

# Sarcopenic obesity: potential therapeutic targets based on exercise

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**Abstract:** In recent years, sarcopenic obesity (SO) has increasingly become one of the serious public health challenges due to the rapid increase in the number of obese people in the world, which has caused a heavy burden on patients' life and social medical care. Challenges and regarding the diagnosis and treatment of SO remain because of its complex pathogenesis and limitations. As a safe and effective way to promote body health, exercise may prevent and treat SO through multiple mechanisms. In this context, this paper systematically summarizes and discusses the possible mechanism of the benefit of SO via exercise, in order to provide novel ideas and theoretical support for the screening of SO therapeutic targets.

**Keywords:** sarcopenic obesity; exercise; mechanism; therapeutic targets

## 1. Introduction

We are currently during a global epidemic of obesity and its related metabolic diseases. Obesity is "invisible killer" of health, which will pose a major threat to human health. Obesity increases lipids and glucose, impairs lipid and glucose metabolism, and is a strong risk factor for atherosclerosis and other cardiovascular complications, as well as many other chronic diseases. In addition, obesity is closely associated with elevated levels of chronic systemic inflammation and a gradual decline in physical activity and cardiopulmonary function, all of which led to a poorer prognosis for diseases and increased risk of muscle mass reduction<sup>[1][2]</sup>. Skeletal muscle is the largest organ in the human body, and its quality and integrity are essential for the proper functioning of the musculoskeletal system and for the homeostasis of glucose and lipid metabolism<sup>[3]</sup>. Persistent obesity causes changes in skeletal muscle structure and function, which can lead to skeletal muscle atrophy characterized by loss skeletal muscle mass, known as "sarcopenic obesity (SO)". In obesity, the loss of skeletal muscle mass can severely impair motor system function, resulting in dyskinesia and impaired glucose and lipid metabolism. This can lead to falls, osteoporosis, dyslipidemia, cardiovascular risk, and metabolic syndrome. Understanding the pathophysiological process of obesogenic muscular atrophy and identifying effective ways to prevent sarcopenic obesity are crucial for improving quality of life. The identification of SO therapeutic targets has received extensive attention. As a safe and effective way to promote body health, exercise is considered to be one of the best means to prevent and treat SO. This article reviews the mechanism of exercise intervention in obesity-induced muscular atrophy, to provide theoretical basis for screening therapeutic targets of SO.

## 2. Obesity and sarcopenia

Skeletal muscle is one of the main organs of glycolipid metabolism in human body and has a wide range of physiological functions. Muscular atrophy is an obvious histological phenomenon in patients with sarcopenia and muscle wasting diseases. A variety of pathologic conditions, including aging, obesity, cancer, and diabetes are characterized by loss of skeletal muscle mass<sup>[4]</sup>. Sarcopenia leads to reduced energy expenditure, decreased physical activity, and altered hormone levels, which lead to obesity. Meanwhile, obesity also accelerate the development of sarcopenia. One study found that the quadriceps muscle cross-sectional area of male SD rats decreased significantly after feeding on a diet<sup>[5]</sup>. In an animal model of hereditary obesity (such as ob/ob or db/db mice), skeletal muscle mass muscle fiber cross-sectional area were smaller than in normal-weight control mice<sup>[6]</sup>. The skeletal weight of mice in a high-fat diet-induced obese animal model (HFD) decreased, and the expression of two muscle-specific ubiquitin ligases MuRF1 and Atrogin-1 genes and proteins increased significantly.

Furthermore, the cross-sectional area of skeletal muscle fibers was significantly decreased of HFD-fed mice, as well as time to fatigue, the distance, and grip strength on animal running platforms, suggesting that high-fat diet-induced obesity is associated with decreased skeletal muscle mass and muscle dysfunction<sup>[7]</sup>. Collins and his colleagues explored that compared with the normal diet control group, the weight and body fat of rats in the high-fat and high-sugar obesity-prone group increased, while the muscle mass of lateral femoris decreased. At the same time, there were fat deposits between and within skeletal muscle fibers, the fibrosis level increased, and the cross-sectional area of muscle fibers were decreased<sup>[8]</sup>. In summary, obesity can lead to sarcopenia.

### 3. Exercise and SO

The pathophysiological mechanism of obesity-induced skeletal muscle atrophy is complex and has not been fully elucidated. People with skeletal muscle atrophy have the decreased muscle strength, the impaired physical function recovery ability, and the limited motor ability, which causing the serious economic burden to themselves and society. Current therapeutic strategies for obesity-induced skeletal muscle atrophy include exercise, nutritional supplementation and drug therapy. However, exercise is one of the safe and effective measures to prevent and treat obesity-induced muscular atrophy.

It is well known that exercise is an important means to reduce obesity and delay the loss of skeletal muscle mass. Increased levels of physical activity not only stimulate skeletal muscle protein synthesis<sup>[9]</sup>, but also promote the release of proteins associated with skeletal muscle metabolism through repeated muscle contraction and relaxation<sup>[10]</sup>. Mechanistically, different types of exercise such as resistance and endurance exercise activate different signaling pathways, leading to specific adaptations of skeletal muscles. Antiresistive exercise reduces systemic inflammation by inhibiting inflammatory proteins and cytokines in aging and cachexia states, and reduces the activation of ubiquitin-ligase in skeletal muscle. Repeated endurance exercise training activates selective cell signaling pathways, promotes mitochondrial biogenesis, stress protein expression, and increases the antioxidant capacity of skeletal muscle fibers during exercise mode. Endurance exercise inhibits skeletal muscle protein breakdown by increasing mTOR signaling, and reduces activation of the ubiquitin-proteasome pathway to promotes skeletal muscle hypertrophy. In general, resistance exercise is more effective than aerobic exercise in maintaining skeletal muscle mass by increasing protein synthesis rather than degradation, and aerobic exercise has beneficial effects on skeletal muscle mass mainly by improving aerobic capacity, promoting mitochondrial biogenesis, increasing oxidase activity and maintaining metabolic homeostasis<sup>[11]</sup>. Although different exercise pathways differ, they all significantly inhibit muscle atrophy, suggesting that different exercise modes may also play a momentous role in obesity-related muscular atrophy.

### 4. The pathways and mechanisms of exercise intervention in SO

#### 4.1 Exercise inhibits abnormal protein degradation pathways

Abnormal activation of muscle protein degradation is a crux factor leading to muscle atrophy, and the UPS pathway plays a key role in this process. Exercise could regulate the levels of UPS related proteins. It has been reported that MuRF-1 in the lateralis femoris muscle is significantly upregulated after acute resistance exercise in healthy young men, while after 24 hours, MuRF-1 mRNA levels returned to basal level<sup>[12]</sup>. Resistance exercise resulted in up-regulation of MuRF-1 at 4 h postexercise, and downregulation of FOXO3a and MAFbx at 12 h postexercise. However, endurance exercise increased FOXO1A, MuRF-4, and MAFbx mRNA expression within 3 hours after exercise, and did not inhibit it at 12-24 hours<sup>[13]</sup>. Another study reported that MAFbx was up-regulated immediately after resistance exercise (with increased phosphorylation of p38 MAPK and decreased phosphorylation of Akt), down-regulated 24 h later, and returned to pre-exercise levels 72 h<sup>[14]</sup>. So, these reported showing that the effects of exercise type, intensity, and post-exercise time processes on MuRF-1 and MAFbx were not the same. Furthermore, exercise also regulate the expression of UPS-related proteins in the disease state to inhibit muscle atrophy process. It has been reported that lifelong aerobic exercise successfully prevents and delays age-induced skeletal muscle atrophy by preventing aging-induced ubiquitin-proteasome system damage by inhibiting key regulatory components of UPS, inhibiting excessive cell apoptosis, and optimizing mitochondrial quality control<sup>[15]</sup>. 4 weeks of endurance training decreased skeletal muscle MuRF-1 levels in patients with heart failure, while 12 weeks of exercise decreased ubiquitin-ligase Rnf28 expression in skeletal muscle in patients with advanced

congestive heart failure, increased skeletal muscle cross-sectional area, and slowed progression of progressive muscle atrophy<sup>[16]</sup>. Therefore, exercise may inhibit sarcopenic obesity by targeting and regulating proteasome activity in the UPS system. The specific targets of different exercise interventions will need to be further studied.

In addition, the disorder of autophagy system also affects the degradation process of muscle protein. Excessive autophagy exacerbates the breakdown of skeletal muscle protein, while inadequate autophagy results in aging, broken or misfolded proteins that cannot be cleared and replaced in a timely manner. Exercise is an effective strategy to counteract the adverse effects of sarcopenia. Exercise has been reported to regulate skeletal muscle metabolism and maintain internal environmental stability by promoting autophagy/mitochondrial autophagy pathways, thereby improving motor function, and preventing skeletal muscle atrophy<sup>[17][18][19]</sup>. However, due to the different effects of exercise intensity, type, and frequency on skeletal muscle contraction, different exercise patterns may lead to different responses to skeletal muscle autophagy<sup>[20]</sup>. Animal studies have shown that 9 weeks of resistance exercise training improve the strength and quality of skeletal muscle, improve muscle strength, and reduce muscle loss in aging rats by activating IGF-1/IGF-R-Akt/mTOR and Akt/FoxO3 signaling pathways, increase the level of autophagy in skeletal muscles<sup>[19]</sup>. Long-term autonomic resistance exercise in middle age (15 months in mice) enhanced the autophagy pathway, and led to soleus hypertrophy, compared with sedentary controls of the same age<sup>[21]</sup>. In addition, during 9 weeks of resistance exercise, autophagy regulatory proteins increased and LC3-II/LC3-I ratio decreased, p62 protein level decreased, which effectively prevented muscle loss and increased muscle strength<sup>[22]</sup>. Endurance exercise promote the expression of mitochondrial phagocytosis markers such as BNIP3 and Parkin in skeletal muscle of the elderly, thereby eliminating oxidative damage and dysfunctional mitochondria through the autophagolysosome pathway<sup>[23]</sup>. Overall, although different exercises have different effects on autophagy, they all significantly inhibit skeletal muscle atrophy. In the future, the role of autophagy in effecting obesity-induced skeletal muscle atrophy by different exercise methods still needs to be studied continuously.

#### ***4.2 Exercise promotes muscle protein synthesis***

Different types of exercise affect skeletal muscle protein synthesis through different mechanisms. Endurance exercise inhibit protein synthesis in skeletal muscle through a variety of molecular signaling pathways, promote protein degradation, produce energy substrates, such as amino acids, for muscle contraction or metabolism, and maintain aerobic endurance levels<sup>[24]</sup>. Resistance training activates Akt and phosphorylates FoxO3 to prevent nuclear translocation, inhibits its double transcriptional activation, and reduces muscle protein degradation<sup>[25]</sup>. Resistance exercise induces the activation of protein synthesis signaling pathways and alleviates skeletal muscle atrophy, and these anabolic effects may be partially eliminated by attenuation of Akt/FOXO1 axis activity<sup>[26]</sup>. Animal studies have shown that nine weeks of resistance exercise training improves skeletal muscle strength and mass in aging rats by activating IGF-1 and its receptor Akt/mTOR and Akt/FoxO3 signaling pathways<sup>[19]</sup>. In addition, 8-week exercise significantly increased the levels of IGF-1/IGF-1R AMPK protein, AMPK phosphorylation and FOXO3a phosphorylation in skeletal muscle of aged rats, and significantly increased muscle mass<sup>[27]</sup>. Endurance exercise training in aging enhance the expression of mitochondrial E3 ubiquitin ligase 1 (MUL1) and MuRF-1 mediated by AMPK/FoxO3, and finally degrade protein in skeletal muscle<sup>[28]</sup>, suggesting that endurance exercise promote the degradation of skeletal muscle dysfunction protein by activating AMPK/FoxO3 signaling pathway. Produce energy substrates for skeletal muscle contraction<sup>[17]</sup>. In brief, different types of exercise promote the production of skeletal muscle protein and delay the process of skeletal muscle atrophy through different types of molecular mechanisms. Future research could focus on whether combined exercise interventions have more striking effects, and whether there is an interaction between targets of different exercise modes.

#### ***4.3 Exercise inhibits inflammation***

Chronic inflammation is one of the considerable mechanisms of sarcopenic obesity. Studies have shown that 12 weeks of aerobic training combined with resistance training significantly increased the expression of muscle cytokine IL-7 secreted by skeletal muscle and significantly reduced inflammation levels in obese rats<sup>[29]</sup>. It has been reported that six weeks of aerobic endurance interval training improved glucose tolerance and insulin sensitivity in high-fat diet-induced obese mice, and significantly down-regulated the gene expressions of inflammatory cytokines such as TNF- $\alpha$ , IL-6 and

CCL2 in skeletal muscle, and tended to balance the expressions of pro-inflammatory and anti-inflammatory cytokines in muscle<sup>[30]</sup>. The gastrectomy muscle of mice showed obvious atrophy 6 weeks after Hindlimb Unloading, accompanied by increased inflammation. Chronic exercise intervention significantly reduce the expression of IL-6, TNF- $\alpha$ , Atrogin-1/MAFbx, inhibit inflammation and alleviate the process of skeletal muscle atrophy<sup>[31]</sup>. Resistance exercise significantly inhibit chronic inflammatory induced muscle atrophy<sup>[26]</sup>. The expressions of IL-6 and STAT3 are significantly increased in skeletal muscle of HFD-fed mice, and the combination of resveratrol and exercise can significantly up-regulate the expression of PI3K/Akt in skeletal muscle of HFD-fed mice, reduce the expression of IL-6 and STAT3, and alleviate skeletal muscle atrophy<sup>[32]</sup>. Recent studies have shown that exercise can prevent musculoskeletal obesity by regulating inflammation levels by altering miRNA expression<sup>[33]</sup>. In a word, exercise inhibits obesity-induced muscular atrophy by inhibiting the expression of inflammatory cytokines, but its targets and mechanisms still need to be further studied. For example, the application of inhibitors of IL-6, TNF- $\alpha$ , IL-7, IL-10 may also be so important as a therapeutic way.

#### 4.4 Exercise improves mitochondrial structure and function in muscles

Mitochondrial quality control is closely related to skeletal muscle mass. It was found that the weight and cross-section area of gastrectomy muscle of mice in 8 weeks HFD group were significantly decreased, SIRT1 protein level in skeletal muscle was significantly decreased compared with normal control group, the content of MyHC II was reduced by 76%, and the expression of atrophy gene-related proteins MuRF1 and Atrogin-1 was significantly increased, and the changes reversed by swimming training<sup>[34]</sup>. These findings suggest that exercise enhances mitochondrial quality control by activating SIRT1 signaling pathways, which may be a potential treatment for HFD-induced muscle dysfunction. An increase of PGC-1 $\alpha$  was found after acute and chronic endurance training in rodents and human aging skeletal muscle<sup>[35]</sup>, suggesting that endurance exercise induce autophagy and mitochondrial biogenesis and improve mitochondrial quality control in skeletal muscle health in the elderly<sup>[36]</sup>. Exercise as a protective intervention plays an important role in regulating the structure and apoptosis of obese skeletal muscle. Obesity is characterized by inducing skeletal muscle remodeling and mitochondria-mediated apoptosis, and exercise is an active regulator of skeletal muscle remodeling and apoptosis. Twelve weeks of aerobic exercise training improved the increase of intramuscular lipid infiltration and the decrease of muscle fiber cross-sectional area caused by obesity by down-regulating the mitochondrial apoptosis signal and cell apoptosis in skeletal muscle of obese mice, and then reduced the weight loss of skeletal muscle caused by obesity<sup>[37]</sup>. The mechanism of exercise to inhibits obesity-induced skeletal muscle atrophy may be involved in control mitochondrial function or in mitochondrial decomposition and fusion.

## 5. Conclusions and prospect

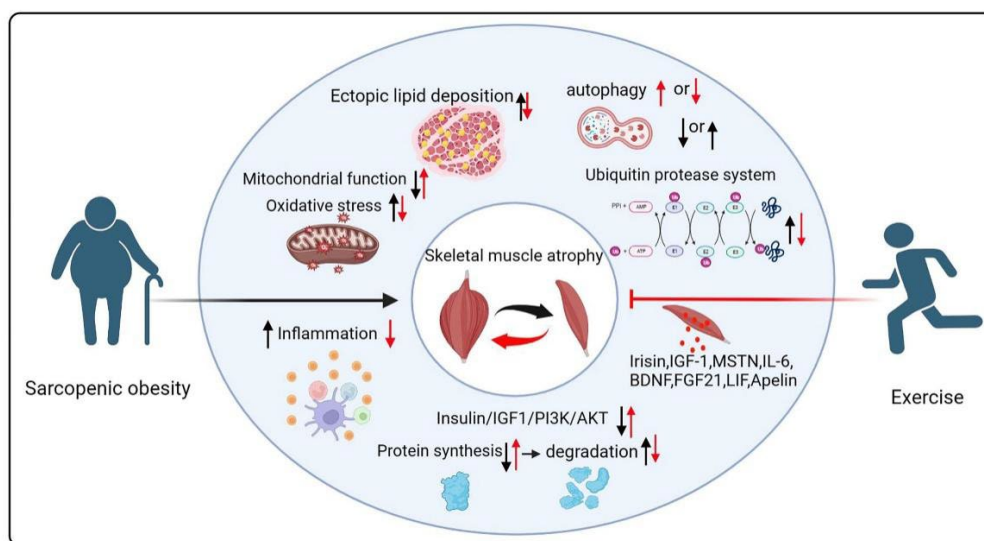


Figure 1. Possible mechanism of exercise induction to improve skeletal muscle atrophy in obesity.

With the increasingly serious global obesity problem, the incidence of SO is also increasing year by year, which has become one of the important challenges of public health security. This article based on the effects of exercise on inhibiting the synthesis of skeletal muscle protein, inhibiting excessive degradation of skeletal muscle protein, anti-inflammatory, improving mitochondrial function and secretion factors in the process of SO, it provide ideas and theoretical basis for screening effective therapeutic targets of SO. SO may have more serious manifestations when combined with cardiovascular diseases and Type 2 diabetes syndrome, and is often combined with a variety of diseases clinically. Therefore, based on existing studies, more attention should be paid to the potential interaction between the signal transduction mechanism of muscle involved in other diseases prevalent in SO and the signal transduction mechanism of SO, which may be an important therapeutic target in SO in the future.(See Figure 1)

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