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REVIEW

Research Progress on the Effect and Mechanism of Exercise Intervention on Sarcopenia Obesity

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Abstract: With the increasingly severe situation of obesity and population aging, there is growing concern about sarcopenia obesity (SO). SO refers to the coexistence of obesity and sarcopenia, which imposes a heavier burden on individuals and society compared to obesity or sarcopenia alone. Therefore, comprehending the pathogenesis of SO and implementing effective clinical interventions are vital for its prevention and treatment. This review uses a comprehensive literature search and analysis of PubMed, Web of Science, and CNKI databases, with search terms including "Sarcopenic obesity", "exercise", "cytokines", "inflammation", "mitochondrial quality control", and "microRNA", covering relevant studies published up to July 2024. The results indicate that the pathogenesis of SO is complex, involving mechanisms like age-related changes in body composition, hormonal alterations, inflammation, mitochondrial dysfunction, and genetic and epigenetic factors. Regarding exercise interventions for SO, aerobic exercise can reduce fat mass, resistance exercise can increase skeletal muscle mass and strength, and combined exercise can achieve both, making it the optimal intervention for SO. The potential mechanisms by which exercise may prevent and treat SO include regulating cytokine secretion, inhibiting inflammatory pathways, improving mitochondrial quality, and mediating microRNA expression. This review emphasizes the effectiveness of exercise interventions in mitigating sarcopenic obesity through comprehensive analysis of its multifactorial pathogenesis and the mechanistic insights into exercise's therapeutic effects. Understanding these mechanisms informs targeted therapeutic strategies aimed at alleviating the societal and individual burdens associated with SO.

Keywords: sarcopenic obesity, exercise, cytokines, microRNA, mitochondrial quality control, inflammation

Introduction

Sarcopenia, a prevalent geriatric syndrome associated with aging, is primarily characterized by reduced muscle mass, muscle strength, and/or physical function.[1] When sarcopenia coexists with obesity, it is defined as SO.[2] Nowadays, with the increasing aging population and rising obesity rates, the prevalence of SO is increasing as well. Statistics indicate that globally, at least one in every ten elderly individuals suffers from SO.[3] Additionally, due to the mutual influence of sarcopenia and obesity on various aspects such as decreased muscle mass and function, increased visceral fat, and metabolic disturbances, they can initiate a vicious cycle.[4] Therefore, compared to pure obesity or sarcopenia, SO may result in more severe health consequences, including lower cardiorespiratory fitness, reduced physical activity, and increased risks of falls, disability, mortality, depression, and cardiovascular metabolic diseases.[5–9]

Exercise, as a safe and cost-effective non-pharmacological intervention, provides a plethora of beneficial effects for SO and is deemed essential in its management.[10] Accumulating evidence indicates that exercise can not only reduce body fat percentage (PBF), increase lean body mass, and muscle strength in SO patients but also improve metabolic syndrome scores, anxiety, and depression levels, thereby reducing the risk of metabolic syndrome and depression to a certain extent.[11–15] Despite the myriad benefits of exercise for SO, research on the specific mechanisms underlying exercise interventions for SO remains relatively scarce. This review examines the intervention effects of various exercise types on SO and delves into exploring the potential intrinsic molecular mechanisms implicated in exercise interventions for SO, with the aim of offering novel insights and references for exercise interventions tailored to SO.

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Diagnostic of so

Diagnosis of Sarcopenia

Diagnosis of sarcopenia varies with age, gender, and race, and undergoes continuous updates.[16] Skeletal muscle mass (SMM) and appendicular skeletal muscle mass (ASM) can be evaluated through dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA). Muscle strength can be assessed with a handgrip dynamometer, while physical function can be measured by gait speed. Sarcopenia is diagnosed based on several criteria:

(1) International Working Group on Sarcopenia (IWGS) criteria: Diagnosis requires a gait speed of <1 m/s and a skeletal muscle mass index (SMI) of ≤7.23 kg/m_2 for men and ≤5.67 kg/m_2 for women.[17]

(2) European Working Group on Sarcopenia in Older People (EWGSOP) criteria: Diagnosis involves reduced muscle mass, strength, and/or physical function. The 2019 updated criteria include SMI (men <7.0 kg/m_2, women <5.5 kg/m_2), handgrip strength (men <27 kg, women <16 kg), and gait speed ≤0.8 m/s for diagnosing severe sarcopen- ia.[1]

(3) Asian Working Group for Sarcopenia (AWGS) criteria: Updated in 2019, the criteria include SMI (men <7.0 kg/m_2, women <5.4 kg/m_2) measured by DXA, or (men <7.0 kg/m_2, women <5.7 kg/m_2) measured by BIA. Additionally, handgrip strength should be (men <26 kg, women <18 kg), and gait speed should be <0.8 m/s.[18]

Diagnosis of Obesity

According to the World Health Organization, obesity is defined by a body mass index (BMI) ≥30, or by waist circumference (≥102 cm for men, ≥88 cm for women), or by body fat percentage (>25% for men, >35% for women).[19] In China, obesity is defined by a BMI ≥28, or by waist circumference (≥85 cm for men, ≥80 cm for women).[20] Due to limitations of the BMI indicator in distinguishing between fat and muscle mass, particularly in older adults, some scholars suggest using relative fat mass (RFM) as a more precise measure to assess body fat percentage, with RFM (≥30% for men, ≥40% for women) indicating obesity.[21]

Diagnosis of so

Currently, there is no standardized diagnostic criteria for sarcopenic obesity, as it is influenced by factors such as race. Typically, the concurrent diagnosis of sarcopenia and obesity suggests the presence of SO.

Pathogenesis of so

The pathogenesis of SO is complex and involves multiple interrelated factors, including age-related changes in body composition, genetic and epigenetic factors, hormonal changes, increased inflammation, and mitochondrial dysfunction.

Age-Related Changes in Body Composition

Influenced by factors such as hormonal changes, decrease due to physical activity barriers, and unhealthy lifestyle habits, the body composition of most individuals undergoes substantial changes as they age.[22–24] Regarding muscle mass, the human body undergoes a decline of approximately 3–8% per decade after reaching 30 years old, with a significant acceleration in the decline rate after 60 years old.[25] Furthermore, as individuals age, there is a noticeable increase in adipose tissue infiltration within skeletal muscle, leading to a decline in muscle quality and function. Regarding adipose tissue mass, most individuals undergo a gradual increase beginning between the ages of 20–25, reaching its peak between 60–75 years old.[25,26] Importantly, this rise in total adipose tissue mass is accompanied by a redistribution of fat tissue, characterized by a decrease in subcutaneous fat and an increase in visceral fat.[25] Consequently, the body composition of older adults consists primarily of adipose tissue rather than muscle tissue.

Hormonal Changes

Hormonal changes associated with aging lead to decreased levels of anabolic hormones such as growth hormone, insulin-like growth factor 1 (IGF-1), and testosterone, which contribute to muscle loss and impaired protein synthesis.[27] Additionally, decreased levels of anabolic hormones result in reduced lean body mass, leading to a decreased metabolic rate and promoting the accumulation of adipose tissue.[28] Concurrently, aging can also lead to increased levels of catabolic hormones such as cortisol.[29] These hormones promote protein breakdown and inhibit protein synthesis,

exacerbating muscle loss, while also stimulating the deposition of adipose tissue, particularly visceral fat accumulation, thereby increasing the risk of obesity and metabolic dysfunction.[30] Consequently, these hormonal changes exacerbate sarcopenia and contribute to the development and progression of obesity, further impacting the pathophysiology of SO.

Inflammation

In aging, heightened oxidative stress induces cellular damage and inflammation.[31] Nuclear factor-kappa B (NF-κB) activation in damaged cells triggers the expression of inflammatory genes, leading to heightened synthesis and release of pro-inflammatory cytokines.[32] Furthermore, obesity results in adipose tissue expansion and alteration, characterized by enlarged adipocytes and infiltration of inflammatory cells.[33] This inflammatory environment stimulates the production and release of pro-inflammatory cytokines within adipose tissue, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), when released into the circulation, can induce systemic inflammation.[34,35] Concurrently, heightened levels of inflammatory cytokines may reduce growth hormone and IGF-1 secretion in plasma and muscle, inhibit the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway, and thereby decrease muscle protein synthesis.[32] Hence, elevated levels of inflammatory cytokines accelerate the decline in muscle mass, strength, and function.

Mitochondrial Dysfunction

Aging, adipose tissue inflammation, insulin resistance, and other factors related to SO all lead to increased production of reactive oxygen species (ROS).[36,37] This elevation in ROS levels heightens oxidative stress, resulting in damage to mitochondrial DNA (mtDNA) and subsequent mitochondrial dysfunction.[38] Meanwhile, ROS regulates NF-κB and forkhead box protein O (FOXO) transcription factors, activating the ubiquitin-proteasome system (UPS) and autophagy-lysosome pathway, which results in mitochondrial biofunctional impairment, increased cell apoptosis, and compromised autophagy, ultimately accelerating skeletal muscle atrophy.[39] Additionally, AMP-activated protein kinase (AMPK) promotes mitochondrial biogenesis in skeletal muscle and enhances cellular energy metabolism by activating peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α).[40] During aging, the PGC-1α-nuclear respiratory factors (NRF1)-mitochondrial transcription factor A (TFAM) pathway is impaired, resulting in decreased mitochondrial function and quantity, thereby contributing to the development of SO.[41]

Genetic and Epigenetic Factors

Although genetic and epigenetic factors are crucial in the development of sarcopenia and obesity, our current understanding of their specific roles in SO remains limited. Research suggests that genetic variations in α-actinin-3 (ACTN3), myostatin-1, vitamin D receptor, methylenetetrahydrof- olate reductase (MTHFR), and nuclear respiratory factor 2 (NRF2) may contribute to the development of sarcopenia.[42–45] These genetic variations may impact muscle mass and strength by affecting individual responses to exercise, muscle protein synthesis, and energy regulation.[42–45] Furthermore, genetic variations linked to obesity, including those in the fat mass and obesity-associated gene (FTO), β-2 adrenergic receptor (ADRB2) gene, melanocortin-4 receptor (MC4R), and leptin receptor (LEPR), may influence metabolic processes, energy expenditure, appetite regulation, thereby leads to excessive accumulation of adipose tissue.[46]

In terms of epigenetics, studies have found that in the lateral femoral muscle of male patients with sarcopenia, DNA methylation regions were enriched in genes related to myotube fusion, oxidative phosphorylation, and voltage-gated calcium channels, and were associated with sarcopenia as well as decreased muscle mass, strength, and function in the elderly, suggesting that changes in DNA methylation in the muscle may contribute to the development of sarcopenia in old age.[47] Additionally, Xu et al conducted an exome-wide association analysis of SO cases in the UK Biobank cohort and found that the long non-coding RNA LYPLAL1-AS1 is co-localized with SO in various tissues such as muscle, subcutaneous fat, and bone. It may be involved in the pathogenesis of SO by targeting multiple signaling pathways, including those related to fat metabolism, muscle synthesis, inflammation, and insulin signaling.[48] Moreover, a meta-analysis revealed that up to 55 microRNAs (miRNAs) are aberrantly expressed in both obesity and sarcopenia. These miRNAs mediate protein homeostasis, mitochondrial dynamics, muscle fiber type transformation, insulin resistance, and adipogenesis, potentially playing crucial roles in the pathogenesis of SO.[49]

Intervention Effects of Different Exercise Types on so

The therapeutic benefits of exercise interventions on SO are widely acknowledged. Studies have indicated that aerobic exercise, resistance training, and a combination of both can effectively ameliorate SO, although their therapeutic effects may vary slightly. The following sections provide a summary of pertinent studies investigating the effects of various exercise types on SO (Table 1).

Aerobic Exercise

Aerobic exercise refers to physical activity in which aerobic metabolism primarily supplies energy during the exercise process. Mason et al randomized postmenopausal women with SO into groups receiving dietary weight loss, aerobic exercise, aerobic exercise combined with dietary weight loss, and control groups for a 12-month intervention. They observed that dietary weight loss resulted in significant reductions in appendicular lean mass (ALM) and SMI compared to the control group.[54] Conversely, aerobic exercise notably preserved ALM and SMI. Furthermore, the addition of

Table 1 Summary of the Effects of Different Exercise Types Interventions on so

Study	Characteristics of Participants	Intervention Protocol	Intervention Effect
Gadelha et al (2016)[11]	F=113 (67.0±5.2 years)	RE,60–80% 1RM, 8–12 reps /set,3 sets, 3 times/ week, 24 weeks	Lean body mass↑ Muscle strength↑
Vasconcelos et al (2016)[50]	F=28 (72.0±4.6 years)	RE,40–75% 1RM, 2 times/ week, 60 min/session, 10 weeks	Knee extensor strength↑ SF-36 score→ Gait speed→ SPPB score→
Huang et al (2017)[51]	F=35 (68.9±4.9 years)	RE with elastic bands, RPE 13, 3 times/week, 40 min/session, 12 weeks	Fat mass↓ Bone density↑
Liao et al (2017)[12]	F=46 (67.3±5.2 years)	RE with elastic bands, RPE 13, 3 times/week, 35–40 min/ session, 12 weeks	Lean body mass↑ Fat-free mass↓ Muscle quality↑ Gait speed↑
Chiu et al (2018)[52]	M=35; F=35 (79.9±7.8 years)	2–5 lbs of sandbag or dumbbell,2 times/week, 60 min/session, 12 weeks	Grip strength↑ PBF→ SMM→
Liao et al (2018)[13]	F=56 (67.3±5.1 years)	RE with elastic bands, RPE 13, 3 times/week, 35–40 min/ session, 12 weeks	Muscle quality↑ ALM↑ SF-36↑ Timed chair rise ↑ Timed Up & Go ↑ Single leg stance time↑
Cunha et al (2018)[53]	F=62 (68.0±4.3 years)	G1S: 1 set, 10–15 reps/set, 3 times/week, 12 weeks G3S: 3 sets, 10–15 reps/set, 3 times/week, 12 weeks	SMM↑ Muscle strength↑ PBF↓ Bone density→
Chang et al (2020)[14]	M=35; F=35 (79.6±7.3 years)	2–5 lbs of sandbag or dumbbell, 2 times/week, 50 min/session, 12 weeks	Anxiety levels↓ Depression levels↓ Quality of life↑
Mason et al (2013)[54]	F=76 (58.0±5.0 years)	AT, 60–85% HR_{max}, 5 times/ week,45 min/session,12 months	SMI↑ ALM↑

(*Continued*)

Table 1 (Continued).

Study	Characteristics of Participants	Intervention Protocol	Intervention Effect
Chen et al (2017)[55]	M=10; F=50 (68.6±3.1 years)	AE: Moderate intensity, 2 times/ week, 60 min/session, 8 weeks; RE:60–70% 1RM, 2 times/ week, 60 min/session, 8 weeks AE+RE: AE and RE performed separately once per week, 8 weeks	Knee extensor strength↑ Grip strength↑ Back extensor strength↑ PBF↓ SMM↑ Visceral fat area↓
Wang et al (2019)[56]	M=43; F=37 (65.1±3.4 years)	AE: Moderate intensity, 2 times/ week, 20 min/session, 8 weeks; RE: Moderate intensity, 2 times/ week, 20 min/session, 8 weeks; AE+RE: RE for 10 min followed by AE for 20 min, 8 weeks	SMM↑ Back extensor strength↑ Grip strength↑ PBF↓ Knee extensor strength↑ Visceral fat area↓
Park et al (2017)[57]	F=60 (74.1±6.1 years)	RE with elastic bands: 12 sets × 8–15 reps, 20–30 min/session, 3 times/week, 24 weeks; Walking: RPE 13–17, 30–50 min, 5 times/week, 24 weeks	CIMT↓ Carotid flow velocity↑ Carotid wall shear ratio↑
Qi et al (2023)[58]	F=20 (67.6±5.2 years)	RE with water: RPE 13–15, 5 min/session, 3 times/week, 12 weeks; AE with water: 90–135 beats/ min HR, 20 min/session, 3 times /week, 12 weeks	PBF↓ Metabolic syndrome score → SMI→
Fang et al (2023)[59]	M=30; F=29 (73.8±7.2 years)	Elastic band and exercise ball: RPE 13–14, 18 min, 12 weeks; Exercise bike: RPE 11–12, 15–20 min, 12 weeks	Grip strength↑ PBF↓ Visceral fat area↓ Quality of life↑

Notes: Age are expressed as mean ± standard deviation; "↑"indicates a significant improvement. (P<0.05); "→"indicates a no significant change; "↓"indicates a significant reduction.

Abbreviations: F, female; M, male; RE, resistance exercise; 1RM, one repetition maximum; PBF, percentage of body fat; SMM, skeletal muscle mass; AE, aerobic exercise; SPPB, short physical performance battery; RPE, rating of perceived exertion; HR_{max}, maximum heart rate; SF-36, short form-36 health survey; ALM, appendicular lean mass; SMI, skeletal muscle mass index; CIMT, carotid intima-media thickness.

aerobic exercise to dietary interventions alleviated the loss of skeletal muscle mass during weight loss.[54] Chen et al implemented 8 weeks of moderate-intensity aerobic exercise in elderly individuals with SO and evaluated the training effects 4 weeks after cessation. The findings revealed notable reductions in body fat percentage and visceral fat area, along with significant increases in skeletal muscle mass and strength, with sustained intervention effects observed 4 weeks after training cessation.[60] Moreover, 8 weeks of moderate-intensity home- based aerobic exercise effectively enhanced skeletal muscle mass and back muscle strength in elderly individuals with sarcopenic obesity, concurrently reducing body mass index and visceral fat area.[56] These findings indicate that aerobic exercise has positive effects on reducing body fat, preserving skeletal muscle mass, and enhancing muscle strength in individuals with SO.

Notably, a recent Cross-sectional study found that older adults exceeding the recommended physical activity guidelines (>300 min/week) had a lower risk of sarcopenia compared to those meeting the WHO's recommended levels (150–300 min/week).[61] This suggests that surpassing the WHO's recommended physical activity levels may be more effective in preventing SO in older adults and offer greater health benefits. Additionally, França et al found that high-intensity aerobic exercise significantly increased muscle mass and reduced fat mass in rat models of SO compared to low-intensity aerobic exercise.[62] Therefore, in preventing and treating SO through aerobic exercise, gradually increasing the intensity and volume of exercise may induce more significant adaptations and maximize adherence. Presently, aerobic exercise prescriptions for individuals with SO commonly involve activities such as walking, jogging, cycling, etc., with intensities

ranging from 70% to 85% of maximum heart rate (HR_{max}) or perceived exertion levels (RPE) of 13 to 17, lasting 20 to 45 minutes per session, and conducted 2 to 5 times per week.[63]

Resistance Exercise

Resistance exercise involves muscle overcoming resistance to perform work. Research has demonstrated that 24 weeks of resistance training markedly augmented lean body mass and muscle strength in elderly female individuals with SO.[11] Elastic band resistance training for 12 weeks elevated lean body mass and enhanced physical function (including gait speed, single-leg standing time, timed up-and-go test, and sit-to-stand test) in individuals with SO,[12,13] along with improved bone density.[51] Furthermore, 12 weeks of progressive resistance training using sandbags or dumbbells not only enhanced the quality of life for individuals with SO in long-term care facilities but also alleviated their anxiety and depression levels.[14]

It is noteworthy that the efficacy of resistance exercise in SO may be influenced by factors such as exercise intensity, volume, and duration. Chiu et al found that while 12 weeks of biweekly training with 2 to 5 pounds of sandbags or dumbbells significantly enhanced grip strength, pinch strength, and self-care ability in sedentary individuals with SO in long-term care facilities, it did not notably impact PBF and SMM, likely owing to the low load and absence of progressive overload during resistance exercise.[52] Cunha et al compared the effects of resistance exercise performed once (G1S) or three times (G3S) per session on comprehensive parameters of osteosarcopenic obesity (OSO) in elderly women. After a 12 weeks intervention, performed three times weekly, both exercise groups demonstrated significant enhancements in SMM and muscle strength, along with reductions in PBF, with no notable alteration in bone density compared to the control group.[53] Additionally, the G3S group exhibited greater enhancements in muscle strength and PBF compared to the G1S group, indicating that improvements in muscle strength and PBF with resistance exercise are associated with exercise volume.[53] Furthermore, Vasconcelos et al observed that following a 10-week progressive resistance training program, there was no significant improvement in Short Physical Performance Battery (SPPB) scores, gait speed, and quality of life among elderly women with SO. Concurrently, significant improvement was observed only in knee extension strength in terms of lower limb strength, power, and endurance, possibly attributable to the relatively short duration of the resistance training intervention.[50] Therefore, to achieve significant improvements in resistance exercise, it is recommended to implement progressive resistance training 2 to 3 times per week, with each session lasting 35 to 45 minutes. The training should commence at a moderate to low intensity (40–60% 1RM) and gradually progress to moderate to high intensity (70–85% 1RM), and last for at least 12 weeks.

Combination Exercise

The combination of resistance exercise and aerobic exercise is commonly known as combination exercise. Studies have demonstrated that a 12-week combination exercise program effectively decreases body fat percentage and visceral fat area in elderly maintenance hemodialysis patients with SO, while concurrently enhancing grip strength, serum albumin levels, and quality of life.[59] Park et al found that 24 weeks combination exercise can reduce the intima-media thickness of the carotid artery in elderly female SO patients, increase carotid artery blood flow velocity, and improve the wall shear rate, thereby effectively reducing the risk of cardiovascular diseases.[57] Qi et al found that a 12-week moderate-intensity combination exercise program (5 min of resistance exercise per session; 20 min of aerobic exercise per session), performed three times a week, significantly reduced fat mass in SO patients, but had no significant effect on SMI and metabolic syndrome scores, suggesting that lower volumes of combination exercise may not effectively improve SMM and metabolic health.[58]

Furthermore, studies have compared the intervention effects of aerobic exercise, resistance exercise, and combination exercise on SO. For example, Chen et al randomized 60 patients with SO into control, aerobic exercise, resistance exercise, and combination exercise groups, with each group receiving an 8-week intervention twice a week. They observed significant reductions in PBF and visceral fat area and significant improvements in SMM and back muscle strength in all exercise groups compared to the control group. However, knee extension strength significantly increased after combination exercise and resistance exercise, whereas grip strength increased only after resistance exercise. Specifically, resistance exercise was more effective in improving muscle strength performance, while combination exercise was more effective in reducing PBF.[60] Similarly, Wang et al obtained similar results in elderly SO patients after aerobic, resistance, and combination exercise interventions.[56] Thus, combination exercise can increase SMM and

muscle strength while reducing PBF. Although slightly less effective than resistance exercise in improving muscle strength, it is more effective in improving body composition.

In summary, both resistance exercise and combination exercise have their advantages in SO exercise therapy. Nevertheless, given that combination exercise may integrate the supplementary advantages of both exercise modalities and boasts higher adherence rates owing to its varied training approaches, it may be the optimal exercise modality for intervening in SO. However, the scarcity of clinical evidence persists due to the limited research on factors such as diverse exercise types, intensities, and durations influencing the intervention outcomes in SO. Therefore, future clinical studies are warranted to delineate the ideal exercise intensity, frequency, and duration to optimize the benefits derived from diverse exercise types, while considering variables such as patients' age, gender, and health status, with the aim of formulating more individualized exercise regimens.

Possible Mechanism of Exercise Intervention in so

Currently, research on the mechanisms underlying exercise intervention in SO is limited and still in its nascent stages. This review aims to offer insights into the potential mechanisms of exercise intervention for SO based on relevant literature.

Exercise Regulates Cytokines to Intervene in so

Exercise Regulates Myokines to Intervene in so

Myokines, cytokines synthesized and secreted by skeletal muscles, can act on various target organs, including skeletal muscle itself, adipose tissue, and bone, through autocrine, paracrine, or endocrine pathways. Evidence suggests that myokines participate in physiological processes such as muscle cell proliferation and differentiation, muscle atrophy, increased mitochondrial function, reduced inflammation, and metabolic homeostasis. Abnormal myokine secretion forms the basis of SO pathogenesis.[64]

IGF-1 is a key regulator of muscle growth and regeneration. On one hand, IGF-1 is involved in synthetic metabolism in skeletal muscle through the PI3K/AKT/mTOR and glycogen synthase kinase-3β (GSK3β) signaling pathways.[65] On the other hand, IGF-1 can inhibit the transcription of FOXO and E3 ubiquitin ligases via the PI3K/Akt signaling pathway, thereby regulating the UPS to reduce skeletal muscle protein degradation.[66] Clinical data indicate that reduced serum IGF-1 levels are independently associated with sarcopenia risk and increased abdominal visceral fat.[64,67] Therefore, IGF-1 may be closely linked to SO pathogenesis.[68]

Exercise can upregulate local IGF-1 expression in skeletal muscle, leading to increased muscle strength and hypertrophy.[69] Studies have shown that 8 weeks of resistance and combined exercises effectively improve body composition and muscle strength in elderly patients with SO, with improvement associated with increased IGF-1 secretion and decreased IL-6 concentrations.[56] Compared with elderly patients with SO who did not undergo exercise, those who underwent resistance and combined exercises showed significant improvements in muscle strength and serum IGF-1 levels after an 8-week intervention, with resistance exercise showing the most significant improvement.[60] Therefore, exercise-induced IGF-1 may be a key myokine for intervening in SO, and an important mediator for improving patient body composition, promoting muscle hypertrophy, and increasing strength.

Irisin is a newly discovered myokine, released into the circulation by fibronectin type III domain-containing protein 5 (FNDC5) after proteolytic cleavage and regulated by PGC-1α.[70] In skeletal muscle, irisin significantly increases IGF-1 expression and decreases myostatin gene expression through the extracellular regulated protein kinases (ERK) signaling pathway, while upregulating the IGF-1/Akt/mTOR signaling pathway to promote muscle hypertrophy.[71,72] In white adipose tissue, irisin stimulates the expression of PGC-1α, UCP1, and other brown fat-related genes through the p38 mitogen-activated protein kinase (MAPK) and ERK pathways, increasing mitochondrial biogenesis, reducing body weight, and improving glucose homeostasis, thus preventing obesity and type 2 diabetes.[73]

Under normal circumstances, the expression level of PGC-1α is low in skeletal muscle, but during exercise, the expression level of PGC-1α rapidly increases, along with increased expression levels of FNDC5 and irisin.[74] Research shows that 10 weeks of aerobic exercise significantly increases FNDC5 mRNA and circulating irisin levels in obese individuals.[75] 16 weeks of low-intensity resistance exercise effectively improves muscle strength and serum irisin levels in the elderly, and circulating irisin can be used as a marker for improving muscle strength after resistance exercise in the elderly.[76] In postmenopausal women with sarcopenia, resistance exercise alone or in combination with aerobic exercise

significantly improves muscle mass and muscle strength, and these improvements are closely related to increased serum irisin concentrations.[77] These studies suggest that exercise-induced irisin not only improves SO by increasing mitochondrial biogenesis, promoting browning of white adipose tissue, and increasing muscle mass and strength, but also serves as a marker for evaluating the effectiveness of exercise rehabilitation for SO.

Exercise Regulates of Adipokines Intervention in so

In addition to myokines, adipokines also play an important role in the improvement of SO through exercise. Adipokines refer to biologically active substances secreted by adipose tissue, such as leptin and adiponectin.

Leptin is a peptide hormone primarily binding to leptin receptors (LepRb) in various hypothalamic neurons, activating janus family tyrosine kinases-2 (JAK2), and subsequently participating in signaling through transcription factor 3 (STAT3), PI3K, and ERK1/2 pathways to regulate energy balance and metabolic homeostasis.[78] Serum leptin levels are significantly higher in SO patients than in non-sarcopenic obese individuals, and they are associated with reduced grip strength and physical function.[79] Furthermore, in aging, fat accumulation leads to increased leptin levels, often resulting in leptin resistance, which reduces fatty acid oxidation in muscles, consequently decreasing muscle quality in SO patients.[80] Exercise effectively reduces serum leptin levels in SO patients and decreases body fat.[81] Animal studies demonstrate that aerobic exercise can partially reverse peripheral leptin resistance induced by high-fat diet in sedentary obese rats.[82] Moreover, even acute exercise can effectively reduce food intake in obese mice and improve central leptin resistance.[83] Therefore, exercise appears to improve SO by reducing high serum leptin levels and improving leptin resistance, thereby reducing body fat and enhancing muscle quality.

Adiponectin (ADN), another important hormone secreted by adipose tissue, signals through receptors (AdipoR1 and AdipoR2), predominantly expressed in skeletal muscle by AdipoR1.[84] Evidence suggests that serum ADN levels decrease with age and progression of obesity.[2] Futuremore, serum ADN levels in patients with sarcopenia are significantly lower than in healthy individuals and are negatively correlated with the risk of developing sarcopenia.[85] Therefore, ADN may also be related to the pathogenesis of SO.[86] Studies have found that 12 weeks of resistance exercise combined with whey protein supplementation significantly increases muscle mass and serum ADN levels in elderly patients with sarcopenia.[85] In the rapid aging mouse model (SAMP10), exercise can improve protein degradation metabolism, synthetic metabolism reactions, oxidative stress-induced cell apoptosis, and ADN/PGC-1α activation-related biogenesis by activating the AMPK/Akt/mTOR signaling pathway dependent on ADN-AdipoR1.[87] Inhibition of AdipoR1 expression leads to decreased PGC-1α expression and deacetylation in skeletal muscle, reduced mitochondrial content and related oxidative enzymes, decreased oxidative type I muscle fibers, and diminished oxidative stress detoxification enzymes, attenuating the beneficial effects of exercise on muscles.[88] It is speculated that exercise can increase serum ADN levels in patients with SO and positively affect muscle hypertrophy, inflammation reduction, and fat oxidation through the ADN-AdipoR1 axis.

Besides the aforementioned cytokines, various others may also play roles in improving SO through exercise, including IL-6, Brain-derived neurotrophic factor (BDNF), Fibroblast growth factor-21 (FGF-21), MSTN, Leukemia inhibitory factor (LIF), Resistin, and Apelin.[10,89]

Exercise Intervenes in so by Inhibiting Inflammatory Pathways

Studies have shown that elevated levels of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β, induced by sarcopenia and obesity, are linked to abnormal activation of NF-κB and Nod-like receptor protein 3 (NLRP3) inflammasome signaling pathways, which can be ameliorated by exercise.[90–92]

Exercise Intervention in so by Inhibiting NF-κB Pathway

NF-κB is a protein complex crucial for regulating immunity and inflammation, especially in mediating the effects of TNF-α and IL-6 on muscle atrophy.[93] Under normal conditions, NF-κB resides in the cytoplasm and binds with inhibitory protein kappa B alpha (IκBα) to form a complex. When activated, IκBα kinase (IKK) phosphorylates IκBα, leading to the release of NF-κB, which then undergoes dimerization (with p50 and p65) and translocates into the nucleus.[93] Studies have shown that NF-κB protein concentration in the muscles of elderly individuals is four times higher

than that in young people, and this elevation is linked to deficiencies in synthetic metabolic signals contributing to muscle atrophy and aging.[94]

Moderate exercise can suppress the IκBα/NF-κB signaling pathway, decrease IL-6 and TNF-α mRNA levels, and concomitantly activate the sirtuin 1 (SIRT1)-AMPKα-PGC1α axis, thereby alleviating muscle atrophy in type 2 diabetic mice.[95] 6 weeks of swimming can activate the AMPK/SIRT1/NF-κB signaling pathway, suppress IL-6 and TNF-α gene expression in skeletal muscles, enhance IL-10 gene expression, and decrease body weight and fasting blood glucose in diabetic mice.[96] Furthermore, 4 weeks of high-intensity interval training (HIIT) can suppress the NF-κB signaling pathway in obese rats, decrease protein levels of TNF-α, IL-1β, and IL-6 in skeletal muscles, mitigate chronic inflammation associated with obesity, and diminish apoptosis of skeletal muscle cells.[97] Thus, exercise could attenuate inflammation by inhibiting the NF-κB signaling pathway, consequently mitigating muscle atrophy and adipose tissue accumulation.

Exercise Intervention in so by Inhibiting the NLRP3 Inflammasome Pathway

Besides NF-κB, the NLRP3 inflammasome, another crucial regulator of inflammation, is closely associated with the onset and progression of sarcopenia and obesity. NLRP3 gene knockout aged mice exhibit significantly attenuated reduction in muscle fiber size during aging compared to aged wild-type mice, indicating the involvement of NLRP3 inflammasome in age-related muscle atrophy.[98] Obese individuals demonstrate significantly higher expression of the NLRP3 gene in adipose tissue compared to non-obese individuals.[99] Therefore, the NLRP3 inflammasome may be overactivated in the skeletal muscles and adipose tissue of patients with SO.

Studies have shown that 12 weeks of moderate-intensity aerobic exercise can decrease the basal expression of NLRP3 inflammasomes and levels of downstream pro-inflammatory factors (IL-1β, TNF-α, and IL-6) in elderly women, thereby alleviating age-related chronic inflammation.8 weeks of treadmill exercise can diminish NLRP3 inflammasome activation in adipose tissue, consequently decreasing IL-1β and IL-18 expression, lowering body weight, mitigating fat accumulation, and alleviating insulin resistance in obese mice.[100] Additionally, 8 weeks of combined resistance and treadmill exercise can enhance protein synthesis levels by activating the PI3K/AKT/FOXO1/NF-κB/NLRP3 signaling pathway, while concomitantly suppressing TNF-α /MSTN/peroxisome proliferator-activated receptor γ (PPARγ)/NF-κB/NLRP3 signaling pathways, leading to reduced lipid droplets and inflammation in skeletal muscles, consequently postponing the onset of SO in high-fat diet-induced aging mice.[101]

The above studies suggest that exercise may hinder the onset and progression of SO by inhibiting the NF-κB and NLRP3 inflammasome signaling pathways, reducing the secretion of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β, thereby reducing muscle atrophy and obesity, thus impeding the occurrence and development of SO.

Exercise Improves Mitochondrial Quality to Intervene in so

Mitochondria, often referred to as the "powerhouses" of cells, are centrally implicated in the pathogenesis of SO due to their dysfunction, regarded as a core mechanism in SO progression.[68] Due to the dual impact of obesity and sarcopenia on patients with SO, some researchers believe that SO patients may experience more severe mitochondrial dysfunction compared to patients with either obesity or sarcopenia alone. For instance, in the respiratory muscles of SO patients, biomarkers of mitochondrial biogenesis such as PGC1-α, mitochondrial fusion markers like mitofusin 1 (Mfn1) and mitofusin 2 (Mfn2), and mitochondrial fission marker dynamin-related protein 1 (DRP1) are significantly lower than normal levels.[102]

Several lines of evidence suggest that mitochondria could represent a crucial target for exercise intervention in SO. Research has demonstrated that 12 weeks of high-intensity interval training (HIIT) markedly augmented mitochondrial biogenesis markers (eg, TFAM), fusion markers (eg, OPA1, Mfn1, and Mfn2), and autophagy markers (eg, Parkin) in the lateral thigh muscles of obese elderly individuals.[103] This increase was associated with improvements in physical function, muscle strength, lean body mass, and reduced waist circumference.[103] Colleluori et al found that under calorie restriction conditions, a 6-month combination of exercise significantly decreased mitochondrial fission, autophagy, and proteostasis regulatory factor expression in the lateral thigh muscles of obese elderly individuals, resulting in enhanced muscle protein synthesis and muscle cell quality, suggesting that combined exercise can preserve lean body mass and muscle cell quality by ameliorating skeletal muscle mitochondrial dysfunction.[104] Furthermore, lifelong aerobic exercise can promote mitochondrial biogenesis, enhance mitochondrial dynamics, activate the AMPK/PGC-1α signaling pathway,

ameliorate aberrant autophagy/mitochondrial autophagy function, attenuate skeletal muscle mass decline in elderly mice, enhance energy metabolism, bolster mitochondrial quality control, and suppress protein ubiquitination to prevent or postpone skeletal muscle atrophy associated with aging.[105]

Recent studies have additionally revealed that exercise can trigger the mitochondrial unfolded protein response (UPRmt), thereby efficiently decreasing mitochondrial burden and restoring mitochondrial function. UPRmt is a protein quality control system found in eukaryotic cells that prevents the accumulation of damaged proteins, preserves mitochondrial homeostasis and function.[106] In the gastrocnemius muscle of mice, mRNA levels of UPRmt-related genes, including YME1-like protein 1 (Yme1L1) and Clp protease proteolytic subunit 1 (CLpP1), decline with aging.[107] Following 4 weeks of aerobic exercise, the expression of these UPRmt-related genes increases, showing a positive correlation with mitochondrial content.[107] Furthermore, 4 weeks of HIIT effectively induces nuclear division imbalance and UPRmt in the skeletal muscle of aged mice, leading to elevated mRNA and protein levels of Yme1L1 and Lon peptidase 1 (LONP1), improved mitochondrial quality (eg, increased PGC-1α expression and citrate synthase level), and enhanced physical function (eg, increased grip strength, maximum running speed, and running distance).[108] Similarly, 4 weeks of treadmill exercise can efficiently activate UPRmt in obese mice, simultaneously elevating protein levels of LONP1 and ClpP, thereby enhancing grip strength and maximum running speed.[109]

The above studies suggest that exercise may improve SO by enhancing mitochondrial biogenesis, optimizing mitochondrial dynamics, improving mitochondrial autophagy, activating UPRmt, thereby strengthening mitochondrial quality control, and reducing mitochondrial dysfunction.

Exercise Regulates miRNA Expression Intervention in so

Exercise can function as an effective activator or inhibitor of gene expression, thereby regulating the expression of miRNAs in skeletal muscle and adipose tissue, and exerting various adaptive effects on the body.[110] Human experiments have shown that miR-628-5p expression rises with age. This miRNA can directly bind to striated muscle activator of rho signalling (STARS), reducing its transcription and impeding muscle cell regeneration.[111] Acute resistance exercise in elderly individuals markedly reduces miR-628-5p expression in skeletal muscle, thereby enhancing muscle regeneration.[111] Pheiffer et al found that exercise can induce the expression of miR-155-5p, miR-329-3p, and miR-377-3p in the subcutaneous adipose tissue of African obese women, stimulating fat breakdown, increasing circulating triglycerides, and simultaneously activating the AKT signaling pathway to improve insulin sensitivity.[112]

Animal studies have demonstrated that aerobic exercise significantly enhances skeletal muscle mass and function, restoring mitochondrial homeostasis in aging skeletal muscle by upregulating the miR-128/IGF-1 signaling pathway in a zebrafish sarcopenia model.[113] Overexpression of miR-761 in skeletal muscle downregulates the PGC-1α and p38 MAPK signaling pathways, thereby inhibiting mitochondrial biogenesis.[114] Xu et al found that 4-week of treadmill exercise can decrease miR-761 expression in mouse skeletal muscle, thereby enhancing energy metabolism.[114] Therefore, exercise can modulate miRNA expression in skeletal muscle and adipose tissue, leading to enhanced mitochondrial quality, improved insulin sensitivity, and decreased muscle atrophy and fat accumulation.

Exercise-mediated miRNAs can also improve SO by reducing inflammation levels. Research indicates that lifelong low-intensity aerobic exercise increases the expression of miR-146d-5p, miR-152-3p, miR-296-3p, and miR-20a-5p in rat gastrocnemius muscle, reducing the IL-6/IL-10 and TNF-α/IL-10 ratios to maintain skeletal muscle function and decrease body fat percentage, thereby impeding the onset and progression of SO.[115] Rosa et al found that rehabilitation exercise in sarcopenic patients increases the expression of miR-355-5p and miR-657, improving physical function while reducing levels of IL-18, IL-37, and c-reactive protein (CRP).[116] MiR-355-5p and miR-657 are known as post-transcriptional regulators of IL-37, and their increased expression significantly lowers IL-37 levels, correlating with improvements in rehabilitation parameters among sarcopenic patients, suggesting that the expression of these miRNAs can be assessed to evaluate disease progression and the efficacy of exercise rehabilitation in SO.[116]

Patients suffering from SO often face difficulties in sample collection and extraction due to muscle atrophy and abundant adipose tissue. Studies have shown that miRNAs can be released into the circulatory system, where they become circulating miRNAs (c-miRNAs).[117] These c-miRNAs are highly stable, easily extractable, and demonstrate high sensitivity and specificity to exercise stimuli.[118] Within skeletal muscle, miR-23a and miR-27a play roles in alleviating

muscle atrophy, whereas miR-133a is involved in maintaining muscle function and promoting myoblast proliferation. Compared to young individuals, circulating levels of miR-23a, miR-27a, and miR-133a are lower in older adults, but resistance exercise can increase the levels of these circulating miRNAs in older adults to levels comparable to those in young individuals.[119] Margolis et al found that acute resistance exercise in older adults reduces the expression levels of circulating miR-19a-3p, miR-19b-3p, miR-20a-5p, miR-26b-5p, miR-143-3p, and miR-195-5p, thereby upregulating the expression levels of phosphorylated Akt and ribosomal S6 kinase 1 (S6K1) potentially enhancing skeletal muscle protein synthesis response.[120] Importantly, certain c-miRNAs associated with aging (miR-19b-3p, miR-206, and miR-486) show strong correlations with markers of body composition and metabolic health, such as serum glucose and triglyceride concentrations.[120] Despite the good health status of elderly participants, these c-miRNAs can still distinguish aging, suggesting that these c-miRNAs may serve as highly sensitive biomarkers for predicting the onset of SO.[120]

The above studies suggest that exercise can promote muscle hypertrophy, reduce inflammation, mitigate muscle atrophy, increase insulin sensitivity, and improve mitochondrial quality by modulating the expression of miRNA, suggesting its potential as a novel target for exercise therapy in SO.

In summary, exercise may intervene in SO by modulating cytokine secretion, inflammation pathways, mitochondrial quality, and miRNA expression (Figures 1 and 2). Nevertheless, since most of the above mechanisms are based on hypotheses and speculations from current relevant research, and many studies are conducted in animal models with relatively lacking clinical evidence, specific molecular mechanisms still need to be further confirmed in more clinical

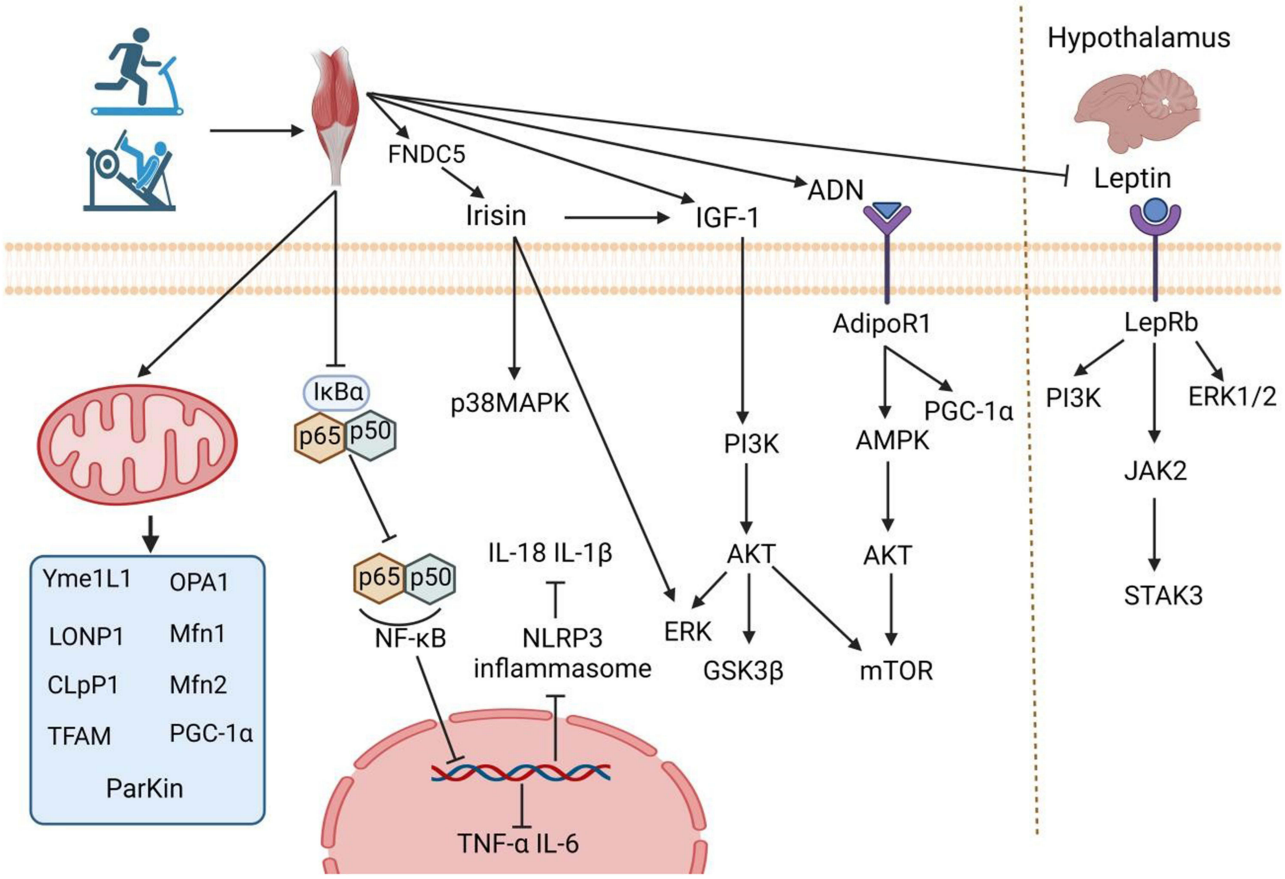

Figure 1 The main possible mechanisms of exercise intervention in SO. Created with BioRender.com.

Abbreviations: FNDC5, fibronectin type III domain-containing protein 5; IGF-1, insulin-like growth factor 1; ADN, adiponectin; LepRb, leptin receptors; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol-3-kinase; ERK, extracellular regulated protein kinases; AKT, protein kinase B; JAK2, Janus family tyrosine kinases-2; STAK3, signaling through transcription factor 3; GSK3β, glycogen synthase kinase-3β; mTOR, mammalian target of rapamycin; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator 1; NF-κB, nuclear factor-kappa B; TFAM, mitochondrial transcription factor A; Yme1L1, YME1-like protein 1; Mfn1, mitofusin 1; Mfn2, mitofusin 2; OPA1, optic atrophy 1; LONP1, Yme1L1 and Lon peptidase 1; CLpP1, Clp protease proteolytic subunit 1; NLRP3, Nod-like receptor protein 3; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; IL-18, interleukin-18; IL-1β, interleukin-1β.

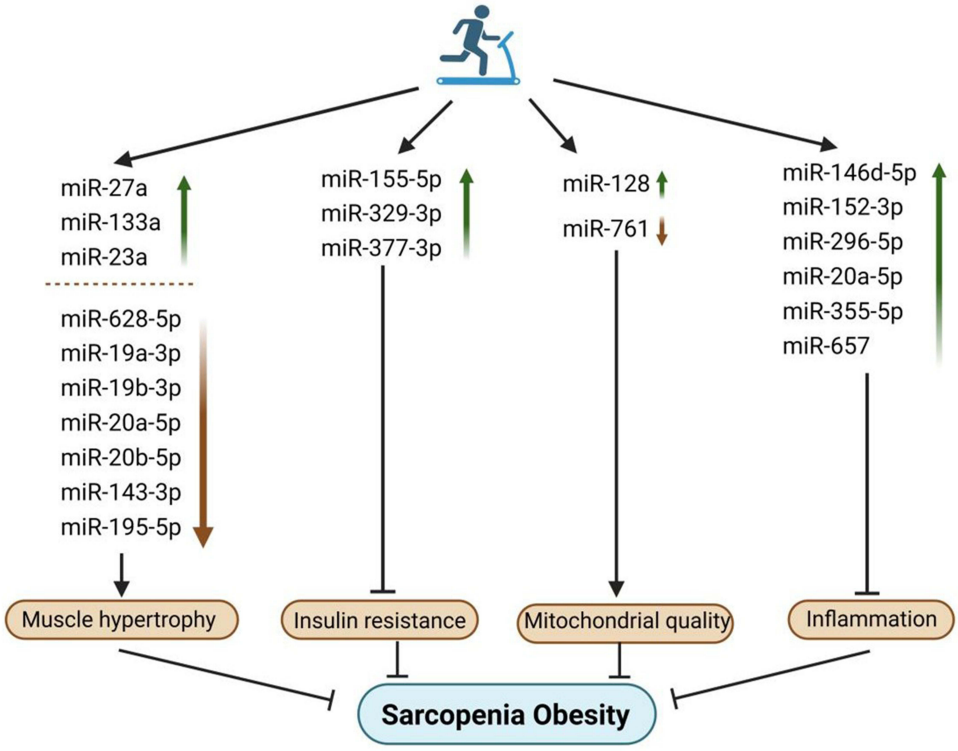

Figure 2 The potential mechanisms of exercise-mediated miRNAs in improving SO. Created with BioRender.com.

experiments. Moreover, individual variances, exercise types, and intensities may also lead to variations in its outcomes. Hence, it is crucial to elucidate the molecular mechanisms underlying exercise intervention in SO from various perspectives in future studies.

Conclusions and Perspectives

SO is a common geriatric syndrome clinically associated with genetic and epigenetic factors, increased inflammation, age-related changes in body composition, hormonal shifts, and mitochondrial dysfunction, among other factors. These factors interact, resulting in muscle atrophy, decreased muscle strength, and increased adipose tissue accumulation in elderly individuals, ultimately leading to SO. Exercise, as a key intervention for preventing and treating SO, can enhance muscle strength and mass, reduce body fat through various physiological pathways, which are important in improving the physical health and quality of life of SO patients. Additionally, engaging in combined exercise two to three times per week, starting with moderate to low intensity (resistance exercise: 40–60% 1RM; aerobic exercise: 50–60% HR_{max}) and gradually increasing to moderate-to-high intensity (resistance exercise: 70–85% 1RM; aerobic exercise: 70–85% HR_{max}), is an effective strategy for preventing and treating SO.

Despite providing a theoretical basis for exercise in preventing and treating SO, current research still faces some unresolved issues: 1) Under clinical conditions, it is not always feasible to perform high-intensity exercise for SO patients. Recent findings suggest that combining low-intensity conventional exercise with blood flow restriction (BFR) can yield comparable benefits to high-intensity exercise, with possesses high safety and compliance. Future research could further investigate the application of BFR in exercise interventions for SO, thereby enriching the exercise prescriptions for SO. 2) Proteomic and genomic studies have identified numerous exerkines and miRNAs in the human body. However, current comprehension and research on these elements may be superficial, necessitating further identification of additional exerkines and miRNAs contributing to SO improvement. 3) Currently, little is known about the mechanisms by which exercise regulates the NLRP3 inflammasome to intervene in SO. More research is needed in the future to elucidate the connection between exercise, the NLRP3 inflammasome, and SO.

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Disclosure

The authors report no conflicts of interest in this work.

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