recorded and the speed of the treadmill was determined and controlled by using the equation (Speed= (belt length)/(complete belt around time). The endurance training protocol was carried out for 8 weeks. the protocol of endurance training was carried out from moderate to intense training intensity, which was performed with progressive intensity and duration, following the principle of gradual overload. 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 meters per minute, 20 minutes in the third week, 14 to 15 meters. per minute for 30 minutes in the fourth week, it increased to 17-18 meters per minute for 30 minutes in the fifth to eighth week.

Measurement of Inflammatory Biomarkers

At the end of the study duration, the rats were anesthetized with intraperitoneally mixture of ketamine and xylazine. Then, the chest was open and the blood samples collected from the left heart ventricle using special tubes. The samples centrifuged and the obtained supernatants were applied to evaluated the concentration levels of amyloid A and fibrinogen using special kits via spectrophotometry method ([xiii]).

Measurement of Inflammatory Cytokines

At the end of the study duration, the rats were anesthetized with intraperitoneally mixture of ketamine and xylazine. Then, the chest was open and blood samples collected from the left heart ventricle using special. In order to evaluate the pro-inflammatory cytokines (IL-6 and TNF-a) and also anti-inflammatory cytokine (IL-10), the samples homogenized in phosphate buffered saline and after centrifuge, the obtained supernatants were applied to evaluated the mentioned factors concentration using ELISA kits and according to the manufacturer's instructions ([xiv]).

Measurement of CRP

At the end of the study duration, the rats were anesthetized with intraperitoneally mixture of ketamine and xylazine. Then, the tissue samples of hearts were collected. In order to evaluate CRP, the samples homogenized in phosphate buffered saline and after centrifuge, the obtained supernatants were applied to evaluated the CRP concentration using ELISA kits and according to the manufacturer's instructions.

Real-Time PCR Genes Expression

In this purpose, the rats were anesthetized. the cardiac tissue samples were collected. Then, in order to evaluate the expression of AP1 and JNK, the RNA in the cardiac tissue was extracted using RNeasy Plus Mini Kit. Then, the cDNA synthesis step was done using the Quantitate 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 ([xv]).

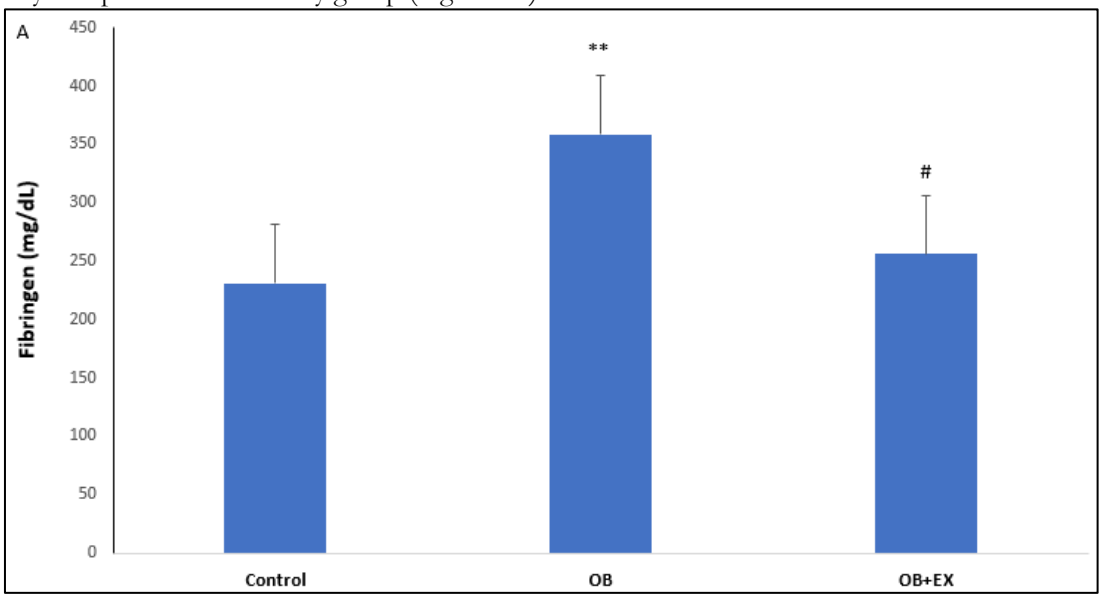
Statistical Analysis

The analysis of the current study data was performed via SPSS software (version 20). in order to check the normality of the data K–S test was performed. Data are demonstrated as the mean ± SD. The data were analyzed using ANOVA followed by Tukey's tests. Finally, $P < 0.05$ was considered as statistically significant.

RESULTS

Exercise Improved Inflammatory Biomarkers in Obesity Rat Model

As it shows in Figure 1A, high fat/fructose diet caused to increases in plasma fibrinogen concentration level compared to control rats. eight weeks-exercise caused to decreases in fibrinogen value in plasma samples of rats compared to the obese group. Moreover, data analysis of the obese rats showed an increase in CRP concentration level compared to control rats. eight weeks-exercise caused to decreases in CRP level in rats compared to the obese rats (Figure 1B). also, evaluating of the serum level of amyloid A in obese rats demonstrated a significant increase compared to the control values. whereas, serum amyloid A concentrations in obesity plus exercise group reduced significantly compared to the obesity group (Figure 1C).



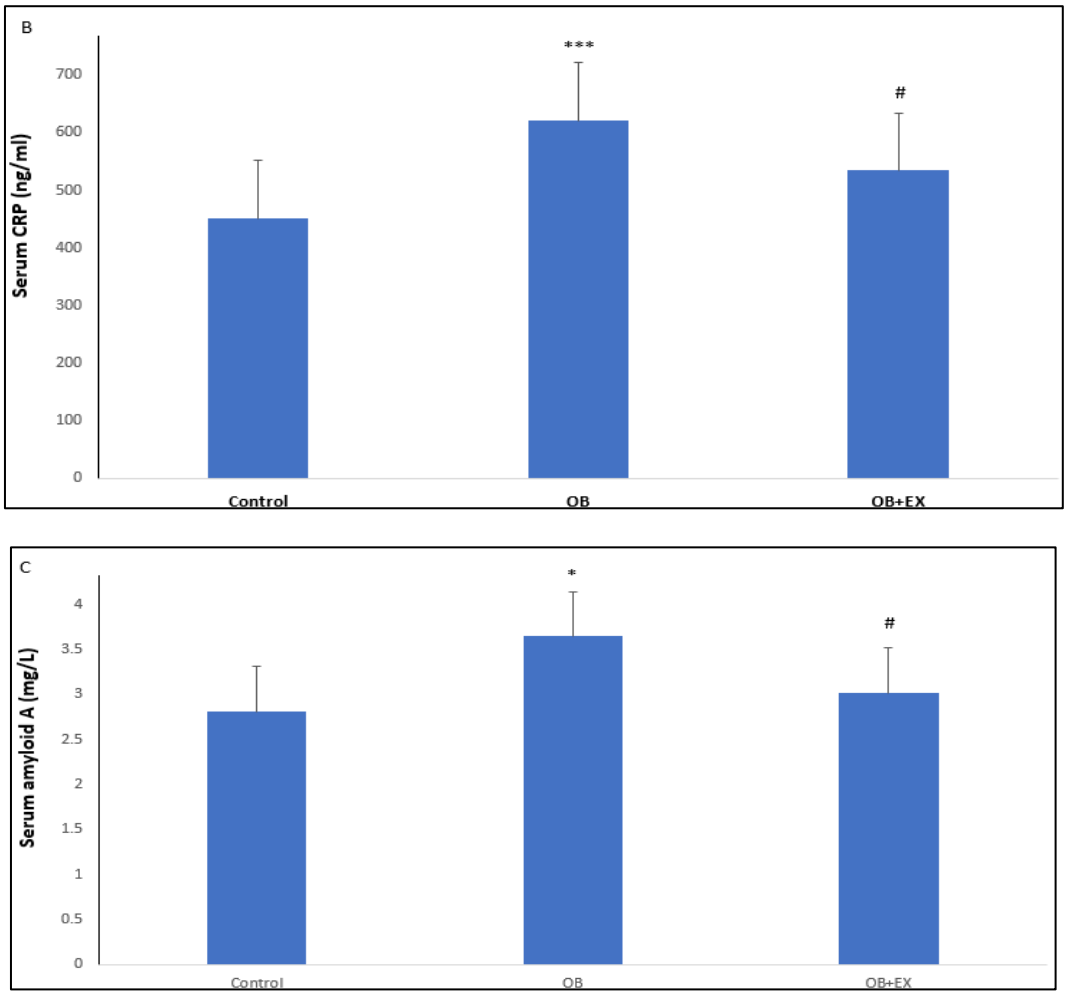
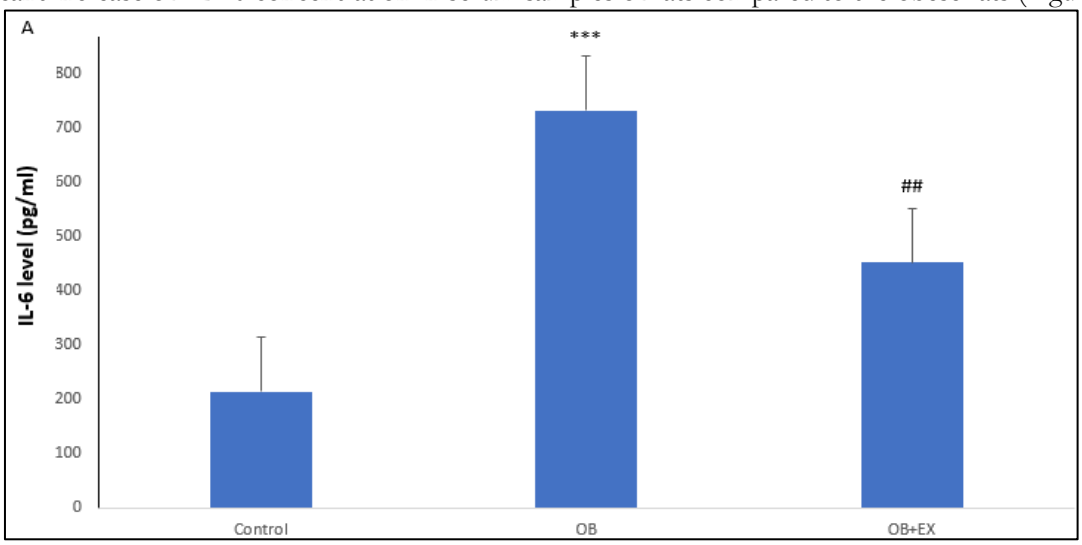


Figure 1. Comparison of plasma fibrinogen (A), CRP (B) and serum amyloid A (C) in different groups, including: Control, OB (high fat/fructose diet) and OB+EX (high fat/fructose diet plus exercise). The comparison of groups has been done by One-Way ANOVA, and HSD. * vs control and # vs OB group.

Exercise Improved Cardiac Inflammatory Cytokines in Obesity Rat Model

In purpose to evaluate the pro/anti-inflammatory cytokines in blood samples, the concentration level of IL-6, TNF-a and IL-10 were measured in all rats. As it shows in Figure 2 A&B, high fat/fructose diet caused to increases of IL-6 and TNF-a concentration level compared to control rats. eight weeks-exercise caused to decreases in pro-inflammatory cytokines compared to the obese group. conversely, data analysis of the obese rats showed significant decrease in IL-10 concentration level compared to control rats. Although, eight weeks-exercise caused to significant increase of IL-10 concentration in serum samples of rats compared to the obese rats (Figure 2C).



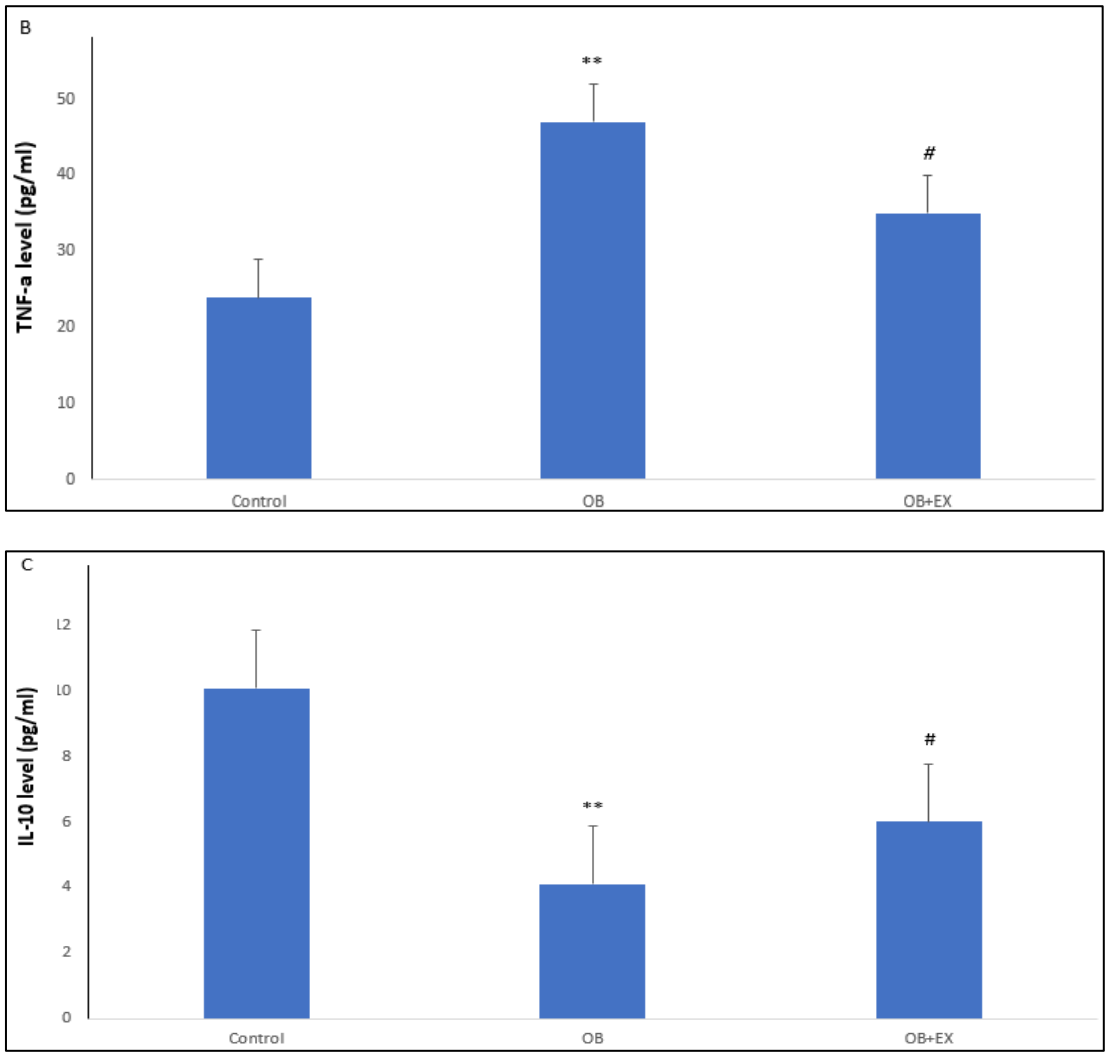
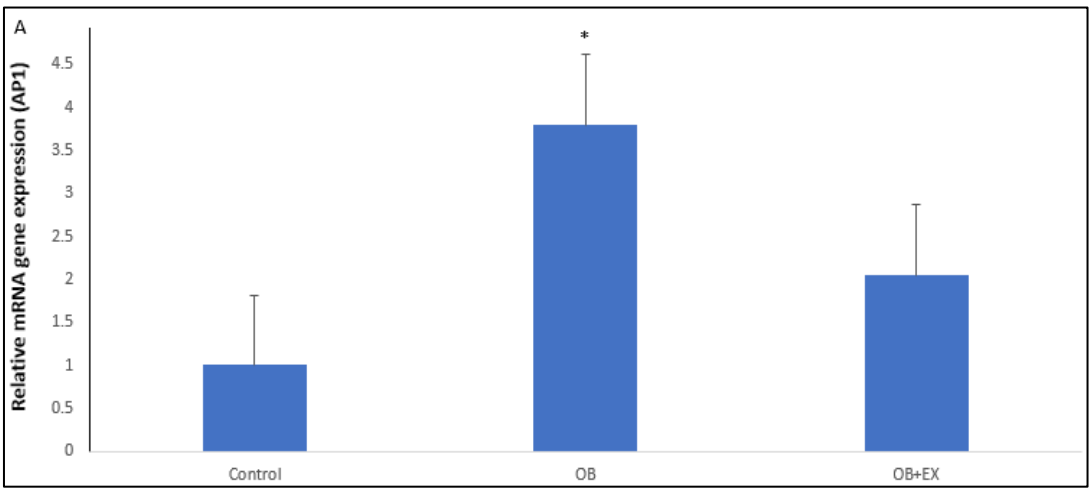


Figure 2. Comparison of concentration level of IL-6 (A), TNF-a (B) and IL-10 (C) in different groups, including: Control, OB (high fat/fructose diet) and OB+EX (high fat/fructose diet plus exercise). The comparison of groups has been done by One-Way ANOVA, and HSD. * vs control and # vs OB group.

Exercise Improved Cardiac AP1-JNK Genes Expression in Obesity Rat Model

As it shows in Figure 3, high fat/fructose diet caused to increases in genes expression of AP1 and JNK in cardiac tissue compared to control rats. However, eight weeks-exercise caused to significant decreases in genes expression of AP1 and JNK in cardiac tissue of rats compared to the obese group.



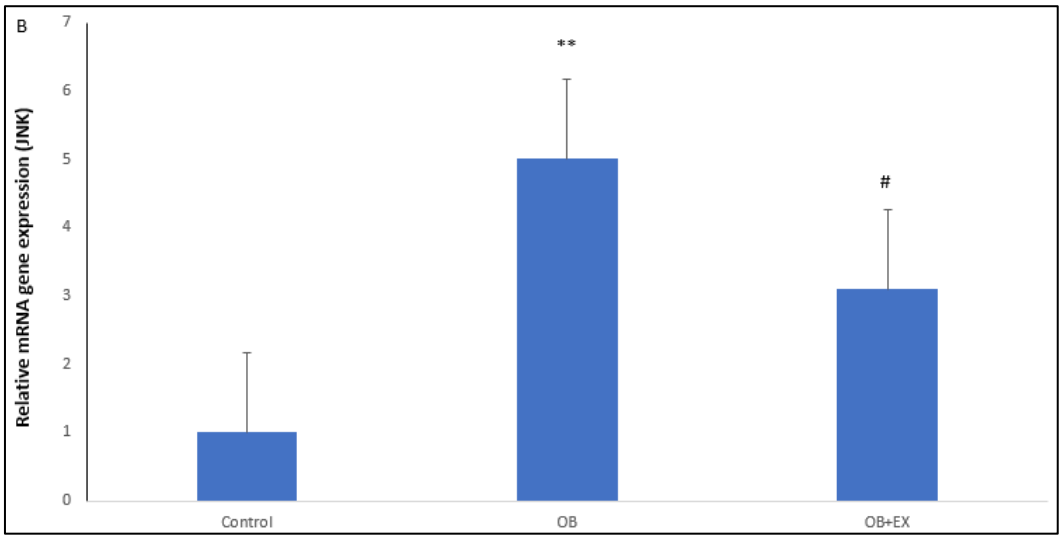


Figure 3. Comparison of cardiac gene expression level of AP1 (A) and JNK (B) in different groups, including: Control, OB (high fat/fructose diet) and OB+EX (high fat/fructose diet plus exercise). The comparison of groups has been done by One-Way ANOVA, and HSD. * vs control and # vs OB group.

DISCUSSION

The results of the current study showed that the high fat plus fructose diet increases the inflammatory conditions in the cardiovascular system. This inflammation was demonstrated by increased inflammatory biomarkers and inflammatory cytokines. These results were associated by the increased in expression of key genes that stimulate inflammatory processes in the cardiac system, including AP1 and JNK. Aerobic exercise for 8 weeks using a rodent treadmill improved inflammatory factors in the obese rats.

Research has shown that a high-fat/fructose diet is associated with obesity, cardiovascular disease, and fatty liver in laboratory animals ([xvi]). These pathological conditions are associated with disturbances in biochemical markers. In this regard, Abol Ghasemi et al. have shown that administration of a high-fat diet for 24 weeks is associated with changes in lipids profile (triglycerides, cholesterol, LDL, and HDL) and an increase in inflammatory markers ([xvii]). There is strong scientific evidence that aerobic exercise can improve these inflammatory disorders. Mohebi et al. showed that 8 weeks of aerobic training was associated with improvement of lipid profile and oxidative stress ([xviii]).

In cardiovascular diseases induced by lipid exacerbation, there is an increased levels of cytokines and free fatty acids which associated by JNK activation in various tissues ([xix]). AP-1 is the functional arm of JNK in part of the JNK signaling pathway ([xx]). The activation of JNK leads to the phosphorylation of the c-Jun part in the AP-1 protein, which could activate inflammatory metabolic pathways leads cell death ([xxi]). Accordingly, a high-fat/fructose diet with stimulation of inflammatory cascade, leads to JNK-AP-1 pathway activation. Janevski et al. showed that even two weeks of high-fructose plus fat diet induction in laboratory animals led to an increase in JNK and AP-1 gene expression. JNK appears to stimulate cytokine production through the transcription of AP-1-related genes ([xxii]). Thus, JNK stimulation leads to increasing in cytokine production and inflammation injuries.

Regular aerobic exercise has various health benefits, especially in people with obesity. However, regardless of weight loss, aerobic exercise can reduce many of the complications induced by obesity, such as the risk of cardiovascular disease. Many studies have shown that aerobic exercise is associated with a reduction in inflammatory markers and lipid profile ([xxiii]).

The obtained data of current study demonstrated that obesity caused to increases of fibrinogen, CRP and amyloid A.

Pervious study showed that fibrinogen as an important marker of inflammation increases in presence of inflammation condition specially in cardiovascular disorders caused by inflammation ([xxiv]). Also, recent studies documented that CRP ([xxv]) and amyloid A ([xxvi]) are biomarkers of progression of inflammatory condition in cardiovascular dysfunction. These findings are in line with obtained results of current study which showed systemic significant increases of inflammatory biomarkers in obesity rat model.

Studies have been shown that aerobic exercise can also lead to improved cardiovascular system performance. Some studies have reported that aerobic exercises can induce protective effects by modulating the AP-1 and JNK genes expression ([xxvii]). In this context, Iemitsu et al. investigated the activation pattern of MAPK downstream enzymes in the cardiovascular system after 12 weeks of running sessions ([xxviii]). In another study by Ávila et al. the

effects of swimming exercise on inflammatory and oxidative stress factors showed the protective effect of exercise to inhibition of inflammatory cytokines releases ([xxix]).

It seems that the positive effects of aerobic exercise on JNK and AP-1 levels have been observed in acute studies as well. Guo et al. investigated the effects of aerobic exercise on JNK expression and activity at 24 h post-exercise time intervals. According to the findings of the mentioned study, the expression of JNK gene increases over time after exercise and reaches a peak at 30 minutes after exercise and turned to the basal level by 8 hours after exercise ([xxx]). In the current study 8 weeks of aerobic exercise leads to downregulation of AP1/JUNK genes which associated with decreases of inflammatory cytokines release. although, it seems that more molecular researches are necessary to clarify the exact mechanism of inflammation suppress in response to exercise in obesity models. However, according to the current data aerobic exercise could be suggested as a preventive or treatment strategy in obese patients in order to relives the cardiovascular disorders.

CONCLUSION

In summary, the findings of the current research showed that inducing obesity in rats with high-fat plus fructose diet increases the cardiac inflammatory biomarkers with upregulation of JNK and AP1. although, 8 weeks of aerobic exercise caused to significant improvement of cardiac inflammation in obese rats with suppression of inflammatory process.

Acknowledgment
There is no found.

Conflict of interest
The authors declare that they have no conflicts of interest.

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