

# A Review of the Molecular Mechanisms of Aerobic Exercise in Modulating Adipose Tissue Apoptosis and Inflammation in Obese with Metabolic Syndrome

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## Abstract

Obesity and inflammation are major risk factors for various diseases, and metabolic syndrome is a complex disorder characterized by insulin resistance, dyslipidemia, hypertension, and abdominal obesity. Aerobic exercise appears to reduce obesity-induced inflammation. The purpose of this study was to review the molecular mechanisms of aerobic exercise in modulating adipose tissue apoptosis and inflammation in individuals with metabolic syndrome. Studies related to the intrinsic apoptotic pathway in women with metabolic syndrome evaluated the effects of aerobic exercise on apoptotic signaling pathways and adipose tissue inflammation. Aerobic exercise appears to increase the expression of the BCL-2 gene and decrease the expression of BAX and caspase-3, thereby delaying the apoptotic process. In addition, aerobic exercise reduced body fat percentage, fasting insulin levels, insulin resistance, and was associated with decreased apoptosis and inflammation of adipose tissue in individuals with metabolic syndrome. The findings indicate that aerobic exercise exerts significant beneficial effects on factors associated with metabolic syndrome and may represent an appropriate and effective strategy for appetite regulation in individuals with metabolic syndrome.

**Keywords:** Inflammation, Metabolic syndrome, Obesity, Aerobic exercise, Women

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## Introduction

Metabolic syndrome, a complex clinical condition involving central obesity, insulin resistance, hypertension, and dyslipidemia, is a significant risk factor for cardiovascular diseases and type 2 diabetes mellitus. It is closely linked to body metabolism and insulin resistance (1). Normally, The gastrointestinal tract and liver break down foods into glucose, which is transported through the bloodstream to body tissues for energy (2). Insulin helps glucose enter cells, but in insulin-resistant individuals, cells do not respond properly to insulin, leading to elevated insulin levels and difficulty in glucose entry. This can eventually lead to diabetes. Even without diabetes, high glucose levels are harmful (3). Increased insulin levels also raise triglyceride levels, increasing the risk of heart disease, stroke, diabetes, and other disorders. Genetic and environmental factors contribute to the insulin resistance, with obesity and physical inactivity being major environmental factors (4-5). Obesity, especially abdominal obesity is associated with insulin resistance in peripheral glucose and fatty acid utilization leads to type 2 diabetes mellitus. Obesity is a multifactorial and complex disease with diverse causes, most of which arise from environmental factors superimposed on a genetic background. Some studies have attributed a limited role to heredity in the development of obesity, suggesting that only about 15% of body fat is determined by genetic inheritance (6). In addition, chronic low-grade inflammation and oxidative stress play key roles in the pathophysiology of metabolic syndrome. Adipose tissue, as an endocrine organ, responds to increased fat mass by releasing pro-inflammatory cytokines such as TNF- $\alpha$ , IL-6, and IL-1 $\beta$ , thereby contributing to systemic inflammatory responses (7). Moreover, mitochondrial dysfunction and increased production of reactive oxygen species (ROS) activate inflammatory pathways such as the NLRP3 inflammasome, creating a self-perpetuating cycle between metabolic

stress and inflammation (8). The rapid increase in obesity prevalence suggests that environmental factors play a predominant role, whereas genetic factors are less influential. A sedentary lifestyle and high-calorie food intake are two major environmental contributors to weight gain. Modern technologies have promoted sedentary lifestyles in most individuals (9). Apoptosis refers to programmed cell death that occurs in an organized and regulated manner. This process is characterized by changes in cellular structures and the emission of signals to neighboring cells and is often associated with tissue preservation and a reduced severe inflammatory response. Molecular and morphological hallmarks of apoptosis include cell shrinkage, membrane blebbing, chromatin condensation, release of cytochrome c from mitochondria into the cytosol, activation of caspases (particularly caspase 3 and 7) and the conversion of pro-caspases into their active forms (10) (Figure 1). Apoptosis is a programmed form of cell death defined by minimal biological disruption and preservation of anti-inflammatory features, such as limited release of intracellular contents into the extracellular space. In healthy tissues, apoptosis facilitates the removal of damaged cells without eliciting a strong immune response. Adipose tissue inflammation is a chronic, low-grade immune response within adipose tissue characterized by the release of cytokines and inflammatory mediators. In obesity, this chronic inflammation plays a central role in metabolic disturbances such as insulin resistance (11).

In obesity, the proportion of enlarged adipocytes and metabolic stress (due to mechanical pressure, high lipid content, and oxidative stress) increases. This condition predisposes adipose tissue to the development of a chronic inflammatory response. Cellular stress and apoptosis, driven by elevated free fatty acids, mechanical stress, and hypoxia in tissue with hypertrophic adipocytes, can lead to apoptotic cell death.

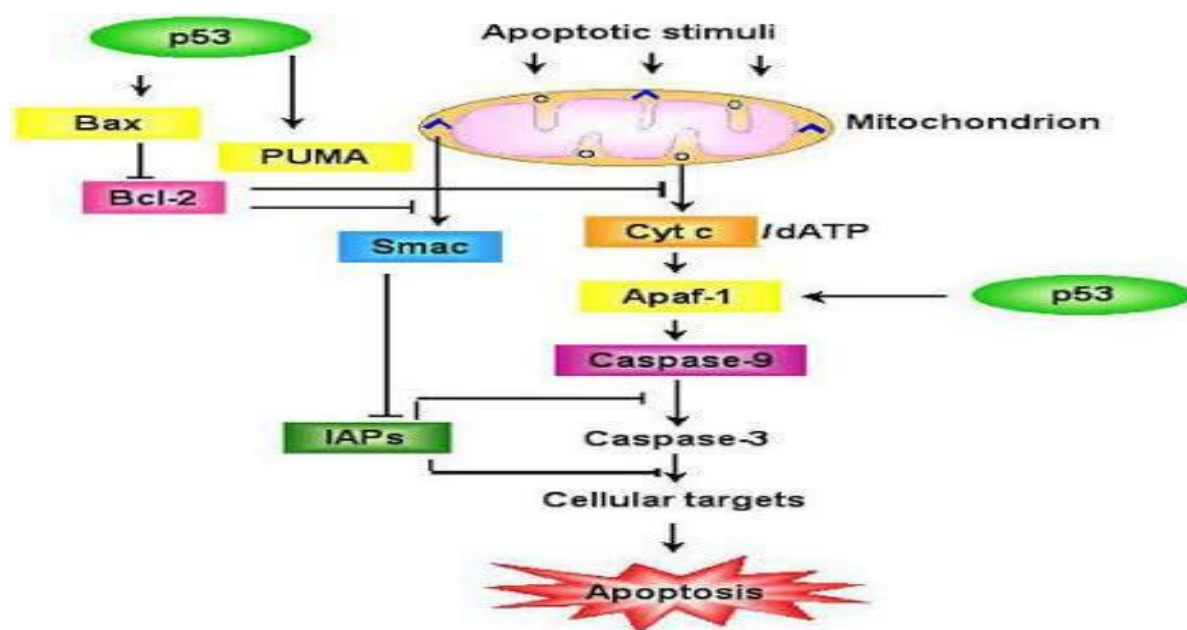


Figure 1. Intrinsic and extrinsic pathways leading to apoptosis via cytochrome c

Initial outcomes include the controlled removal of damaged cells, typically without extensive release of intracellular contents; however, under many conditions, chronic demands may result in deleterious spillover effects (12). The inflammatory response to apoptosis occurs when adipocytes are chronically driven toward apoptosis or when large numbers of dead cells remain within the tissue. In such cases, cellular contents from dead cells leak into the interstitial space and release immune-related factors such as HMGB1 and other DAMPs, which can recruit macrophages. Adipose tissue macrophages (ATMs) engulf dead tissue. Under chronic conditions, this process can induce a phenotypic switch of macrophages from the supportive/anti-inflammatory M2 phenotype to the pro-inflammatory M1 phenotype. This phenotypic shift leads to the release of cytokines such as TNF- $\alpha$ , IL-6, MCP-1, and other inflammatory mediators (13) (Figure 2). Activation of interleukin responses, including TNF- $\alpha$  and IL-6, through signaling pathways such as NF- $\kappa$ B and JAK-STAT, is classically associated with the development of insulin resistance in target tissues (muscle and liver).

Chronic adipose tissue inflammation is linked to reduced insulin sensitivity in muscle and liver and may ultimately lead to type 2 diabetes and cardiovascular diseases. Oxidative stress in adipose tissue damages lipoproteins and protein complexes and can promote apoptosis and abnormal immune responses. Chronic adipose tissue inflammation is one of the central axes of insulin resistance in obesity (14) (Figure 2). The chronic inflammatory phase of adipose tissue is a major driver of insulin resistance, type 2 diabetes, metabolic syndrome disorders, and cardiovascular diseases. The association between hypertension and metabolic syndrome is partly attributable to inflammatory effects on the vascular system and metabolism. The severity and duration of adipose tissue inflammation can alter the prognosis of blood pressure, blood glucose levels, and cardiovascular risk. Dysregulation of adipose tissue immune responses may improve in some individuals through weight loss, physical activity, or anti-inflammatory treatments, while remaining resistant in others (15).

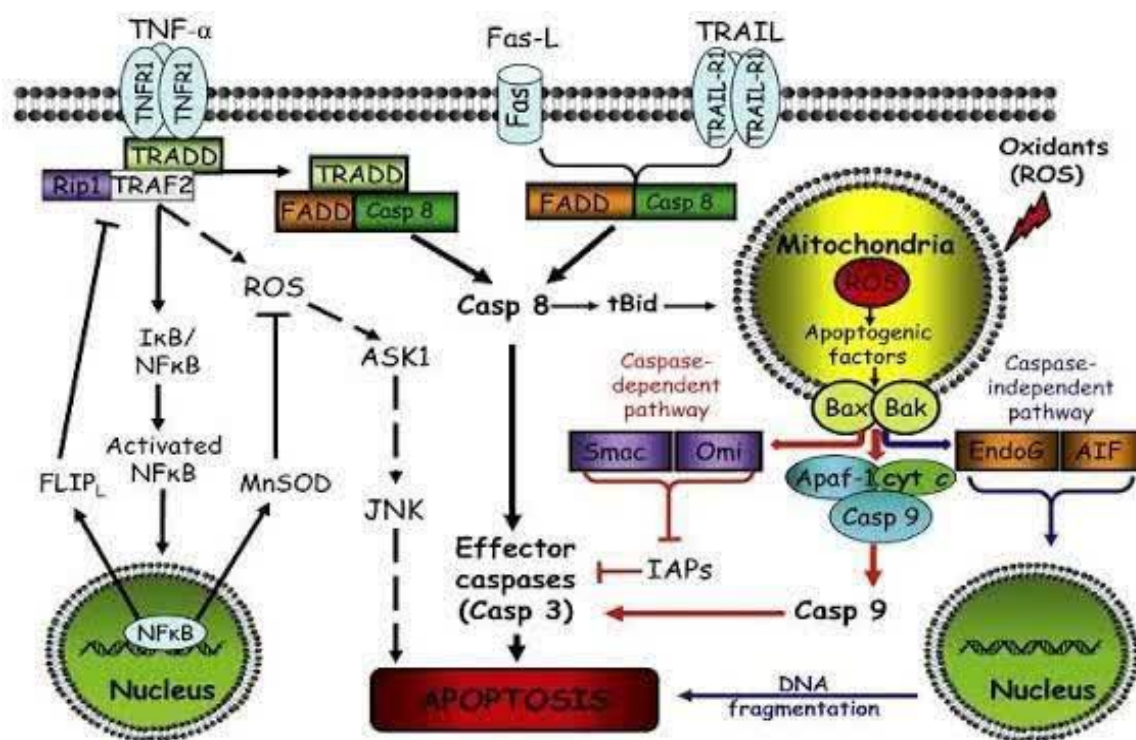


Figure 2. Extrinsic (receptor-mediated, red) and intrinsic (mitochondrial) apoptotic pathways

Aerobic exercise is recognized as a non-pharmacological intervention that improves inflammatory markers and reduces oxidative stress. Numerous studies have demonstrated that, in addition to lowering pro-inflammatory cytokine levels, aerobic exercise enhances mitochondrial function and reduces oxidative stress. Moreover, modulation of apoptotic processes (programmed cell death) through reduction of inflammatory burden may play an important role in improving adipose tissue function and reducing metabolic complications (16).

Aerobic exercise is widely associated with improvements in metabolic indices and reductions in adipose tissue inflammation. By increasing oxygen consumption and mitochondrial content, aerobic exercise improves IRS-1/PI3K/Akt signaling and reduces insulin resistance. Reductions in local and systemic TNF- $\alpha$  and IL-6, as well as alterations in adipokine profiles such as increased adiponectin occur through multiple interacting mechanisms. Improved tissue

oxygenation and reduced oxidative stress may decrease the release of DAMPs and ameliorate apoptotic responses (17).

Weight loss and reductions in abdominal fat decrease sources of free fatty acids, metabolic stress, and mechanical load on adipose tissue, thereby lowering the risk of chronic inflammation. Aerobic exercise also improves endothelial function and reduces blood pressure, which in turn decreases the likelihood of tissue damage and inflammation (18).

In this review article, based on studies published between 2010 and 2025, the effects of aerobic exercise on the modulation of apoptosis and inflammation in women with metabolic syndrome are comprehensively examined. The present work aims to elucidate, based on experimental and molecular evidence, the role of physical activity in regulating inflammatory responses and modulating apoptotic pathways.

## Discussion

Based on the systematic search of scientific databases, 275 articles were identified. After removing duplicate records, 187 articles remained for initial screening. Following title and abstract screening, 64 articles were selected for full-text review. After further evaluation, 38 articles were excluded based on the inclusion and exclusion criteria. Ultimately, 26 studies were included in the final analysis. The characteristics of the included studies are presented in Table 1. All studies were published between 2005 and 2025 and investigated the effects of aerobic exercise on participants with metabolic syndrome. In all included studies, the diagnosis of metabolic syndrome and the calculation of the metabolic syndrome Z score were performed based on the ATP III criteria. Notably, 471 participants were allocated to aerobic exercise and control groups, with a median age of 26 years (range: 21-32 years). Among the included studies, four studies investigated both women and men, two studies included only women, and two studies included only men. The exercise modalities employed across the studies included walking, running, and cycling. In addition, exercise intensity ranged from moderate (corresponding to maximal fat oxidation) to high intensity (up to 80% of maximal heart rate). It is noteworthy that all studies implemented supervised exercise programs; however, in some studies, a portion of the weekly sessions consisted of unsupervised training. Metabolic syndrome, characterized by a combination of central obesity, insulin resistance, hypertension, and dyslipidemia, is more prevalent in women, particularly in middle-aged and premenopausal groups, and is associated with complex metabolic outcomes. Increased body fat, especially visceral adiposity, is linked to chronic inflammation and metabolic disturbances and plays a key role in the development of cardio metabolic diseases (3-18). Women are at particular risk for metabolic syndrome due to hormonal differences, fat distribution patterns, and

distinct metabolic responses. Studies have shown that visceral fat accumulation in women can exacerbate inflammatory responses, and obese women respond differently to changes in adipokine markers compared to men. Therefore, a focused examination of obese women, particularly those with metabolic syndrome, is essential for a precise understanding of molecular and clinical mechanisms (19). Adipose tissue is an active endocrine organ that not only stores energy but also secretes adipokines and cytokines, playing a critical role in regulating metabolism and immune responses. Key adipokines include leptin, adiponectin, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- $\alpha$ ). TNF- $\alpha$  is primarily produced by macrophages and visceral adipocytes and contributes to reduced insulin sensitivity in muscle and liver cells (10). This mechanism is a major contributor to insulin resistance in obese individuals and those with metabolic syndrome. IL-6 is a pleiotropic cytokine; in chronic and prolonged elevations, it acts as a pro-inflammatory agent, whereas in response to acute aerobic exercise, it can exert anti-inflammatory effects. IL-6 promotes insulin sensitivity by stimulating adiponectin secretion and reducing TNF- $\alpha$  level. Inflammation is a complex biological response to cellular damage, infection, or metabolic stress (20). In obesity and metabolic syndrome, a persistent, low-grade inflammatory state often referred to as low-grade systemic inflammation develops. This inflammation arises from the activation of macrophages and immune cells in adipose tissue and leads to elevated levels of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-6, and MCP-1. Chronic inflammation disrupts insulin signaling and alters the adipose tissue microenvironment, ultimately reducing insulin sensitivity and metabolic function (21). Apoptosis, or programmed cell death, is an essential process for maintaining tissue homeostasis. In adipose tissue, apoptosis plays a critical role in regulating adipocyte number and maintaining the balance between cell

growth and cell death (22). Increased adipocyte size and number in obesity, combined with metabolic stress, can lead to abnormal apoptosis. Such dysregulated apoptosis promotes the release of inflammatory factors, tissue fibrosis, and impaired metabolic function (23). Moreover, abnormal apoptosis in visceral adipose tissue is associated with elevated TNF- $\alpha$  and IL-6 production, creating a self-perpetuating cycle of chronic inflammation and cellular dysfunction. Aerobic exercise is a form of physical activity that utilizes oxygen to produce energy, resulting in increased heart rate and oxygen consumption in muscles. Aerobic exercises include running, brisk walking, swimming, cycling, and dancing, and can be performed at moderate to high intensity (24). These exercises are associated with reductions in pro-inflammatory cytokines, improvements in mitochondrial function, enhanced insulin signaling, and modulation of apoptotic pathways, all of which contribute to improved adipose tissue function and reduced metabolic complications in women with metabolic syndrome (25).

Furthermore, one study demonstrated that aerobic exercise is associated with reduced local expression of pro-apoptotic markers (BAD and BAX) and increased expression of anti-apoptotic markers (BCL-2 and BCL-XL). Aerobic exercise, by modulating apoptotic-signaling pathways, provides enhanced protective effects (26). Regular aerobic exercise improves cardiorespiratory capacity, oxygen consumption, reduces fat mass, and enhances insulin sensitivity. At the molecular level, aerobic exercise can decrease TNF- $\alpha$  production, induce short-term anti-inflammatory increases in IL-6, and modulate apoptotic pathways and adipose tissue remodeling (27). Studies indicate that aerobic exercise, by reducing body fat volume particularly visceral fat can diminish chronic adipose tissue and systemic inflammation. Additionally, regular exercise may improve adipose tissue structure and function by enhancing the expression of genes related to

apoptosis and angiogenesis (28). Considering that chronic inflammation and dysregulated apoptosis are key pathways in metabolic disturbances in obese women, aerobic exercise can play an important preventive and therapeutic role by modulating these pathways. Obesity and metabolic syndrome are characterized by visceral fat accumulation, elevated inflammatory cytokines, and abnormal adipocyte apoptosis. This creates a vicious cycle: increased fat  $\rightarrow$  elevated TNF- $\alpha$  and IL-6  $\rightarrow$  abnormal apoptosis  $\rightarrow$  chronic inflammation  $\rightarrow$  metabolic dysfunction (29). Aerobic exercise, as a non-pharmacological intervention, can disrupt this cycle by reducing fat mass, regulating cytokines, modulating apoptosis, and improving inflammatory responses, thereby enhancing metabolic health in obese women. Despite the clinical and epidemiological importance of obesity and metabolic syndrome in women, existing studies on the effects of aerobic exercise on adipose tissue apoptosis and inflammation are limited and fragmented. Many human studies have small sample sizes or focus on plasma markers rather than adipose tissue data (30). A systematic review of the available evidence allows the identification of overarching trends, strengths and weaknesses of previous research, and gaps in knowledge, facilitating the design of targeted clinical interventions and future research. Therefore, the objective of this systematic review is to collect and analyze existing evidence on the effects of aerobic exercise on apoptosis and adipose tissue inflammation in obese women with metabolic syndrome, providing a comprehensive overview of these molecular and metabolic processes and identifying research gaps.

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**Conflict of Interest**

There are no conflicts of interest.

**Authors' contributions**

R.A and M.GH: Idea presentation, software, methodology, data curation, writing-original

draft, writing review and editing. Supervision, project administration, Idea presentation, and preparation of the first draft. Cooperation in implementation, methodology

## References

1. Han TS, Lean ME. Metabolic syndrome. *Medicine*. 2015;43(2):80-7.
2. Samson SL, Garber AJ. Metabolic syndrome. *Endocrinology and Metabolism Clinics*. 2014;43(1):1-23.
3. Toalson P, Ahmed S, Hardy T, Kabinoff G. The metabolic syndrome in patients with severe mental illnesses. Primary care companion to the *Journal of clinical psychiatry*. 2004;6(4):152.
4. You T, Arsenis NC, Disanzo BL, LaMonte MJ. Effects of exercise training on chronic inflammation in obesity: current evidence and potential mechanisms. *Sports Medicine*. 2013;43(4):243-56.
5. Emamaullee JA, Shapiro AJ. Interventional strategies to prevent  $\beta$ -cell apoptosis in islet transplantation. *Diabetes*. 2006;55(7):1907-14.
6. Fock KM, Khoo J. Diet and exercise in management of obesity and overweight. *Journal of gastroenterology and hepatology*. 2013;28:59-63.
7. Jakicic JM, Rogers RJ, Davis KK, Collins KA. Role of physical activity and exercise in treating patients with overweight and obesity. *Clinical chemistry*. 2018;64(1):99-107.
8. Pereira BC, Da Rocha AL, Pauli JR, Ropelle ER, De Souza CT, Cintra DE, et al. Excessive eccentric exercise leads to transitory hypothalamic inflammation, which may contribute to the low body weight gain and food intake in overtrained mice. *Neuroscience*. 2015;311:231-42.
9. Nicklas BJ, Beavers KM. Exercise, weight loss, and effects on inflammation. *Current Cardiovascular Risk Reports*. 2010;4(4):284-92.
10. Morawin B, Tylutka A, Chmielowiec J, Zembron-Lacny A. Circulating mediators of apoptosis and inflammation in aging; physical exercise intervention. *International Journal of Environmental Research and Public Health*. 2021;18(6):3165.
11. Phaneuf S, Leeuwenburgh C. Apoptosis and exercise. *Medicine & Science in Sports & Exercise*. 2001;33(3):393-6.
12. Azar JT, Maleki AH, Moshari S, Razi M. The effect of different types of exercise training on diet-induced obesity in rats, cross-talk between cell cycle proteins and apoptosis in testis. *Gene*. 2020;754:144850.
13. Marinho R, Munõz VR, Pauli LS, Ropelle EC, de Moura LP, Moraes JC, et al. Endurance training prevents inflammation and apoptosis in hypothalamic neurons of obese mice. *Journal of cellular physiology*. 2019;234(1):880-90.
14. Samari Ebrahimzadeh, Azamian Jezi, Akbarpour Bani. The effect of 12 weeks of multicomponent exercise training on serum levels of interferon gamma and interleukin-17 in elderly men. *Journal of Exercise Physiology and Physical Activity*. 2025. doi: 10.48308/joeppa.2025.240980.1386.
15. Bradley RL, Jeon JY, Liu FF, Maratos-Flier E. Voluntary exercise improves insulin sensitivity and adipose tissue inflammation in diet-induced obese mice. *American Journal of Physiology-Endocrinology and Metabolism*. 2008;295(3):E586-94.
16. Tayebi SM, Poorhabibi H, Heidary D, Amini MA, Sadeghi A. Impact of aerobic exercise on chronic inflammation in older adults: a systematic review and meta-analysis. *BMC Sports Science, Medicine and Rehabilitation*. 2025;17(1):229.
17. Rauramaa R, Halonen P, Väisänen SB, Lakka TA, Schmidt-Trucksäss A, Berg A, et al. Effects of aerobic physical exercise on inflammation and atherosclerosis in men: the DNASCO Study: a six-year randomized, controlled trial. *Annals of internal medicine*. 2004;140(12):1007-14.
18. Attarzadeh Hoseini SR, Rahimiyan Mashhad Z. Comparison the effect of aerobic training and diet on Body Composition and Metabolic Syndrome Indexes in overweight and obese women. *Applied Research of Sport Management*. 2012;1(2):27-36.(in Persian)
19. Alménning I, Rieber-Mohn A, Lundgren KM, Shetelig Løvvik T, Garnæs KK, Moholdt T. Effects of high intensity interval training and strength training on metabolic, cardiovascular and hormonal outcomes in women with polycystic ovary syndrome: a pilot study. *Plos one*. 2015;10(9):e0138793.
20. Benham JL, Booth JE, Corenblum B, Doucette S, Friedenreich CM, Rabi DM, et al. Exercise training and reproductive outcomes in women with polycystic ovary syndrome: a pilot randomized controlled trial. *Clinical endocrinology*. 2021;95(2):332-43.
21. Radmehr S., Riyadh Al-ani R., Abbas Oleiwi Rfeash S., Ali Hassan S., Nabil Mohamed Ibrahim Salem M. Effect of aerobic exercise on the expression of inflammation-related genes TNF- $\alpha$ , IL-6, and IL-10 in overweight individuals. *JEOCT*, 2025; 5(4): 180-197. doi: 10.22122/jeoct.2025.561902.1181. (in Persian)
22. Costa EC, Sá JC, Stepto NK, Costa IB, Farias Junior LF, Moreira SD, Soares EM, Lemos TM, Browne RA, Azevedo GD. Aerobic training improves quality of life in women with polycystic ovary syndrome. 2018;50(7):1357-66.
23. Vigorito C, Giallauria F, Palomba S, Cascella T, Manguso F, Lucci R, et al. Beneficial effects of a three-month structured exercise training program on cardiopulmonary functional capacity in young women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology & Metabolism*. 2007;92(4):1379-84.

24. Patel V, Menezes H, Menezes C, Bouwer S, Bostick-Smith CA, Speelman DL. Regular mindful yoga practice as a method to improve androgen levels in women with polycystic ovary syndrome: a randomized, controlled trial. *Journal of Osteopathic Medicine*. 2020;120(5):323-35.
25. Ribeiro VB, Pedroso DC, Kogure GS, Lopes IP, Santana BA, Dutra de Souza HC, et al. Short-term aerobic exercise did not change telomere length while it reduced testosterone levels and obesity indexes in PCOS: a randomized controlled clinical trial study. *International Journal of Environmental Research and Public Health*. 2021;18(21):11274.
26. Orio F, Muscogiuri G, Giallauria F, Savastano S, Bottiglieri P, Tafuri D, et al. Oral contraceptives versus physical exercise on cardiovascular and metabolic risk factors in women with polycystic ovary syndrome: a randomized controlled trial. *Clinical endocrinology*. 2016;85(5):764-71.
27. Wang X, Wang Z, Tang D. Aerobic exercise alleviates inflammation, oxidative stress, and apoptosis in mice with chronic obstructive pulmonary disease. *International journal of chronic obstructive pulmonary disease*. 2021:1369-79.
28. Ahmadi P, Ghahramani M. A review of apoptosis in diabetic patients with the approach of exercise activity. *EBNESINA*. 2024;26(3):86-99.(in Persian)
29. Ghahramani M, Setooni zadeh fard S E, Ghahramani M. Molecular Mechanisms of Aerobic Exercise in Modulating Cardiac Apoptosis: A Systematic Review in Cardiovascular Patients. *Journal of Advanced Biomedical Sciences*. 2025; 15 (4) :325-336.(in Persian)
30. Lu K, Wang L, Wang C, Yang Y, Hu D, Ding R. Effects of high-intensity interval versus continuous moderate-intensity aerobic exercise on apoptosis, oxidative stress and metabolism of the infarcted myocardium in a rat model. *Molecular medicine reports*. 2015 ;12(2):2374-82.