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The effect of aerobic exercise on insulin sensitivity in brown adipose tissue

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Abstract

In order to reduce obesity complications, brown adipose tissue (BAT) plays a very important role. This tissue increases energy consumption through thermogenesis by absorbing and oxidizing glucose and fatty acids. It controls weight and reduces obesity. Physical activities, especially aerobic exercise, can reduce obesity by improving BAT function. Despite the contradictory results evidence shows that aerobic exercise enhances glucose uptake and oxidation in BAT by enhancing insulin sensitivity. Aerobic exercise increases insulin sensitivity by stimulating beta-adrenergic receptor activity and stimulating the production and release of growth differentiation factor 15 (GDF15) and prevents hyperglycemia complications caused by inactivity. Based on this, it is determined that the improvement of insulin sensitivity in brown fat tissue is one of the mechanisms justifying the positive effect of aerobic exercise on reducing obesity complications, which shows the importance of brown fat tissue in health development.

Keywords

Brown adipose tissue, aerobic exercise, insulin sensitivity, GDF15

Introduction

Due to the changes made in the lifestyle, obesity has been widely developed in many societies. Statistics show that in 2022, 2.5 billion adults will be overweight and more than 890 million adults will be obese. Although the prevalence of obesity has increased worldwide, its prevalence in geographical areas does not follow the same pattern. For example, its prevalence was in America (67%), while it was reported in Southeast Asia and Africa at about 31%. The prevalence of obesity worldwide more than doubled between 1990 and 2022(1). It is well known that obesity is a complex phenomenon and various factors play a role in its occurrence, one of the most important of which is reducing the amount of physical activity and increasing calorie intake. In recent years, the attention of researchers has been drawn to the role of regular physical activities on brown fat tissue in controlling obesity. Adipose tissue (AT) is an organ composed of different cells located in the intercellular matrix. These cells include adipocytes, preadipocytes, adipose stem cells (ASCs), fibroblasts, as well as endothelial, neural, and immune cells. There are two types of white adipose tissue (WAT) and brown adipose tissue (BAT), which have significant differences in terms of origin, function and morphology. WAT is the predominant type of AT in adult humans, which is distributed in a specific pattern throughout the body. Although the main function of WAT is to store energy, it also has different roles, including the control of metabolism (2). BAT is important for temperature regulation in small mammals. In humans, it is present in abundance in infants, BAT is believed to be absent in adult humans, however, recently with evidence from nuclear medicine (3), it has been shown that BAT is active in adult humans and plays a role It is very important in health. It has been reported that body mass index (BMI) has an inverse relationship with BAT activity. Therefore, any disturbance in BAT activity can lead to the development of obesity (4). Increasing the activity and volume of BAT can increase energy consumption by increasing thermogenesis and prevent the development of obesity and its complications (5). For this reason, BAT should be used as a target to control obesity and metabolic diseases caused by obesity (6,7). Studies conducted in recent years show that BAT can autocrine and paracrine regulate energy metabolism through the production and release of messenger molecules called cytokines.The evidence shows that exposure to cold, regular

physical activities and some phytochemical compounds by affecting the function of BAT control obesity and its complications (8). Studies show that physical activities, especially aerobic exercises It has increased the activity of BAT and increased the number of beige adipocytes, which indicates one of the important anti-obesity mechanisms of physical activities (9). Based on this, in the present study, the effect of aerobic exercise on the insulin signaling pathway of brown adipose tissue was examined.

The effect of aerobic exercise on insulin sensitivity in brown adipose tissue

Adipose tissue is a very dynamic tissue whose main task is to store energy when it is in excess (in satiety conditions) and to release it when it is needed (energy crisis) (10). In obesity, due to the changes that occur in the insulin signaling pathway in WAT, the sensitivity of this tissue to insulin is reduced and the ability to absorb glucose is disturbed, and the process of diabetes develops (11). Although insulin dysfunction is very common in skeletal muscle tissue, WAT and liver, it has been reported that this process may also occur in BAT (12,13). Evidence shows that β3-adrenergic receptor (AR) agonist can stimulate human BAT and increase the ability of insulin or β3-AR agonist to stimulate glucose absorption and thermogenesis, thereby controlling obesity (14). Regular physical activities, especially aerobic exercises, are one of the important stimuli for changing the function of WAT and BAT, and it is known that adipose tissue shows significant flexibility in response to physical activity (15). In general, regular physical activities, especially aerobic exercises, improve glucose absorption and insulin sensitivity in WAT, improve mitochondrial activity, regulate lipolysis, increase the production and release of anti-inflammatory adipokines, and reduce inflammatory adipokines, hypoxia and inflammation. The set of these changes improves the performance of WAT, and since the performance of this tissue affects the performance of other tissues, it ultimately leads to the development of health. However, the effect of aerobic exercise on BAT has not been investigated as much as on WAT. As mentioned, aerobic exercise increases insulin sensitivity in adipose tissue (16,17,18). Studies show that aerobic exercise increases the amount of glucose and fatty acid uptake and oxidation in BAT to increase oxidation and heat production (19). The amount of glucose uptake by BAT plays an important role in the homeostasis of this tissue (20). Activation of BAT by increasing the oxidation of glucose and fatty acids for heat

generation increases energy consumption and controls blood glucose (21). It has been reported that aerobic exercise in rodents has increased the expression of insulin signaling pathway proteins that facilitate glucose uptake in BAT (22,23). The effect of aerobic exercise on BAT glucose uptake is somewhat contradictory. Some studies have reported a decrease in glucose uptake by BAT following aerobic exercise (23,24,25). It seems that the reason for this phenomenon is not related to the weakening of the insulin signaling pathway in BAT, but the reason for it is the increase in the uptake of circulating glucose by skeletal muscle to supply the contraction energy needed to maintain muscle contraction (23). As a result, the rate of glucose uptake by BAT decreases to maintain the glucose required for skeletal muscle (26,27). On the other hand, eight weeks of aerobic training (running on a treadmill) in rodents (rats) caused the upregulation of insulin signaling pathway proteins in BAT, which indicates the effect of training on increasing insulin sensitivity in this tissue (28). The positive effect of aerobic exercise on BAT sensitivity to insulin in rats fed a high-fat diet was reported by Fu et al (2021). After feeding with high-fat food, the insulin signaling pathway was negatively regulated, and four weeks of training could reduce these changes and increase insulin sensitivity in this tissue (9). Aerobic exercise along with the up-regulation of the insulin signaling pathway also up-regulated the expression of lipid metabolism signaling pathway genes and down-regulated the inflammation signaling pathway in this tissue. These findings show that aerobic exercise activates the oxidation process of glucose and fatty acids in BAT and reduces the inflammation caused by obesity that can have a negative effect on BAT function. These results show that aerobic exercise reduces negative side effects. Obesity on BAT can prevent the development of obesity and its complications. From a molecular point of view, regular aerobic exercise increased insulin receptor expression and p42/p44 phosphorylation in BAT, which indicates that regular aerobic exercise can increase insulin sensitivity in this tissue. In addition, aerobic exercise increases the IRA/IRB ratio and increases glucose uptake in BAT (28).

The effect of aerobic exercise on GDF15 and insulin sensitivity in brown adipose tissue

Another mechanism by which aerobic exercise can improve insulin signaling in BAT tissue is the release of cytokines. Growth differentiation factor 15 (GDF15) is a protein belonging to

the family of transforming growth factor-β (TGF-β). Its receptor is expressed mainly in the brain and in WAT (29). Although the main origin of GDF15 is in the liver circulation, other tissues such as skeletal muscle, WAT and BAT also release GDF15 into the blood circulation (30). GDF15 is secreted from brown and beige adipocytes in response to thermogenic activity and reduces local inflammation, especially in BAT tissue (31). It has been reported that aerobic exercise increases the circulating levels of GDF15 after aerobic exercise (32,33). GDF15 reduces food intake, body weight and obesity and improves glucose tolerance by improving insulin action at the tissue level (34). On the other hand, increasing the circulating levels of GDF15 prevents obesity and insulin resistance by modulating metabolic activity by increasing the expression of thermogenic and lipolytic genes in BAT and WAT (35). Increased expression of thermogenic and lipolytic genes due to GDF15 activity is likely responsible for improved glucose uptake, increased insulin sensitivity, reduced WAT, and reduced obesity. Confirming the role of GDF15 in the control of obesity and insulin sensitivity reported in the knockout of GDF15 in rodents Body weight increased significantly along with insulin resistance, which indicates the role of GDF15 in controlling obesity and its complications, especially insulin resistance and diabetes (36).Based on this, it is clear that aerobic training improves glucose homeostasis and insulin sensitivity in BAT by increasing the expression and release of GDF15 and reduces obesity-related complications (37,38).

Conclusion

The study of the effect of aerobic exercise on insulin sensitivity in brown adipose tissue showed that, despite the contradictory results, aerobic exercise increased insulin sensitivity in BAT and increased glucose uptake by upregulating the proteins of the insulin signaling pathway in BAT. Aerobic exercise increases insulin sensitivity in BAT by increasing sympathetic stimulation and GDF15 expression, which can improve systemic glucose homeostasis, reduce insulin resistance, and then the complications caused by insulin resistance.

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Conflicts of interest

There are no conflicts of interest, according to the authors.

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