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Molecular Mechanisms of Age-Related Sarcopenia and Their Modulation by Exercise: A Narrative Review

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A B S T R A C T

Background: Sarcopenia is the progressive loss of muscle mass and strength with ageing and is a major cause of disability, reduced quality of life, and increased mortality in older adults. While exercise is widely recommended as a treatment, the molecular mechanisms by which it protects muscle remain incompletely understood. This review examines the key molecular pathways involved in age-related muscle wasting and evaluates how exercise therapy can modify these pathways.

Aim: To provide a narrative review of the molecular mechanisms underlying sarcopenia in the elderly and to assess the potential of exercise therapy to reverse these mechanisms and improve clinical outcomes. We focus on three interrelated pathways: (1) myostatin signaling, (2) TNF-α and inflammation, and (3) oxidative stress and endothelial dysfunction, with particular attention to their convergence on the IGF-I–Akt–mTOR pathway that regulates muscle protein synthesis.

Methods: A systematic search of PubMed/MEDLINE was conducted using MeSH terms and free-text keywords related to sarcopenia, ageing, molecular mechanisms, and exercise. Studies examining molecular alterations in skeletal muscle and cardiac tissue in elderly individuals with sarcopenia were analyzed, with emphasis on the direct and indirect roles of exercise in restoring molecular balance.

Results: Exercise-based interventions, particularly resistance and aerobic training, modulate the key molecular pathways involved in muscle wasting. Resistance training reduces myostatin expression and TNF-α levels, while aerobic exercise improves redox balance and endothelial function. These molecular changes are associated with increased muscle mass, strength, and functional capacity. Exercise also enhances signaling through the IGF-I–Akt–mTOR pathway, promoting muscle protein synthesis and inhibiting degradation. Nutritional supplementation (e.g., leucine, creatine, protein) may complement these effects by further activating anabolic signaling.

Conclusion: Sarcopenia results from the convergence of multiple molecular pathways, including myostatin, TNF-α, and oxidative stress, all of which impair muscle protein synthesis and promote degradation. Exercise therapy counteracts these mechanisms at the molecular level, improving muscle mass, strength, and function. While exercise is currently the cornerstone of sarcopenia management, personalized prescriptions and combined interventions hold promise for optimizing outcomes in older adults.

Keywords: Sarcopenia, Molecular Mechanisms, Exercise Therapy, Myostatin, TNF-α, Oxidative Stress, Muscle Wasting.

Introduction

Sarcopenia is the progressive and generalized skeletal muscle wasting and strength loss and is one of the most significant public health challenges of ageing populations worldwide. Muscle wasting is a significant, multifaceted condition associated with ageing, chronic diseases, and prolonged immobilization. This condition reduces quality of life (QOL), increases morbidity, and raises mortality. Muscle mass and strength fluctuate throughout life (1). Even minor but sustained imbalances between muscle protein synthesis and degradation can reduce muscle mass if anabolic processes do not offset them (2).

A significant research challenge is the limited understanding of molecular disruptions to skeletal muscle homeostasis associated with ageing. After age 50, muscle mass and strength decline by approximately 1–2% and 1.5–5% per year, respectively (3) . Concurrently, muscle wasting in older adults leads to reduced cardiac function, as evidenced by an approximately 1% annual decline in maximal aerobic capacity (4). This decline is attributed to reductions in

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muscle mass, maximal cardiac output, and skeletal oxidative capacity.

A lower skeletal muscle index (SMI) impairs peak stroke volume (SV) (5) , resulting in decreased muscle strength and exercise tolerance. These changes contribute to increased weakness and greater dependence on daily activities. Particularly, cardiomyocyte loss may accompany muscle wasting during ageing (6), suggesting a potential cardio-sarcopenia syndrome affecting both systems. Sarcopenic individuals usually show smaller left ventricular (LV) and left atrial (LA) sizes, preserved LV function, reduced wall thickness, lower ventricular mass, and less muscle mass and handgrip strength (6). Yet, some studies suggest that ageing may also increase LV wall thickness, sometimes with ventricular myocyte hypertrophy (7) .

Multiple molecular pathways likely connect muscle wasting to cardiac decline in ageing. These include impaired oxygen utilization in tissues, elevated myostatin levels, and increased production of TNF-α (8).The oxidative-stress axis, common to both skeletal and cardiac muscle, underpins these interconnected mechanisms. Impaired oxygen utilization, resulting from oxidative stress, diminishes exercise capacity and underscores the importance of redox balance in mitigating muscle degradation and improving cardiac health. These pathways converge into a complex network that influences both muscular and cardiovascular ageing, warranting further investigation into their interactions.

Elevated myostatin levels reduce muscle mass and increase weakness, raising the risk of falls and hospitalizations. Elevated TNF-α levels drive systemic inflammation, which exacerbates muscle wasting and increases hospital admission rates. Although key participants in these pathways have been identified, the complete set of molecular links between low skeletal muscle mass (SMM) and poor cardiorespiratory fitness (CRF) remains unclear. An integrative signaling cascade involving TNF-α, myostatin, and oxidative stress converging on dysregulation of the Akt/Mammalian Target of Rapamycin (Akt/mTOR) pathway may clarify the causal relationships in muscle wasting. Muscle atrophy arises from inflammation, oxidative stress, and dysregulation of signaling molecules (9). Atrophy occurs when protein synthesis decreases or protein breakdown increases, but the precise mechanisms, particularly in response to exercise therapy, are not fully understood. Previous studies have demonstrated that skeletal muscle exhibits plasticity, enabling phenotypic changes in response to mechanical or metabolic stimuli, resulting in alterations in muscle fiber size (9).

To address this knowledge gap, this review is guided by the following research question: "What are the molecular mechanisms by which exercise therapy modulates muscle wasting in elderly individuals with sarcopenia, and how do these mechanisms translate into improvements in muscle mass, strength, and functional capacity?"

This question has two interconnected components:

1. Mechanistic component: What molecular pathways are dysregulated in sarcopenia (specifically myostatin, TNF-α, oxidative stress/endothelial dysfunction, and the IGF-I–Akt–mTOR axis), and how does exercise modulate these pathways?
2. Translational component: How do these exercise-induced molecular changes correlate with clinically meaningful outcomes, including muscle mass, strength, and functional capacity?

This Review Aimed to:

1. Identify and describe the key molecular pathways dysregulated in sarcopenia, focusing on myostatin, TNF-α, oxidative stress/endothelial dysfunction, and the IGF-I–Akt–mTOR axis.
2. Evaluate the evidence on how exercise therapy (resistance, aerobic, and combined training) modulates these pathways at the molecular level.
3. Assess the translational relevance of these molecular changes by examining their association with clinical outcomes (muscle mass, strength, and functional capacity).
4. Identify knowledge gaps and propose future research directions, including personalized exercise prescriptions and combined exercise-nutrition interventions.

Methods

Review Design

This narrative review was conducted using a systematic search strategy to synthesize evidence on the molecular mechanisms of sarcopenia and exercise modulation. We followed the STARLITE framework for reporting literature searches.

The STARLITE framework is specifically designed for narrative reviews and includes items on sampling strategy, type of studies, approaches, range of years, limits, inclusion/exclusion criteria, terms used, and electronic sources

Rationale for STARLITE: Unlike PRISMA 2020, which is designed for systematic reviews and meta-analyses, STARLITE provides appropriate reporting guidance for narrative reviews that employ systematic search methods but do not perform quantitative synthesis

Search Strategy

PubMed/MEDLINE was searched from inception to December 2025 using the following search string: ("sarcopenia" OR "muscle wasting" OR "age-related muscle loss") AND ("elderly" OR "older adults" OR "ageing") AND ("molecular mechanisms" OR "pathophysiology" OR "oxidative stress" OR "inflammation" OR "mitochondrial dysfunction" OR "myostatin" OR "TNF-α" OR "IGF-1") AND ("exercise" OR "physical activity" OR "rehabilitation" OR "resistance training" OR "aerobic training"). We applied Boolean operators (AND/OR).

Inclusion and Exclusion Criteria

Studies were included if they: (1) examined molecular mechanisms of sarcopenia in humans or animal models; (2) evaluated exercise interventions (resistance, aerobic, or combined); (3) reported outcomes related to muscle mass, strength, or function; and (4) were published in peer-reviewed journals. Studies were excluded if they: (1) focused exclusively on pharmacological interventions; (2) lacked molecular outcome data; or (3) were not available in English.

Data Extraction and Synthesis

Data were extracted on study design, population, exercise

modality, molecular outcomes (myostatin, TNF-α, oxidative stress markers, Akt/mTOR signaling), and clinical outcomes. Findings were synthesized narratively and organized around three molecular pathways.

Results

A total of 1,247 records were identified from PubMed/ MEDLINE. After removal of 312 duplicates, 935 records were screened. Of these, 847 were excluded based on title and abstract review. Eighty-eight full-text articles were assessed for eligibility. Forty-three articles were excluded: no molecular outcomes (n = 18), no exercise intervention (n = 12), conference abstract/review (n = 8), and not in English (n = 5). Forty-five studies were included in the final review. A total of 45 studies were included in the final review, as illustrated in Figure 1.

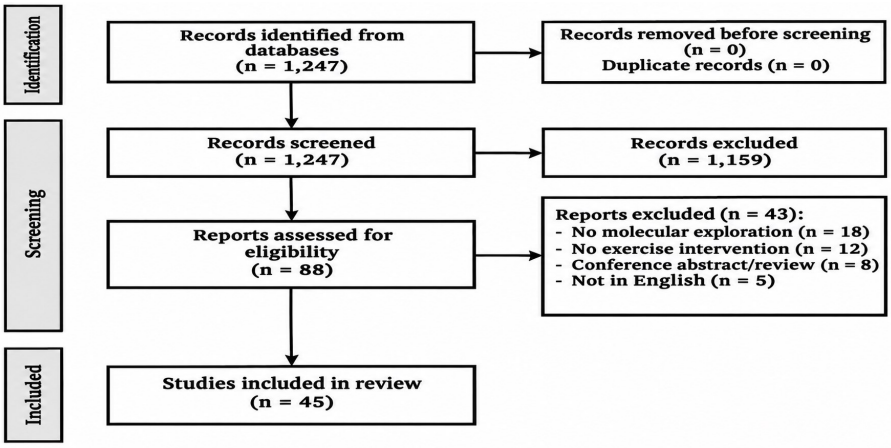


Figure 1. PRISMA Flow Diagram of Study Selection.

Myostatin

Myostatin is a primary negative regulator of muscle mass, and its increased expression directly addresses one of the molecular mechanisms underlying sarcopenia (10). Myostatin levels vary with disease states and physical activity, and muscle myostatin mRNA correlates with markers of insulin resistance and inflammation (11). Resistance training has been shown to downregulate myostatin levels in older adults with sarcopenia. This downregulation is linked to improved muscle mass and strength, making resistance training an essential component of treatment strategies (11).

It acts autocrinally in skeletal muscle and is present in plasma, reflecting its systemic role as a transforming growth factor-family protein produced by various organs. In healthy hearts, myostatin appears at low levels in Purkinje fibers (11). Its concentration increases in heart failure, leading to high plasma myostatin and reduced skeletal muscle mass (12). Around 68% of heart failure patients develop skeletal muscle atrophy, resulting in muscle weakness and exercise intolerance (13). Notably, myostatin may contribute to the association among handgrip strength (HGS), peak VO_2, and cardiovascular risk factors, though the mechanism remains unclear (5).

In healthy individuals, peak VO_2 is negatively linked to muscle myostatin (11) . Furthermore, muscle myostatin mRNA correlates positively with fasting insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA2-IR), TNF-α, Interleukin 6 (IL-6), fat mass, and triglyceride levels (11), indicating its broader metabolic involvement. Myostatin is a key catabolic factor in the UPS (14).

Its role is contrasted with TNF-α, another critical factor in both muscle and cardiac function. While TNF-α amplifies inflammation and promotes catabolic pathways by suppressing the Akt/ mTOR pathway (8) it also has systemic effects on myocardial and skeletal muscle tissues. This comparison highlights the interplay between myostatin and TNF-α, suggesting their combined impact on muscle degradation.

Mechanism of Action

Myostatin is part of the transforming growth factor-β (TGF-β) family. It negatively regulates skeletal muscle growth. Overexpression leads to muscle wasting (15). Myostatin, its inhibitor follistatin, and growth/differentiation factor 11 (GDF11) may influence biological age (16). Follistatin prevents myostatin from binding to activin type II B (ActRIIB) and helps normalize myostatin levels in circulation (17). GDF11 is a circulating age-associated factor with several proposed roles (18). The stimulus for increased myostatin production in skeletal muscle is still unknown. This pathway includes Smad, Akt, and mTOR, simplified here in three steps:

1. Active myostatin binds to ActRIIB receptors and the ALK4 and/or ALK5 coreceptor, triggering Smad2/3 phosphorylation, which subsequently blocks Myoblast determination protein 1 (MyoD) transactivation in an autoregulatory feedback loop (19).

2. Activated Smad2/3 impairs protein synthesis by inhibiting Akt function (20).

3. IGF-I-Akt-mTOR pathway can counteract myostatin-dependent signaling. IGF-I regulates protein kinase Akt. Its downstream target, mTOR, is crucial for translation initiation and muscle size (21) .

Additionally, TNF-α inhibits IGF-I. This process indirectly promotes muscle catabolism by reducing growth hormone (GH) and IGF-I concentrations (6) . Lower levels of IGF-I and GH fail to activate the signalling pathways (Akt, mTOR, STAT5, etc.) necessary for protein synthesis. Reduced Forkhead box O (FoxO) regulation by Akt leads to the overexpression of Atrogin-1 and Muscle ring finger protein (MuRF). This leads to protein breakdown in sarcopenic muscle (6).

Myostatin may serve as a blood biomarker for frailty and sarcopenia. Some studies have examined relationships between blood myostatin and factors such as age or physical interventions. Few studies have used validated frailty scales (22) or precise methods like dual-energy X-ray absorptiometry (DEXA) to assess sarcopenia. Accurate measurements by mass spectrometry and larger, well-defined studies are needed. Researchers must also determine the optimal timing for assessing physical exercise and blood sampling (23). Future studies should use these approaches to clarify myostatin's value as a biomarker. Practical concerns include the cost, availability, and variability of myostatin assays compared to current frailty markers. Comparative analysis of these factors will guide clinical adoption. Studies about assay reliability and performance in different clinical settings are crucial for routine use.

The TNF-α

It is a pro-inflammatory cytokine that stimulates additional cytokine secretion and amplifies inflammation. Elevated TNF-α is linked to chronic low-level inflammation in age-related sarcopenia and contributes to muscle wasting by suppressing the Akt/mTOR pathway (8). In parallel, TNF-α is also produced in the myocardium and may play a significant role in ischemic heart disease by promoting atherosclerotic plaque formation, progression, and rupture (24) . The dual impact of TNF-α on skeletal muscle and cardiac tissues underscores the systemic threat of inflammation. Serum levels of TNF-α, IL-1-beta, and IL-6 correlate with functional impairment and 6-minute walk test performance in patients with chronic heart failure (CHF) (25).

Mechanism of Action

The in vivo mechanisms of TNF-α are not fully understood. Indirectly, TNF-α promotes muscle wasting by altering hormone levels that regulate muscle growth, such as reducing GH and IGF-I concentrations, and by decreasing tissue sensitivity to these factors. It also stimulates catabolic cytokine production and can induce anorexia. Directly, TNF-α may contribute to muscle catabolism by inhibiting myoblast differentiation, inducing apoptosis, and exerting catabolic effects on differentiated muscle (26). The transcription of pro-inflammatory cytokines is primarily regulated by nuclear factor-KB (NF-KB) (26) Age-related disturbances in intracellular redox balance contribute to chronic low-level inflammation, with NF-KB increasing IL-6 and TNF-α levels in ageing (26).

Reactive oxygen species (ROS) act as second messengers for TNF-α in skeletal muscle, activating NF-KB directly or indirectly. Both FoxO and NF-KB activate the proteasome pathway by upregulating E3 ubiquitin ligases, such as muscle ring finger protein-1 (MuRF-1) and muscle atrophy F-box-1 (MAFbx-1), leading to muscle atrophy. Particularly, aerobic and resistance training have been shown to downregulate NF-KB, serving as countermeasures against these catabolic effects, which foreshadow their potential role in the later intervention sections discussed. However, the exact intensity threshold required for aerobic training to effectively downregulate NF-KB remains uncertain (26). This highlights the need for targeted future trials that specifically explore the dose-response relationship and clarify this intensity threshold. Future research should investigate exercise intensities ranging from 40-80% heart rate reserve (HRR) to determine the precise NF-KB threshold, turning this gap into a future research question.

Peripheral Oxygen Utilization

Ageing causes central and peripheral hemodynamic changes that affect arterial compliance, blood pressure, and vascular response to exercise. Reduced blood flow limits oxygen delivery to active muscles, contributing to functional decline. Studies have linked age-related reductions in VO_2 max to muscle wasting, as measured by 24-hour urinary creatinine excretion (27). This decline results from reduced arteriovenous oxygen differences due to diminished blood flow and decreased oxygen extraction. Endothelial dysfunction and low cardiac output may also lead to repeated skeletal muscle ischemia.

Mechanism of Action

The vascular endothelium produces several biologically active molecules, especially nitric oxide (NO) (28). Generalised vascular dysfunction results from multiple overlapping mechanisms. Oxidative stress is central to both normal vascular ageing and the pathology and prognosis of heart failure (29) (32). Increased oxidative stress results from overexpression of radical-producing enzymes, decreased activity of radical scavenger enzymes, and reduced expression and phosphorylation of endothelial nitric oxide synthase (eNOS) (30). Ageing leads to deterioration in peripheral vascular function, likely due to redox imbalance and oxidative stress affecting endothelial function (31). Free radicals reduce NO bioavailability, impairing vasodilation and blood flow. For example, a 10% reduction in vascular function may reduce an older adult's capacity to climb an additional flight of stairs, illustrating how molecular changes translate into tangible declines in physical capability. This reduction in NO bioavailability exemplifies how molecular changes can lead to tangible declines in physical capabilities, emphasizing the need for clinical focus on maintaining endothelial health. Although free radical production increases with age (32) the full impact on vascular function, oxygen delivery, and exercise intolerance in older adults is not yet fully understood.

Endothelial dysfunction may contribute to the increased risk of cardiovascular disease with age (33). Oxidative stress primarily affects the vascular endothelium through interactions between NO and free radicals. Overproduction of free radicals, especially superoxide (O_2-) rapidly binds to and inactivates NO. This accelerates NO inactivation and promotes endothelial cell apoptosis, compromising endothelial integrity and function (34). As a result, less NO is available for smooth muscle relaxation, impairing NO-dependent vasodilation. Inflammation and increased oxidative stress are major contributors to reducing NO bioavailability and the development of endothelial dysfunction, which is independently associated with poor long-term outcomes in the elderly (33). Excess free radicals also impair muscle function and induce apoptosis in skeletal muscle fibers, leading to muscle wasting; they further pro-

mote endothelial cell apoptosis, compromising vascular integrity and function (35).

Three interrelated pathways drive muscle wasting: myostatin signaling, TNF-α inflammation, and oxidative stress. These pathways converge on the IGF-I–Akt–mTOR axis, leading to reduced muscle mass, strength, and functional capacity, as summarized in Figure 2.

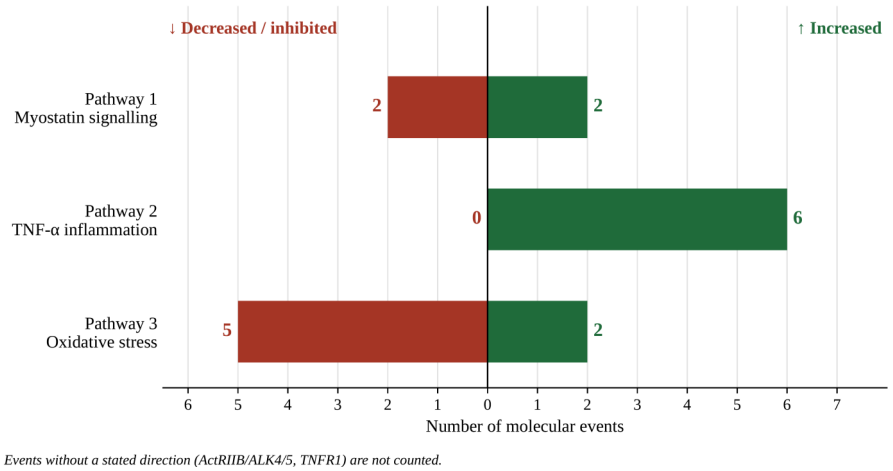


Figure 2. Molecular pathways converging on the IGF-I–Akt–mTOR axis and their translational outcomes.

Discussion

Role of Exercise Training in The Elderly With Sarcopenia

The molecular mechanism behind exercise training in the elderly is fundamental to understanding how physical activity can combat sarcopenia. Recent guidelines strongly recommend physical activity, particularly progressive resistance exercise, as a primary treatment for sarcopenia. Exercise training is also effective for patients with sarcopenic obesity (35). Rehabilitation through exercise, alone or with nutritional supplementation, can reduce muscle wasting or promote skeletal muscle hypertrophy (36).

Sarcopenic individuals often experience varying degrees of malnutrition, possibly due to inflammatory cytokines that contribute to anorexia. Effective prevention and management of sarcopenia require combining exercise with adequate protein and energy intake (37). Large-scale trials, such as the European SPRINT trial, are evaluating exercise and nutritional interventions for sarcopenia (38). Studies show that exercise combined with amino acid supplementation (3 g leucine-amino acid twice daily) may improve muscle strength, mass, and walking speed in sarcopenic participants (29). Furthermore, leucine, a branched-chain amino acid, plays a crucial role in activating the mTOR pathway, which is essential for protein synthesis and muscle growth. The activation of mTOR by leucine complements the effects of resistance training by enhancing anabolic responses, thereby potentially increasing the efficacy of exercise interventions. This synergy between nutrition and exercise provides a compelling rationale for combined interventions, which could persuade practitioners to adopt such approaches for managing sarcopenia effectively. Resistance exercise with nutritional support increases muscle mass and strength more than exercise alone. Low-dose creatine combined with resistance exercise has been shown to improve lean mass in the elderly within three months. Providing amino acids plus glucose before or during recovery from exercise enhances skeletal muscle protein synthesis, with the greatest effect when nutrients are consumed immediately before exercise (39). Lifestyle modifications, including exercise and diet, can help minimize the negative effects of sarcopenia. Adequate dietary protein is essential for muscle protein synthesis and survival at any age, especially since older adults are at increased risk of protein-energy malnutrition due to reduced food intake (40). Higher protein intake (1.0 to 1.3 g $kg^{-1}\cdot d^{-1}$) is recommended to improve muscle protein anabolism and delay atrophy progression in older adults (41). However, one study found that combining protein intake (1.01 ± 0.47 g $kg^{-1}\cdot d^{-1}$) with high-velocity resistance training (HVRT) for 20 weeks did not significantly change serum myostatin levels or lean mass in the elderly (42).

Particularly, muscle strength, a more functional measure, was not assessed in this study. While these interventions might not have altered morphology, they could still offer functional benefits such as improvements in gait or balance, which are crucial for maintaining independence in everyday activities. Despite the potential benefits of combining protein supplementation with physical activity, the certainty of evidence remains low due to limited sample sizes, few trials, and potential biases (43). Another study found that circulating plasma myostatin and follistatin negatively affect muscle function in the elderly. Follistatin showed an inverse relationship with peak power output (Pmax), power relative to body mass (Pmax·kg^{-1}), and 70% leg press power. At the same time, myostatin was negatively correlated with left handgrip strength and optimal shortening velocity (U opt). These findings suggest that circulating myostatin and follistatin may influence muscle power and shortening velocity more than isometric strength. GDF11 was also negatively correlated with body mass, body mass index, waist circumference, fat mass, and body fat percentage (44). Exercise and stretching enhance NO response, a key messenger that activates muscle satellite cells (SCs) (44). SCs are essential for muscle maintenance, growth, and repair (45). Follistatin levels increase after resistance training in older women, and performance improvements have been linked to inhibition of degradation pathways via follistatin (44).

A 2024 systematic review and meta-analysis demonstrated that resistance training significantly reduces myostatin levels in older adults with sarcopenia (46). The study found that resistance training inhibits NF-KB pathway activity by reducing pro-inflammatory factors, thereby indirectly decreasing myostatin transcription. Subgroup analysis revealed that older sarcopenic adults were more likely to activate the mTOR pathway via resistance training to inhibit myostatin expression. Exercise training improves endothelial function and reduces total peripheral resistance, which may help alleviate skeletal muscle ischemia during exercise. This effect is mediated by increased expression of eNOS, resulting in greater NO production and reduced local oxidative stress. Exercise also enhances superoxide dismutase expression in vascular smooth muscle cells and modulates the extracellular redox state (19).

Exercise training can partially reverse cardiovascular disease -related changes by reducing Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity and increasing eNOS expression and phosphorylation. Research suggests that engaging in exercise training at a frequency of at least three sessions per week, maintaining an intensity of 60–70% HRR, is beneficial for achieving these endothelial improvements. The PI3K/Akt pathway, activated by exercise and regulated by IGF-I and insulin signaling, is central to promoting protein synthesis and inhibiting protein degradation through inactivation of FOXO transcription factors (47). This focus on the PI3K/Akt pathway highlights its pivotal role as a key signaling axis, enhancing muscle protein synthesis and offering potential therapeutic avenues in the management of sarcopenia.

The PI3K/Akt pathway, activated by exercise and regulated by IGF-I and insulin signaling, is central to promoting protein synthesis and inhibiting protein degradation through inactivation of FOXO transcription factors. Recent evidence confirms that IGF-1 increases skeletal muscle protein synthesis via PI3K/Akt/mTOR and PI3K/Akt/GSK3 β pathways, and that IGF-1/Akt can inhibit myostatin signaling via Smad pathway inhibition (48). Furthermore, IGF-1 can dominantly overcome myostatin-induced inhibition of Akt in muscle cells (49).

High-velocity resistance training (HVRT) promotes anabolism, helps maintain lean mass, and improves functional fitness in older adults (50). HVRT achieves these benefits by inhibiting myostatin signaling and enhancing regulation of the mTOR pathway, which is critical for muscle mass maintenance during ageing (51). Exercise training also reduces systemic TNF-α levels, increases bone marrow-derived progenitor cell numbers, lowers the proapoptotic impact on endothelial cells, and raises plasma levels of Stromal cell-derived factor 1 (SDF-1), Vascular endothelial growth factor (VEGF), and cluster of differentiation 34 (CD34), all of which are associated with capillary formation in skeletal muscle (39).

Despite extensive research on exercise training in older adults with sarcopenia, there is still limited evidence regarding optimal exercise prescriptions, including frequency and intensity, tailored to this population to prevent adverse outcomes such as musculoskeletal complaints. Figure 3 summarizes these changes.

Limitations

This review has several limitations. First, as a narrative review, it does not employ the quantitative synthesis methods of a systematic review, and the potential for selection bias exists. Second, the heterogeneity of study designs, populations, exercise protocols, and outcome measures across the included studies limits the comparability of findings. Third, many of the mechanistic studies were conducted in animal models or cell culture, and extrapolation to human sarcopenia should be done with caution. Fourth, the evidence base for exercise-induced molecular changes in sarcopenia is limited by small sample sizes and few randomized controlled trials. Finally, publication bias may have influenced the available evidence. These limitations should be considered when interpreting the findings of this review.

Resistance training downregulates myostatin and Smad2/3, relieving inhibition of Akt and permitting mTOR-mediated protein synthesis. Aerobic training reduces TNF-α and NF-ΚB activation while increasing eNOS expression, NO bioavailability, and redox balance. High-velocity resistance training (HVRT) combines myostatin suppression with mTOR activation to promote anabolism, lean mass, and functional fitness. Nutritional supplementation (leucine, creatine, protein) serves as an adjunct to exercise by further activating anabolic signaling.

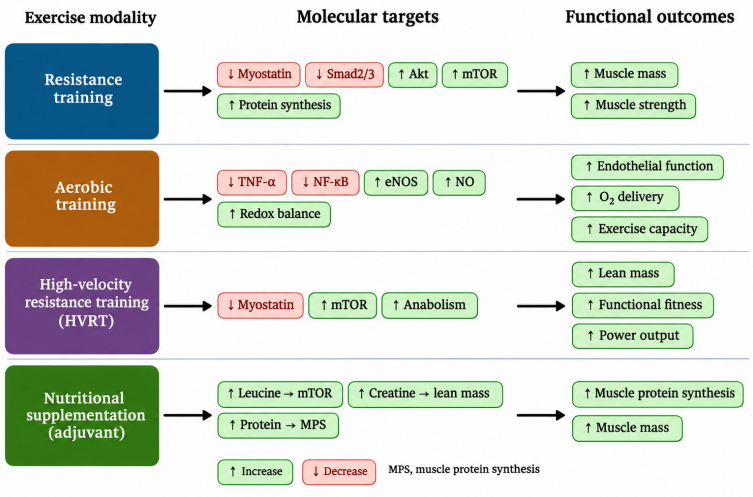


Figure 3. Exercise intervention modalities and their molecular targets in sarcopenia.

Conclusion

Sarcopenia is associated with dysregulation of three interrelated molecular pathways: myostatin signaling, TNF-α-mediated inflammation, and oxidative stress/endothelial dysfunction. These pathways converge on the IGF-I–Akt–mTOR axis, which regulates the balance between muscle protein synthesis and degradation. However, the precise mechanisms by which these pathways interact in human sarcopenia remain incompletely understood.

Exercise therapy, particularly resistance training, has been shown to modulate these pathways in older adults with sarcopenia. Resistance training downregulates myostatin expression and may permit mTOR-mediated protein synthesis. Aerobic and resistance training reduce TNF-α levels and inhibit NF-KB activation, potentially limiting inflammation-driven catabolism. Exercise also improves redox balance, enhances eNOS expression, and increases nitric oxide bioavailability. These molecular changes are associated with improvements in muscle mass, strength, and functional capacity in some studies, though the certainty of evidence varies.

Important gaps remain. The optimal exercise prescription—including frequency, intensity, and type—for frail older adults with sarcopenia has not been established. The role of myostatin as a clinically useful biomarker requires validation through larger, well-designed studies using standardized assays. The direct mechanisms by which TNF-α contributes to muscle atrophy in humans remain incompletely understood. Furthermore, the clinical significance of exercise-induced molecular changes requires confirmation in adequately powered longitudinal studies. Nonetheless, exercise remains the most accessible and evidence-based intervention for managing sarcopenia, and further research is warranted to optimize exercise prescriptions and identify which patients benefit most from specific intervention strategies.

Future Directions

Future research should priorities the following areas, ranked by clinical impact:

1. Personalized exercise prescriptions for frail individuals. Tailoring exercise interventions to individual needs can maximize benefits and minimize risks.
2. Myostatin as a clinical biomarker. The stimulus for increased myostatin production in muscle atrophy remains unknown. Future studies should use validated frailty scales and precise measurement methods (e.g., DEXA, mass spectrometry) to clarify myostatin's value as a biomarker
3. Peripheral vascular function and ageing. The relationship between ageing and impaired peripheral vascular function requires further study to inform strategies for preventing cardiovascular disease in sarcopenic individuals.
4. Direct mechanisms of TNF-α in muscle atrophy. The in vivo mechanisms of TNF-α are not fully understood. Future research should elucidate these mechanisms and explore the potential of anti-inflammatory treatments.
5. Longitudinal studies of combined interventions. Longitudinal studies are crucial to assess the impact of exercise training alone or combined with nutritional supplementation (e.g., leucine, creatine, protein) on muscle mass, strength, and functional capacity in sarcopenic older adults.

Conflict of Interest

None.

Data Sharing

All data, documentation, and Arduino program code used in this will be made available upon reasonable request to the corresponding author

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Ethics Approval and Consent to Participate

Not applicable .

Declaration of AI-Assisted Tools

"During the preparation of this manuscript, the authors used [DeepSeek] for paraphrasing. The authors carefully reviewed and verified the content and take full responsibility for the accuracy, originality, and integrity of the published work."

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