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Narrative Review

Sarcopenia in older adults: A narrative review of current concepts in diagnosis and treatment

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SUMMARY

Sarcopenia is a multifactorial geriatric syndrome characterized by progressive declines in skeletal muscle strength, muscle mass, and physical performance. It is associated with disability, loss of independence, and increased mortality in older adults. Despite being recognized as distinct disease entity, heterogeneity in diagnostic criteria, assessment methods, and therapeutic approaches continue to hinder the translation of research findings into routine clinical practice.

This review aims to provide a comprehensive and integrated overview of current knowledge on sarcopenia, highlighting advances in pathophysiology, diagnostic assessment, and emerging therapeutic strategies. Key biological mechanisms underlying sarcopenia include anabolic resistance, neuromuscular degeneration, chronic inflammation, hormonal dysregulation, mitochondrial dysfunction, as well as systemic regulators such as the renin–angiotensin system and microRNAs. Contemporary diagnostic frameworks remain heterogeneous with respect to definitions, terminology, and assessment components. In this context, the Global Leadership Initiative on Sarcopenia (GLIS) has proposed a conceptual framework that seeks to distinguish the core biological components from downstream clinical outcomes.

Resistance exercise and nutritional optimization remain the cornerstone of sarcopenia management, while pharmacological and molecular strategies targeting anabolic and metabolic pathways are considered adjunctive or investigational. Although many pharmacological agents demonstrate increases in muscle mass, the translation of these gains into consistent and clinically meaningful improvements in muscle strength and physical performance remains limited. This review underscores the need for harmonized diagnostic concepts and individualized, multimodal treatment strategies, and suggests that future advances in sarcopenia management will likely depend on refined phenotyping and targeted combination therapies rather than single-target interventions.

1. Introduction

Sarcopenia is a complex and multifactorial geriatric syndrome characterized by a progressive decline in skeletal muscle strength, muscle mass, and physical performance. This condition contributes to impaired mobility, loss of independence, and adverse health outcomes in older adults [1] and frequently coexists with other geriatric syndromes — such as frailty and cognitive impairment — further amplifying vulnerability and complicating clinical management [2,3]. A growing body of evidence demonstrates a significant association between sarcopenia and cognitive impairment, including dementia and depression. A meta-analysis reported that sarcopenia was associated with an increased risk of cognitive impairment (adjusted OR 2.25, 95% CI 1.70–2.97) [4]. In a pooled analysis of 35 studies comprising 58,404 participants, the global prevalence of sarcopenia was estimated at 10.0% in both men (95% CI: 8–12%) and women (95% CI: 8–13%) [5]. In addition to its clinical consequences, sarcopenia imposes a substantial healthcare and socioeconomic burden due to increased risk of falls, hospitalization, disability, and long-term care dependency in aging populations [6]. Reflecting its clinical importance, sarcopenia has been recognized as a distinct disease entity and was assigned a specific diagnostic code in the International Classification of Diseases (ICD-10) in 2016. More recently, a meta-analysis published in

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2023 demonstrated that sarcopenia is associated with a 36% increase in all-cause mortality (RR = 1.36, 95% CI: 1.28–1.44), highlighting its prognostic relevance [7]. Despite increasing awareness, important challenges persist in both the diagnosis and management of sarcopenia. Substantial heterogeneity in diagnostic definitions, assessment tools, and outcome measures has limited comparability across studies and complicated translation into routine clinical practice [8]. Concurrently, accumulating evidence suggests that traditional single-target approaches are insufficient to capture the clinical complexity of sarcopenia, highlighting the need for outcome-oriented diagnostic frameworks and integrated, multimodal treatment strategies [9]. Unlike previous narrative reviews focusing primarily on either diagnostic criteria or single therapeutic domains, this review integrates the evolving conceptual framework of sarcopenia (GLIS), contemporary diagnostic heterogeneity, and emerging combination-based therapeutic strategies, emphasizing the persistent dissociation between muscle mass gains and functional outcomes.

2. Literature search strategy

A narrative literature search was performed using major biomedical databases, including PubMed, Scopus, and Web of Science. The search covered studies published between January 2000 and February 2026. Search terms included combinations of keywords such as “sarcopenia”, “muscle mass”, “muscle strength”, “aging”, “nutrition”, and “exercise”. Titles and abstracts were screened to identify relevant studies, and the reference lists of key reviews and consensus statements were also examined to identify additional publications. Priority was given to consensus statements, systematic reviews, randomized controlled trials, and large observational studies. Earlier seminal studies were also included to provide historical context and to illustrate the evolution of conceptual definitions of sarcopenia.

3. Pathophysiology

Sarcopenia arises from the interaction of multiple biological mechanisms rather than a single defining pathway. These include impaired protein homeostasis (reduced protein synthesis and increased protein degradation), disrupted neuromuscular integrity, alterations in satellite cell function, mitochondrial dysfunction, chronic inflammation, hormonal dysregulation, activation of the renin–angiotensin system (RAS), microRNAs, gut dysbiosis, and behavioral factors [9].

Aging is commonly associated with anabolic resistance, primarily driven by impaired mechanistic target of rapamycin (mTOR) signaling and diminished responsiveness to insulin, insulin-like growth factor-1 (IGF-1), and dietary amino acids. Concurrently, muscle protein degradation is increased through activation of the ubiquitin–proteasome system, calpain- and caspase-mediated pathways, and enhanced autophagy [10]. Neuromuscular changes, including motor neuron loss, disruption of the neuromuscular junction, and incomplete reinnervation—further contribute to muscle weakness, particularly through preferential loss of fast-twitch type II fibers [11].

In parallel, the satellite cell pool, which is essential for muscle repair and regeneration, progressively declines in both number and self-renewal capacity [12]. Persistent low-grade inflammation, characterized by elevated levels of tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), C-reactive protein (CRP), and oxidative stress, promotes catabolic signaling and facilitates intramuscular fat infiltration and fibrosis [13]. Age-related hormonal changes, including reductions in testosterone, estrogen, growth hormone, dehydroepiandrosterone, and IGF-1, along with increased cortisol levels, further exacerbate muscle loss and metabolic dysfunction [14].

Systemic pathways also play an important modulatory role, as activation of the classical RAS pathway is associated with oxidative damage and muscle atrophy, whereas the non-classical pathway appears to exert protective effects [15]. Additional contributors include microRNA dysregulation, gut microbiota alterations, and aging-associated anorexia, each influencing muscle metabolism through interconnected mechanisms [9,10].

Overall, sarcopenia represents a multifactorial, network-level disruption of muscle homeostasis, in which metabolic, neural, inflammatory, endocrine, and systemic factors interact to drive the progressive loss of muscle mass and function.

4. Diagnostic assessment of sarcopenia

In clinical practice, screening and case-finding tools are increasingly used to identify individuals at risk of sarcopenia in routine care. Brief questionnaires, such as SARC-F and its modified version incorporating calf circumference (SARC-CalF), as well as simple anthropometric measures, facilitate early recognition, particularly in community and outpatient settings [16]. The diagnostic performance of these tools varies substantially across studies due to differences in populations, reference standards, and cut-off values. Meta-analyses indicate that although SARC-F demonstrates moderate-to-high specificity, its sensitivity remains low to moderate, leading to potential under-recognition of sarcopenia [17]. Accordingly, screening is best regarded as a case-finding strategy rather than a stand-alone diagnostic approach, prompting subsequent standardized assessment of muscle strength, muscle quantity, and physical performance.

4.1. Muscle strength assessment

Muscle strength is a central component of contemporary sarcopenia definitions and is most assessed using handgrip strength (HGS) and the five-times sit-to-stand (STST) test, reflecting upper- and lower-extremity strength, respectively [1]. Handgrip strength is typically measured using handheld dynamometers, with the Jamar dynamometer widely regarded as the reference device in research settings. Nevertheless, its size and grip design may limit usability in individuals with arthritis, leading to the frequent use of alternative devices in clinical and epidemiological studies [18]. Inter-device variability should therefore be acknowledged when interpreting results [19].

4.2. Muscle mass assessment

Skeletal muscle mass can be assessed using a variety of imaging and body composition techniques, including computed tomography (CT), magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), and ultrasonography (US) [20]. Although CT and MRI are considered reference standards for assessing skeletal muscle mass, their use in routine practice is limited [1]. Comprehensive assessment requires summation of muscle areas across multiple axial slices; this approach is time-consuming and, in the case of CT, is additionally associated with radiation exposure. Accordingly, standard CT or MRI protocols typically rely on contiguous or semi-contiguous axial slices (approximately 8-mm slice thickness with 2–3-mm interslice gaps), from which muscle area or volume is calculated using validated formulas. Therefore, research studies have adopted surrogate approaches, most commonly the measurement of skeletal muscle area at the third lumbar vertebra (L3) level. Muscle area measured at this level—including the psoas major, erector

spinae, quadratus lumborum, and abdominal wall muscles—shows a strong correlation with total body skeletal muscle volume ($r \approx 0.85–0.95$). In contrast, reliance on isolated psoas muscle area alone yields a weaker, though still moderate to strong, correlation with whole-body muscle mass ($r \approx 0.65–0.80$) [21].

DXA represents a widely available and validated method for estimating appendicular skeletal muscle mass; however, its use may be limited in routine clinical practice due to equipment availability, the need for patient transfer, and susceptibility to inter-device variability and hydration status [22]. In contrast, BIA offers a rapid, noninvasive, and bedside-applicable approach that is particularly suitable for outpatient, inpatient, and community settings. However, BIA provides indirect estimates of muscle mass and is highly influenced by hydration status [23].

Ultrasound has increasingly been recognized as a promising bedside tool for muscle assessment, enabling evaluation of muscle thickness, cross-sectional area, echogenicity, and architectural features. For ultrasound-based estimation of skeletal muscle mass and quality, measurements are typically obtained from selected representative muscles rather than the entire musculature. Commonly examined muscles include the rectus femoris, gastrocnemius medialis, biceps brachii, forearm flexors, and abdominal wall muscles, as these sites are easily accessible, reproducible, and show robust correlations with whole-body muscle mass, muscle strength, and physical performance, supporting their widespread use in both clinical and research settings [24–29]. However, ultrasound-based muscle assessment is inherently operator-dependent, and measurement reliability may be influenced by probe positioning, applied pressure, and examiner experience, underscoring the need for standardized protocols and adequate training.

More recently, the D_3-creatine (D_3-Cr) dilution method has emerged as a potentially relevant alternative for estimating total body skeletal muscle mass in vivo. This technique is based on administering a small oral dose of deuterium-labeled creatine and measuring the enrichment of D_3-creatinine in subsequent urine samples to estimate the total creatine pool, which is predominantly located in skeletal muscle (~95%). The total body creatine pool size can then be converted into an estimate of muscle mass using established conversion factors, providing a direct, noninvasive, and radiation-free measure of skeletal muscle mass. Studies have shown strong correlations between D_3-Cr–estimated muscle mass and MRI or other reference imaging measurements, and this approach has been associated with clinically relevant outcomes such as disability, mobility limitations, falls, fractures, and mortality in older adults. However, the accuracy of the D_3-creatine dilution method may be influenced by assumptions regarding uniform creatine concentration per unit of muscle mass, as well as by the timing of urine sampling, particularly in older individuals with altered muscle composition [30]. At present, ultrasound and D_3-creatine dilution should be regarded as complementary or research-oriented tools rather than universally applicable diagnostic standards.

4.3. Physical performance assessment

Physical performance reflects the functional consequences of reduced muscle mass and strength and is commonly quantified using gait speed, the Timed Up and Go (TUG) test, and the Short Physical Performance Battery (SPPB) [1]. The SPPB integrates gait speed, balance, and chair-stand performance into a composite score ranging from 0 to 12, with lower scores indicating poorer physical performance. Low physical performance tests have been consistently associated with adverse outcomes, including disability, hospitalization, and mortality [31].

Following Rosenberg's original description of sarcopenia, multiple consensus groups have proposed diagnostic criteria integrating muscle mass, muscle strength, and physical performance. However, the lack of a unified conceptual hierarchy among these components has led to variability in how sarcopenia is defined and assessed across research and clinical contexts [8].

Prior to the introduction of formal consensus definitions, sarcopenia—initially described as age-related loss of muscle mass [32], — was largely regarded as a descriptive concept without standardized diagnostic criteria or clear clinical operationalization.

The publication of the first European Working Group on Sarcopenia in Older People (EWGSOP) criteria in 2010 marked a major milestone by integrating reduced muscle mass and decreased muscle strength into a formal diagnostic framework [33]. Even so, routine assessment of muscle mass proved impractical in many outpatient and clinical settings, limiting real-world applicability. Moreover, this approach inadequately classified individuals with preserved muscle mass but impaired physical performance, as well as those with reduced muscle strength in the absence of overt functional limitation.

To address these limitations, subsequent consensus definitions adopted different conceptual orientations. The Asian Working Group for Sarcopenia (AWGS) primarily adapted existing criteria by modifying cut-off values to reflect anthropometric differences in Asian populations, without introducing a fundamentally new conceptual model [34]. In contrast, the International Working Group on Sarcopenia (IWGS) placed impaired physical performance at the center of the sarcopenia definition, emphasizing functional decline over structural measurements [35].

A more explicit conceptual shift occurred with the publication of the revised EWGSOP2 criteria in 2019, which introduced the concept of “probable sarcopenia” based on reduced muscle strength. Within this framework, low handgrip strength (e.g., <27 kg in men and <16 kg in women) is considered sufficient to identify individuals with probable sarcopenia, prompting further evaluation. Physical performance measures, such as usual gait speed (<0.8 m/s), were repositioned as indicators of disease severity rather than core diagnostic components. Confirmation of sarcopenia requires evidence of reduced muscle quantity or quality. According to EWGSOP2, low muscle mass is defined by an appendicular lean mass adjusted for height squared (ALM/height^2) of <7.0 kg/m^2 in men and <5.5 kg/m^2 in women when assessed by DXA. While these thresholds provide a reference standard, alternative techniques such as BIA, CT and MRI use modality- and population-specific cut-offs [1]. The 2019 update of the AWGS criteria largely aligned with this approach, retaining population-specific cut-offs while adopting a strength-first diagnostic strategy [36]. While consensus groups such as EWGSOP and AWGS have proposed region-specific thresholds for muscle strength and muscle mass, the generalizability of these cut-offs to other populations remain uncertain. Applying thresholds derived primarily from European or Asian cohorts to other ethnic groups may therefore lead to misclassification or inconsistent prevalence estimates. Future research should focus on validating and refining population-specific diagnostic thresholds across diverse global populations. The key conceptual differences between major consensus definitions of sarcopenia are summarized in Table 1.

In contemporary clinical practice, sarcopenia assessment can be framed as a stepwise workflow comprising screening (case-finding), assessment of muscle strength, confirmation by measures of muscle quantity or quality, and evaluation of physical performance for severity staging.

However, in real-world clinical settings, the implementation of this stepwise approach may vary depending on patient characteristics, clinical context, and resource availability. In the absence

Table 1
Comparison of major consensus definitions and conceptual frameworks of sarcopenia.

Consensus group	Core components	Diagnostic sequence	Role of physical performance	Cut-off philosophy
EWGSOP (2010)	Muscle mass, muscle strength, physical performance	Combined assessment of low muscle mass plus low muscle strength or low physical performance	Part of diagnostic criteria	Fixed cut-offs derived from young reference populations (≈2 SD below mean); primarily European cohorts
IWGS (2011)	Muscle mass and physical performance	Performance-oriented approach: low gait speed required, combined with low appendicular lean mass	Central diagnostic component (gait speed ≤1.0 m/s mandatory)	Function-based cut-offs aimed at identifying individuals at increased risk of mobility disability
AWGS (2014)	Muscle strength, muscle mass, physical performance	EWGSOP-based framework	Part of diagnostic criteria (6-m gait speed, chair stand)	Population-specific cut-offs adapted to Asian body composition and anthropometry
EWGSOP2 (2019)	Muscle strength, muscle mass/quality, physical performance	Stepwise approach: low muscle strength defines *probable sarcopenia*; diagnosis confirmed by low muscle mass/quality	Indicator of disease severity rather than a primary diagnostic criterion	Standardized cut-offs with modality-specific thresholds; emphasis on clinical feasibility
AWGS (2019)	Muscle mass, muscle strength, physical performance	Strength-first, stepwise approach, EWGSOP-based framework	Integral part of severity assessment (6-m gait speed, chair stand)	Population-specific cut-offs adapted to Asian body composition and anthropometry
GLIS initiative	Muscle mass and muscle strength	Conceptual framework rather than diagnostic algorithm	Considered a downstream clinical outcome rather than part of the core definition	Does not propose specific cut-offs; aims to harmonize conceptual definitions

Table Notes: EWGSOP, European Working Group on Sarcopenia in Older People; IWGS, International Working Group on Sarcopenia; AWGS, Asian Working Group for Sarcopenia. EWGSOP2 refers to the revised European consensus published in 2019; GLIS, Global Leadership Initiative on Sarcopenia.

of advanced imaging modalities, the diagnostic process often relies on simplified and pragmatic adaptations of existing consensus recommendations. Such approaches should be regarded as context-specific clinical applications rather than standardized diagnostic algorithms.

Given the substantial clinical and pathophysiological overlap between sarcopenia and frailty, the latter should be systematically considered in the evaluation of older adults with suspected sarcopenia. While these constructs are not interchangeable, sarcopenia is widely regarded as a key biological substrate of physical frailty, particularly within the framework of Fried's phenotype model. Their coexistence is common and has important prognostic implications, as individuals with both conditions exhibit a markedly higher risk of adverse outcomes, including disability, hospitalization, and mortality [2].

Importantly, frailty status may modify both the clinical expression and the trajectory of sarcopenia. In people living with frailty, sarcopenia is more likely to be associated with multidimensional deficits, including impaired resilience, reduced physiological reserve, and increased vulnerability to stressors. This has direct implications for management, as treatment responses to nutritional and exercise interventions may be attenuated or require a more individualized and gradual approach in frail patients [37].

Therefore, in geriatric practice, frailty assessment should be integrated alongside sarcopenia evaluation as part of a comprehensive geriatric assessment (CGA). This approach allows clinicians to interpret muscle impairment within the broader context of multimorbidity, functional decline, nutritional status, and psychosocial vulnerability, thereby supporting more accurate risk stratification and personalized care planning.

Despite these refinements, the coexistence of multiple diagnostic frameworks has resulted in substantial diagnostic discordance across clinical and research settings, contributing to variability in terminology, prevalence estimates, and clinical interpretation. In response to this persistent heterogeneity, the Global Leadership Initiative on Sarcopenia (GLIS) was established to harmonize conceptual definitions and standardize terminology rather than to introduce new diagnostic cut-off values [38].

A key point of discussion within the GLIS framework is the exclusion of physical performance from the core conceptual definition of sarcopenia [39]. This differs from earlier consensus definitions such as EWGSOP and AWGS, in which physical performance was incorporated either as a diagnostic component or as an indicator of disease severity [1,36].

While this approach emphasizes muscle strength as the primary determinant, physical performance remains an important predictor of disability, functional decline, and mortality [40].

Collectively, GLIS should be viewed not as a finalized diagnostic system, but as an evolving, outcome-oriented framework that prioritizes conceptual clarity and outcome validation, thereby providing the necessary groundwork upon which future harmonized definitions and, potentially, diagnostic thresholds may be developed.

5. Treatment of sarcopenia: current and emerging strategies

Current management of sarcopenia relies primarily on resistance exercise and nutritional optimization, whereas pharmacological and emerging molecular approaches remain adjunctive or investigational [1,41].

5.1. Resistance exercise

Resistance exercise represents the cornerstone of non-pharmacological management of sarcopenia. Its benefits may be further enhanced when combined with adequate protein and energy intake; however, the synergistic effects of combined interventions are discussed in a separate section [41,42].

Current guidelines recommend that resistance training be performed 2–3 times per week, targeting major muscle groups, with moderate-to-high intensity (approximately 60–80% of one-repetition maximum), with 1–3 sets of 8–12 repetitions and progressive overload as tolerated [43]. Supervised training programs

may be particularly beneficial in frail or mobility-limited individuals to ensure safety, optimize adherence, and individualize exercise prescription [41].

Resistance exercise is consistently associated with significant improvements in muscle strength and physical performance, whereas its effects on muscle mass are generally more modest [42]. This discrepancy likely reflects age-related anabolic resistance and impaired muscle protein synthesis in older adults. Nevertheless, given its robust and reproducible functional benefits, resistance exercise remains the central component of multimodal sarcopenia management. Implementation in routine clinical practice remains challenging, particularly in frail and hospitalized populations.

5.2. Nutritional strategies

Nutritional strategies play a complementary and essential role in supporting anabolic responses in older adults with sarcopenia. Early identification of malnutrition using validated tools (e.g., GLIM criteria) enables timely intervention [44,45]. In addition, upstream social determinants such as food insecurity may increase the risk of malnutrition and contribute to the development of geriatric syndromes in older adults, which may indirectly predispose to sarcopenia [46].

Adequate energy intake is essential to avoid negative energy balance, which can blunt the anabolic effects of both dietary protein and resistance exercise. In older adults, a daily energy intake of approximately 25–30 kcal/kg is generally recommended, with individual adjustments based on clinical condition and physical activity level [47]. Importantly, weight management strategies should prioritize fat mass reduction while preserving skeletal muscle, as excessive caloric restriction may accelerate muscle loss and increase the risk of sarcopenia [48].

Protein intake represents the key nutritional determinant of muscle maintenance and anabolic responsiveness. According to ESPEN, a protein intake of at least 1.0 g/kg/day is recommended for healthy older adults, increasing to 1.2–1.5 g/kg/day in those with acute or chronic illness, particularly in people living with frailty or those with inadequate intake, in whom oral nutritional supplements may be required. Intakes of up to 2.0 g/kg/day may be considered in malnourished or critically ill individuals, provided that renal function is closely monitored [47]. While Kidney Disease: Improving Global Outcomes (KDIGO) Guideline traditionally suggests lower protein intake (0.8 g/kg/day) in non-dialysis chronic kidney disease, these restrictions should not be applied rigidly in older adults with frailty or sarcopenia; in such cases, preserving muscle mass and function takes priority, and a more liberal, individualized protein approach is recommended with close clinical monitoring [49].

Protein quality is also clinically relevant. Essential amino acid–rich proteins, particularly those derived from animal sources, demonstrate greater anabolic potential due to their leucine content and favorable amino acid profile. Dairy products are particularly effective in stimulating muscle protein synthesis. Nevertheless, plant-based protein sources may also support muscle maintenance when appropriately planned to ensure adequate essential amino acid intake [50].

Among specific nutritional supplements, β-hydroxy-β-methylbutyrate (HMB), a bioactive metabolite of leucine, has been extensively studied. Randomized controlled trials and meta-analyses indicate that supplementation with approximately 3 g/day for at least 12 weeks may result in modest improvements in muscle mass and strength; however, its effects on physical performance outcomes appear limited [51].

Vitamin D has also been widely investigated in the context of sarcopenia. Current evidence suggests that vitamin D supplementation alone does not exert a consistent disease-modifying effect on muscle strength, muscle mass, or functional performance. Therefore, vitamin D should be considered an adjunct within a multimodal treatment strategy, particularly in individuals with deficiency, rather than a standalone intervention [52].

Overall, nutritional strategies primarily support muscle mass preservation, whereas consistent improvements in muscle strength and physical performance are more frequently achieved when nutritional optimization is combined with resistance exercise.

5.3. Combined exercise-nutrition approaches

Combined exercise–nutrition strategies represent the most effective approach for the management of sarcopenia, as they target complementary mechanisms underlying muscle loss. While resistance exercise is the primary stimulus for muscle protein synthesis, adequate protein and energy intake are required to sustain and amplify this anabolic response [41]. Evidence consistently demonstrates that the combination of resistance training and protein supplementation leads to greater improvements in muscle strength, muscle mass, and physical performance compared with either intervention alone [42]. This synergistic effect is particularly relevant in older adults, in whom anabolic resistance limits the efficiency of isolated nutritional or exercise interventions.

From a practical perspective, integrating nutritional support with structured exercise programs is essential. Protein intake should be optimized in proximity to exercise sessions to maximize muscle protein synthesis, although the precise timing and distribution of protein intake remain areas of ongoing investigation. In frail or malnourished individuals, oral nutritional supplementation combined with supervised resistance exercise may further enhance adherence and functional outcomes [41].

Overall, combined exercise–nutrition interventions provide the most consistent improvements in muscle strength and physical performance, supporting their central role in multimodal sarcopenia management [53].

5.4. Hormonal therapies

Sex-related differences play an important role in the epidemiology and clinical expression of sarcopenia. Men typically exhibit higher absolute muscle mass but experience age-related declines in anabolic hormones such as testosterone, whereas women demonstrate accelerated muscle loss following menopause, partly due to reduced estrogen levels. These differences may influence both disease trajectory and response to therapy.

Sex steroid hormones regulate skeletal muscle metabolism through nuclear receptor–mediated pathways that promote protein synthesis, enhance myogenic differentiation, and suppress proteolysis. Accordingly, hormone-based strategies—including testosterone replacement therapy, selective androgen receptor modulators (SARMs), and estrogen-related interventions—have been explored as potential therapeutic approaches in sarcopenia [14].

Evidence from randomized controlled trials and meta-analyses indicates that testosterone therapy may increase lean body mass and modestly improve muscle strength in older men with low or low–normal serum testosterone levels; however, its effects on physical performance remain inconsistent [54]. In addition, potential risks—including cardiovascular events, erythrocytosis, and

prostate-related complications—necessitate careful patient selection and close monitoring [55].

Although both testosterone and SARMs have demonstrated anabolic effects on muscle mass, their translation into clinically meaningful functional improvements remains limited [56]. Similarly, the use of estrogen-based therapies and selective estrogen receptor modulators (SERMs) has been constrained by safety concerns, including thromboembolic and hormone-related risks [57].

Overall, hormonal therapies may provide modest benefits in muscle mass in selected populations, but their impact on muscle strength and physical performance is less consistent. Therefore, they should be considered adjunctive or investigational approaches rather than first-line treatments in the management of sarcopenia.

5.5. Metabolic therapies

Beyond hormonal modulation, increasing attention has been directed toward metabolic pathways linking insulin resistance, glucose homeostasis, and skeletal muscle health, particularly in older adults with type 2 diabetes mellitus [58]. Improvement of glycemic control has been associated with modest benefits in muscle mass and mobility. In the MUSCLES-DM study, reductions in HbA1c were associated with improvements in skeletal muscle index and gait speed, although no significant changes were observed in muscle strength [59]. Similarly, observational data from the KORA-Age study suggest that type 2 diabetes is associated with muscle mass decline, whereas insulin therapy may contribute to the preservation of muscle mass, without consistent improvements in strength or physical performance [60].

Metformin has attracted interest due to its effects on AMP-activated protein kinase (AMPK) activation, mitochondrial biogenesis, and modulation of mTOR signaling. However, despite these mechanistic considerations, the MET-PREVENT trial demonstrated no significant effects on handgrip strength, physical performance (SPPB), or appendicular muscle mass in older adults [61].

Although sodium–glucose cotransporter-2 inhibitors exert favorable metabolic effects and promote weight loss, meta-analytic evidence suggests that these benefits may be accompanied by reductions in lean and skeletal muscle mass, thereby raising concerns about a potential sarcopenia risk in vulnerable populations [62].

Similarly, glucagon-like peptide-1 (GLP-1) receptor agonists improve metabolic parameters and reduce inflammatory signaling but are also associated with substantial weight loss, a proportion of which is attributable to lean mass. Notably, current evidence does not demonstrate consistent improvements in physical performance outcomes with these agents [63].

Overall, while metabolic therapies may support muscle mass and overall metabolic health, their effects on muscle strength and physical performance remain inconsistent. These findings underscore that metabolic modulation alone is insufficient and should be integrated with resistance exercise and nutritional strategies for optimal sarcopenia management.

5.6. Emerging molecular therapies

Beyond currently available nutritional, hormonal, and metabolic interventions, increasing attention has focused on novel pharmacological strategies targeting specific molecular pathways involved in muscle homeostasis, inflammation, and regeneration.

Among these, myostatin–activin pathway inhibition has emerged as a major therapeutic target. Bimagrumab, a monoclonal antibody that blocks activin type II receptors (ActRIIA/ActRIIB), suppresses Smad- and MAPK-mediated catabolic signaling pathways associated with muscle atrophy. Clinical trials and meta-analyses have demonstrated that bimagrumab significantly increases muscle volume and fat-free mass; however, these gains have not consistently translated into meaningful improvements in muscle strength or physical performance. Therefore, despite its potent anabolic effects, bimagrumab remains an investigational agent rather than a routine therapeutic option for sarcopenia [64].

Classical RAS pathway blockades, including perindopril and losartan, have demonstrated limited benefits on muscle strength and physical performance [15]. In contrast, activation of the non-classical RAS pathway has emerged as a potential therapeutic target for sarcopenia. BIO101, a Mas receptor activator, demonstrated significant improvements in walking speed in the SARA-INT phase 2b trial, particularly among slow walkers, individuals with obesity, and those with low chair-stand performance. Although secondary strength outcomes did not reach statistical significance, its favorable safety profile and mechanistic rationale support further investigation [65].

Another promising target is the Growth Differentiation Factor-15 (GDF-15) pathway. In a phase 2 trial, ponsegromab produced dose-dependent weight gain and improvements in appetite, physical activity, and skeletal muscle mass in patients with cancer cachexia, suggesting potential relevance for muscle-wasting conditions [66].

Overall, emerging pharmacological therapies frequently lead to increases in muscle mass; however, translating these changes into consistent and clinically meaningful improvements in muscle strength and physical performance remains a major challenge. This limitation underscores the multifactorial nature of sarcopenia and highlights the need for multimodal strategies that integrate targeted pharmacological interventions with resistance exercise, nutritional optimization, and individualized patient assessment. Future progress will likely depend on refined patient phenotyping and combination-based therapeutic approaches rather than single-target interventions.

6. Conclusion

Sarcopenia represents a major contributor to functional decline and adverse health outcomes in older adults. In conclusion, improving conceptual clarity and distinguishing core biological features from downstream clinical outcomes are essential for harmonizing sarcopenia research and supporting outcome-oriented care. Although several pharmacological agents have demonstrated the capacity to increase muscle mass, these changes do not consistently translate into meaningful improvements in muscle strength or physical performance.

Accordingly, current evidence strongly supports a multimodal management strategy that integrates resistance exercise, adequate nutritional support, and optimization of underlying metabolic and hormonal conditions. Such an approach is essential to address the complex and multifactorial nature of sarcopenia and to achieve clinically relevant functional outcomes.

Future research should prioritize interventions that not only enhance muscle mass but also effectively improve strength, physical performance, and patient-centered outcomes. In parallel, emerging international initiatives such as the Global Leadership Initiative on Sarcopenia (GLIS) are expected to harmonize diagnostic criteria and assessment frameworks, thereby improving comparability across studies and facilitating translation into clinical practice.

Author contributions

MG: Conceptualization; Writing – original draft; Writing – review & editing.

CB: Conceptualization; Writing – review & editing; Supervision.

Generative AI declaration

During the preparation of this manuscript, the authors used generative artificial intelligence tools (ChatGPT and QuillBot) solely for language editing and grammatical improvement. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication. The literature selection, interpretation, and synthesis of the evidence, as well as all conclusions, were entirely performed by the authors.

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Conflict of interest

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