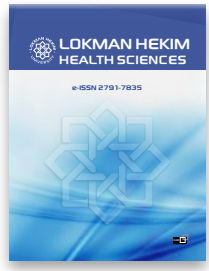
LOKMAN HEKIM HEALTH SCIENCES

DOI: 10.14744/lhhs.2026.74130
Lokman Hekim Health Sci 2026;6(4):749–758



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INVITED REVIEW

Sarcopenia: The Emerging Geriatric Syndrome of the 21st Century

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Abstract

Sarcopenia is a progressive generalized disorder of skeletal muscle defined by declines in muscle mass, strength, and function, resulting in increased risk of falls, fractures, disability, dependency, reduced quality of life, and mortality. It primarily affects older adults, with prevalence rising with age, but can also develop secondary to chronic diseases, prolonged immobilization, malnutrition, or systemic inflammatory conditions. Early identification is crucial, as sarcopenia is a preventable and potentially reversible condition when appropriate interventions are implemented. Diagnosis involves sequential assessment of muscle strength, quantity, and physical performance, with the European Working Group on Sarcopenia in Older People2 recommending the find–assess–confirm–severity approach to ensure standardized evaluation across clinical and research settings. Lifestyle-based interventions remain the cornerstone of management, including resistance and aerobic exercise, adequate protein intake, Vitamin D supplementation, and high-quality dietary patterns. Nutritional supplements, including leucine, β-hydroxy-β-methylbutyric acid, and omega-3 fatty acids, provide additional support. Pharmacological options are limited, with testosterone demonstrating benefits in deficiency states, and emerging agents such as a mas receptor agonist, BIO101, showing potential as future therapeutic interventions. Given its multifactorial pathophysiology – including hormonal changes, chronic inflammation, neuromuscular decline, and lifestyle-related factors – effective sarcopenia management requires a comprehensive, multi-targeted approach addressing both lifestyle and underlying mechanisms.

Keywords: Geriatrics; Muscle strength; Older adults; Sarcopenia

The human body contains over 600 skeletal muscles, which constitute a major proportion (45–55%) of total body mass, and the majority of them are located in the lower extremities. With advancing age, both the size and function of these muscles undergo substantial changes.[1] Sarcopenia is a generalized skeletal muscle disorder defined by progressive decline in muscle mass and function and related to increased risk of negative outcomes such as falls, fractures, functional loss, and mortality.[2] Sarcopenia is predominantly associated with aging but may also develop secondary to chronic conditions such as prolonged immobilization or systemic inflammatory diseases.[3,4]

Why it is Important

Sarcopenia imposes substantial individual, social, and financial burdens if left untreated. Clinically, it increases the risk of falls, bone fractures, mobility disorders, and disability in activities of daily living, and is associated with

Cite this article as: *Yurt MŞ, Ülger Z. Sarcopenia: The Emerging Geriatric Syndrome of the 21st Century. Lokman Hekim Health Sci 2026;6(4):749–758.*

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cardiovascular, respiratory, and cognitive impairments. These consequences lead to reduced quality of life, dependency, institutionalization, and increased mortality. Sarcopenia leads to significantly higher healthcare expenditures, as affected individuals experience higher rates of hospitalization and markedly greater inpatient costs. Early recognition is crucial, as sarcopenia is a preventable and potentially reversible condition when appropriate intervention strategies are implemented.[2]

Sarcopenia is a Geriatric Syndrome

Geriatric syndromes are characterized by complex, multifactorial conditions that arise from interactions between genetic, environmental, and physiological factors, and do not fit neatly into traditional disease categories. They are frequent in older adults and are associated with multiple comorbidities, disability, and diminished quality of life.

Sarcopenia meets the main criteria of a geriatric syndrome:

- It is highly prevalent, affecting about 30% of individuals over 65 and more than 50% over 80 years of age
- It results from multiple contributing factors, including aging, genetics, lifestyle, environmental influences, and chronic diseases
- It is related to functional decline, disability, poor life quality, and death
- Managing individual risk factors alone does not reverse its clinical manifestations.

Therefore, sarcopenia represents a multifactorial condition reflecting vulnerability due to impairments in multiple systems, fitting the definition of a geriatric syndrome rather than a single disease entity. Considering sarcopenia as a geriatric syndrome facilitates its recognition and the assessment of associated risk factors.[1]

This review aims to provide a comprehensive and up-to-date overview of sarcopenia as an emerging geriatric syndrome, focusing on its definition, epidemiology, pathophysiology, diagnostic approaches, management strategies, and preventive interventions, based on current evidence from the literature.

The literature search was conducted using the PubMed database. Articles were identified using the keywords "sarcopenia," "older," and "elderly," along with related terms such as "grip strength," "gait speed," "frailty," and "geriatric syndrome." In addition, reference lists of relevant articles were manually screened to identify further eligible studies. The search included studies published between 1997 and 2025. Original articles and review papers addressing the definition, epidemiology, pathophysiology, diagnosis, management, and prevention of sarcopenia in older adults were considered. Only studies published in English and involving human subjects were included. Articles not directly related to the topic or based on animal models were excluded.

Definition

Sarcopenia was initially used to describe low muscle mass. "Sarx" means muscle, and "penia" means loss in Greek.[5] The concept of sarcopenia has evolved over time, first with the inclusion of muscle function – shown to better predict clinical outcomes than muscle mass – and later with its formal recognition as an independent disease through the assignment of an International Classification of Diseases, Tenth Revision, Clinical Modification code (M62.84) in 2016.[6] Moreover, with the implementation of the 11th revision of the ICD in 2022, the diagnostic code for sarcopenia was updated to FB32.Y.[3]

The European Union Geriatric Medicine Society (EUGMS) established a Sarcopenia Working Group in 2009 with the aim of developing standardized definitions and diagnostic criteria applicable to both clinical and research.[7] In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) offered a definition of sarcopenia that gained global acceptance and significantly contributed to progress in the recognition and management of individuals at risk for, or affected by, the condition.[7] The EWGSOP advised that sarcopenia should be diagnosed by the concurrent presence of reduced muscle mass and impaired muscle function, either in terms of strength or physical performance.[7]

The EWGSOP was most recently updated in 2019 and identified reduced muscle strength as the principal criterion for sarcopenia,[2] as declines in strength were reported to precede reductions in mass and serve as stronger predictors of adverse outcomes.[8] Nevertheless, reduced muscle mass remains an essential criterion that supports the diagnosis of sarcopenia. A further revision was made in which the concept of muscle mass was refined and replaced by muscle quantity or quality to better capture the multifaceted nature of sarcopenia. Recent evidence indicates that, beyond alterations in muscle mass, various factors contributing to muscle quality – such as composition, fatty or fibrotic changes, metabolism, and aerobic performance – may also play a critical role in the reduction of muscle function. Notably, deterioration in muscle quality may occur before the decline in muscle

Table 1. 2019 EWGSOP2 definition of sarcopenia[2]

1. Reduced muscle strength
2. Reduced muscle quantity or quality
3. Reduced physical performance
(1)=probable sarcopenia
(1)+(2) = confirmed sarcopenia
(1)+(2)+(3) = severe sarcopenia

EWGSOP: European Working Group on Sarcopenia in Older People.

mass. For this reason, early detection of muscle quality is important, particularly among middle-aged adults who may benefit from timely interventions aimed at preserving or enhancing muscle function.[9] With ongoing advancements in the assessment of muscle quality, this measure is expected to assume a more prominent role in defining sarcopenia.[2]

According to the EWGSOP2 criteria, reduced muscle strength represents "probable sarcopenia" (Table 1). A definite diagnosis requires confirmation of reduced muscle quantity or quality with various methods. When both of these criteria are present, the condition is defined as "confirmed sarcopenia." With the additional presence of reduced physical performance, it is classified as "severe sarcopenia."[2] In the 2010 EWGSOP criteria, physical performance was considered a defining component of sarcopenia.[7] After the 2019 revision, it was reclassified as a marker of the disease's severity.

Because of the lack of a universally accepted definition of sarcopenia, an international initiative called global leadership initiative in sarcopenia (GLIS) was established to standardize the terminology commonly used in sarcopenia, for both clinical practice and research purposes. The initiative brings together leading investigators in the field to develop a single, globally applicable definition of sarcopenia. As a first step, GLIS aims to create a common glossary of terms that will provide consensus on the universal definition and support consistent interpretation of clinical and research findings.[4,10]

According to the GLIS committee, sarcopenia is recognized as a generalized disorder of skeletal muscle, and its prevalence increases progressively with advancing age. Experts largely agree that the conceptual definition of sarcopenia should remain consistent across different healthcare settings, such as inpatient and outpatient environments, and should not differ based on age or comorbid conditions. Moreover, it is widely accepted that the definition should be unified for both clinical practice and research purposes. Importantly, sarcopenia is viewed as a condition that holds the potential to be reversible with appropriate interventions. There is strong consensus that muscle strength, muscle mass, and muscle-specific strength – such as the ratio of muscle strength to muscle size – are the key components of sarcopenia. Finally, sarcopenia leads to multiple adverse outcomes, such as poor physical performance, mobility limitations, falls, fractures, loss of independence in daily activities, increased hospitalizations, new admissions to long-term or nursing care facilities, poorer quality of life, and higher mortality risk. Impaired physical performance is considered an outcome of sarcopenia rather than a defining component.[11]

Epidemiology

Sarcopenia affects 10–27% of adults over 60 years[12] and nearly 30% of those over 80 years.[13] Severe sarcopenia was reported in 2–9% of individuals. Based on EWGSOP2, men had a higher prevalence of sarcopenia (11% vs. 2%).[12] Prevalence is expected to rise in Europe due to increased life expectancy.[13] Obesity and decreased physical activity exacerbate this trend, leading to sarcopenic obesity (SO). Sarcopenia may also develop before age 60 in patients with cancer, metabolic disorders, renal or liver disease, or rheumatologic conditions, and serves as a prognostic marker. Reducing the prevalence of sarcopenia may substantially lower healthcare expenditures. Exact estimation of the prevalence is challenging due to differences in diagnostic criteria, age of study population, clinical settings, and assessment methods.[13]

Pathophysiology

The pathophysiology underlying sarcopenia is incompletely understood. Both intrinsic and systemic factors contribute to the structural and functional decline of muscle tissue.[3] In affected individuals, multiple pathways may act concurrently, and their contributions can vary throughout the disease course. Identifying these mechanisms is crucial for the development of targeted intervention strategies.[7] Primary alterations underlying sarcopenia involve an imbalance in muscle protein synthesis and breakdown, fatty infiltration, impaired neuromuscular function, changes in the satellite cells, mitochondrial dysfunction, chronic systemic low-grade inflammation, hormonal changes (decrease in sex hormones, growth hormone, and insulin-like growth factor-1 [IGF-1]), activation of the classical renin-angiotensin system (RAS) pathway, microRNAs, dysbiosis, anorexia of aging, and physical inactivity.[3]

Case Finding and Diagnosis

Case Finding

As current screening tools lack sufficient accuracy, universal screening is not recommended for sarcopenia.[14] EWGSOP2 recommends a case finding strategy rather than screening. Sarcopenia should be considered when patients exhibit symptoms suggestive of sarcopenia, such as falls, generalized weakness, slowness, or unintentional weight/muscle loss. In these situations, further diagnostic evaluation for sarcopenia is advised.[2]

The application of the SARC-F questionnaire as a patient-reported screening instrument is recommended to recognize individuals susceptible to sarcopenia. It has been validated in multiple populations, demonstrating reliability and consistency for identifying individuals at risk of sarcopenia-related adverse outcomes. SARC-F exhibits low-to-moderate sensitivity but very high specificity, primarily detecting more severe cases. It is inexpensive, convenient, and suitable for use in community and clinical settings, reflecting patient-perceived limitations that are meaningful for care.[2] SARC-F is an acronym that stands for five components whose first letters are highlighted in the following way – strength, need for walking assistance, ability to rise from a chair, stair climbing, and falls – selected to reflect functional decline associated with sarcopenia. Scores range from 0 to 10 (0–2 per item), with higher scores indicating greater impairment, and are commonly categorized into symptomatic (≥4) versus non-symptomatic (0–3) status. The scores ≥4 were associated with more instrumental activities of daily living deficits, lower grip strength, slower chair-stand times, reduced physical performance, slower gait, higher hospitalization risk, and higher mortality.[15]

Diagnosis

The assessment of sarcopenia typically involves measuring muscle strength, mass, and physical function. Although definitions generally include two or more of these indicators, variability in threshold values complicates standardization and clinical application. The EWGSOP2 proposes a structured, sequential approach to improve diagnosis.[2,14]

Measurement of Muscle Strength

Measurement of handgrip strength is recommended as a practical, quick, and cost-effective method for evaluating muscle function. It is validated and reliable in older adults.[16] Reduced grip strength has been consistently shown to predict adverse clinical outcomes, including prolonged hospitalization, functional decline, diminished quality of life, and increased mortality. Accurate assessment requires a calibrated handheld dynamometer and standardized testing procedures, along with reference values derived from appropriate populations. According to the EWGSOP2 criteria, cut-off values for grip strength are <27 kg for men and <16 kg for women (Table 2).[2] If grip strength is under the reference thresholds for sex or those defined by consensus guidelines, sarcopenia should be considered as a potential diagnosis. Early recognition of diminished grip strength is clinically important, as it serves as a strong predictor of multiple adverse health outcomes.[8,14,17]

Table 2. Sarcopenia cut-off values according to EWGSOP2[2]

	Men	Women
Muscle strength		
Grip strength (kg)	<27	<16
Chair stand	>15 s for five rises	
Muscle quantity (DXA, BIA)		
ASM	<20 kg	<15 kg
ASM/height^2	<7.0 kg/m^2	<5.5 kg/m^2
Physical performance		
4-m walking speed	≤0.8 m/s	
TUG test	≥20 s	

EWGSOP: European Working Group on Sarcopenia in Older People; DXA: Dual-energy X-ray absorptiometry; BIA: Bioelectrical impedance analysis; ASM: Appendicular skeletal muscle mass; TUG: Timed-up and go.

Grip strength demonstrates a moderate correlation with strength in other muscle groups and thus serves as a useful proxy for overall muscle strength. In cases where grip assessment is not feasible due to hand impairments (e.g., severe arthritis, neurologic conditions), isometric torque measurements of the lower limbs can be applied as substitutes. The chair stand test – also referred to as the chair rise test – provides an indirect estimate of lower-limb muscle strength, particularly of the quadriceps. It involves measuring the time taken to rise from a seated position five consecutive times without arm support, or alternatively, counting repetitions within a 30-s interval.[2,18] According to EWGSOP2, a time >15 s for five chair rises indicates low muscle strength (Table 2).

Measurement of Muscle Quantity

After detecting reduced muscle strength, the second step is evaluation of the muscle quantity to confirm the diagnosis of sarcopenia. Various methods have been employed to assess muscle mass; however, each presents significant limitations, such as variability in measurements, inconsistency in the application of cut-off values, and a weak correlation between muscle mass and adverse clinical outcomes.[14]

Magnetic Resonance Imaging (MRI) and Computed Tomography (CT)

MRI and CT are regarded as the gold-standard modalities for the non-invasive evaluation of muscle quantity. Nevertheless, their application in primary care settings is limited due to factors such as higher costs, restricted portability, and the need for specialized personnel to operate the devices. In addition, standardized threshold values for defining reduced muscle mass using the mentioned imaging modalities have not yet been clearly established.[2] MRI and CT are primarily reserved for research purposes or for the monitoring of other medical conditions, such as in patients undergoing cancer evaluation or treatment.[14] Lumbar L3 cross-sectional area, mid-thigh muscle area, and psoas muscle measurements are commonly used as imaging-based proxies to estimate total body muscle composition.[2]

Dual-energy X-ray Absorptiometry (DXA)

Among the available approaches, DXA remains the most reliable modality for estimating lean body mass.[14] It is an extensively used, non-invasive technique for assessing muscle quantity, reported as either total body lean tissue mass or appendicular skeletal muscle mass (ASM). On the other hand, measurements may vary across different DXA device brands. A notable limitation of DXA is its lack of portability for community-based use, and its measurements can be influenced by the individual's hydration level. Despite these limitations, DXA remains a preferred method among clinicians and researchers due to its ability to provide rapid and reproducible estimates of ASM when the same instrument and cut-off values are applied.[2]

Bioelectrical Impedance Analysis (BIA)

BIA provides an indirect estimation of muscle mass by assessing total body electrical conductivity and applying population-specific prediction equations calibrated against DXA-measured lean mass. Although BIA is affordable, portable, and widely available, its accuracy varies across devices, reference populations, and hydration states. While BIA offers practical advantages over DXA, its precision is restricted by the population- and device-specific nature of predictive equations and cut-off thresholds, as well as the absence of standardization. Further validation of prediction models in diverse populations is required.[2,14]

Ultrasound

Since 2018, ultrasound has been suggested as a practical and accessible method for assessing muscle mass in clinical settings. However, the technique remains non-standardized and currently lacks validated cut-off points.[14] It allows bedside evaluation of muscle morphology by trained clinicians, demonstrating high intra- and inter-observer reliability. Measurements of muscle thickness and cross-sectional area, particularly in pennate muscles, for example, quadriceps femoris, can identify early changes in muscle mass, supporting its clinical applicability.[2] The EuGMS sarcopenia group[19] has recommended a consensus protocol standardizing ultrasound parameters, including muscle thickness, cross-sectional area, fascicle length, pennation angle, and echogenicity. Ultrasound is a valid technique and comparable to DXA, MRI, and CT for estimating muscle mass. However, further research is required to refine prediction equations across diverse clinical and functional populations.[20]

The widespread implementation of sarcopenia assessment is constrained by limited access to DXA, BIA, and ultrasound, as these techniques are not available in all healthcare centers. Cost, infrastructure requirements, and the need for trained personnel further limit their routine use, particularly in primary care settings. Consequently, simpler and more widely applicable screening tools, such as handgrip strength and calf circumference measurements, are often preferred in routine clinical practice.

Because muscle mass is correlated with body size, skeletal muscle mass (SMM) or ASM is often adjusted using indices such as weight (ASM/weight), height^2 (ASM/height^2), or body mass index (ASM/BMI). Although no universal recommendation exists regarding which adjustment should be applied, normalization may be appropriate when reference data from relevant populations are available. Height-adjusted values (ASM/height2) are most commonly used to establish diagnostic cut-offs. However, variability among studies in defining these cut-off points has resulted in inconsistent thresholds and challenges in standardizing sarcopenia diagnosis. Therefore, in its updated definition, the EWGSOP chose a practical strategy by selecting straightforward and easily applicable cut-off values based on the best available evidence (Table 2).[2,14]

Anthropometry

Anthropometric measures are not good indicators of muscle mass. Nevertheless, calf circumference has been identified as an indicator of physical performance and survival in this population, with a proposed cut-off value of <31 cm.[21] Different cut-off values are present according to sex and ethnicity. In clinical settings where direct assessment of muscle mass is not feasible, calf

circumference may serve as a practical surrogate marker for sarcopenia screening in older adults.[2]

Creatine Dilution

It is possible to estimate total body muscle mass using creatinine excretion rate. In the creatine dilution test, a fasting individual ingests a deuterium-labeled creatine (D3-creatine) tracer, and subsequent measurements of labeled and unlabeled creatine/creatinine in urine allow calculation of total body creatine and muscle mass. This method correlates well with MRI and moderately with BIA and DXA. Currently, the test is primarily used in research, and further development is needed for routine clinical application.[2]

Muscle Quality Measurement

Muscle quality may be a more clinically relevant indicator of sarcopenia than muscle mass; however, it has not yet been adequately defined for routine use in clinical settings.[14] Ultrasound echogenicity is used as an indicator of muscle quality due to its correlation with myosteatosis. In research settings, advanced imaging modalities such as MRI and CT have been employed to evaluate muscle quality, for example, by assessing intramuscular fat infiltration. Other approaches include calculating the ratio of muscle strength to ASM or muscle volume and using BIA-derived phase angle measurements. Currently, no standardized method exists for routine practice, yet muscle quality evaluation is expected to become a standard part of treatment decision-making and follow-up.[2]

Assessment of Physical Performance

Physical performance in older adults can be evaluated using various tests, including gait speed, the short physical performance battery (SPPB), the timed-up-and-go (TUG) test, and the 400-m walk test. Among these, gait speed (mostly 4-m walking speed) is a quick, safe, and reliable measure. EWGSOP2 recommends a gait speed cut-off of ≤0.8 m/s to indicate severe sarcopenia.[2] Gait speed is preferred for routine sarcopenia assessment due to its convenience and predictive value for adverse outcomes such as disability, falls, cognitive decline, institutionalization, and mortality.[22] The SPPB, TUG, and 400-m walk tests also predict adverse outcomes but are more often used in research or specialized settings due to longer administration time or space requirements.[2] Limitations can be faced in patients with cognitive impairment, gait disorders, or balance problems. Cut-off values of commonly used parameters are listed in Table 2.

Ethnic Variability and Population-based Cut-off Values for Sarcopenia in the Turkish Population

Ethnic variability is an important consideration in the interpretation of sarcopenia-related cut-off values, as muscle strength, muscle mass, and physical performance are influenced by anthropometric characteristics, genetic background, lifestyle, and environmental factors. Cut-off values derived from Western populations may not be directly applicable to Asian or Middle Eastern populations, leading to potential misclassification. The higher cut-off values proposed by AWGS 2019 compared with EWGSOP2 emphasize the role of ethnic variability in defining diagnostic criteria. According to the AWGS 2019 criteria, low muscle strength is defined as handgrip strength <28 kg in men and <18 kg in women, while low physical performance is identified by a 6-m gait speed <1.0 m/s, an SPPB score ≤9, or a 5-time chair stand test ≥12 s. ASM/height2 cut-offs <7.0 kg/m^2 in men and <5.4 kg/m^2 in women by DXA; <7.0 kg/m^2 in men and <5.7 kg/m^2 in women by BIA, and calf circumference <34 cm in men and <33 cm in women.[23]

At present, there are no nationally established consensus cut-off values for the diagnosis of sarcopenia in the Turkish population, and population-based studies have reported varying threshold values. In a community-dwelling older population, the cut-off thresholds for SMM index (SMMI) were 9.2 kg/m^2 for men and 7.4 kg/m^2 for women by BIA. Corresponding handgrip strength cut-off values were 32 kg for men and 22 kg for women, while a calf circumference threshold of 33 cm was applied for both sexes.[24] In another population-based study including 1,150 older adults, the SMMI cut-off values were defined as 8.33 kg/m^2 for men and 5.70 kg/m^2 for women by BIA. In the same study, handgrip strength thresholds were determined as 28 kg for men and 14 kg for women, based on measurements obtained from a healthy young adult reference population.[25]

The EWGSOP2 proposes a practical diagnostic pathway for sarcopenia, known as the find–assess–confirm–severity strategy.[2] It is recommended for use in both clinical practice and research.

1) Find: Identify individuals susceptible to sarcopenia according to the SARC-F questionnaire or according to clinical suspicion
2) Assess: Evaluate muscle strength using the grip strength or chair stand test
3) Confirm: Confirm the diagnosis by measuring low muscle quantity and quality using DXA, BIA, CT, and MRI

Table 3. Classification of sarcopenia[2,7,14]

Primary=Age-related
Secondary
Nutritional
Low protein or energy intake
Micronutrient deficiency
Malabsorption
Drug-related anorexia or anorexia of aging
Obesity
Inactivity
Bed rest or immobility
Sedentary lifestyle
Disease-associated
Inflammatory conditions (e.g. malignancy, advanced organ failure)
Endocrine diseases (androgen deficiency)
Neurological disorders
Bone and joint diseases

4) Severity: Determine the severity of sarcopenia by assessing physical performance (e.g., gait speed or the TUG test).

Classification of Sarcopenia

After diagnosis of sarcopenia, it is crucial to identify the mechanism underlying the condition. Common causes of sarcopenia are listed in Table 3.

Sarcopenia-Like Conditions

SO

SO refers to the coexistence of sarcopenia and obesity.[26] SO is predominantly observed in older adults. The presence of obesity accelerates the progression of sarcopenia, promotes intramuscular fat infiltration, impairs physical function, and increases the risk of mortality.[2] The risk of mortality and functional decline may increase with the loss of SMM in individuals with obesity, particularly during periods of weight loss.[14]

Evaluation of SO involves two main levels: screening and diagnosis, followed by staging to determine disease severity. SO screening is based on the simultaneous presence of increased BMI or waist circumference and risk of sarcopenia. A confirmed diagnosis requires abnormalities in both skeletal muscle function and body composition. After diagnosis, two stages of SO are defined. Stage I: No complications linked to altered muscle or fat composition. Stage II: Existence of one or more complications, such as metabolic disorders, functional disability, or cardiovascular/respiratory diseases. SO is thus a multifactorial condition requiring combined functional and compositional assessment for correct diagnosis and management.[26]

Dynapenia

Dynapenia is defined as the age-related decline in muscle strength.[27] It is measured with handgrip strength, and a value <16 kg for women, <27 kg for men indicates dynapenia.

Frailty

Frailty is a clinical condition characterized by heightened vulnerability to increased dependency and/or mortality when an individual faces stressors. It may develop as a consequence of various diseases or medical conditions.[28] According to Fried et al.,[29] is a clinical syndrome defined by the presence of ≥3 of the following five criteria: unintentional weight loss, exhaustion, reduced physical activity, slowness, and weakness. Its physical phenotype overlaps with sarcopenia, sharing features such as reduced handgrip strength, slower walking, and weight loss, which also contribute to sarcopenia. Treatment strategies for both conditions, including optimal protein intake, vitamin D supplementation, and physical exercise, are similar. Nevertheless, frailty represents a broader concept encompassing multiple physiological systems, whereas sarcopenia is a specific skeletal muscle disease.[2]

Treatment of Sarcopenia

The management of sarcopenia is mainly based on non-pharmacologic strategies. There is no known pharmacologic therapy specifically approved for sarcopenia. Due to the complex underlying pathophysiology, developing an effective treatment for sarcopenia remains challenging. Multiple therapeutic modalities have been investigated for the treatment of sarcopenia. Among them, the only treatment options shown to be beneficial are Vitamin D supplementation, exercise, and adequate nutrition.[3] In addition, testosterone supplementation has been shown to have potential benefits on muscle tissue in men with testosterone deficiency.[30]

Nutritional approaches, including adequate calorie, protein, and micronutrient intake, are important for optimal muscle function. European Society for Clinical Nutrition and Metabolism guidelines recommend a daily protein consumption of 1.0–1.2 g/kg body weight (BW) to preserve muscle health in older adults. Protein requirements increase to 1.2–1.5 g/kg BW during the state of acute or chronic illness and may reach up to 2.0 g/kg BW critical

illness or malnutrition states.[31] If combined with resistance exercise, whey protein, particularly doses above 20 g per meal, effectively stimulates muscle protein synthesis.[13]

Leucine, one of the essential amino acids, is fundamental for the triggering of muscle protein synthesis. Leucine-rich protein supplements support lean body mass, but supplementation alone without exercise is insufficient. β-hydroxy-β-methylbutyric acid (HMB) is a metabolite of leucine, and HMB supplementation (3 g/day) has been demonstrated to improve muscle strength and body composition in older adults, particularly in untrained or immobilized individuals.[32]

Evidence suggests that Vitamin D supplementation improves muscle strength and physical performance, particularly in women with vitamin D deficiency (<25 nmol/l).[30] Vitamin D supplementation is also associated with decreased mortality in older adults.[33] Omega-3 (n3-PUFA) supplementation may also improve muscle mass, volume, strength, and physical performance, particularly at higher doses (>2 g/day).

Other nutrients, including selenium, magnesium, inorganic nitrate, Vitamin C and E, calcium, probiotics, collagen, and polyphenols, have been investigated for their potential effects on muscle performance and physical activity in older adults.[3,32] In a cross-sectional study, low magnesium levels were found to be associated with dynapenia in malnourished older women even after adjusting for nutritional status.[34]

Physical exercise, particularly resistance training, is a highly effective approach to improve muscle mass and function. Aerobic exercise is beneficial not only for muscle mass and function but also for endurance and cardiovascular health,[3] with an additional protective role against mitochondrial dysfunction.[35] Beyond stimulating muscle protein synthesis, exercise also enhances the effects of nutritional interventions.[13] A combined exercise program, including resistance and aerobic training, is the best strategy to counteract sarcopenia.[35]

High-quality dietary patterns, for example, the Mediterranean and Nordic diets, have been shown to improve muscle strength and reduce sarcopenia risk, likely due to their antioxidant and anti-inflammatory properties. Nutrient timing is crucial for optimizing dietary effects in sarcopenia. The circadian clock regulates metabolic processes, and an early breakfast modulates peripheral clock genes that enhance glucose metabolism and muscle protein synthesis. Disruptions in clock-gene expression increase the risk of obesity and sarcopenia. Similarly, late-afternoon resistance exercise influences the circadian rhythm of anabolic and catabolic hormones. It alternates the testosterone to cortisol balance and promotes skeletal muscle protein synthesis.[13]

Various pharmacological agents have been investigated for treatment of sarcopenia, including testosterone, selective androgen receptor modulators, selective estrogen receptor modulators, dehydroepiandrosterone, growth hormone, IGF-1, insulin, anti-diabetic drugs, ghrelin and ghrelin receptor agonists, myostatin and activin II receptor inhibitors, RAS inhibitors, mas receptor agonists, mechanistic target of rapamycin inhibitors, espindolol, indoxyl sulfate, fast skeletal muscle troponin activators, elamipretide, and anti-tumor necrosis factor drugs. Among these agents, none have demonstrated efficacy in sarcopenia, except for testosterone in patients with testosterone deficiency. In addition, a mas receptor agonist, BIO101, is considered a leading candidate with the potential to become the first approved therapeutic agent for the treatment of sarcopenia.[3]

Despite continued research on sarcopenia management, the most effective strategies for prevention and treatment remain lifestyle interventions. Due to the complex and multifactorial nature of the disease, focusing on a single causative mechanism is unlikely to be effective, and multi-targeted interventions may be required.[3]

In routine clinical practice, adherence to exercise programs and difficulties in accessing adequate amounts of high-quality dietary protein represent major barriers to the implementation of sarcopenia prevention and management strategies. Older age, comorbidities, functional limitations, lack of motivation, and limited access to supervised exercise facilities have been shown to negatively affect long-term compliance with exercise interventions.[2,36,37] Socioeconomic constraints, food insecurity, and limited availability of protein-rich foods may prevent older adults from meeting recommended protein intake levels, particularly in community-dwelling and resource-limited settings.[2,38] These barriers may compromise the effectiveness of combined exercise and nutritional interventions and should be considered when translating evidence-based recommendations into routine clinical practice.

Conclusion

Sarcopenia is a multifactorial geriatric syndrome with significant clinical, social, and economic consequences. Early identification and intervention are essential to prevent adverse outcomes, including functional decline, institutionalization, and mortality. Current evidence supports lifestyle-based strategies, particularly exercise combined with adequate

nutrition, as the cornerstone of sarcopenia management. While pharmacological therapies remain limited, emerging agents such as a mas receptor agonist BIO101 offer potential for future treatment. A comprehensive, multi-dimensional approach addressing muscle strength, mass, quality, and physical performance is critical for effective prevention and management of sarcopenia in aging populations.

Ethics Committee Approval: Ethical approval was not required for this study since this is a review article.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: Not declared.

Authorship Contributions: Concept: ZÜ, MŞY; Design: ZÜ, MŞY; Supervision: ZÜ, MŞY; Resource: ZÜ; Analysis or Interpretation: ZÜ; Literature Search: MŞY; Writing: MŞY; Critical Review: ZÜ, MŞY.

Peer-review: Double blind peer-reviewed.

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