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REVIEW

# Exploration of Pathogenesis and Cutting-Edge Treatment Strategies of Sarcopenia: A Narrative Review

Yin Gao[1,2,*], Di Liu[1,2,*], Qixian Xiao[1,*], Shan Huang[1,2], Li Li[2], Baocheng Xie[3], Limin Zhou[3], Yi Qi[2], Yanzhi Liu[1]

[1]Key Laboratory of Traditional Chinese Medicine for the Prevention and Treatment of Infectious Diseases, Institute of Clinical Medicine, Zhanjiang Central Hospital, Guangdong Medical University, Zhanjiang, 524037, People's Republic of China; [2]Marine Medical Research Institute of Zhanjiang, School of Ocean and Tropical Medicine, Guangdong Medical University, Zhanjiang, 524023, People's Republic of China; [3]Department of Pharmacy, The Tenth Affiliated Hospital of Southern Medical University (Dongguan People's Hospital), Dongguan, 52305, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yanzhi Liu; Yi Qi, Email liuyanzhi@gdmu.edu.cn; qiyi7272@gdmu.edu.cn



**Abstract:** Sarcopenia a progressive and multifactorial musculoskeletal syndrome characterized by loss of muscle mass and function, poses a significant global health challenge, particularly in aging populations. Epidemiological studies reveal that sarcopenia affects approximately 5–10% of the general population, with prevalence rates escalating dramatically after age 60 to reach 10–27% in older adults. This age-associated increase contributes significantly to healthcare burdens by elevating risks of disability, frailty, and mortality. Despite its profound impact, current clinical approaches to sarcopenia remain limited. While resistance exercise and protein supplementation form the cornerstone of management, their efficacy is often constrained by poor long-term adherence and variable individual responses, highlighting the urgent need for more comprehensive and personalized treatment strategies. The pathogenesis of sarcopenia is complex and influenced by various factors, including aging, inflammation, nutritional deficits, physical inactivity, and mitochondrial dysfunction. However, the precise molecular mechanisms underlying this condition are still not fully understood. Recent research has made significant strides in elucidating the intricate mechanisms contributing to sarcopenia, revealing novel insights into its molecular and cellular underpinnings. Notably, emerging evidence points to the pivotal role of mitochondrial dysfunction, altered myokine profiles, and neuromuscular junction degeneration in sarcopenia progression. Additionally, breakthroughs in stem cell therapy, exosome-based treatments, and precision nutrition offer promising avenues for clinical intervention. This review aims to synthesize the latest advancements in sarcopenia research, focusing on the novel contributions to its pathogenesis and treatment strategies. We explore emerging trends such as the role of cellular senescence, epigenetic regulation, and targeted therapeutic interventions that could reshape future approaches to managing sarcopenia. By highlighting recent breakthroughs and cutting-edge research, we hope to advance the understanding of sarcopenia and foster the translation of these findings into effective clinical therapies.

**Keywords:** sarcopenia, muscle, aging, skeleton

## Introduction

Sarcopenia, first described by Rosenberg in 1997, is a clinical syndrome characterized by the progressive decline in muscle mass and function, predominantly associated with aging.[1] The European Working Group on Sarcopenia in Older People (EWGSOP) defines sarcopenia as a gradual, generalized loss of skeletal muscle mass and strength that leads to reduced physical capability, diminished quality of life, and increased mortality.[2] Similar definitions have been proposed by the International Sarcopenia Working Group, the Asian Working Group for Sarcopenia (AWGS), and the Chinese Society of Osteoporosis and Bone Mineral Research.[3–5] The AWGS introduced regional guidelines tailored for Asian populations in 2014, which were updated in 2019.[4,6] China currently adheres mainly to the EWGSOP definition.



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Contemporary sarcopenia diagnosis relies on a tripartite assessment framework encompassing muscle mass, muscle strength, and biomechanical performance. The current gold standard quantifies muscle mass index (ASMI) via dual-energy X-ray absorptiometry (DXA), with sex-specific thresholds defining pathology (<7.0 kg/m² males; <5.4 kg/m² females). Dynamometric evaluation of maximal grip strength establishes functional reserve boundaries (<26 kg males; <18 kg females), while ambulatory capacity is objectively measured through standardized gait analysis, where velocities below 0.8 m/s signify clinically relevant impairment. Diagnostic confirmation necessitates concurrent abnormalities in ≥2 domains, as per international consensus guidelines.[7] As the understanding of sarcopenia continues to evolve, the Global Leadership Initiative in Sarcopenia (GLIS) recently suggested that muscle mass, muscle strength, and muscle-specific strength should be considered the core components of sarcopenia, while impaired physical performance should be viewed as an outcome rather than a component of the syndrome.[8] Epidemiological studies reveal that sarcopenia affects approximately 5–10% of the general population[9] and with prevalence rates escalating dramatically after age 60 to reach 10–27% in older adults.[10] Another report estimated that 10–16% of the global elderly population is affected by sarcopenia.[11] A meta-analysis involving 41 studies and 34,955 participants found that the prevalence of sarcopenia among community-dwelling individuals was 11% in men and 9% in women.[12] Systematic analysis suggest that the overall prevalence of sarcopenia in the elderly ranges from 5% to 37%.[13] Among specific groups, prevalence rates are reported to be 41–59% in nursing home residents and 12.9–40.4% in community-dwelling older adults.[14] Community-dwelling adults exhibit prevalence rates of 8–13% in men and 7–11% in women (EWGSOP/AWGS/IWGS criteria).[15] Certain populations demonstrate disproportionately elevated sarcopenia prevalence, including 40.7% in liver transplant recipients, 51% in male nursing home residents and 23–24% in hospitalized populations.[15] These populations exhibit robust high-risk to sarcopenia, strongly correlating with adverse clinical outcomes such as prolonged hospitalization and mortality. Previous reports reveal significant variations in sarcopenia prevalence among older populations, with estimates ranging from 10% to 27% across studies employing different diagnostic classifications and cut-off points. Notably, geographical disparities emerge, with Oceania demonstrating the highest rates when applying EWGSOP criteria, while European populations show the lowest prevalence under EWGSOP2 guidelines. Studies reveal an 8.3% prevalence in Beijing[16] (AWGS-2019 criteria) and a striking age-dependent increase from 1.5% (60–69 years) to 33.1% (≥80 years) in Chinese men.[17] Age-stratified data indicate a progressive increase from around 8% in adults under 60 years to 10–27% in those aged 60 and above. Intriguingly, sex-specific patterns differ substantially based on diagnostic frameworks: while EWGSOP2 identifies higher prevalence in males, IWGS criteria conversely report elevated rates among females.[2] The observed heterogeneity in prevalence estimates reflects methodological disparities in diagnostic frameworks. Existing consensus guidelines (AWGS, EWGSOP, IWGS, FNIH) demonstrate variable sensitivity profiles, with particularly limited detection capability for incipient sarcopenia. While advanced imaging techniques (eg, DXA/BIA) represent the current diagnostic gold standard, their implementation barriers in resource-constrained environments necessitate the development of validated, point-of-care assessment tools. This critical gap has prompted international calls for unified diagnostic standards to enhance early identification and targeted therapeutic interventions. In this work, we performed a systematic search across three major databases (PubMed, Web of Science, and Cochrane Library) for collecting relevant publications from January 2015 to December 2023. The inclusion criteria were peer-reviewed clinical trials, meta-analyses, and mechanistic studies published in English. The exclusion criteria contained case reports, non-human studies, and editorials. A three-phase screening process was employed, which involved title and abstract review, full-text evaluation, and quality assessment, with dual independent verification at each stage.

The observed heterogeneity in prevalence estimates primarily reflects methodological disparities in diagnostic frameworks. Existing consensus guidelines (AWGS, EWGSOP, IWGS, FNIH) demonstrate variable sensitivity profiles, with particularly limited detection capability for incipient sarcopenia. While advanced imaging techniques (eg, DXA/BIA) represent the current diagnostic gold standard, their implementation barriers in resource-constrained environments necessitate the development of validated, point-of-care assessment tools. This critical gap has prompted international calls for unified diagnostic standards to enhance early identification and targeted therapeutic interventions.

Sarcopenia manifests as a multisystemic risk multiplier, demonstrating significant pathophysiological linkages to cardiovascular compromise, respiratory insufficiency, neurocognitive deterioration, frailty syndrome.[18] This musculoskeletal degeneration also substantially elevates clinical risks including injurious falls (particularly fragility fractures),

unplanned hospital admissions, and all-cause mortality.[19] The cumulative disease burden poses significant risks to patients' functional independence and psychosocial well-being. Emerging evidence positions the SarQoL® questionnaire as a validated multidimensional tool[20] for quantifying sarcopenia-specific health-related quality of life (HRQoL) impairments.[21] Comparative analyses reveal pronounced health-related quality of life deficits in sarcopenic populations versus their non-sarcopenic counterparts.[22] A significantly lower HRQoL was observed for sarcopenic individuals compared with non-sarcopenic ones.[23,24] A meta-analysis demonstrated that sarcopenia is associated with lower health-related quality of life measured with SarQoL. Subgroup analyses revealed substantial impact of regions, clinical settings, and diagnostic criteria on the difference in health-related quality of life between sarcopenic and non-sarcopenic individuals.[24] This metric now facilitates therapeutic monitoring in clinical trials evaluating sarcopenia interventions–from pharmacological agents like metformin to the effect of pathophysiological states like leaky gut.[25] Despite this, sarcopenia is still underdiagnosed and poorly managed in clinical. Standardizing diagnostic criteria and improving measurement techniques are crucial steps toward advancing sarcopenia management.[26]

The primary risk factors for sarcopenia include aging, chronic diseases, physical inactivity and malnutrition (Figure 1). However, a recent study suggests that the risk factors for sarcopenia in younger individuals differ somewhat from those in older adults. In younger populations, sarcopenia is more closely associated with metabolic and endocrine disorders, while genetic predisposition, physical inactivity, vitamin D deficiency, and poor nutrition are common risk factors across all age groups.[27]

This comprehensive review critically examines recent breakthroughs in sarcopenia research, with particular emphasis on mechanistic insights into disease pathogenesis and evolving therapeutic paradigms. By highlighting recent breakthroughs and cutting-edge research, we hope to advance the understanding of sarcopenia and foster the translation of these findings into effective clinical therapies.

# Risk Factors

## Aging and Sarcopenia

Muscle physical functions decline with aging, accompany with a decrease in anti-inflammatory cytokines and an accumulation of inflammatory factors. The inflammatory microenvironment contributes to muscle loss, atrophy, and reduced functionality. Aging also triggers reductions in autophagy and endogenous hormone secretion, impairing muscle growth and regeneration (Figure 2).

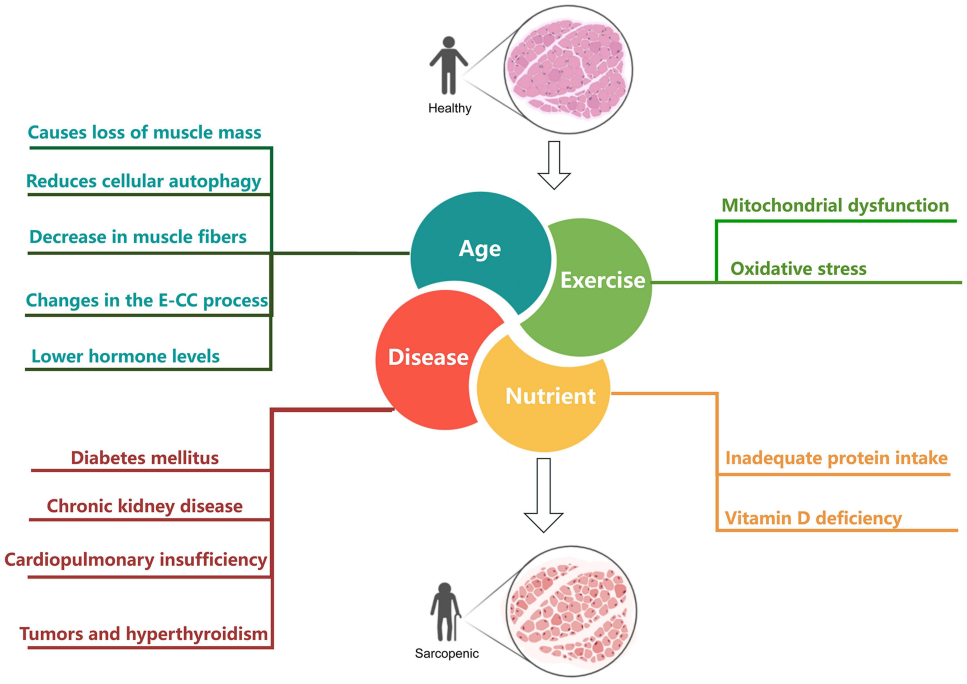


**Figure 1** Major risk factors of sarcopenia.


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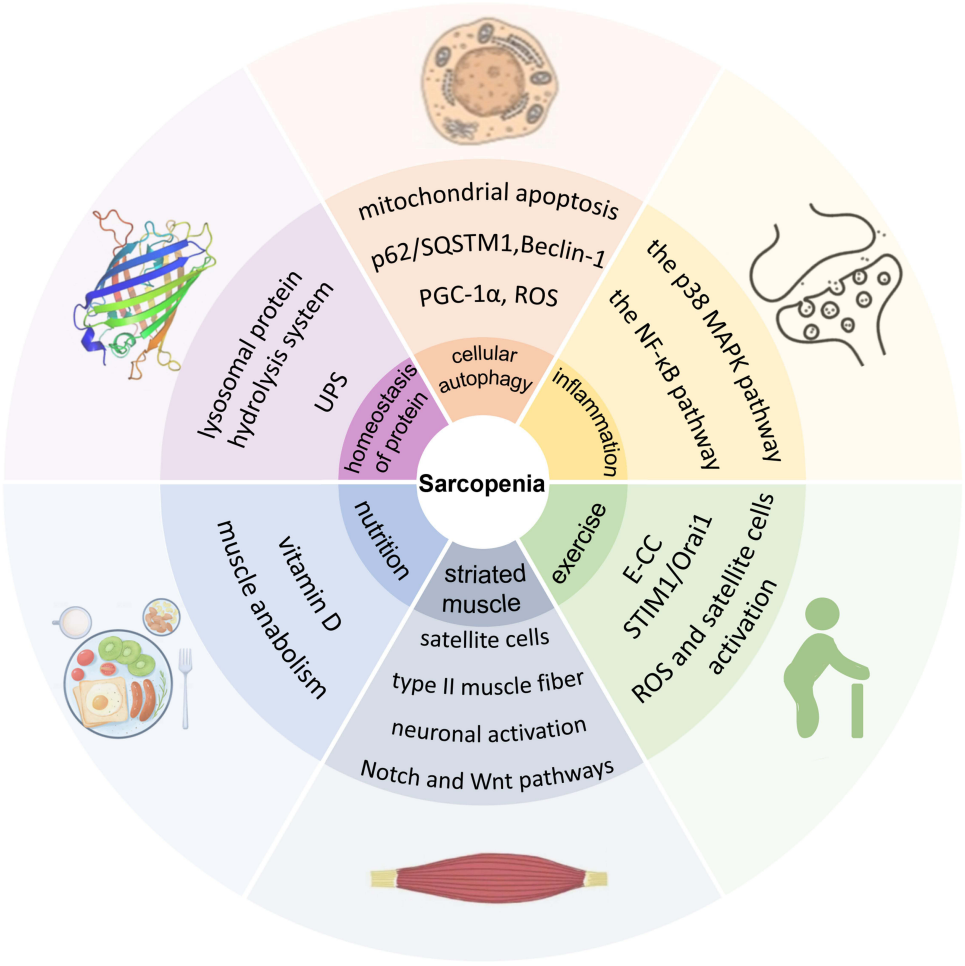


**Figure 2** Signals and factors involved in sarcopenia development due to aging.

## Aging-Induced Muscle Mass Decline and Fiber Degradation

Previous studies reported muscle mass declines by 1–2% annually after the age of 50,[28] with higher rates observed in individuals over 75—ranging from 0.64–0.70% in women and 0.80–0.98% in men.[29] Prolonged inactivity accelerates muscle atrophy, increasing the risk of sarcopenia.

Aging also affects muscle fiber composition, particularly the fast-twitch type II fibers, which are essential for power and speed. Type II fibers shrink in both size and number as people aging, and their functionality is compromised. Clinical studies show a 10–40% reduction in type II fibers among older adults compared to younger populations.[30–32]

Skeletal muscle harbors a specialized population of adult stem cells known as satellite cells, which predominantly exist in a quiescent state under homeostatic conditions. These cells exhibit limited proliferative activity, primarily responding to replace damaged myofibers resulting from routine physiological stress while simultaneously preserving the progenitor pool necessary for long-term muscle maintenance. Recent evidence indeed suggests that satellite cell depletion in knockout models does not significantly accelerate sarcopenia progression, indicating that impaired myogeneration through type II myonecrosis may not be the primary driver of age-related muscle loss. Instead, accumulating data support that sarcopenia develops through multifactorial processes including neuromuscular junction remodeling with motor unit reorganization[33] (shifting from type II to type I fiber predominance), chronic low-grade inflammation,[34] and altered muscle protein turnover.[35] While satellite cells may not be essential for maintaining muscle mass during aging under basal conditions, their dysfunction likely contributes to sarcopenia through paracrine mechanisms affecting the muscle microenvironment.[36] Emerging research demonstrates that skeletal muscle exhibit altered crosstalk with immune cells (particularly macrophages),[37] fibroblasts, and other stromal components,[38] disrupting the coordinated signaling

required for effective muscle maintenance and repair.[39,40] Epigenetic alterations in Polycomb/Trithorax group protein activity impair the temporal regulation of myogenic gene expression during regeneration.[41] These reports suggest that satellite cell dysfunction in aging primarily manifests as impaired microenvironmental communication rather than an absolute loss of regenerative potential. (Figure 3).

Previous analysis highlight five novel hallmarks that are particularly consequential for age-related skeletal muscle decline: chronic low-grade inflammation, progressive neural dysfunction, extracellular matrix remodeling, diminished vascular perfusion, and disrupted ionic homeostasis, each representing promising therapeutic targets for sarcopenia intervention.[39] Building upon this framework, newly work on meta-hallmarks of aging revealed the meta-hallmarks of aging and their intersection with cancer biology, particularly their conceptual expansion of the original hallmarks of aging to include impaired macroautophagy, sustained inflammaging, and gut microbiome dysbiosis - all highly relevant to sarcopenia pathophysiology - interact to drive muscle deterioration.[42] These works collectively provide a comprehensive roadmap for developing targeted interventions that address both local tissue changes and organism-wide aging processes contributing to sarcopenia progression.

In conclusion, the combined effects of reduced muscle fiber number, atrophy, and satellite cell dysfunction are central contributors to sarcopenia.

## Aging and Excitation-Contraction Coupling (E-CC)

Aging not only reduces muscle mass but also weakens muscle strength at both the single-fiber and whole-muscle levels.[43,44] A key reason for this is the disruption of excitation-contraction coupling (E-CC), the process by which neural signals trigger muscle contractions. Impaired $Ca^{2+}$ release from the sarcoplasmic reticulum (SR) is a potential mechanism behind this decline.[45] Additionally, aging decreases the expression of the voltage-gated $Ca^{2+}$ channel α1 subunit (Cav1.1), which is essential for E-CC. Research by Zhang et al found that genetic knockout of fast skeletal muscle troponin T3 (TnT3) downregulates Cav1.1. In aged sedentary mice, preventing TnT3 fragmentation led to a 20–30% increase in gastrocnemius muscle mass.[46] These findings suggest that targeting E-CC abnormalities could help reverse age-related declines in muscle strength and mass.

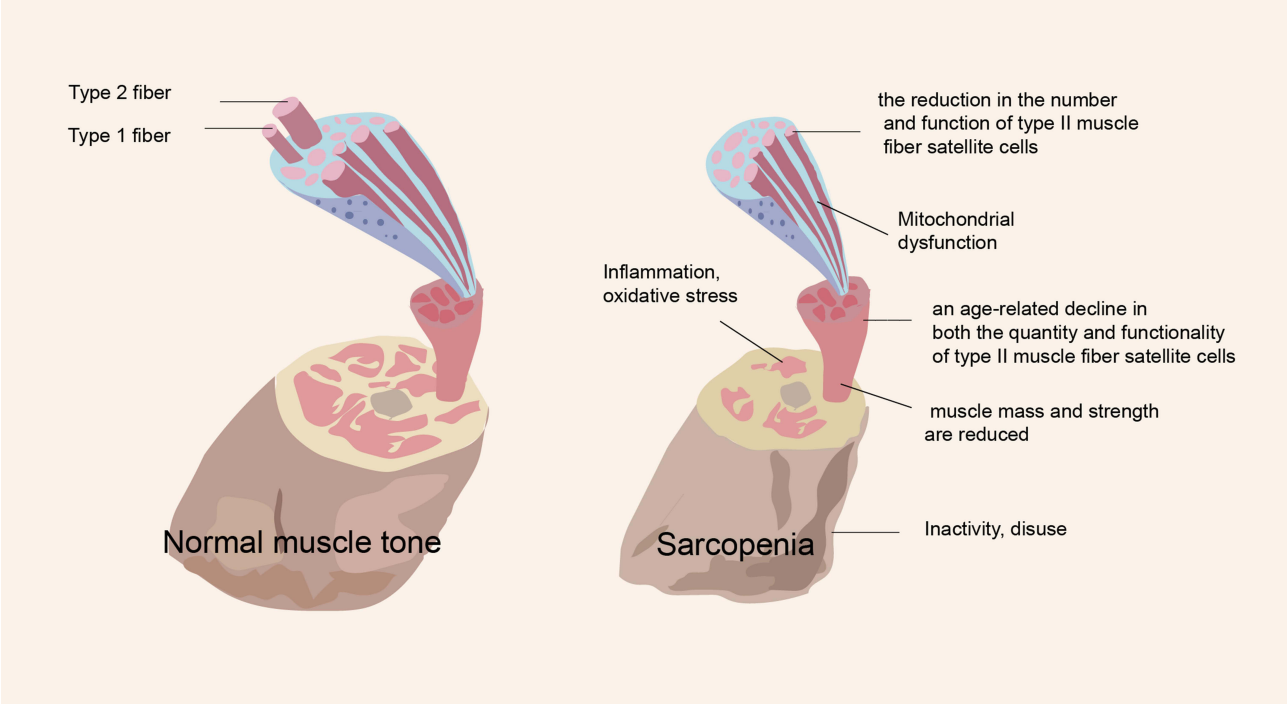


**Figure 3** Aging-induced loss of muscle mass and degeneration of muscle fibers.


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## Aging and Autophagy Reduction

Aging reduces the number of MuSCs in skeletal muscle and disrupts their regulation. This results in impaired muscle regeneration and increased vulnerability to age-related decline.[47] Autophagy plays a key role in muscle regeneration, supporting both stem cells and muscle fibers.[48] Aged muscle stem cells often exhibit autophagy deficiencies, leading to elevated reactive oxygen species (ROS) levels, which impair regenerative capacity.[49] Additionally, excessive ROS damages muscle tissue integrity, further contributing to muscle decline. A decrease in Myf5-positive cells, can lead to muscle defects. Research by Sakuma et al found an increase in autophagy-related molecules, such as p62/SQSTM1 and Beclin-1, in aged mice. However, there was no significant change in the autophagy protein LC3, suggesting a defect in autophagic capacity in aged mice.[50] This deficiency contributes to impaired muscle regeneration, metabolic defects, and the progression of sarcopenia.

## Aging and Inflammation

Chronic low-grade inflammation is a major driver of sarcopenia. As the body ages, increased fat tissue leads to the accumulation of pro-inflammatory macrophages and immune cells. This imbalance reduces anti-inflammatory cytokines and elevates pro-inflammatory molecules such as leptin, TNF-α, IL-1, and IL-6.[50,51] Markers of inflammation, including C-reactive protein and erythrocyte sedimentation rate, are elevated in sarcopenic patients, particularly those with hip fractures.[52] Pro-inflammatory cytokines accelerate muscle protein degradation, leading to a loss of muscle mass, strength, and function.[53] The ratio of IL-6 to IL-10 is used as an indicator of inflammation in sarcopenia elderly patients.[54] This imbalance promotes muscle degradation through pathways such as the ubiquitin-proteasome system and the lysosomal autophagy system. TNF-α could inhibit the Akt/mTOR pathway, triggering muscle degradation via the NF-κB signaling pathway.[55] Therefore, chronic inflammation is a significant factor contributing to sarcopenia in the elderly.

## Aging and Hormonal Decline

Hormonal changes play a key role in muscle loss with aging. Declining levels of hormones such as growth hormone, testosterone, thyroid hormone, and insulin-like growth factor reduce muscle regeneration and promote atrophy.[56] Muscle loss is further exacerbated by increased catabolic signaling mediated by pro-inflammatory cytokines like TNF-α and IL-6.[57] Hormonal deficiencies, including lower levels of insulin, estrogen, and androgens, are major contributors to the development of sarcopenia (Table 1).

**Table 1** The Relationship Between Hormones and Sarcopenia

| Hormones | Relationship to Sarcopenia |
|---|---|
| Growth Hormone (GH) | GH can promote the increase of insulin-like growth factor 1 (IGF-1), which positively regulates the serine/threonine protein kinase B pathway, promotes protein synthesis, and inhibits protein degradation.[58] IGF-1 induces myoblast proliferation by regulating the expression of Myogenic Regulatory Factor (MRF) and Pax3/7 genes, and affects muscle development during secondary muscle development.[59] |
| Androgens | The decline in androgen levels leads to reduced skeletal muscle protein synthesis and may be one of the mechanisms of sarcopenia. Androgens can stimulate the mitotic activity of muscle satellite cells and influence muscle hypertrophy by increasing IGF-1 expression.[60] |
| Estrogens | Estrogen is an antioxidant and muscle fiber membrane stabilizer that mainly enhances the sensitivity of skeletal muscle to anabolic stimuli, maintains skeletal muscle contractility, and resisting degenerative changes in skeletal muscle.[61] Estrogen has a direct effect on muscle mass. |
| Vitamin D | Prolonged low vitamin D level primarily causes type II muscle fiber atrophy, leading to decreased muscle strength and increased fall risk in the elderly.[62] |

(*Continued*)

**Table 1** (Continued).

| Hormones | Relationship to Sarcopenia |
|---|---|
| Thyroid Hormone (TH) | TH is an important regulator of muscle fibers, especially regulate fibers phenotype and muscle fibers composition. Hypothyroidism leads to a shift from fast to slow muscle fibers, while hyperthyroidism shifts in the opposite direction.[63] Thus, a reduction in T3 decreases the expression and activity of the signaling protein calmodulin phosphatase and its downstream transcription factors, leading to changes in muscle strength and function in the early stages of sarcopenia.[64] |
| Creatine | Accelerate the proliferation process of satellite cells, promote the efficient repair of muscle fibers, ensure the rapid generation of ATP, enhance the body's training adaptability, and indirectly reduce the degree of inflammation through the approach of improving muscle bioenergetics.[65] |

## Physical Inactivity and Sarcopenia

Physical inactivity is a key risk factor for sarcopenia.[66] Muscle fiber decline typically begins around age 50, and sedentary individuals experience more pronounced reductions in muscle mass and strength than those who are physically active.[67] Exercise activates various signaling pathways that promote muscle regeneration, enhancing both strength and mass.[68] It has been shown to transiently elevate IL-6, which may stimulate the chronic expression of anti-inflammatory mediators such as IL-1 receptor antagonists and IL-10, while suppressing pro-inflammatory mediators like TNFα and IL-1β.[69] In a study by Reid et al[70] total daily sedentary time was found to be positively correlated with lower lean body mass percentage (−1.70% [95% CI: −2.30, −1.10]) and higher fat mass (2.92 kg [95% CI: 1.94, 3.30]) among 123 elderly individuals living independently. Frequent interruptions in sitting time were associated with a 45% reduction in the risk of pre-sarcopenia (OR = 0.55, 95% CI: 0.34, 0.91), indicating a strong association between sedentary behavior and greater declines in muscle mass and strength. Another cross-sectional study in a Japanese population used logistic regression analysis to explore the relationship between exercise habits and sarcopenia. The study considered factors such as skeletal muscle mass index (SMI), grip strength, walking speed, chair stand time, and single-leg standing time as dependent variables, while middle-aged exercise habits served as independent variables. The results showed significant positive correlations between middle-aged exercise habits and grip strength, walking speed, and single-leg standing time in older adults.[71] This suggests that regular exercise during middle age acts as a protective factor against sarcopenia later in life. In summary, individuals who engage in less physical activity are more likely to experience reductions in muscle mass and strength, significantly increasing the risk of sarcopenia.

## Mitochondrial Dysfunction and Oxidative Stress in Sarcopenia

Mitochondrial quantity, function, and morphology are closely linked to muscle mass and performance.[72] The accumulation of damaged mitochondria and impaired mitochondrial autophagy are common during aging and strongly associated with sarcopenia development.[73]

In sarcopenia, mitochondrial function declines, with reduced capacity to eliminate defective mitochondria and decreased adenosine triphosphate (ATP) synthesis. This results in lower ATP production and increased oxidative stress. These physiopathological changes are key contributors to muscle weakness and fatigue.[74]

As aging progresses, the mitochondrial quality-control system undergoes complex molecular changes, including downregulation of genes related to mitochondrial biogenesis, slowed biogenesis rates, mitochondrial DNA mutations, deletions, or copy number variations, and impaired mitochondrial respiratory chain function, leading to increased ROS production.[75] Studies suggest that endurance exercise can improve muscle regeneration by modulating mitochondrial metabolism, which promotes satellite cell self-renewal and activation.[76] Maintaining a functional mitochondrial network is essential for skeletal muscle health throughout life. Tamaki et al observed that mitochondrial dysfunction occurs at the onset of muscle mass and function decline, highlighting its central role in sarcopenia.[77] Oxidative stress and mitochondrial dysfunction lead to DNA fragmentation,[78] accelerate cellular denervation, decrease cellular regeneration and differentiation, and ultimately contribute to muscle loss (Figure 4).

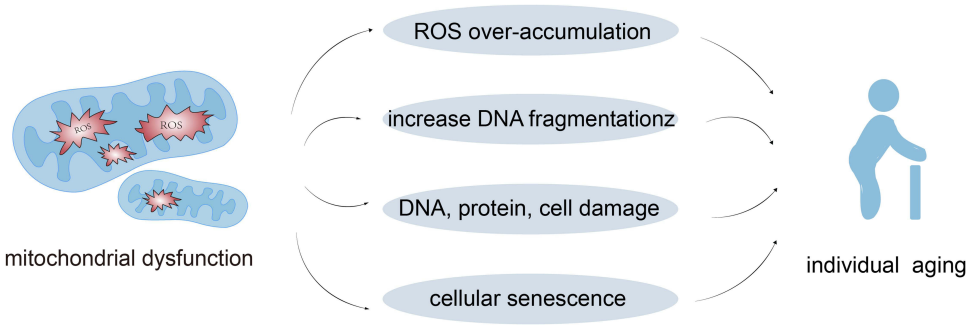


**Figure 4** Mitochondria dysfunction and aging.

Growing evidence highlights the critical role of mitochondria in sarcopenia progression. Key features of sarcopenia include reduced muscle fiber diameter, decreased myosin heavy chain expression, increased activation of the ubiquitin-proteasome system (UPS), and elevated ROS levels.[79] Mitochondria are the primary source of ROS,[80] and oxidative phosphorylation (OXPHOS) during intense skeletal muscle contractions. With aging, mitochondrial function declines, leading to bioenergetic failure, increased fatigue, and excessive ROS production.[81] This disrupts redox homeostasis and impairs cellular signaling.[82] Mitochondrial quality control can be enhanced through mitophagy, the selective degradation of damaged mitochondria, which can be promoted by bioactive components or lifestyle interventions like exercise.[83]

Defective mitochondrial autophagy and the accumulation of damaged mitochondria also induce inflammation, leading to persistent energy imbalances and increased muscle protein catabolism, which further contribute to sarcopenia (Figure 5). [84] During aging, the reduced capacity of mitochondria in muscle cells is a major factor in the development of sarcopenia,[85] and targeting mitochondrial dysfunction may offer new therapeutic approaches for treating sarcopenia.

## Malnutrition and Sarcopenia

Adequate protein intake and optimal vitamin D levels are essential for maintaining skeletal muscle. Nutritional deficiencies, particularly low protein intake, are major contributors to muscle loss and sarcopenia.

### Insufficient Protein Intake

Research indicates that muscle mass declines at rates of 3–8% per decade after age 30, accelerating to 1.1–1.4% per year after 50, and reaching 2.3% per year after 60. Muscle strength and power decline at a rate of 1.5% per year.[86] The key factors behind this loss include reduced energy availability and inadequate protein intake. Protein consumption is crucial for preserving skeletal muscle mass, yet malnutrition is common among the elderly. In a study of 836 elderly individuals over 60, Hai et al[87] found a strong association between poor nutritional status and sarcopenia. Aging leads to physiological deterioration, reduced protein intake and synthesis, and the accumulation of non-contractile proteins like lipofuscin and cross-linked proteins in muscle. To maintain muscle health, the elderly is recommended to consume 1.0–1.2 g/kg of high-quality protein daily.[88] Insufficient protein intake is a significant risk factor for sarcopenia.

### Vitamin D Deficiency

Vitamin D deficiency is associated with reduced muscle strength, especially in the elderly, who often experience decreased vitamin D synthesis due to limited sun exposure and metabolic disorders. Studies have shown that treating muscle cells with 100 nM Vitamin D3 for 1–12 days enhances the expression of myogenic regulatory factors, promoting muscle fiber differentiation.[89] Nakamura et al demonstrated that low vitamin D levels lead to muscle fiber reduction and muscle atrophy in mice.[90] Vitamin D plays a critical role in muscle tone and contraction.[91] Overexpression of the vitamin D receptor (VDR) in rats has been shown to promote muscle hypertrophy, increasing muscle cross-sectional area and enhancing anabolic signaling pathways such as the mTOR complex 1 (mTORC1), which stimulates protein synthesis.[92] Prolonged vitamin D deficiency primarily affects type II muscle fibers, leading to muscle atrophy, reduced strength, and an elevated risk of falls in the elderly.[93] Harvey et al[94] reported that vitamin D supplementation reduces the risk of falls by 8%–22%. Additionally, vitamin D has been shown to increase serum IGF-1, which may mitigate muscle atrophy by

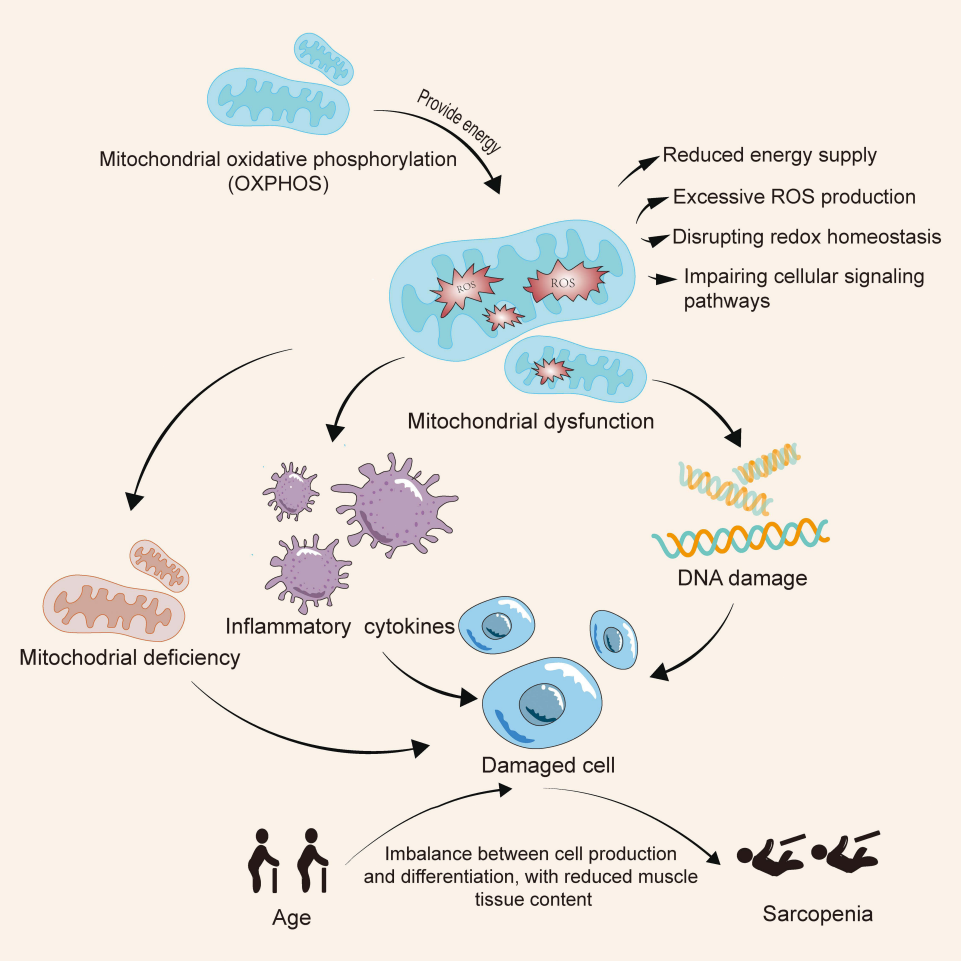


**Figure 5** Mitochondrial dysfunction in aging: ROS accumulation, inflammation, and muscle senescence.

inhibiting NF-κB and Smad signaling, thereby enhancing muscle growth.[95,96] Extensive research has established a significant association between suboptimal serum 25-hydroxyvitamin D (25(OH)D) levels (<50 nmol/L) and impaired muscle protein synthesis, reduced muscle strength, and accelerated progression of sarcopenia, as documented in multiple clinical studies.[97–100]

## Chronic Diseases and Sarcopenia

Many older adults suffer from chronic diseases such as chronic kidney disease, heart failure, lung dysfunction, cancer, diabetes, and hyperthyroidism. These conditions contribute to muscle deterioration, leading to atrophy and functional decline.[101–103]

### Diabetes Mellitus (DM) and Dyslipidemia in Sarcopenia

High blood glucose levels are a risk factor for age-related muscle loss and dysfunction[104] Insulin resistance, elevated glucose levels, and increased glucocorticoids accelerate muscle atrophy.

### Chronic Kidney Disease and Sarcopenia

Chronic kidney disease impairs muscle precursor (satellite) cell function, reducing myogenesis and contributing to sarcopenia.[105] Other factors, such as prolonged dialysis, comorbid diabetes, elevated phosphate levels, and malnutrition, further increase the prevalence of sarcopenia.[106]


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## Cancers and Sarcopenia

In cancer patients, oncogenic drivers (eg, MYC, RAS, HIF-1α) promote tumor progression through metabolic reprogramming and oxidative damage.[107] Concurrently, aging-associated epigenetic alterations (aberrant DNA methylation, dysregulated histone modifications) and genetic defects (telomere attrition, mitochondrial DNA mutations) further exacerbate genomic instability.[42] These synergistic mechanisms not only drive tumorigenesis but also induce metabolic imbalance, directly impairing muscle protein homeostasis and suppressing muscle regenerative capacity, thereby accelerating the development of sarcopenia. Sarcopenia in this population is driven by cancer-related anorexia, malignancy, surgical stress, and the adverse effects of chemotherapy.[108] Inflammatory cytokines triggered by cancer can induce muscle breakdown, exacerbating muscle loss.[109] A study using tumor mouse models revealed that activation of the receptor for advanced glycation end-products (RAGE) by S100B induces muscle atrophy, suggesting that chronic RAGE activation in cancer patients is linked to systemic inflammation and muscle degradation. Anticancer treatments also worsen physical frailty, contributing to sarcopenia.[110]

## Heart and Lung Dysfunction and Sarcopenia

In heart failure, continuous metabolic demand depletes skeletal muscle protein, increasing the risk of sarcopenia.[111] In postoperative non-small cell lung cancer patients, obstructive ventilatory impairment (FEV1% <70%) is an independent risk factor for skeletal muscle loss.[112]

## Hyperthyroidism and Sarcopenia

Hyperthyroidism is a well-known cause of sarcopenia.[113] Animal studies show that hyperthyroid mice experience greater muscle fatigability, and the muscle mass and tone decrease in Slc16a2 knockout mice (Mct8KO), which may due to elevated muscle thyroid hormone levels.[114,115] Clinically, hyperthyroid patients often present with exercise intolerance, cramps, muscle pain (myalgia), and muscle weakness, likely due to increased calcium ion circulation.[116]

## Genetic Factors and Sarcopenia

The pathogenesis of sarcopenia is multifactorial, with genetic factors playing a key role alongside environmental influences. Recent studies emphasize the impact of genetic variations in structural and metabolic proteins, growth factors, hormones, and inflammatory cytokines.[117] Heritability accounts for up to 64% of muscle strength variability in aging populations.[118] Studies have identified the COL15A1 gene as one of the genes with shared genetic co-localization evidence related to sarcopenia, and increased expression of the COL15A1 contributed to sarcopenia development.[119] Specific gene polymorphisms, such as in the ACTN3 gene, which influences fast-twitch muscle fibers, are associated with differences in muscle mass and performance in older adults.[120] Emerging evidence underscores the critical involvement of epigenetic regulation in the pathogenesis and progression of sarcopenia.[121] Age-related hypermethylation of DNA and elevated histone deacetylase (HDAC) activity have been shown to suppress myogenic gene expression and impair protein biosynthesis pathways essential for muscle homeostasis.[122] Epigenome-wide analyses have revealed 176 differentially methylated CpG sites and 141 distinct methylomic regions significantly associated with sarcopenic phenotypes, with functional enrichment observed in pathways governing myotube fusion dynamics, mitochondrial oxidative phosphorylation, and voltage-gated calcium channels.[123] Simultaneously, epigenetic regulators including DNA methylation and HDACs reciprocally modulate miRNA expression, forming an integrated regulatory network wherein miRNAs cooperate with other epigenetic factors to coordinately govern skeletal muscle development and functional adaptation.[124] Myogenic miRNAs (including the pro-myogenic miR-1/133/206 cluster and muscle-specific miR-208b) exert central regulatory functions in skeletal muscle development by targeting and suppressing inhibitory factors such as HDAC4 and Pax7, while establishing positive feedback loops with key myogenic transcription factors MyoD and MEF2.[125] These genetically related pathophysiological mechanisms interact to exacerbate muscle atrophy and increase the risk of sarcopenia. Clinically significant methylation alterations have been identified in sarcopenic cohorts, including 17 differentially methylated CpG sites and 7 differentially methylated regions (DMRs) were confirmed between patients with sarcopenia and control individuals; hypomethylation at specific FGF2_30 that demonstrates progressive reduction correlating with disease severity. Such epigenetic signatures hold promise as diagnostic biomarkers for sarcopenia risk stratification and therapeutic monitoring.[126] Emerging therapeutic strategies focus on epigenetic reprogramming interventions targeting these dysregulated pathways to restore musculoskeletal integrity, offering novel approaches for sarcopenia management.[127]

## Hydration and Muscle–Water Balance and Sarcopenia

Hydration plays a vital role in muscle function and health. Intracellular water (ICW) and extracellular water (ECW) are crucial to maintaining muscle integrity. ICW supports intracellular homeostasis, protein synthesis, and metabolic function. ECW, distributed in interstitial spaces and blood, facilitates nutrient transport and metabolic waste removal.[128] The balance between ICW and ECW is regulated by aquaporins, ion channels, and transporters et.al. Disruption of this balance can lead to muscle atrophy, reduced contractility, and weakness—hallmarks of sarcopenia.[129]

## Neuromuscular Junction Transmission and Sarcopenia

Recent studies highlight changes in the neuromuscular junction (NMJ) as a central factor in sarcopenia pathogenesis.[130] The NMJ, comprising presynaptic motor neuron terminals, the synaptic cleft, and postsynaptic muscle membranes, relies on acetylcholine (ACh) release for efficient neurotransmission. ACh binds to nicotinic acetylcholine receptors (nAChRs) on the muscle membrane, initiating muscle contraction.[131] The C-terminal Agrin fragment(CAF) plays a crucial role in the function of NMJ. Studies have shown that the CAF has higher concentrations in older adults and patients with muscular dystrophy, it is associated with decreased muscle strength and function.[132,133] CAF levels correlate with age-related sarcopenia and pathological conditions (eg, diabetes, chronic inflammation).[134] Previous analysis demonstrated CAF has been identified as a marker for early diagnosis and monitoring of sarcopenia.[135] The differential impact of CAF is associated with sarcopenia subtypes the primary (age-related) and secondary sarcopenia (eg, disuse atrophy, cachexia) demonstrated different utilization value on CAF's diagnostic and prognostic utility. Exercise and pharmacological agents that may modulate CAF levels, highlighting its potential as a therapeutic target. As age progresses, the loss of motor neurons leads to muscle fiber denervation and NMJ fragmentation, impairing neurotransmission. Additionally, mitochondrial dysfunction and oxidative stress damage NMJ components.[136] At the molecular level, the agrin-muscle-specific kinase (MuSK) pathway is critical for NMJ stability. Aging decreases agrin levels and MuSK activation, disrupting NMJ integrity. Similarly, the neuregulin-1 (NRG1)-ErbB2/4 signaling axis, essential for motor neuron and muscle fiber function, diminishes with age, contributing to NMJ degeneration.[137]

These findings uncover molecular mechanisms of NMJ degeneration and suggest potential therapeutic targets, such as agrin and MuSK regulation for sarcopenia. However, translating these insights into clinical practice requires further research to evaluate their safety and efficacy in humans.

## Gut Microbiota and Sarcopenia

Emerging evidence has elucidated the critical involvement of gut microbiota dysbiosis in sarcopenia pathogenesis via the gut-muscle axis,[138] with recent mechanistic investigations revealing novel therapeutic targets. Microbial-derived metabolites, particularly short-chain fatty acids (SCFAs)[139] and quorum-sensing peptides (QSPs), have emerged as key mediators influencing skeletal muscle homeostasis. SCFAs, generated through bacterial fermentation of dietary fibers, exhibit dual regulatory functions: they promote muscle protein synthesis via mTOR pathway activation[140] while simultaneously enhancing mitochondrial biogenesis and metabolic flexibility through AMPK/PGC-1α signaling.[141] Interestingly, pediatric studies suggest gut microbial composition and fecal SCFA levels correlate with musculoskeletal parameters in a body fat-dependent manner.[142] Preclinical models reveal butyrate supplementation mitigates cachexia-related muscle wasting through gut barrier stabilization and macrophage polarization modulation.[143] Previous study systematic screening of 75 microbial quorum-sensing molecules identified 30 bioactive compounds affecting C2C12 myocyte dynamics, substantiating microbiota-derived QSPs as gut-muscle axis mediators.[144] Specific QSPs, like iAM373,[145] impair muscle regeneration through concurrent suppression of myogenic differentiation and activation of ubiquitin-proteasome degradation. Notably, multi-omics analyses demonstrate that fecal microbiota transplantation from juvenile rodents preserves gut barrier function, enhances mitochondrial performance, and attenuates age-related sarcopenia in senescent recipients, suggesting microbiota-modulating approaches may offer viable therapeutic strategies for musculoskeletal aging.[146] These findings collectively underscore the therapeutic potential of modulating specific microbial metabolites while highlighting the need for further research to establish causality in human populations and develop targeted interventions.

## Sarcopenia Therapies

The primary goal in treating sarcopenia is to alleviate or reverse the decline in muscle mass and function. Traditional approaches have focused on nutritional interventions, exercise, and pharmacotherapy. Recently, innovative strategies such as stem cell and exosome therapy have been explored, offering new avenues for sarcopenia treatment. The evolving therapeutic approaches for sarcopenia are summarized as follows (Figure 6 and Table 2).

### Exercise Intervention

Among the various sarcopenia interventions, physical activity is a cornerstone in both the prevention and treatment of sarcopenia. Resistance training and aerobic exercise are particularly effective in reducing the risk of chronic conditions and enhancing functional mobility in older adults. Current evidence indicates that individualized exercise prescriptions adhering to the FITT framework (Frequency, Intensity, Time, and Type) demonstrate therapeutic efficacy in ameliorating sarcopenia-related muscle weakness and functional decline in older adults.[147] Dual-task, and power training may be particularly effective for reducing the C-terminal Agrin fragment—improving neuromuscular junction integrity, and suppressing sarcopenia progression.[133] Studies have shown that aerobic exercise is mostly performed in the form of walking, stepping, and bicycle ergometry. For people with musculoskeletal problems, stretching of the upper, trunk, and lower limbs should be recommended to reduce the chance of injury in older adults.[148] The most effective strategies for clinically meaningful increase in muscle mass of sarcopenic individuals involve either progressive resistance training protocols or targeted nutritional interventions combining extra energy with adequate protein intake. Current evidence strongly supports structured resistance exercise programs, particularly when combined with leucine-fortified essential

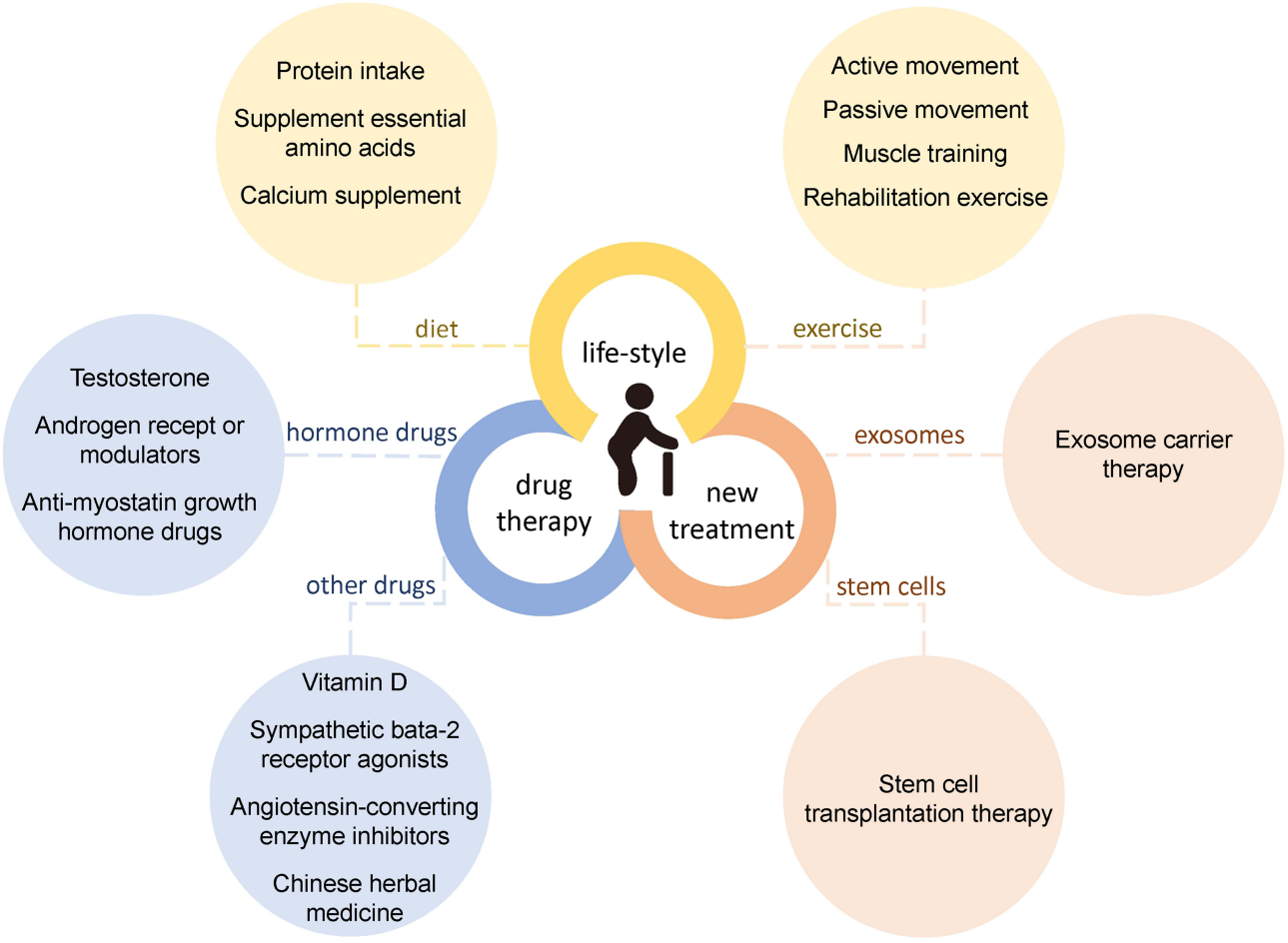


**Figure 6** Treatments for sarcopenia.

**Table 2** Advantages and Disadvantages of Sarcopenia Treatment Methods

| Treatments | Advantages | Disadvantages |
|---|---|---|
| Exercise | Physical exercise and physical stimulation therapies can prevent the onset and progression of sarcopenia by building muscle mass and strength and improving body function and balance. | These are mainly preventive and improvement measures with long treatment cycles and cannot treat cure sarcopenia. |
| Nutritional Intervention | Adequate protein intake and amino acid supplementation, combined with exercise therapy, can increase muscle protein synthesis, thereby treating sarcopenia. Supplementing calcium and vitamin D is crucial for musculoskeletal disorders. | The treatment duration is long, thus it can only serve as an adjunct therapy. |
| Medication | Medications can enhance the proliferation and differentiation of muscle cells, osteoblasts, and muscle fibers, increasing muscle mass and strength, which in turn promotes muscle growth and hypertrophy. | There are numerous side effects and a lack of direct evidence regarding their efficacy on skeletal muscle. |
| Exosomes | Exosomes can facilitate muscle regeneration following skeletal muscle injury and improve muscle protein synthesis and thickness. | The potential pathways for treating sarcopenia are not yet fully understood. |
| Stem Cell Transplantation | Modifying the internal microenvironment to promote muscle and nerve tissue repair and regeneration. It can restore muscle strength and alleviate sarcopenia. | The treatment is expensive, and may require steroid therapy to enhance the survival rate of cell transplants, which can be detrimental to patients' health. |

amino acid supplementation or whey protein administration in cases of dietary protein inadequacy, as foundational therapeutic approaches for sarcopenia management.[149] Importantly, comprehensive exercise interventions incorporating progressive resistance training as a core component demonstrate consistent efficacy in improving muscle strength and physical function among older adults with both frailty and sarcopenia, with meta-analytic data confirming superior outcomes compared to single-modality approaches.[150] These multimodal strategies work synergistically by simultaneously stimulating muscle protein synthesis through mechanical loading while providing the necessary substrate availability for tissue remodeling, thereby addressing both the anabolic resistance and nutritional deficiencies characteristic of age-related muscle loss. Resistance training, a cornerstone in managing muscle-wasting diseases,[151] has been shown to improve muscle strength, mass, and function—key factors in mitigating sarcopenia.[152] Evidence suggests that a resistance training regimen consisting of upper- and lower-body exercises, performed with moderate to high effort for 1–3 sets of 6–12 repetitions, can be highly effective.[153] These exercises may involve resistance machines, free weights, bodyweight movements, or resistance bands.[154] Importantly, resistance training can be both enjoyable and tolerable for older adults, further reinforcing its effectiveness in sarcopenia treatment. This is exemplified by the Reablement Strategies targeting Sarcopenia (ReStart-S) program, a intervention specifically developed for long-term care residents. The ReStart-S framework integrates current evidence on sarcopenia pathophysiology with practical considerations for frail populations, offering healthcare providers an evidence-based template for developing tailored rehabilitation programs, have yielded promising results that warrant further investigation through large-scale randomized controlled trials to establish its effectiveness in mitigating age-related muscle decline.[155] The epidemiological profile of sarcopenia demonstrates significant variability across clinical and community settings, with the highest prevalence rates consistently observed among institutionalized older adults in long-term care facilities. Current diagnostic criteria established by AWGS provide a standardized framework for classifying disease severity, enabling clinicians to distinguish between preclinical, established, and severe sarcopenia stages. This stratification is particularly crucial for developing targeted exercise interventions, as emerging evidence indicates that prescriptive parameters including intensity, frequency, and modality must be precisely calibrated to an individual's diagnostic category and functional capacity to achieve optimal therapeutic outcomes. The ReStart-S program's methodological framework offers particularly valuable insights into implementing targeted exercise interventions tailored to different stages of sarcopenia severity. Exercise interventions significantly improve muscle strength (SMD=0.62), muscle mass (SMD=0.28), and physical performance (gait speed


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+0.08 m/s, SPPB +1.2 points) in older adults with sarcopenia. High-intensity progressive resistance training (>70% 1-RM for ≥12 weeks) demonstrates optimal efficacy, while combined training yields particularly significant functional benefits, with favorable safety profile (AE rate <5%).[156] Importantly, These exercises are both pleasant and tolerable for the elderly, further strengthening their effectiveness in treating sarcopenia.[157,158] Additionally, physical stimulation, such as Whole Body Vibration Training (WBVT), has proven beneficial in the early stages of sarcopenia. WBVT stimulates bone progenitor cell activity, enhances osteoblast function, and increases levels of sex hormones and cytokines, ultimately improving bone density and muscle function.[159,160] In conclusion, physical activity and physical stimulation therapies, are vital components for the prevention and management of sarcopenia.

## Nutritional Intervention: Protein and Vitamin D Supplementation

### Protein Intake

Malnutrition, particularly inadequate protein intake, is a key contributor to sarcopenia. Insufficient dietary protein impairs the synthesis of muscle proteins, exacerbating muscle loss. While the current recommended dietary allowance (RDA) for protein in adults is 0.8 g/kg of body weight per day,[161] this is often insufficient for the elderly to maintain muscle mass and function. Recent expert guidelines suggest that elders should consume 1.0–1.5 g/kg/day of high-quality protein, especially from animal sources such as eggs and meat, to support muscle hypertrophy when combined with resistance training.[162] Higher protein intake has been linked to better physical function, with positive associations between protein consumption and physical activity, as well as negative correlations with sedentary behavior.[163] Leucine-rich protein supplements, such as whey protein, can help prevent muscle loss, particularly during periods of bed rest or inactivity.[164] Given the common decline in protein intake with age,[165] it is recommended that older adults aim for around 1.6 g/kg/day to combat sarcopenia.[166] Nutrient intake can also be affected by oral health. Logistic regression analysis indicated that the prevalence of sarcopenia is increased among patients diagnosed with reduced oral function (odds ratio: 1.59, 95% confidence interval: 1.02–2.47).[167] A cross-sectional study targeting community-dwelling older adults reveals that the prevalence of reduced oral function is 34.3% (n = 427) in the robust group and 65.2% (n = 178) in the sarcopenic group.[168] With advancing age, poor oral health status exerts a significant negative impact on food intake, which in turn leads to muscle loss and a decline in muscle strength.[169] It is recommended to engage in daily oral function training and undergo regular oral examinations to ensure adequate protein intake.[170] Ensuring attention to oral health status provide adequate protein intake, are essential for maintaining muscle health and mitigating sarcopenia in older adults.

### Vitamin D Supplementation

Vitamin D deficiency is a major risk factor for muscle atrophy, falls, and fractures in the elderly. Individuals with insufficient vitamin D levels often experience muscle weakness and reduced mobility. This deficiency is particularly common in older adults with limited sun exposure.[171] Vitamin D plays a crucial role in muscle metabolism, facilitating calcium absorption and maintaining serum calcium and phosphate levels, which are essential for muscle function.[172] Studies suggest that vitamin D supplementation, particularly in combination with leucine, may enhance muscle function and physical performance by promoting protein anabolism. Maintaining optimal serum 25-hydroxyvitamin D levels (50–75 nmol/L) is crucial for preserving muscle strength and supporting muscle protein synthesis. It is recommended that older adults receive 800–1000 international units of vitamin D per day to support musculoskeletal health and reduce the risk of disease.[173] Intervention studies indicate that daily supplementation with 1000 IU vitamin D effectively enhances anabolic response, muscle mass, and physical performance in community-dwelling older adults (≥60 years), particularly when baseline levels are deficient, with demonstrated efficacy in elevating 25(OH)D concentrations from suboptimal (28.1 ng/mL) to therapeutic ranges.[174] Emerging evidence suggests that combined nutritional strategies incorporating vitamin D3 with whey protein, leucine, calcium, and structured exercise programs yield superior musculoskeletal outcomes compared to monotherapy approaches.[173] Importantly, dose-response studies reveal a plateau effect in therapeutic benefits, with high-dose supplementation (3750 IU/day) showing no additional advantage over standard doses (600 IU/day) in overweight elderly populations (>65 years), suggesting the existence of endocrine regulatory mechanisms that maintain vitamin D homeostasis.[175]

Contrasting these findings, recent randomized controlled trials demonstrate that pharmacological interventions using active vitamin D metabolites fail to produce clinically meaningful improvements in key sarcopenia parameters—including handgrip strength, timed-up-and-go performance, appendicular lean mass, or muscle function—among older adults without severe deficiency.[176,177] Notably, even high-dose supplementation (2000 IU/day vitamin D3) showed no significant effects on lower extremity power, muscle strength, or physical performance in functionally impaired elderly individuals (aged 65–89). These contradictory observations highlight critical knowledge gaps regarding the therapeutic application of vitamin D in sarcopenia management, particularly concerning: (1) the necessity of pre-existing deficiency for clinical efficacy, (2) potential differential effects between native vitamin D and active analogs on vitamin D receptor signaling pathways in muscle tissue, and (3) the physiological importance of endogenous 1α-hydroxylation in renal and extrarenal tissues for optimal musculoskeletal outcomes. Resolution of these outstanding questions through carefully designed mechanistic studies will be essential for developing evidence-based vitamin D supplementation strategies tailored to specific sarcopenia phenotypes and metabolic states.

It is important to acknowledge that the Endocrine Society has recently revised its position on defining vitamin D status, as articulated in their latest Guideline Communication.[178] After thorough evaluation of existing clinical trial data, the expert panel concluded that current evidence does not support establishing specific 25(OH)D thresholds that reliably predict clinically meaningful benefits from vitamin D supplementation. The Society explicitly withdrew its previous classifications of vitamin D "sufficiency" (≥30 ng/mL [75 nmol/L]) and "insufficiency" (20–30 ng/mL [50–75 nmol/L]), citing substantial limitations in the available evidence and assigning very low certainty to these historical cutoffs. This paradigm shift introduces significant challenges for clinical decision-making regarding vitamin D supplementation in sarcopenia management. The absence of validated biochemical thresholds complicates the identification of patients who might benefit from intervention, particularly given the current lack of consensus on how to interpret serum 25(OH)D levels in the context of musculoskeletal health.

## Pharmacological Treatment

Currently, the development of drugs for sarcopenia remains in its early stages. To date, no approved pharmacological agents specifically targeting sarcopenia have been developed, and the management of sarcopenia primarily focuses on strength-training exercises as well as an increased intake of energy-dense foods and a diet rich in protein.[179] However, the "Sarcopenia Consensus" highlights several promising agents, including anabolic steroids, vitamin D, growth hormone, β-receptor agonists, angiotensin-converting enzyme inhibitors, myostatin inhibitors, and activin receptor antagonists. These drugs, though not yet widely used for sarcopenia, represent potential therapeutic avenues for future clinical interventions (Table 3).

## Exosome Therapy

In recent years, microvesicles and exosomes have gained significant attention for their promising applications in tissue repair, particularly skeletal muscle regeneration.[210] Exosomes secreted by skeletal muscle cells, which carry miRNAs and other regulatory molecules, have been identified as critical regulators of muscle homeostasis.[211] For example, a study by Li et al[212] demonstrated that exosomes from skeletal muscle cells increased muscle strength by 30% in a mouse model of sarcopenia, underscoring their role in regulating muscle function. Ma et al reported that the use of exosomes derived from human umbilical cord MSCs significantly improved grip strength and increased muscle mass in muscular dystrophy mice.[213] Exosomes derived from adipose tissue mesenchymal stem cells (AD-MSCs) have also shown novel paracrine effects on skeletal muscle repair. A study revealed that these exosomes, rich in cytokines, chemokines, and growth factors, enhanced muscle repair by 50% in areas of muscle damage, highlighting their potential in promoting muscle healing.[214] Recent research further suggests that exosomes can stimulate muscle regeneration following injury and promote muscle protein synthesis.[215] Williams et al[216] found that exosome treatment after exercise led to a 25% increase in muscle fiber size and a 20% improvement in muscle strength in aged rats, demonstrating their potential to enhance exercise-induced muscle health.

Although the precise mechanisms through which exosomes exert these effects are not fully understood, ongoing studies are uncovering their therapeutic potential in treating sarcopenia.

**Table 3** Current Status and Pros and Cons of Drug Treatments for Sarcopenia

| Drugs | Advantages of the Drug | Current Limitations of the Drug |
|---|---|---|
| Testosterone | Testosterone therapy(TRT) can promote protein synthesis by stimulating the Akt/mTORC1 pathway and inhibit protein degradation by suppressing FoxO-targeted gene expression.[180] Treatment with testosterone in a Phase II trial improved patients' rapid gait speed at 3 and 12 months and knee strength at 12 months.[181] Testosterone replacement therapy greatly (TRT) improves patients' muscle mass, lean body mass and physical activity, as well as their quality of life.[182,183] | TRT improves physical performance but does not increase muscle strength and is associated with a range of adverse effects such as allergic reactions, thrombosis and prostate cancer.[184,185] |
| Synthetic steroids / Selective Androgen Receptor Modulators (SARMs) | SARM interacts with the androgen receptor and promotes nuclear translocation of the complex, thereby enhancing muscle mass.[186] SARMS binding to androgen receptors in the prostate and seminal vesicles is partially agonistic, whereas it is fully agonistic in muscle and bone. Meanwhile, several clinical trials found that SARM increased muscle mass and decreased fat mass.[187] Another selective androgen receptor modulator, S42, promotes protein synthesis and muscle hypertrophy through the activation of the Akt/mTORC1/p70S6K signaling pathway. Additionally, S42 reduces protein degradation by suppressing MuRF1 and atrogin1 expression, mitigating muscle atrophy.[188] | SARMs do not demonstrate superiority over testosterone. |
| Growth hormone (GH) | GH is essential for growth and development of muscle.[189] GH replacement therapy promoted an increase in skeletal muscle protein synthesis and mitochondrial biogenesis pathways. At the same time, the expression of inhibitory factors that inhibit skeletal muscle regeneration and the protein degradation was reduced.[190] Endogenous ligands for the growth hormone secretagogue receptor stimulate the release of growth hormone and IGF-1, while also inhibiting the inflammatory response, alleviating sarcopenia.[191] | GH drugs can increase muscle mass and enhance muscle strength; However, side effects are also evident, including joint pain, soft tissue edema, carpal tunnel syndrome and diabetes. |
| Active vitamin D | Vitamin D interact with nuclear receptors (VDR) improves muscle function and mass by regulating the expression of target genes via VDR mediation.[192] Vitamin D supplements, either alone or in combination with other treatments, improved muscle mass or increased physical function.[193] Vitamin D deficiency is associated with decreased muscle mass; Approximately 50% of individuals over the age of 65 have low vitamin D levels.[194] Vitamin D supplement increase muscle mass (whole body and lower extremities). | Vitamin D supplement regimens improve muscle mass and lower limb function in people with sarcopenia This health benefit cannot be attributed to vitamin D alone. Clinicians are advised to make judgements about the use of vitamin D supplements due to racial and age differences.[195] |

(*Continued*)

**Table 3** (Continued).

| Drugs | Advantages of the Drug | Current Limitations of the Drug |
|---|---|---|
| Anti-myostatin agents | The active form of muscle growth inhibitor (MSTN) binds to activator receptor type 2B (ActR2B), and thereby activates protein degradation signaling through Smad2/3-mediated transcription. Smad activates the inhibition of muscle protein synthesis by blocking Akt signaling. Targeting MSTN/Activin-ActR2B pathway have been shown to prevent loss of muscle mass and strength.[196–198]<br>LY2495655 is a humanised recombinant immunoglobulin antibody targeting muscle growth inhibitors. Becker et al[199] found that monthly subcutaneous injections of 315 mg of LY over a 20-week period resulted in significant improvements in lean body mass and several tests of physical function.<br>Intramuscular injection of follicle arresting hormone (ACE-083) can increase lean body mass and thigh muscle mass in postmenopausal women.[200] The anti-myostatin ActRIIb antibody bimagrumab (BYM338) can enhance physical function in sarcopenia patients and increase muscle mass in COPD patients with cachexia.[201] | Muscle growth inhibitors may cause off-target effects including nosebleeds, bleeding gums, and skin vasodilation.[202] Although no serious safety concerns arose in the trials, more research is needed to confirm the potential benefit of MSTM in sarcopenia patients. |
| β-adrenergic agonists | β2 receptor agonists promote muscle growth through the insulin/insulin-like growth factor-1 signaling pathway, enhancing anti-proteolytic and hypertrophic capacity by mediating β2 adrenergic receptor activation and possibly FOR-induced protein synthesis.[203] β2 adrenergic receptor agonists can effectively prevent skeletal muscle atrophy and oxidative stress in uremic mice.[204] The β2 receptor agonist clenbuterol increases skeletal muscle strength and mass by mediating the β-inhibin 1 signaling pathway.[205] | The effectiveness of β-adrenergic agonists in treating sarcopenia is currently under investigation. |
| Angiotensin-converting enzyme inhibitors | ACE inhibitors (ACEIs) increased muscle mass and grip strength. ACEIs not only improve mitochondrial function and elevate IGF-1 but also promote skeletal muscle glucose uptake and activate IGF-1/IGFR by downregulating NF-κB and FoxO.[206] Activation of PKB by ACEIs can increase protein synthesis via mTOR-dependent pathways, reduce autophagy,[207] and suppress inflammatory responses, improving skeletal muscle function. | The ACEI's effects on skeletal muscle in elderly individuals remains lack direct evidence. |
| Acetylcholinesterase inhibitors | Reduce the muscle weakness caused by sarcopenia.[208] | Side - effects related to acetylcholine in aspects such as the gastrointestinal tract and the nervous system. |
| Anti-inflammatory therapies | Have the potential to enhance the process of muscle regeneration and simultaneously slow down the phenomenon of muscle atrophy.[209] | Older patients are more likely to have significant side - effects when using it. |

## Stem Cell Therapy

Mesenchymal stem cells (MSCs) therapy offers a promising approach for substantial diseases due to their self-renew and differentiation potential into various somatic cells.[217] Upon injury or stress, MSCs are rapidly activated and quickly proliferate to replenish damaged muscle cells and repair of the muscle fibers structure. Notably, MSCs not only proliferative and differentiation to replace myogenic cells and repair damaged structure, but also secrete paracrine factors that enhance MSC activity and muscle regeneration.[218]

MSC therapy has demonstrated potential in sarcopenia treatment. For example, Xu et al[219] reported a 25% increase in muscle strength and 15% increase in muscle mass in sarcopenic rats treated with MSCs, highlighting their regenerative potential. Additionally, MSC therapy has been shown to restore mitochondrial function in aging muscles.[220] Zhao et al[221] found a 40% increase in mitochondrial enzyme activity and a 30% reduction in oxidative stress markers in aged muscle tissue following MSC treatment, underscoring its effectiveness in addressing mitochondrial dysfunction associated with sarcopenia.

The extracellular matrix (ECM) and MSCs are crucial for muscle regeneration.[222] Disruption of ECM components is associated with impaired muscle regeneration in sarcopenia.[223] Previous study suggest that targeting ECM composition —such as using matrix metalloproteinase inhibitors—may improve muscle regeneration.[224] Additionally, the myostatin signaling pathway is critical for regulating MSC activity and muscle repair. Myostatin monoclonal antibodies and receptor antagonists can block this pathway, promoting muscle regeneration.[225] Ongoing clinical trials are evaluating the efficacy and safety of myostatin inhibitors in elderly sarcopenic patients.

Induced pluripotent stem cells (iPSCs) derived from reprogrammed somatic cells also offer promise, particularly for generating patient-specific stem cells for autologous transplantation, reducing the risk of immune rejection.[226]

In summary, while traditional treatments for sarcopenia remain limited, emerging evidence supports stem cell therapy as a viable option for enhancing muscle regeneration and restoring mitochondrial function, offering new tools for improved management of sarcopenia.

## Critical Unmet Needs and Future Directions

Despite considerable advances in sarcopenia research, several critical challenges persist. First, the absence of universally accepted diagnostic criteria continues to hamper clinical translation, with current tools demonstrating variable sensitivity (particularly for early-stage detection) and limited feasibility in resource-constrained settings. Second, while emerging therapies (eg, exosome-based interventions) show preclinical promise, robust long-term efficacy and safety data from randomized controlled trials remain lacking—a gap further compounded by the paucity of standardized outcome measures. Third, the field would benefit from mechanistic studies elucidating tissue-specific responses to novel interventions across diverse patient populations. Addressing these limitations will require coordinated efforts to: (1) establish validated biomarkers for disease staging; (2) develop pragmatic diagnostic tools for community settings; and (3) implement unified endpoints in therapeutic trials.

# Conclusion

The global prevalence of sarcopenia is rising with an aging population, underscoring the urgent need for effective prevention and treatment strategies. Its clinical manifestations are often subtle, making early detection challenging. By the time symptoms become noticeable, significant muscle loss and dysfunction may have already occurred, increasing the risk of falls, fractures, and other complications. Therefore, early screening is crucial. Despite growing awareness, understanding of sarcopenia remains limited, with current diagnostic methods lacking standardization and insufficient evidence on the safety and efficacy of pharmacological treatments.

Emerging therapies, including stem cell and exosome-based approaches, are still under investigation and subject to ongoing debate. While emerging therapeutic modalities—particularly stem cell-derived extracellular vesicles and engineered exosome platforms—show preclinical potential, their translation requires rigorous evaluation through multicenter trials addressing three pivotal questions: (1) long-term safety profiles in metabolically compromised aging cohorts; (2) cost-benefit ratios relative to conventional interventions; and (3) practical implementation barriers across diverse healthcare systems. Concurrently, diagnostic

standardization efforts must reconcile sensitivity (particularly for early-stage detection) with clinical feasibility, potentially through multimodal algorithms integrating biochemical markers with functional assessments.

In general, greater emphasis is needed on early screening and the development of comprehensive, multidisciplinary treatment strategies to mitigate the widespread impact of sarcopenia.

## Data Sharing Statement

This is a review of the literature, and no research data are reported. Further inquiries can be directed to the corresponding author.

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## Disclosure

The authors report no conflicts of interest in this work.

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