Physical Activity and Hormones (J Physic Act Horm)
Vol. 6 Autumn 2025

Aerobic exercise affects hepatic APAF-1 gene expression in rats fed a high-fat diet

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ABSTRACT

Introduction: A high-fat diet (HFD) impairs liver function by inducing pathological apoptosis. Evidence suggests that aerobic exercise modulates apoptotic signaling proteins and inhibits this process. However, the effect of aerobic exercise on hepatic apoptosis protein activator-1 (Apaf-1) gene expression in HFD-fed rats has not been investigated. Therefore, this study aimed to determine the effect of aerobic exercise on hepatic APAF-1 gene expression in HFD-fed rats.

Material & Methods: In an experimental study, 18 female Wistar rats were randomly assigned to three groups: Normal Diet Control (Control-ND), High-Fat Diet Control (Control-HFD), High-Fat Diet - Aerobic Exercise (Aerobic Exercise -HFD). Control-ND and Aerobic Exercise -HFD groups received HFD for 4 weeks before and 4 weeks during the exercise intervention. The NDC group consumed a standard diet for 8 weeks. Aerobic exercise involves treadmill running at a moderate intensity, 3 sessions/week for 4 weeks. Twenty-four hours after the final exercise session and a 12-hour fast, rats were anesthetized (ketamine/xylazine), and liver tissue was extracted for Apaf-1 gene expression analysis via Real-Time PCR. Two-way analysis of variance was used to analyze the data.

Results: Apaf-1 gene expression in the Control-HFD group was significantly higher than in the Control-ND group (P=0.001). On the other hand, Apaf-1 gene expression in the Aerobic Exercise-HFD group was significantly lower than in the Control-HFD group (P=0.003).

Conclusion: Based on the findings of the present study, it is concluded that HFD stimulates hepatocyte apoptosis by increasing Apaf-1 expression and aerobic exercise reduces Apaf-1 expression, indicating its protective role against HFD-induced hepatic apoptosis.

Keywords: Aerobic Exercise, Apaf-1, High-Fat Diet.

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Received: Aug 2025; **Revised:** Sept 2025; **Accepted:** Oct 2025.

DOI: https://doi.org/10.71878/jpah.2025.1211388

1. Introduction

One of the most serious causes of liver disorders is obesity, especially metabolic dysfunction-associated steatotic liver disease (MASLD) (1). As a consequence of obesity, liver cells become insulin resistant, inflammatory, oxidative, and apoptotic (2,3). MASLD and other liver disorders are promoted by a high-fat diet (HFD), which increases the rate of apoptosis in hepatocytes. Apoptosis of hepatocytes plays an important role in acute and chronic liver damage, which can be prevented by understanding the molecular mechanism that causes it (6). The proapoptotic protein BAX is activated by HFD fatty acids, and the antiapoptotic protein BCL-2 is inhibited by them. As a result, mitochondrial membrane permeability increases and cytochrome C enters the cytosol and binds to apoptosis protein activator-1 (Apaf-1). After oligomerization, Apaf-1 binds caspase-9 and forms an activation complex. Hepatocytes undergo apoptosis as a result of the activation of downstream caspase-3/6/7 by this complex (7,8). The expression of Apaf-1 is significantly increased in HFD and enhances apoptosis induced by HFD (9,10,11). An important role is played by Apaf-1 in the apoptotic process. Evidence shows that loss of Apaf-1 impairs the apoptotic response, which highlights Apaf-1's essential role in regulating apoptosis during normal development and disease (12). According to a literature review, aerobic exercise reduces the negative effects of HFD in liver tissue by inhibiting pathological apoptosis (13,14,15). Although aerobic exercise reduces Apaf-1 expression in skeletal muscle (16), its effect on hepatic Apaf-1 gene expression is unknown. In fact, inhibition of pathological apoptosis can prevent structural and functional disorders of liver tissue in HFD. For this reason, this study can test the role of aerobic exercise in hepatoprotection. Consequently, the present study examined the effect of aerobic exercise on hepatic APAF-1 gene expression in rats fed a high-fat diet.

2. Methodology

2.1. Materials and methods

In a preclinical trial.

2.2. Participants

Eighteen female Wistar rats were selected from the animal house of Islamic Azad University's Central Tehran Branch for an experimental study. They were randomly divided into 3 groups: Control-Natural diet, Control-High-fat diet, and High-fat diet-Aerobic exercise. During the experiment, all animals were kept in autoclavable transparent polycarbonate cages at a temperature of (20-22°C), relative humidity of 55 percent, and free access to food and water. All procedures performed in this study were carried out in accordance with laboratory animal guidelines.

2.3. Measurements

Animal sacrifice and tissue collection: To control the acute effects of aerobic exercise, rats were anesthetized with ketamine and xylazine twenty-four hours after their last aerobic exercise session and after twelve hours of fasting. In the next step, the chest was opened and the left ventricle's blood was collected. To measure the expression of Apaf-1, liver tissue was immediately removed and homogenized in cold phosphate-buffered saline (10% w/v).

Apaf-1 gene expression measurement: To measure Apaf-1 gene expression, the Real-Time PCR technique and GAPDH reference gene were used using the 2-ΔCt formula. Table 1 presents primer sequences for measured genes.

Table 1. *Sequence of primers used to determine Apaf-1 gene expression*

Gene	*Forward*	*Reverse*
Apaf-1	ATTTGGGATTCTGGGACTGG	TGGTTGCTCTTATTGGTGAAATG
GAPDH	AACCCATCACCATCTTCCAG	CCAGTAGACTCCACGACATAC

Apaf-1: apoptosis protein activator-1, GAPDH: Glyceraldehyde 3-phosphate dehydrogenase

2.4. Intervention

High-fat diet: In the present study, a high-fat diet was used according to Od-Ek et al (2020) (17). For four weeks before aerobic exercise and for four weeks along with aerobic exercise, subjects in the high-fat diet control group and the high-fat diet-aerobic exercise group were fed a high-fat diet, while rats in the control-normal diet group were fed a normal rat diet for eight weeks.

Aerobic exercise program: Nikbin et al (2020) guidelines were used to design and implement the aerobic exercise program in the present study (18). Consequently, the rats in the high-fat diet-aerobic exercise group had been familiarized with treadmill running for two weeks. Then, they ran on the treadmill for four weeks, five sessions per week, at 55 to 65% of their maximum oxygen consumption.

Sensorimotor Function Assessment: To evaluate motor performance, the inclined plane test was employed. This apparatus could be adjusted from 0 to 90 degrees. In this test, each animal was placed on the inclined surface, which was gradually elevated in 5-degree increments. The maximum angle at which the animal was able to maintain its position for at least 5 seconds was recorded as its score (17) (Khodaee, 2013).

Tissue collection: 48 hours after the last training session and in a 12-hour fast, rats were first anesthetized using ketamine (50 mg/kg) and xylazine (20 mg/kg) prepared from Alphasan, Netherlands. To ensure anesthesia, rats were tested by pain sensation and foot squeeze tests. After ensuring complete anesthesia, the cranial cavity of the rats was first opened using a cutter and then the brain tissue of the rats was carefully separated; immediately after extraction, the brain tissue was placed in special tissue preservation cryotubes and then transferred to a temperature of -70°C.

2.5. Statistical Methods

Data obtained from the Apaf-1 gene expression assay were reported as mean and standard deviation. The normality of data distribution and homogeneity of variance were tested using the Shapiro-Wilk and Levene tests, respectively. A one-way variance analysis was used to test for differences between groups. To determine where significant differences were found, groups were compared pairwise using the Bonferroni test. Calculations were also evaluated with a significance level of (p 0.05). A SPSS 25 program was used to perform all calculations.

3. Results

Compared to Control-ND, Apaf-1 gene expression was significantly higher in Control-HFD (P=0.001). Aerobic Exercise-HFD, however, significantly reduced Apaf-1 gene expression (P=0.003) in comparison to Control-HFD. Despite the fact that aerobic exercise significantly reduced Apaf-1 gene expression, this gene was significantly higher in the Aerobic Exercise-HFD group than in the Control-ND group (P=0.001). Fig. 1.

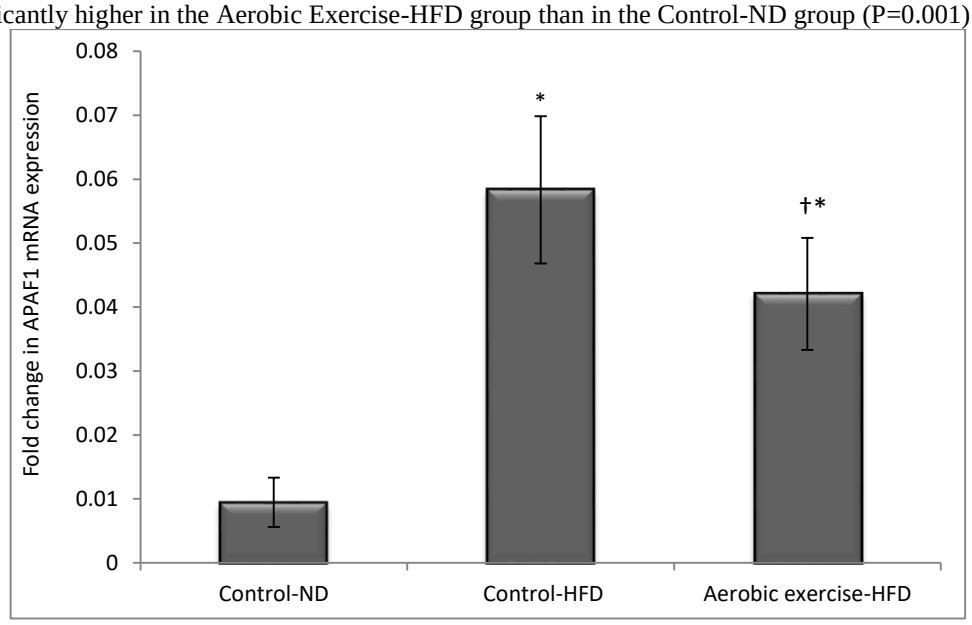

Figure 1. Expression of APAF1 gene in liver tissue in the studied groups. * Indicates a significant difference compared to the Control-ND group. † Significant difference compared to the Control-HFD group. Data are reported based on mean and standard deviation.

4. Discussion

In the present study, the expression of the proapoptotic gene APAF-1 in liver tissue was significantly increased after consuming HFD. Liver damage can be caused by various factors such as alcohol consumption, viral infection, drug abuse, and the consumption of HFD, especially saturated fatty acids (19). Saturated fatty acids accumulate in liver cells and lead to cell death through various death modes, including apoptosis, necrosis, and necroptosis (20, 21). As an adaptive process, the accumulation of FFAs increased mitochondrial fatty acid oxidation, the tricarboxylic acid cycle, and oxidative phosphorylation, while reactive oxygen species (ROS) were produced. Continuous production of ROS attacks and unsaturates fatty acids and leads to aldehyde byproducts including MDA, which enhance oxidative stress. Under these conditions, dysfunction of fatty acid oxidation, mitochondrial DNA damage, and mitochondria-mediated apoptosis will occur. Apoptosis is initiated by the breakdown of mitochondrial membrane potential and the release of apoptotic factors, especially cytochrome C, followed by the formation of the apoptosis complex and activation of the caspase cascade. It is well established

that prolonged high-fat feeding, especially saturated fatty acids, strongly induces the apoptosis of liver cells (22). HFD stimulates the intrinsic mitochondrial pathway and the extrinsic death receptor pathway. As mentioned, in the present study, HFD stimulated the intrinsic apoptosis pathway in liver cells. This was observed with a significant increase in the expression of the gene Apaf-1 as a pro-apoptotic factor compared to the control group fed a normal diet. In addition, free fatty acids increase the permeability of the lysosomal membrane, which may lead to mitochondrial dysfunction, so exogenous lipids activate the intrinsic apoptosis pathway by affecting the lysosomes (23,24). On the other hand, fatty acids in HFD increase gene expression of apoptotic factors and decrease pro-apoptotic factors, causing pathological apoptosis in liver tissue. These changes indicate that high-fat food intake can predispose to liver diseases, especially liver fibrosis, by promoting inflammation and apoptosis (25). On the other hand, in the present study, aerobic exercise significantly reduced the expression of the proapoptotic gene Apaf-1 in liver tissue. It is well established that HFD is associated with many diseases, including liver damage. Saturated fatty acids induce hepatic apoptosis and increases inflammation (26). In active and obese NAFLD patients, aerobic exercise reduces the circulating markers of hepatocyte apoptosis. This reduction is associated with reduced lipid oxidation capacity in liver tissue (27). In addition, Goncalves et al. (2016) show that endurance exercise prevented the release of cytochrome C from mitochondria, decreased membrane potential instability, and thus decreased the release of apoptosis signals by mitochondria in the hepatocytes of high-fat-fed mice, leading to a reduction in pathological apoptosis in liver tissue (28). Rowan et al. (2021) reported that aerobic exercise in rats fed a high-fat diet reduced BAX expression and increased BCL-2, ultimately decreasing apoptosis in liver tissue (29). Evidence shows that under HFD, free fatty acids and oxidative stress in tissue increase. As a result, Bax synthesis increases and moves outside of the mitochondrial membrane. This causes the opening of the mitochondrial permeability transition pore and the release of cytochrome C. On the other hand, Bcl-2 is mainly distributed in the outer mitochondrial membrane. Its homodimers suppress the opening of the permeability transition pore. The ratio of the Bax/Bcl-2 protein complex is directly related to apoptosis. Under these conditions, cytochrome C release into the cytosol activates Apaf-1, which stimulates caspase activation. It seems that aerobic exercise on HFD increases fatty acid uptake by active muscles. This reduces circulating levels of fatty acids, thus reducing apoptosis activation in liver tissue. In this condition, the cytochrome C release from mitochondria is diminished, thereby decreasing Apaf-1 expression and activation. Therefore, aerobic exercise appears to prevent apoptosis by downregulating the intrinsic apoptotic pathway. Overall, in the present study, aerobic exercise decreased the expression of a key apoptotic protein, which—based on previous studies—can minimize apoptosis by eliminating hepatic lipid accumulation, enhancing beta-oxidation of fatty acids, inducing autophagy, improving glucose control, and increasing insulin sensitivity, thereby mitigating liver injury induced by a high-fat diet (30). In addition, aerobic exercise suppresses the excessive production of reactive oxygen species and upregulates several antioxidant enzymes and anti-inflammatory mediators. These changes are associated with reduced apoptosis activation (31, 32).

5. Conclusion

The findings of the present study demonstrate that HFD stimulates hepatocyte physiological apoptosis by upregulating the expression of the Apaf-1 gene. This is a pivotal protein in the intrinsic apoptotic signaling pathway. In contrast, aerobic exercise reduced Apaf-1 expression, indicating that aerobic exercise can attenuate HFD-induced hepatocyte apoptosis. Therefore, aerobic exercise protects liver tissue in the context of HFD. Accordingly, aerobic exercise is suggested to reduce liver complications in obesity caused by HFD.

6. Acknowledgment

This study is derived from a doctoral thesis in exercise physiology. It was approved by the Department of Exercise Physiology, Islamic Azad University, Central Tehran Branch. The authors of this article would like to thank the officials of the Faculty of Physical Education, Islamic Azad University, Physical Education Branch, for their assistance.

Conflict of interests: The authors of this article declare no conflicts of interest.

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