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*Research Article*

# The effect of aerobic exercise on the oxidative stress of brown adipose tissue

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## Abstract

Brown adipose tissue (BAT) plays a very critical role in controlling obesity and metabolic complications due to thermogenesis (fatty acid conversion into heat). Just as this tissue's natural activity prevents obesity, obesity can also disrupt its function through several mechanisms. This is especially due to the increase in oxidative stress. Many studies have shown that aerobic exercise improves the thermogenic function of BAT and exert an anti-obesity effect. However, aerobic exercise not only improves brown fat tissue function, but also protects it from oxidative damage by increasing its antioxidant defense capacity. Since aerobic exercise with moderate intensity can cause a physiological increase in reactive oxygen species (ROS), molecular studies have shown that ROS produced following aerobic exercise can enhance the expression of HSP72, Nrf-2 and SIRT3, and following It enhances the expression of antioxidant enzymes such as SOD, CAT, GPX and hemooxygenase in BAT. Considering that these enzymes (as enzymatic antioxidant defense) inhibit and neutralize all kinds of ROS, BAT's antioxidant defense capacity is increased and disruption of its biological functions is prevented.

**Keywords:**
Aerobic exercise, brown adipose tissue, Nrf-2 and SIRT3

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## 1. Introduction

Adipose tissue is very critical for health due to its multiple biological roles. Adipose tissue is the main organ for storing excess energy in the form of triglycerides (1). There are three distinct types of adipose tissue in humans and rodents, including white adipose tissue (WAT), brown adipose tissue (BAT), and beige adipose tissue. WAT is primarily composed of white adipocytes and the stromal vascular fraction (SVF), which is composed of multiple cell types, including progenitor cells and immune cells. WAT consists of single-cavity fat cells that store large amounts of triglycerides as chemical energy (2). Adipose tissue is now fully recognized as an active metabolic organ. Historically, adipose tissue was thought to be the only source of fuel or insulation for the organs and act as a connective tissue. Studies in the last two decades have shown that adipose tissue plays a crucial role in systemic metabolic health. While adipose tissue is actually the primary site of energy storage in the form of lipids, it is also a major endocrine organ. It produces and secretes adipose tissue-specific hormones known as adipokines. In addition to hormones, adipose tissue produces and secretes various forms of genetic material, lipids and proteins, all of which contribute to its endocrine activity. Adipose tissue also responds to a variety of circulating metabolites and hormones, including lipids, growth hormone, cortisol, insulin, catecholamines, and many others. In addition, adipose tissue is recognized as a major metabolic organ, along with the liver and skeletal muscle. This is critical for maintaining proper glucose homeostasis (3). any of the three main functions of adipocytes (fat storage, endocrine function, and insulin Disruption of response) can have major effects on overall metabolic health.

In positive energy balance, adipocytes are hypertrophied and their normal function is disturbed. In this situation, due to the production and release of many inflammatory mediators, it provides the basis for many obesity-related diseases such as type 2 diabetes, cardiovascular disease, hepatic steatosis and numerous cancers (4,5,6). In contrast to WAT, BAT is composed of multicellular brown fat containing numerous mitochondria that mediate thermogenesis and protect against hypothermia and obesity. It has been reported that BAT's oxidative metabolism plays a crucial role in the energy consumption of the whole body. For this reason, increasing the activity of this tissue is directly related to fat mass control and prevents obesity and its complications (7). BAT maintains body temperature through a process called non-shivering thermogenesis and dissipates energy as heat. Thermogenesis occurs through brown adipocyte-specific uncoupling protein 1 (UCP1), also called thermogenin, in response to adrenergic signaling through the sympathetic nervous system (8). Environmental stimuli, such as cold and physical activity, activate the adrenergic receptors in BAT. This is followed by an activated signaling cascade that leads to lipolysis of TG stores and release of fatty acids (FAs), and finally, activation becomes UCP1. The UCP1 protein is located in the inner mitochondrial membrane (IMM) and transports H+ ions across the mitochondrial inner membrane in the presence of FA and glucose, leading to the uncoupling of cellular respiration and ATP synthesis, resulting in heat release instead of ATP production (9). In fact, stored free fatty acids are converted into heat, water and oxygen, which decreases the body's fat content and causes weight loss.

Therefore, BAT plays a natural role in obesity. It is well known that physical activities, especially long-term aerobic exercises, combat obesity. Aerobic exercises can reduce obesity by increasing fatty acid oxidation in skeletal muscle. In addition, they reduce fat absorption in the digestive system and reducing appetite. One of the other mechanisms by which aerobic exercise exerts its anti-obesity effect is its effect on BAT (10). Aerobic exercise can activate thermogenesis signaling pathways in BAT and increase energy consumption. However, aerobic exercise can improve BAT function by decreasing oxidative stress and inflammation. By improving the function of this tissue, it can reduce obesity. Studies show that aerobic exercise simultaneously reduces oxidative stress and systemic and tissue inflammation (11,12). Compared to other tissues, aerobic exercise's effect on oxidative stress and inflammation in BAT has been less investigated. Most studies have been conducted in recent years. Based on this, the present study aims to investigate the effect of aerobic exercise on oxidative stress in BAT.

**The effect of aerobic exercise on BAT oxidative stress**

Aerobic exercise is a proven approach to fighting obesity and its associated diseases. It improves metabolic abnormalities in peripheral tissues such as skeletal muscle, the liver and white adipose tissue. However, aerobic exercise's effects on obesity-induced oxidative stress and inactivity in BAT have been less investigated. Oxidative stress occurs when antioxidant defense against free radicals, especially reactive oxygen species (ROS), is low. In this condition, ROS react with cell biomolecules such as membrane lipids, intracellular proteins and DNA and disrupt cell function. Evidence shows that oxidative stress is the basis of many cellular disorders, followed by numerous diseases of the earth (13,14).

The accumulation of ROS can disrupt the function of this tissue, especially thermogenesis, by affecting many signaling pathways in brown fat tissue. This disorder is very common in obese, inactive and elderly people (15,16). Despite ROS negative effects, their role in the cell is dual. Evidence shows that ROS are important signaling molecules. ROS at physiological levels enhance cyclic adenosine monophosphate (cAMP)/p38 mitogen-activated protein kinase (MAPK) signaling to induce UCP1 expression and subsequent thermogenesis development in mouse BAT (17). Sestrin2, which is a stress-inducible protein, plays a role in this process (18). However, overexpression of Sestrin2 reduces ROS accumulation in mice, leading to dysregulation of UCP1 in BAT. In addition, the excessive increase of antioxidants in BAT by inhibiting ROS inhibits UCP1 expression in mouse BAT (19). Based on this, it is concluded that excessive suppression of ROS production is harmful for BAT normal function. Therefore, it seems that maintaining physiological levels of ROS is beneficial for BAT metabolism (17). Thus, moderate-intensity aerobic exercises that produce moderate levels of ROS at the tissue level are beneficial to human health. Obesity increases ROS production through several mechanisms and exerts negative effects. It has been reported that in obese animals, the production of ROS in BAT is twice as high as in lean animals (20). It has been reported that BAT oxidative stress is increased in obese mice. Twenty weeks of aerobic exercise reduce oxidative stress by enhancing antioxidant proteins including HSP72, nuclear factor erythroid-related factor 2 (Nrf2), and Mn-SOD in BAT. These results indicate an increase in BAT enzymatic antioxidant defense capacity in response to aerobic exercise (21). Since BAT has a very high oxidative capacity,

the increase in energy consumption is associated with the production of large amounts of ROS, which, if increased excessively, can have negative effects on BAT. Regular aerobic exercise controls cell and tissue oxidative homeostasis through two mechanisms. This is both at the tissue level and in the blood circulation. The first mechanism is to reduce the excessive production of oxygen species and the second mechanism is to increase the antioxidant capacity of cells, which can protect tissues from oxidative damage (22). Aerobic exercise can affect intracellular proteins. It has been reported that HSP72 modulates oxidative stress-activated signals by directly inhibiting JNK (23). It is thought that the increase in HSP72 caused by aerobic exercise in BAT may also suppress JNK activation. This may exert its antioxidant effect. On the other hand, aerobic exercise increases Nrf2 expression as one of the most significant factors regulating antioxidant gene expression at the cellular level (24). As mentioned, Nrf2 is a transcription factor sensitive to ROS and NO (25). Exposure of cells to oxidative or nitrosative stress causes Nrf2 to be translocated from the cytoplasm to the nucleus. It binds to the antioxidant response element for defense. An antioxidant that protects cells against cytotoxic and oxidative damage (25). Nrf2 coordinates antioxidant responses to stress by activating the gene expression of antioxidant enzymes. In confirmation of the effect of Nrf2 on increasing the capacity of the enzymatic antioxidant defense system following aerobic exercise, it has been reported that inhibition of Nrf2 in the skeletal muscle of aged rats inhebited the increase in the mRNA level of antioxidant enzymes in the skeletal muscle after aerobic exercise (running on a treadmill). This results indicated decreased skeletal muscle antioxidant defense capacity after aerobic exercise (26). Nrf2 is the key regulator of cellular oxidation at the transcriptional level, which directly controls SOD, HO-1 and CAT concentrations (27).HO-1 helps convert heme to biliverdin, which is converted to bilirubin, a powerful antioxidant (28). When ROS accumulate excessively, Nrf2 is activated and accumulates in the cytoplasm (29). Nrf2-deficient mice show severe vulnerability to oxidative stress in liver and stomach tissues (30). By improving Nrf2 activity in the body, oxidative stress damage can be prevented (31). In vivo studies have shown that Nrf-2 activation reduces oxidative stress at the cell surface. As a result, it prevents cellular oxidative damage and reduces fatigue by affecting mitochondrial oxidation (32). It has been reported that aerobic exercise increases antioxidant capacity in BAT by increasing gene expression of antioxidant enzymes (33). Another molecular mechanism by which aerobic exercise can develop antioxidant defense capacity in BAT is the increase in the myokine irisin released from active skeletal muscles. Irisin has antioxidant effects. It seems that irisin exerts its antioxidant effect by activating a set of signaling pathways on the surface of cells, especially BAT. Numerous evidences show that sequestosome-1 protein, due to its multifunctional binding sites, affects downstream metabolic signaling pathways, including adipogenesis and BAT thermogenesis and acts as a central regulator of metabolic diseases (34). In addition, sequestosome-1 has putative binding sites for activating the Nrf2, a key regulator of HO-1 expression (34). It has been reported that aerobic exercise increases the release of erysin from skeletal muscle through the activation of sequestosome-1 and increases the nuclear translocation of Nrf2. This is followed by the up-regulation of hemooxygenase-1 and other antioxidant enzymes in BAT(34). As mentioned, Nrf2 plays a pivotal role in regulating a set of genes that encode the antioxidant defense system in the face of oxidative stress to deal with ROS (35,36). A number of studies have demonstrated the beneficial effects of Nrf2 on tissue protection against oxidative damage (37, 38).

In mice fed a high-fat diet, reported four weeks of aerobic training significantly activated the Nrf2 pathway and Keap1 expression in the tissue. Musculoskeletal decreased (39). Another mechanism by which aerobic exercise controls oxidative stress at the tissue level is the inhibition of NF-κB by Nrf2. Nrf2 and NF-κB signaling pathways interact to control downstream target protein transcription or function (40). NF-κB can directly inhibit Nrf2 antioxidant signaling (41), while Nrf2 negatively regulates NF-κB signaling pathway by increasing antioxidant defense (42). It has been shown that Nrf2 may be associated with the induction of NF-κB, IL-1ß and TNF-α expression, all of which activate inflammatory pathways at the tissue level (43). It has been confirmed that in mice lacking Nrf2, NF-kB expression was activated, causing inflammation, oxidative stress, and insulin resistance in the liver (44). Therefore, aerobic exercise may exert its tissue-protective effect by activating Nrf2 and suppressing the NF-kB pathway, which are the main regulators of inflammation and oxidative stress (42). Aerobic exercise can also enhance brown fat tissue's antioxidant defense capacity by affecting Sirtuin 3 expression (45). One of the most important regulators of BAT function is SIRT3. SIRT3 is a mitochondrial sirtuin deacetylase. SIRT3 regulates the expression of many mitochondrial proteins in BAT, including UCP-1 (46). Aerobic exercise is one of the most important SIRT3 stimulators. It has been reported that its expression increases greatly in competitive athletes (47). The increase in SIRT3 expression in animal models has also been reported (48). Aerobic exercise can increase SIRT3 protein expression in BAT. This is associated with an increase in the number of mitochondria and cristae density, and indicates the role of SIRT3 is in the biogenesis of mitochondria.

In this condition, brown fat tissue's energy production capacity is increased. As a result of enhancing ATP availability, the function of this tissue is developed.Additionally, SIRT3 is known to protect against oxidative stress and enhance mitochondrial function (49). MnSOD is a very critical antioxidant enzyme and inhibitor of ROS produced in mitochondria that can be activated by SIRT3 (50). SIRT3 has been reported to directly upregulate MnSOD such that inhibition of SIRT3 leads to increased ROS through decreased MnSOD activation (51). There are several studies showing the relationship between SIRT3 and MnSOD (SOD2) and improved aerobic performance. In fact, this relationship is two-way, in such a way that SIRT3 can improve aerobic performance, and vice versa, aerobic exercise can lead to an increase in SIRT3 expression (52,53). The results show that aerobic exercise can increase the activity of the antioxidant enzyme MnSOD by enhancing the expression of SIRT3. This will develop antioxidant defense capacity.

## 2. Conclusion

BAT plays a crucial role in maintaining health, so any dysfunction can lead to metabolic diseases. This is due to the reduction in energy consumption and the development of obesity. Pathological increase in systemic oxidative stress, as it is very common in obesity, old age and some diseases, can also induce oxidative stress in brown fat tissue. The main function of this tissue is thermogenesis and increased energy consumption, followed by condition control. It disturbs the whole metabolism. The review of studies shows that aerobic exercise can neutralize reactive oxygen species by increasing antioxidant defense capacity and reducing the oxidative stress in brown fat tissue. Aerobic exercise can enhance the antioxidant defense capacity of brown adipose tissue through various molecular mechanisms. The increase in HSP72, Nrf-2 and SIRT3 following aerobic exercise enhances the expression of antioxidant enzymes such as SOD, CAT, GPX and hemooxygenase and improves the capacity to inhibit reactive oxygen species and other free radicals in BAT. Protect this tissue from oxidative stress.

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## Compliance with ethical standards

**Conflict of interest** None declared.

**Ethical approval** the research was conducted with regard to the ethical principles.

**Informed consent** Informed consent was obtained from all participants.

## Author contributions

Conceptualization: N.R, M.A.A, S.R.A, M.P, H.F; Methodology: N.R, M.A.A, S.R.A, M.P, H.F ; Software: N.R, M.A.A, S.R.A, M.P, H.F ;Validation: N.R, M.A.A, S.R.A, M.P, H.F; Formal analysis: N.R, M.A.A, S.R.A, M.P, H.F; Investigation: N.R, M.A.A, S.R.A, M.P, H.F; Resources: N.R, M.A.A, S.R.A, M.P, H.F.; Data curation: N.R, M.A.A, S.R.A, M.P, H.F; Writing - original draft: N.R, M.A.A, S.R.A, M.P, H.F; Writing - review & editing: N.R, M.A.A, S.R.A, M.P, H.F; Visualization: N.R, M.A.A, S.R.A, M.P, H.F.; Supervision: N.R, M.A.A, S.R.A, M.P, H.F; Project administration: N.R, M.A.A, S.R.A, M.P, H.F; Funding acquisition: N.R, M.A.A, S.R.A, M.P, H.F.

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