

Review

Sarcopenia as a Disorder of Skeletal Muscle Homeostasis: A Five-Pillar Translational Framework Linking Mechanisms, Diagnosis, and Treatment

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Abstract

Sarcopenia is a progressive skeletal muscle disorder in which clinically relevant muscle failure is expressed primarily as reduced muscle strength, with low muscle quantity or quality used to confirm the diagnosis and impaired physical performance indicating greater severity in the EWGSOP2 (European Working Group on Sarcopenia in Older People 2) framework. This narrative review first defines the clinical phenotype and its current diagnostic operationalization and then uses an author-proposed five-pillar framework: energy, structure, regeneration, neuromuscular control, and systemic communication, to organize the interacting biological mechanisms that may generate that phenotype. The framework is intended as a translational heuristic rather than a validated classification and is positioned within broader geroscience and hallmarks-of-ageing concepts. Particular emphasis is placed on the distinction between muscle mass, strength, power, and physical performance; context-dependent mTORC1 signaling; the limited specificity of candidate biomarkers; and the uncertain causal direction of several mechanistic associations. Resistance exercise and adequate energy and protein intake remain the foundations of management, whereas pharmacological and regenerative strategies have not yet demonstrated sufficiently consistent improvements in patient-relevant functional outcomes to replace these interventions. Linking biological mechanisms to measurable muscle failure may improve interpretation of current evidence and help define priorities for future mechanistic and clinical studies.

Keywords: sarcopenia; skeletal muscle homeostasis; muscle strength; muscle power; physical performance



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1. Introduction

Sarcopenia is a progressive and generalized skeletal muscle disorder associated with falls, fractures, physical disability, loss of independence, and mortality. Contemporary clinical definitions increasingly conceptualize sarcopenia as a form of muscle failure rather

than as low muscle mass alone. In the EWGSOP2 algorithm, low muscle strength is the principal feature that identifies probable sarcopenia; low muscle quantity or quality confirms the diagnosis, and poor physical performance indicates severe sarcopenia. The 2025 Asian Working Group for Sarcopenia (AWGS) update addresses Asian populations and uses region-specific thresholds and case-finding concepts that should not be merged uncritically with European criteria [1,2]. This diagnostic hierarchy is clinically important because muscle mass, maximal strength, muscle power, and global physical performance represent related but non-equivalent domains of muscle health. In particular, muscle power, the ability to generate force rapidly, may decline disproportionately and has direct relevance to balance recovery, rising from a chair, stair climbing, and other time-dependent activities of daily living [3]. Recent reviews have already described mitochondrial dysfunction, oxidative stress, impaired proteostasis, satellite-cell dysfunction, neuromuscular degeneration, inflammation, metabolic dysregulation, the gut–muscle axis, and emerging therapies [4–8]. The unresolved translational problem is therefore not simply to catalogue additional pathways, but to explain how interacting biological disturbances converge on the measurable clinical phenotype and why changes in muscle quantity do not necessarily predict changes in strength, power, or function. To address this gap, we use a five-pillar framework, energy, structure, regeneration, control, and communication, as an author-proposed organizational model. It is not an established classification and the pillars are neither biologically independent nor assumed to be exhaustive. Instead, they are intended to provide complementary translational lenses through which recurrent mechanisms can be mapped to the clinical domains of strength, power, muscle quantity/quality, and physical performance. This approach complements geroscience models that link sarcopenia to interacting hallmarks and biological determinants of ageing [9,10]. The clinical boundaries of sarcopenia also require caution. Validated diagnostic frameworks were developed primarily for older adults, although AWGS 2025 additionally provides a defined midlife context for Asian populations [2]. Muscle loss in younger adults or children with chronic disease may reflect secondary sarcopenia in selected settings, but it may also represent cachexia, malnutrition, disuse atrophy, treatment-related myopathy, disease-specific muscle wasting, or growth-related abnormalities. These entities should not be considered biologically or diagnostically equivalent without appropriate age- and population-specific criteria. Accordingly, the aim of this narrative review is to connect the clinical phenotype and diagnostic hierarchy of sarcopenia with an integrated, critically appraised five-pillar model of skeletal muscle homeostasis and to examine how established and investigational interventions affect clinically meaningful outcomes.

2. Methodology

This article is a narrative review. To improve transparency, literature supporting the conceptual framework and the present revision was identified through structured searches of PubMed/MEDLINE and backward reference screening, updated through 8 August 2026. Search concepts included combinations of “sarcopenia”, “muscle strength”, “muscle power”, “muscle mass”, “muscle quality”, “mitochondrial dysfunction”, “proteostasis”, “autophagy”, “satellite cells”, “neuromuscular junction”, “inflammation”, “gut–muscle axis”, “exercise”, “nutrition”, “pharmacotherapy”, and “biomarkers”. English-language consensus statements and guidelines, systematic reviews and meta-analyses, randomized trials, and longitudinal human studies were prioritized for clinical statements; experimental cell and animal studies were used when human mechanistic evidence was unavailable and are interpreted accordingly. No formal risk-of-bias instrument was applied and the search was not designed to satisfy systematic-review methodology. The five-pillar framework was generated as a structured narrative synthesis of recurrent biological domains and

was selected for translational organization rather than as a validated or evidence-derived taxonomy; alternative hallmarks-of-ageing and geroscience frameworks were considered when interpreting overlap, causal uncertainty, and conceptual completeness [9,10].

3. Clinical Phenotype and Diagnostic Operationalization

3.1. Diagnostic Framework

Sarcopenia should be identified according to the sequence specified by the applicable consensus rather than by treating muscle mass as the conceptual starting point. In EWG-SOP2, reduced muscle strength establishes probable sarcopenia, low muscle quantity or quality confirms the diagnosis, and poor physical performance identifies severe disease [1]. EWG-SOP2 recommends handgrip strength or the five-repetition chair-stand test for the strength domain. AWGS recommendations were developed for Asian populations and use region-specific thresholds and case-finding pathways; the 2025 update also explicitly addresses midlife assessment and should be interpreted within that geographical and demographic context [2]. European and Asian thresholds should therefore be presented separately rather than combined into a single universal algorithm. Muscle power is not yet a core diagnostic criterion in either framework, but it captures the velocity component of force generation and may identify clinically important neuromuscular impairment that is not fully represented by muscle quantity or maximal strength alone [3].

3.2. Assessment Methods

3.2.1. Muscle Strength and Power

Muscle strength is the entry point of the EWG-SOP2 diagnostic algorithm because it is closely associated with adverse outcomes and can be assessed rapidly in clinical practice [1]. Handgrip dynamometry is widely used, while the five-repetition chair-stand test provides an alternative assessment that is particularly relevant to lower-limb function. The tests should be performed using standardized positioning, equipment, and instructions, and results should be interpreted using consensus- and population-specific thresholds. Muscle power should be distinguished from maximal strength. Power reflects force multiplied by contraction velocity and is especially relevant to rapid functional tasks such as recovering balance, rising from a chair, climbing stairs, and preventing a fall. Evidence suggests that power may decline earlier or more steeply than maximal strength in ageing, but standardized clinical thresholds and its formal role in sarcopenia diagnosis remain under development [3].

3.2.2. Muscle Quantity and Quality

Low muscle quantity or quality is used to confirm sarcopenia after reduced strength has been identified in EWG-SOP2 [1]. Appendicular skeletal muscle mass (ASM) is commonly measured and can be normalized to height squared to derive the Appendicular Skeletal Muscle Mass Index (ASMI). Dual-energy X-ray absorptiometry (DXA) is an imaging-based method that estimates regional lean soft tissue mass. Bioelectrical impedance analysis (BIA), in contrast, is not an imaging technique; it estimates body composition from tissue electrical impedance and is practical for repeated bedside or outpatient measurements, although results depend on device-specific equations and hydration status [11–13]. Computed tomography and magnetic resonance imaging can provide detailed information on muscle cross-sectional area and tissue composition in selected clinical or research settings. Measures of muscle quality, including myosteatosis, are clinically relevant because preserved or increased body weight can coexist with substantial functional muscle impairment [14].

3.2.3. Physical Performance

Physical performance integrates skeletal muscle capacity with balance, cardiorespiratory reserve, neurological function, motivation, and environmental demands. In EWGSOP2, poor physical performance is used to grade sarcopenia as severe rather than to establish the initial diagnosis [1]. Common measures include gait speed and the Short Physical Performance Battery (SPPB), which combines standing balance, gait speed, and repeated chair-rise performance. Wearable accelerometers and inertial sensors can additionally quantify real-world gait speed, activity, and movement variability, but their incremental diagnostic value and standardized thresholds remain under evaluation [15]. Because physical performance is influenced by multiple organ systems, abnormal results should be interpreted in the context of comorbidity and not assumed to reflect skeletal muscle pathology alone (Table 1).

Table 1. Comparison of the diagnostic hierarchy used by EWGSOP2 and AWGS 2025 [1,2].

Consensus and Intended Context	Diagnostic Hierarchy	Selected Tests, Cut-Offs, and Interpretive Notes
EWGSOP2—European framework, primarily older adults	Probable sarcopenia: low strength. Confirmed sarcopenia: low muscle quantity or quality. Severe sarcopenia: additional poor physical performance.	Strength: handgrip < 27 kg (men), <16 kg (women), or five-chair-rise time > 15 s. Quantity: ASMI < 7.0 kg/m ² (men), <5.5 kg/m ² (women). Performance: gait speed ≤ 0.8 m/s or SPPB ≤ 8.
AWGS 2025—Asian populations; includes explicit midlife assessment in addition to older adults	Uses AWGS-specific case-finding and diagnostic categories; low strength and low muscle mass are interpreted with region- and age-appropriate thresholds. Physical performance is an important clinical outcome and contextual measure.	Handgrip thresholds differ by age group (e.g., ≥65 years: <28 kg men, <18 kg women; midlife thresholds are higher). AWGS-specific muscle-mass indices and cut-offs should be used. Do not substitute EWGSOP2 cut-offs for Asian populations.
Clinical interpretation	Consensus frameworks should not be merged into one universal algorithm.	Muscle power is clinically informative but is not yet a core stand-alone diagnostic criterion; all measurements require standardized technique and population-appropriate reference values.

Abbreviations: ASMI—Appendicular Skeletal Muscle Mass Index; AWGS—Asian Working Group for Sarcopenia; EWGSOP2—European Working Group on Sarcopenia in Older People 2.

3.3. Diagnostic Challenges and Clinical Boundaries

A major diagnostic challenge is the absence of a single universally applicable set of reference values. Consensus-specific thresholds reflect population differences in body size, body composition, age distribution, ethnicity, and testing procedures [16,17]. BIA introduces additional variability because device algorithms and hydration status can affect estimated muscle mass. Sarcopenic obesity and myosteatosis further illustrate why body mass index alone is inadequate: normal or high body weight may conceal low muscle quantity, poor tissue quality, and clinically important weakness [14,18]. Comorbid neurological, renal, cardiac, respiratory, metabolic, oncological, and inflammatory diseases can affect strength and performance through mechanisms that are not specific to sarcopenia, so diagnostic findings must be interpreted in context rather than attributed to a single disorder.

Particular caution is required in children, adolescents, and younger adults. There is no universally accepted pediatric definition comparable with EWGSOP2 or AWGS, and muscle mass and strength change continuously with age, sex, height, pubertal stage, and growth [19–22]. Muscle loss in pediatric cancer, inflammatory bowel disease, inherited

metabolic disorders, transplantation, or other chronic illnesses may instead reflect growth failure, malnutrition, cachexia, treatment toxicity, disease-related myopathy, or physical inactivity. Similarly, in younger adults, the term sarcopenia should be used only when an explicit operational definition appropriate to the study population is applied. These boundaries are essential to avoid conflating sarcopenia with other forms of secondary muscle wasting.

3.3.1. Emerging Directions

Biomarkers

No circulating biomarker is currently validated or recommended as a stand-alone diagnostic test for sarcopenia. Candidate markers should therefore be classified according to their intended role (mechanistic marker, risk marker, diagnostic adjunct, prognostic marker, or treatment-response marker) and the biological matrix in which they are measured. Circulating C-terminal agrin fragment (CAF) and neurofilament light chain (NfL) may reflect neuromuscular or axonal injury, but neither is sarcopenia-specific and both can be affected by neurological disease, renal function, physical inactivity, and ageing [23–27]. Inflammatory mediators such as IL-6, TNF- α , and CRP likewise lack disease specificity. Myostatin, activin A, follistatin, irisin, and metabolomic or lipidomic signatures remain research candidates whose assays, thresholds, and incremental clinical value require validation [27–29]. By contrast, PGC-1 α , MyoD, myogenin, MuRF1, and MAFbx/Atrogin-1 are most appropriately regarded as tissue-level or mechanistic markers in muscle or experimental systems rather than routine circulating diagnostic biomarkers. Their inclusion in translational studies may clarify mechanism, but it should not imply current clinical diagnostic utility (Table 2).

Table 2. Candidate biomarkers in sarcopenia research: biological domain, sample matrix, and current interpretive limitations.

Marker(s)	Biological Domain	Typical Matrix	Current Interpretation/Limitation
CAF; NfL	Neuromuscular/axonal injury	Serum or plasma	Mechanistic, risk, or prognostic candidates; limited specificity and important neurological/renal confounding.
IL-6; TNF- α ; CRP	Chronic inflammation	Blood	Nonspecific inflammatory markers; not diagnostic of sarcopenia.
Myostatin; activin A; follistatin; irisin	Endocrine/myokine signaling	Blood	Research candidates; assay standardization and validated thresholds are lacking.
Metabolomic/lipidomic panels	Systemic metabolism	Blood	Promising multianalyte signatures; require prospective validation and proof of incremental value.
PGC-1 α ; MyoD; myogenin	Mitochondrial biology/myogenesis	Muscle tissue; experimental systems	Predominantly tissue-level or mechanistic markers, not routine blood diagnostics.
MuRF1; MAFbx (Atrogin-1)	Protein degradation	Muscle tissue; experimental systems	Mechanistic markers of proteolytic signaling; not validated clinical diagnostic tests.
ROS-related markers	Oxidative stress	Blood and/or tissue	Biologically relevant but nonspecific and method-dependent.
Marker(s)	Biological domain	Typical matrix	Current interpretation/limitation

Abbreviations: CAF—C-terminal agrin fragment; NfL—neurofilament light chain; IL-6—interleukin-6; TNF- α —tumor necrosis factor-alpha; ROS—reactive oxygen species; PGC-1 α —peroxisome proliferator-activated receptor gamma coactivator-1 alpha; MyoD—myogenic differentiation 1; MuRF1—muscle RING finger protein 1; MAFbx (Atrogin-1)—muscle atrophy F-box protein.

Microbiota Potential

The gut–muscle axis is a biologically plausible contributor to muscle ageing, but current evidence is predominantly associative and heterogeneous. Sarcopenia has been associated with altered microbial diversity, differences in bacterial taxa, intestinal-barrier dysfunction, systemic inflammation, and reduced abundance of short chain fatty acid producing organisms [30–34]. These observations are influenced by diet, medications, geography, frailty, comorbidity, and physical activity, and no microbiome signature is validated as a diagnostic test for sarcopenia. Next-generation sequencing should therefore be regarded as a research tool rather than an established case-finding method. Probiotics, postbiotics, urolithin A, and fecal microbiota transplantation are being investigated as potential modulators of the gut–muscle axis, but evidence for clinically meaningful improvements in strength, power, or physical performance remains insufficient for routine therapeutic recommendations [30,35].

4. Sarcopenia as a Loss of Skeletal Muscle Homeostasis: Five-Pillar Framework

The five-pillar framework used here is an author-proposed translational heuristic rather than an established classification of sarcopenia. It organizes recurrent mechanisms into five overlapping domains: energy, structure, regeneration, neuromuscular control, and systemic communication. The model complements geroscience and hallmarks-of-ageing approaches, which emphasize interacting processes such as mitochondrial dysfunction, altered nutrient sensing, loss of proteostasis, cellular senescence, stem-cell exhaustion, inflammation, and impaired intercellular communication [9,10]. The pillars are not biologically discrete: mitochondrial dysfunction can modify inflammatory signaling and regeneration; inflammation can alter proteostasis and neuromuscular function; denervation changes mitochondrial demand and muscle-fiber phenotype; and endocrine or metabolic signals modify nearly every other domain. Accordingly, the framework is best interpreted as a network of bidirectional feedback loops rather than as five independent causal pathways (Figure 1). Its proposed translational value is to connect these mechanisms with the observable phenotype, reduced strength and power, low muscle quantity or quality, and impaired physical performance, while recognizing that no single pillar maps one-to-one onto a diagnostic criterion.

4.1. Energy Pillar—Mitochondrial Dysfunction and Oxidative Stress

Skeletal muscle depends on mitochondrial ATP production, metabolic flexibility, redox control, and mitochondrial quality control [5,36]. Ageing and clinically defined sarcopenia are associated with reduced mitochondrial content or function, impaired oxidative phosphorylation, altered mitochondrial dynamics, and increased oxidative stress, but the temporal and causal direction of these changes remains incompletely resolved [6,37]. Physical inactivity, denervation, malnutrition, chronic disease, and established muscle atrophy can themselves reduce mitochondrial demand and remodeling; therefore, cross-sectional mitochondrial abnormalities should not automatically be interpreted as initiating lesions. Excess reactive oxygen species (ROS) can damage proteins, membrane lipids, and mitochondrial DNA (mtDNA), while impaired mitochondrial renewal may reduce energetic reserve and contribute to fatigability [5–7,38]. Mitochondrial damage can also release mtDNA and other danger-associated molecular patterns. In experimental models, these signals may participate in NLRP3 inflammasome activation, which canonically promotes caspase-1-dependent maturation of IL-1 β and IL-18. TNF- α should not be considered a direct downstream product of NLRP3; instead, TNF- α is generated through broader inflammatory pathways and can activate NF- κ B and JNK signaling, thereby contributing

to catabolic responses and anabolic resistance [7]. Reduced PGC-1 α activity, impaired PINK1/Parkin-mediated mitophagy, and increased susceptibility to mitochondrial apoptosis provide additional candidate links between energetic failure and muscle decline [5,6,36]. Importantly, age-related alterations in autophagy and mitophagy are better described as dysregulated quality-control flux than as a uniformly increased or decreased process across all tissues and disease stages. Low vitamin D status is common in frail and sarcopenic populations, and VDR signaling can influence mitochondrial biology [7,39]. However, the association between vitamin D deficiency is strongly confounded by age, obesity, reduced outdoor activity, malnutrition, chronic disease, and functional limitation. Thus, mechanistic plausibility does not establish vitamin D deficiency as a defining causal component of sarcopenia. Collectively, mitochondrial abnormalities provide a plausible contribution to reduced energetic reserve, contraction velocity, endurance, and recovery, but the evidence supports an interacting and context-dependent mechanism rather than a universal unidirectional cause of sarcopenia (Figure 2).

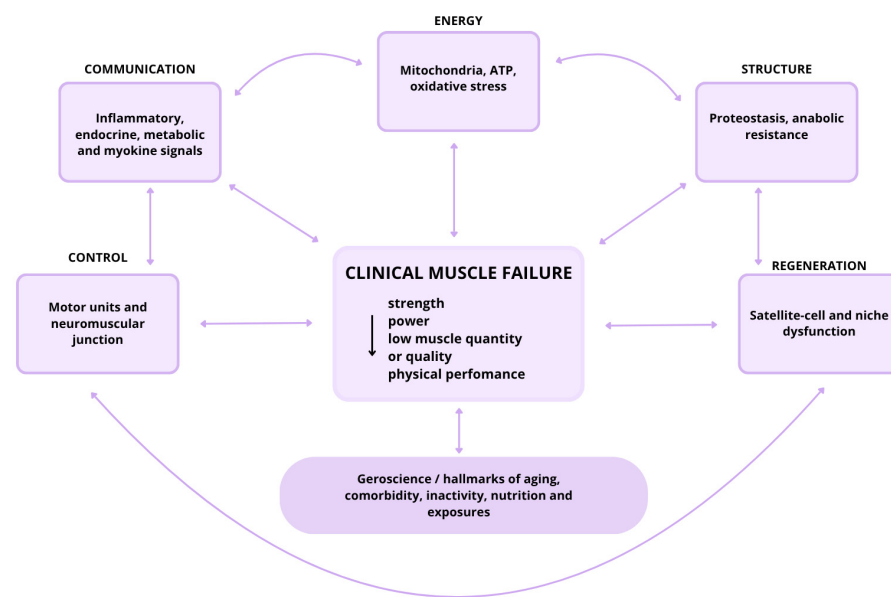


Figure 1. Integrated translational representation of the five-pillar framework. The five domains are overlapping heuristic lenses linked by bidirectional cross-talk and situated within broader geroscience, comorbidity, lifestyle, and exposure contexts. Clinical muscle failure emerges from their combined disruption rather than from a one-to-one mapping between a single pillar and a diagnostic criterion.

4.2. Structural Pillar—Impaired Muscle Proteostasis

Skeletal muscle proteostasis depends on the balance between protein synthesis, protein degradation, folding, repair, and organelle quality control [40,41]. In sarcopenia, net protein balance can shift toward loss, but this phenotype is heterogeneous and may reflect ageing, reduced mechanical loading, inadequate energy or protein intake, systemic inflammation, endocrine disease, hospitalization, or chronic organ failure rather than a single molecular defect [5,41]. Insulin and IGF-1 signaling through PI3K/Akt/mTORC1 participates in anabolic responses to nutrition and exercise. Ageing muscle frequently shows a blunted acute mTORC1 response to anabolic stimulation, contributing to anabolic resistance [5,42,43]. This should be distinguished from inappropriate or persistent basal mTORC1 activity in specific cellular contexts, which may inhibit autophagy. Basal signaling, stimulus-induced responsiveness, cell type, nutritional state, and timing are therefore critical when interpreting apparently opposing mTOR observations. Protein degradation is mediated in part by the ubiquitin–proteasome system (UPS). Reduced Akt signaling can permit nuclear translocation of FoxO transcription factors and increase MuRF1 and MAFbx/Atrogin-1

expression, while inflammatory pathways can further promote catabolic signaling [44–48]. Autophagy requires equally careful interpretation. Sarcopenic and ageing muscle may exhibit defective autophagic initiation, impaired lysosomal clearance, or reduced autophagic flux, leading to accumulation of damaged proteins and organelles; this is mechanistically different from excessive autophagic degradation [41,49,50]. These processes can coexist with increased UPS activity or other catabolic pathways. The clinically relevant result is not simply reduced muscle quantity but deterioration of myofibrillar integrity and muscle quality, which can contribute to loss of force generation and poorer functional reserve (Figure 3).

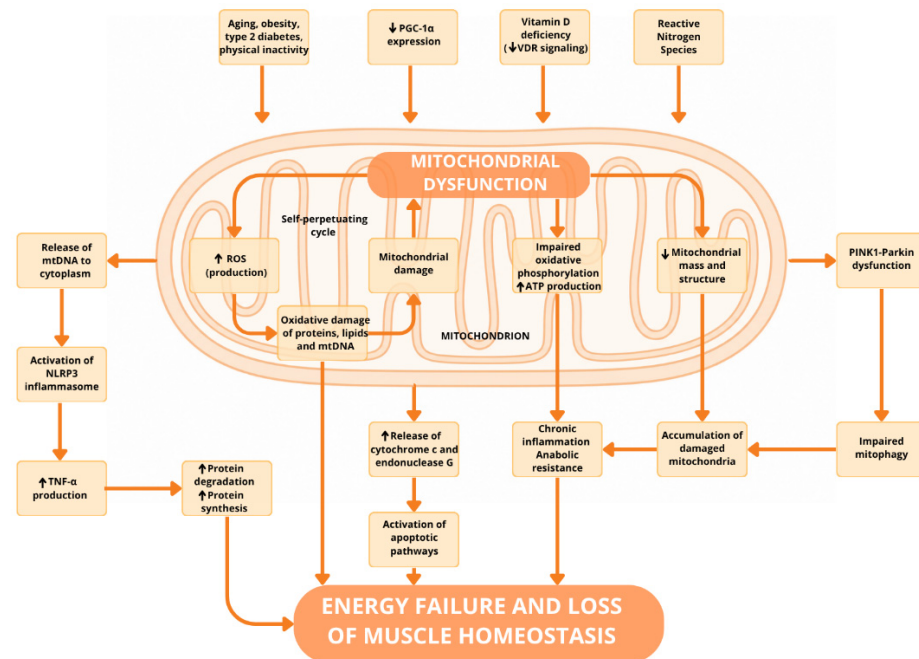


Figure 2. Schematic representation of the molecular mechanisms leading to mitochondrial dysfunction, energy failure, and loss of skeletal muscle homeostasis during sarcopenia. Abbreviations: PGC-1 α —peroxisome proliferator-activated receptor gamma coactivator 1-alpha; VDR—vitamin D receptor; ROS—reactive oxygen species; mtDNA—mitochondrial DNA; NLRP3—NOD-like receptor family pyrin domain-containing protein 3; TNF- α —tumor necrosis factor-alpha; ATP—adenosine triphosphate; PINK1—PTEN-induced kinase 1; Parkin—E3 ubiquitin-protein ligase Parkin.

4.3. Regeneration Pillar—Satellite Cell Exhaustion and Impaired Muscle Repair

Satellite cells (SCs) are resident skeletal muscle stem cells that contribute to repair and adaptation after injury or loading [5,51]. Their behavior cannot be reduced to a fixed binary sequence in which minor injury always induces asymmetric division and extensive injury always induces symmetric division. Division orientation, self-renewal, commitment, differentiation, and return to quiescence depend on injury severity, anatomical niche, extracellular-matrix composition, inflammatory signaling, mechanical loading, developmental stage, and experimental model [51–53]. Pax7 is important for maintenance of the satellite-cell pool, whereas MyoD and myogenin participate in myogenic commitment and differentiation. Ageing is associated with quantitative and functional changes in SCs, but the extent to which satellite-cell depletion is a primary driver of clinically defined sarcopenia versus a marker of the ageing tissue environment remains uncertain [5,53]. Several candidate regulators, including SIRT1/SIRT2-dependent pathways, p16INK4A, FGF2, AMPK/p27 signaling, autophagy, TGF- β , and JAK/STAT signaling, have been implicated in stem-cell ageing or impaired myogenesis [50–55]. Much of this evidence derives from experimental ageing models, isolated cell systems, or injury paradigms and should not

be presented as a single coordinated mechanism proven in humans with sarcopenia. The apparent discrepancy between reduced anabolic Akt/mTORC1 responsiveness in mature myofibers and persistent mTORC1 activity reported in some satellite-cell contexts further illustrates the importance of cell type, timing, and basal versus stimulus-induced signaling. Clinically, impaired regeneration is most plausibly expressed as reduced capacity to recover from illness, unloading, or injury and as progressive loss of muscle quality and reserve rather than as a stand-alone diagnostic feature (Figure 4).

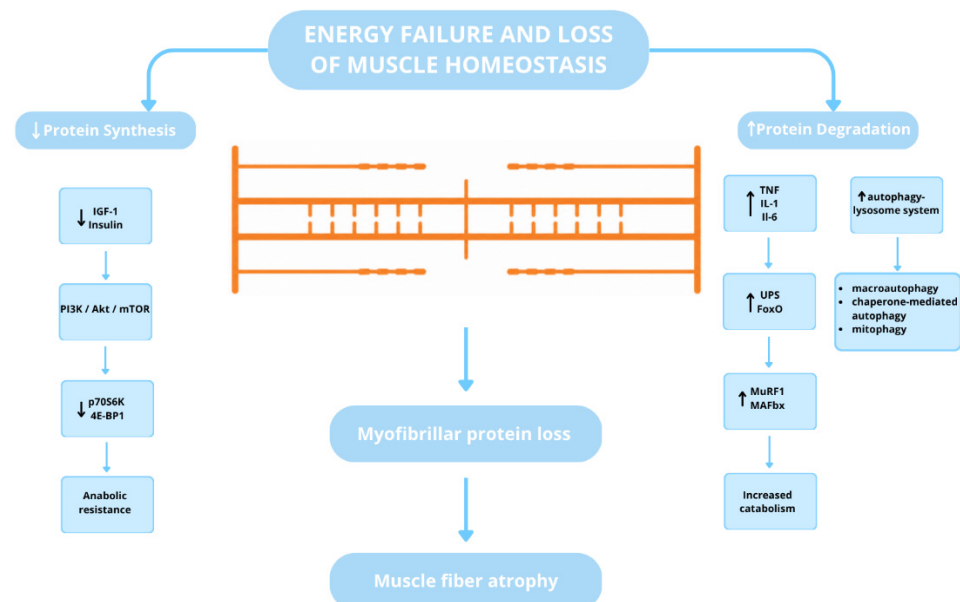


Figure 3. Schematic representation of the imbalance between muscle protein synthesis and degradation leading to proteostasis disruption and muscle fiber atrophy in sarcopenia. Abbreviations: IGF-1—insulin-like growth factor 1; PI3K—phosphoinositide 3-kinase; Akt—protein kinase B; mTOR—mechanistic target of rapamycin; p70S6K—70-kDa ribosomal protein S6 kinase; 4E-BP1—eukaryotic translation initiation factor 4E-binding protein 1; TNF—tumor necrosis factor; IL-1—interleukin-1; IL-6—interleukin-6; UPS—ubiquitin–proteasome system; FoxO—Forkhead box O transcription factors; MuRF1—muscle RING finger protein 1; MAFbx (Atrogin-1)—muscle atrophy F-box protein.

4.4. Control Pillar—Neuromuscular Degeneration and Loss of Muscle Power

Muscle function depends on the integrity of motor neurons, motor units, neuromuscular junctions (NMJs), muscle fibers, and central motor drive. Age-related motor-neuron loss, denervation, incomplete collateral reinnervation, NMJ remodeling, and preferential vulnerability of type II fibers can reduce the ability to recruit muscle rapidly and efficiently [5,23,56–59]. These changes provide a direct translational bridge from cellular ageing to the clinical phenotype: impaired motor-unit recruitment and contraction velocity may reduce muscle power before changes in muscle quantity become prominent, while progressive denervation and fiber atrophy contribute to reduced maximal strength, slower chair-rise performance, gait impairment, falls, and loss of independence [3,57,58,60]. Myosin isoform shifts and hybrid fibers are therefore clinically relevant primarily insofar as they reflect altered motor-unit identity, contractile velocity, and force production rather than as isolated histological phenomena. Circulating NfL and CAF have been studied as markers of axonal injury and agrin cleavage/NMJ remodeling [23–25]. However, NfL is a general marker of neuroaxonal injury and can be influenced by neurodegenerative disease, stroke, peripheral neuropathy, traumatic injury, renal dysfunction, and ageing; CAF may likewise be affected by neurological disease, renal clearance, inactivity, and denervation from other causes. Neither marker is sufficiently specific to establish sarcopenia or dis-

tinguish it reliably from frailty, dynapenia, neuropathy, or other causes of weakness [26]. Neuromuscular degeneration also interacts with mitochondrial stress, oxidative damage, inflammation, and reduced physical activity, creating bidirectional feedback rather than a separate linear pathway [5,7,61].

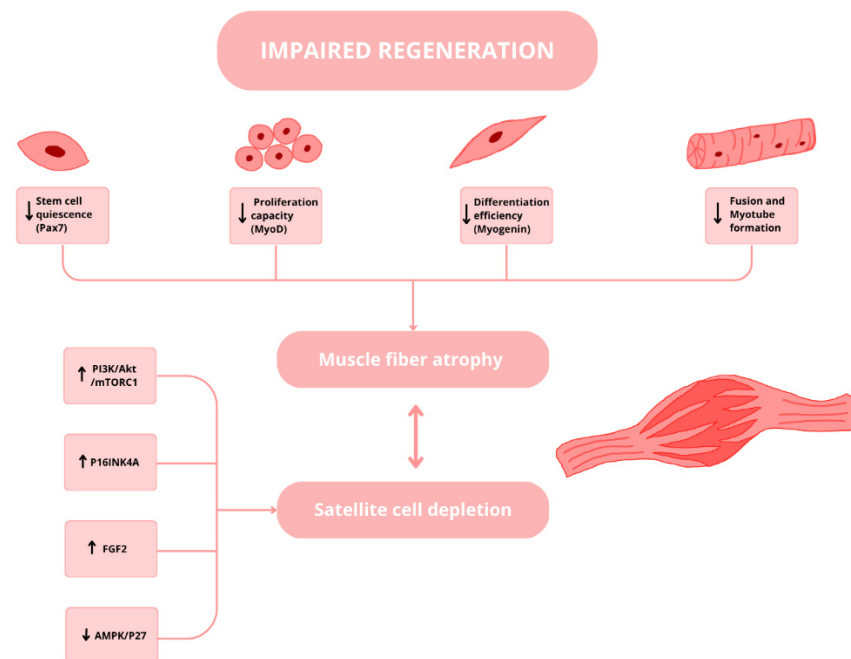


Figure 4. Schematic representation of satellite cell depletion, impaired muscle regeneration and progressive muscle fiber atrophy in sarcopenia. Abbreviations: Pax7—paired box protein Pax7; MyoD—myogenic differentiation 1; PI3K—phosphoinositide 3-kinase; Akt—protein kinase B; mTORC1—mechanistic target of rapamycin complex 1; p16INK4A—cyclin-dependent kinase inhibitor 2A (CDKN2A); FGF2—fibroblast growth factor 2; AMPK—AMP-activated protein kinase; P27—cyclin-dependent kinase inhibitor 1B (CDKN1B).

4.5. Communication Pillar—Inflammation, Hormonal Changes, and Metabolic Signaling

The communication pillar integrates endocrine, immune, metabolic, neural, adipose-tissue, gut-derived, and muscle-derived signals. Chronic low-grade inflammation (“inflammaging”) is associated with higher circulating TNF- α , IL-6, and CRP and can activate NF- κ B, STAT3, and related pathways that favor proteolysis and impair anabolic signaling [7,62–64]. These effects overlap directly with the structural and regenerative pillars, illustrating why the five domains should not be interpreted as independent. Myosteatosis, insulin resistance, hyperglycemia, and advanced glycation end products can further impair glucose utilization, mitochondrial function, tissue quality, and anabolic responsiveness [65,66]. Conversely, loss of muscle mass and activity can worsen whole-body glucose disposal, creating a bidirectional muscle–metabolic relationship. Age-related changes in testosterone, estrogens, GH, and IGF-1 may reduce anabolic support, but endocrine effects are heterogeneous and hormone replacement is not an established treatment for sarcopenia in the absence of an appropriate endocrine indication [56]. Skeletal muscle itself acts as an endocrine organ through myokines, and adipokines and gut-derived metabolites provide additional systemic signals. The clinically important consequence is the convergence of these pathways on reduced anabolism, increased catabolism, impaired tissue quality, and diminished neuromuscular reserve. Because the same inflammatory and metabolic signals also influence mitochondria, proteostasis, satellite cells, and the NMJ, communication is best viewed as a network-level modifier of all other pillars (Figure 5).

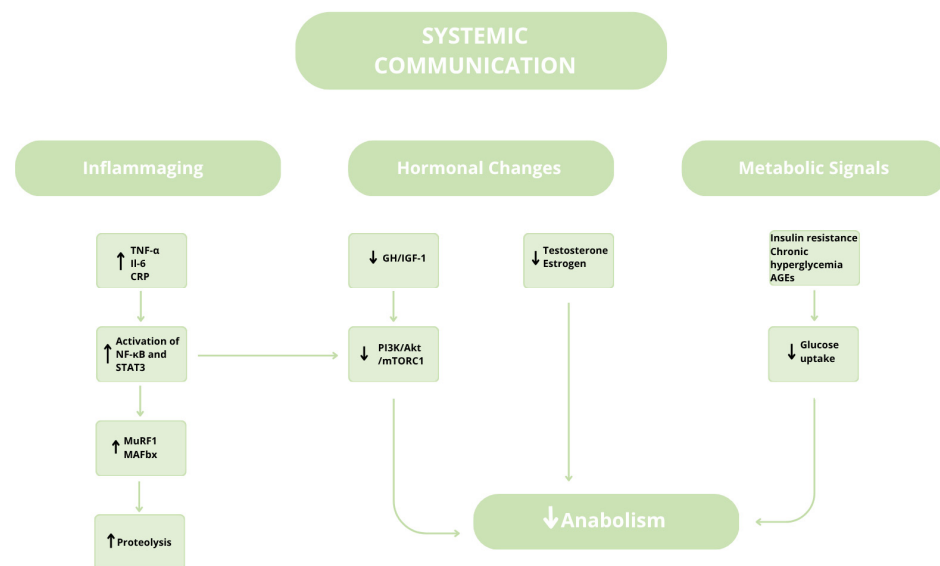


Figure 5. Schematic representation of the interactions between inflammatory, endocrine, and metabolic signaling pathways contributing to the loss of skeletal muscle homeostasis in sarcopenia. Abbreviations: TNF- α —tumor necrosis factor- α ; IL-6—interleukin-6; CRP—C-reactive protein; NF- κ B—nuclear factor kappa B; STAT3—signal transducer and activator of transcription 3; MuRF1—muscle RING finger protein 1; MAFbx (Atrogin-1)—muscle atrophy F-box protein; GH—growth hormone; IGF-1—insulin-like growth factor 1; PI3K—phosphoinositide 3-kinase; Akt—protein kinase B; mTORC1—mechanistic target of rapamycin complex 1; AGEs—advanced glycation end products.

5. Treatment

5.1. Physical Activity

Progressive resistance exercise is the best-established exercise intervention for sarcopenia and should be prescribed according to functional capacity, comorbidity, safety, and prior training experience [67,68]. A pragmatic program commonly targets whole-body exercise with emphasis on major lower-limb muscle groups approximately twice weekly; patients with very low baseline function may begin with one supervised session per week and progress as tolerated. A typical progression uses one to three sets of approximately 6–12 repetitions per exercise, beginning at moderate loads (around 40–60% of one-repetition maximum [1RM] or a comparable perceived-exertion range) and progressing toward higher loads (approximately 70–85% 1RM) when technique and tolerance permit, with at least 48 h of recovery between sessions [68]. Exercise selection, range of motion, volume, and progression should be individualized, and supervision is particularly important in frail patients or those with neurological, cardiovascular, or severe functional limitations. Resistance training can improve strength and functional performance through neural adaptation, muscle hypertrophy, and improved anabolic responsiveness. Combined programs may add balance and aerobic/endurance components to address falls, cardiorespiratory fitness, and mitochondrial capacity [67–70]. Once movement technique and safety are established, high-velocity or power-oriented resistance exercise can be considered because rapid force production is directly relevant to chair rising, stair climbing, and balance recovery. Mechanistic observations involving mTORC1, PGC-1 α , BDNF, agrin, or AChR expression are biologically informative, but evidence from animal models or healthy older adults should not be assumed to demonstrate the same mechanism in clinically diagnosed sarcopenia. Treatment success should therefore be evaluated across strength, power, gait or chair rise performance, falls, disability, adherence, and safety—not by increased muscle mass alone.

5.2. Nutritional Interventions

Nutritional treatment should correct inadequate energy and nutrient intake rather than rely on a universal single-dose protein threshold. ESPEN guidance recommends at least approximately 1.0 g protein/kg body weight/day for older adults, with intake individualized according to nutritional status, physical activity, disease, renal function, and tolerance; intakes around 1.0–1.2 g/kg/day are commonly suggested for healthy older adults and approximately 1.2–1.5 g/kg/day for many older adults with acute or chronic illness, provided that clinical circumstances permit [71]. Adequate total energy intake is essential because amino acids cannot efficiently support anabolism when energy requirements are not met. Oral nutritional supplements or protein-enriched foods can be used when usual intake is insufficient to reach individualized targets. Protein and resistance exercise have complementary but separable effects. Protein provides amino-acid substrate and anabolic signaling, whereas exercise provides mechanical and neural stimuli; the combination often produces greater benefit than either intervention alone, but changes in muscle protein synthesis should not be equated automatically with improvements in mass, strength, power, disability, or falls [72–76]. Leucine and leucine-rich proteins can activate mTORC1-related anabolic signaling, while HMB, creatine, vitamin D, and omega-3 fatty acids have been studied as adjuncts [74–79]. The clinical evidence is heterogeneous, and supplementation should be targeted to deficiency, inadequate intake, or a specific indication rather than presented as universally effective. In particular, vitamin D supplementation is appropriate to correct deficiency and support bone and muscle health, but it should not be framed as a stand-alone treatment that reliably reverses sarcopenia.

5.3. Pharmacotherapy

No pharmacological therapy currently substitutes for progressive exercise and adequate nutrition as routine treatment for sarcopenia. Interpretation of drug studies requires separation of regulatory status, clinical indication, change in muscle quantity, and patient-relevant functional outcomes. Testosterone can increase lean mass and strength in selected patients with documented hypogonadism, but it is not an approved treatment for sarcopenia itself and carries hematological, prostate, and cardiovascular considerations [80]. Selective androgen receptor modulators (SARMs) remain investigational and have unresolved hepatic and cardiovascular safety concerns [81]. Myostatin-, activin-, or ActRIIB-pathway inhibitors can produce substantial increases in lean mass, yet functional gains in strength, power, gait, or disability have often been smaller, inconsistent, or absent [82,83]. This dissociation demonstrates why lean mass should not be treated as a sufficient surrogate for clinically meaningful recovery. ACE inhibitors and β 2-adrenergic agonists have biological or observational rationale but are not established sarcopenia therapies; β 2-agonists are further limited by cardiovascular adverse effects [84–86]. Evidence regarding SGLT2 inhibitors and GLP-1 receptor agonists largely derives from populations treated for diabetes or obesity rather than trials targeting sarcopenia. Their effects on muscle quantity and quality must be interpreted alongside overall weight loss, cardiometabolic benefit, nutritional status, and physical function [87]. Future pharmacological trials should therefore report a common set of outcomes spanning muscle quantity/quality, maximal strength, muscle power, physical performance, falls, disability, patient-reported function, and safety rather than focusing primarily on anabolic changes in body composition.

5.4. Future Therapies

Regenerative and cell-free approaches remain investigational. Mesenchymal stromal/stem cells and cell-derived extracellular vesicles or exosomes can influence inflammatory signaling, myogenesis, mitochondrial biology, and intercellular communication in

experimental models [88–91]. However, the current evidence base is predominantly preclinical and does not establish clinically meaningful improvements in strength, power, mobility, disability, or other patient-important outcomes in sarcopenia. Exosome preparations are heterogeneous with respect to cell source, culture conditions, isolation and purification methods, cargo, potency, dose, biodistribution, and batch reproducibility. Potential off-target effects, immunogenicity, tumor-promoting effects, long-term safety, manufacturing standards, and regulatory requirements remain unresolved. These technologies should therefore be presented as research platforms requiring standardized production, mechanistic validation, dose-finding, and controlled clinical trials rather than as inherently targeted, immunologically safe, or readily standardized therapies.

6. Clinical Boundaries and Life-Course Modifiers of Muscle Health

The term sarcopenia should remain anchored to explicit operational criteria rather than being used as a synonym for any loss of muscle in modern populations. Ageing remains the dominant clinical context for validated sarcopenia definitions, while selected consensus frameworks now address defined middle-aged populations [2,92]. In children, adolescents, and many younger adults with chronic disease, reduced muscle mass or function may reflect growth failure, malnutrition, cachexia, treatment-related myopathy, disuse atrophy, endocrine disease, organ failure, or disease-specific muscle wasting [19–22,93–96]. These conditions can share biological mechanisms with sarcopenia without being diagnostically interchangeable. Physical inactivity, obesity, chronic inflammatory disease, diabetes, chronic kidney disease, cancer therapy, and other life-course exposures can accelerate muscle decline through reduced mechanical loading, inflammation, insulin resistance, energetic stress, and impaired regenerative reserve [8,68,92,94–100]. Sarcopenic obesity represents a specific example in which impaired muscle parameters coexist with excess adiposity and should be assessed using dedicated consensus criteria rather than body mass index alone [101–106]. Social and environmental determinants, including access to nutritious food, opportunities for physical activity, socioeconomic conditions, social isolation, and the built environment, may influence these exposures and thereby modify muscle-health trajectories. However, the available evidence does not justify treating “modern society” itself as a distinct causal category. A more clinically useful approach is to identify modifiable exposures and comorbid mechanisms while maintaining clear diagnostic boundaries between sarcopenia and other forms of muscle loss.

7. Conclusions and Future Perspectives

Sarcopenia is best understood clinically as muscle failure expressed across several related but distinct domains. Contemporary operational frameworks prioritize low muscle strength, use low muscle quantity or quality to confirm the diagnosis, and incorporate physical performance to characterize severity; muscle power provides an additional clinically meaningful dimension that warrants further standardization [1,3]. This hierarchy should guide interpretation of pathophysiology and treatment because changes in lean mass alone do not necessarily translate into improved force generation, movement velocity, mobility, or independence. The five-pillar framework proposed in this review is intended as a translational heuristic, not a validated disease classification. Energy failure, proteostasis disturbance, impaired regeneration, neuromuscular degeneration, and systemic communication are extensively interconnected and overlap with broader hallmarks-of-ageing and geroscience models [9,10]. The strength of evidence is not uniform across pathways: several molecular mechanisms are supported predominantly by experimental models, many human data are cross-sectional, and causal direction may vary with disease, inactivity, nutritional state, cell type, and timing. Future work should therefore test the

framework prospectively rather than assume that each pillar represents an independent causal mechanism. Diagnostic innovation also requires restraint. No circulating biomarker or microbiome signature currently replaces standardized assessment of strength, muscle quantity/quality, and physical performance. Candidate biomarkers should be evaluated according to intended use, matrix, specificity, reproducibility, and incremental value beyond conventional testing. Treatment should likewise prioritize patient-relevant functional outcomes. Progressive resistance exercise and adequate energy and protein intake remain the foundations of care, whereas pharmacological, microbiome-directed, stem-cell, and exosome-based strategies require stronger evidence of benefit in strength, power, mobility, falls, disability, and safety. A phenotype-first, mechanism-informed approach may therefore provide a more rigorous path toward personalized research and care while preserving the validated clinical boundaries of sarcopenia.

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