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DIAGNOSTIC CRITERIA OF SARCOPENIA: A NARRATIVE REVIEW FROM CLINICAL, BIOCHEMICAL, LABORATORY, AND EPIGENETIC PERSPECTIVES

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SUMMARY

Sarcopenia is a progressive, generalized skeletal muscle disorder characterized by accelerated loss of muscle mass, strength, and physical function. This narrative review comprehensively evaluates the diagnostic criteria for sarcopenia across clinical, biochemical, laboratory, and epigenetic domains. Clinically, diagnosis hinges on structured assessments such as grip strength protocols, physical performance batteries, and validated imaging techniques such as muscle ultrasound. Biochemically, chronic systemic inflammation—potentiated by cytokines and the NLRP-3 inflammasome—is identified as a critical pathophysiological driver of muscle catabolism. Laboratory advancements emphasize the utility of circulating metabolomic signatures in detecting early metabolic dysregulation, while epigenetic studies elucidate how cellular senescence and microRNA alterations drastically accelerate muscle aging, particularly in oncological and post-menopausal contexts. By systematically synthesizing evidence from exactly 15 selected high-quality peer-reviewed articles, this review identifies the current unmet need for a globally standardized diagnostic consensus. Bridging this gap requires the integration of multi-domain parameters to optimize early risk stratification and tailor therapeutic interventions.

KEYWORDS: Sarcopenia; Diagnostic Criteria; Inflammaging; Epigenetics; Metabolomics; Ultrasound; Muscle Atrophy.

INTRODUCTION

Sarcopenia represents a significant global health challenge, defined clinically as a progressive and generalized skeletal muscle disorder involving the accelerated loss of muscle mass and function. Historically, the definition of sarcopenia focused predominantly on muscle mass.[12] However, modern consensus guidelines, such as those from the European Working Group on Sarcopenia in Older People (EWGSOP2),[10] the Asian Working Group for Sarcopenia (AWGS),[11] and the Sarcopenia Definition and Outcomes Consortium (SDOC),[14] have rightfully shifted the primary diagnostic focus towards muscle strength and physical performance, given their superior predictive value for adverse clinical outcomes.

Despite these advancements, the extreme variability in operational definitions and cut-off values hinders the harmonization of clinical data. Standard clinical measures often fail to capture the underlying molecular and metabolic deterioration preceding observable functional decline. Consequently, there is an urgent need to integrate biochemical markers, metabolomic profiles, and epigenetic indicators into the standard diagnostic framework. The objective of this study is to systematically examine and synthesize the current diagnostic criteria for sarcopenia across a definitively selected corpus of literature.

Methods

A comprehensive literature search was conducted to identify relevant studies addressing the diagnostic criteria of sarcopenia from clinical, biochemical, laboratory, and epigenetic perspectives. The selection was restricted to English-language articles published in peer-reviewed journals. To ensure maximum congruence and focus, exactly 15 high-quality studies were ultimately selected and integrated into this review. The search identified an initial pool of 125 articles. After screening titles and abstracts, 80 were excluded. Full-text assessment of 45 articles led to the exclusion of 30 due to lack of specific diagnostic criteria focus. The 15 included articles comprise a mix of consensus guidelines, prospective cohort studies, systematic reviews, and translational in-vitro/in-vivo research. The selection process is detailed in the flow chart below.

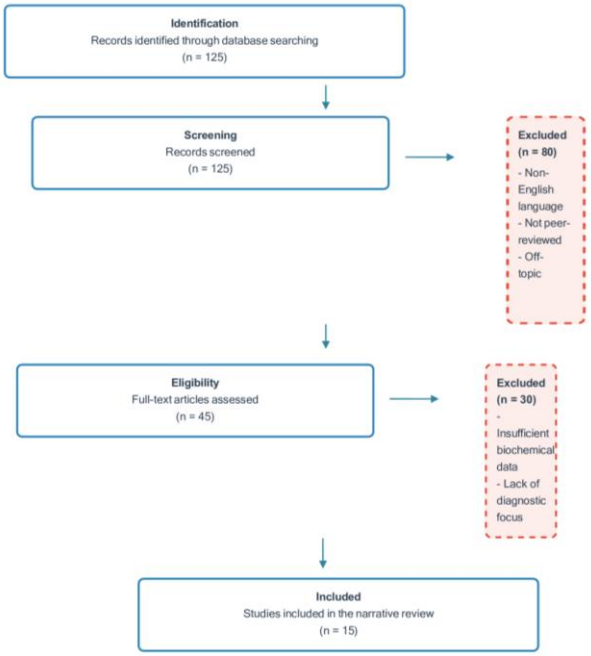

Fig. 1: Flow-Chart.

RESULTS

Clinical Perspectives

The clinical diagnosis of sarcopenia relies heavily on the triad of muscle strength, muscle mass, and physical performance.[10,11] Grip strength has emerged as a robust, easily applicable surrogate for overall muscle strength.

However, maintaining high reliability demands strict adherence to standardized protocols, encompassing specific participant posture and standardized dynamometry equipment.[9] The Foundation for the National Institutes of Health (FNIH) established robust, data-driven cut-offs linking grip strength and appendicular lean mass to incident mobility impairment, further refining diagnostic precision.[13] International clinical practice guidelines continue to endorse screening tools such as SARC-F followed by confirmatory strength and mass assessments.[15] To assess muscle mass, imaging techniques are indispensable. Recently, point-of-care nutritional ultrasound of the rectus femoris has been validated as a highly sensitive tool for detecting sarcopenia in hospitalized patients.[4] Specific cross-sectional area (CSA) and axis cut-off values have been established, allowing for rapid stratification of probable, confirmed, and severe sarcopenia.[4]

Biochemical Perspectives

Systemic low-grade inflammation, or "inflammaging," is a biochemical hallmark of sarcopenia. Elevated circulating levels of pro-inflammatory cytokines and advanced glycation end-products (AGEs) are consistently correlated with diminished muscle mass, particularly in metabolic conditions such as Type 2 Diabetes Mellitus (T2DM).[2]

Furthermore, the activation of the nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP-3) inflammasome significantly drives myocyte apoptosis and suppresses mitochondrial biogenesis, accelerating muscle catabolism.[5] Interventions targeting these pathways, such as soluble guanylate cyclase (sGC) activators like vericiguat, have demonstrated robust anti-sarcopenic potential by modulating MyD-88 and NLRP-3 cascades.[5] In oncological settings, tumor-induced systemic inflammation heavily accelerates epigenetic aging and muscle catabolism, leading to severe cancer-related sarcopenia.[7]

Laboratory and Epigenetic Perspectives

Laboratory assessments have expanded to include untargeted and targeted metabolomics. A distinct metabolomic signature—comprising 86 metabolites including alterations in branched-chain amino acids (BCAAs), specific lipid subclasses, and glycolytic intermediates—has been identified as a reliable tracking mechanism for muscle decline in postmenopausal cohorts.[1] Pathological states such as malignancies drastically accelerate this epigenetic aging process.[7] Animal models, specifically zebrafish, have corroborated these molecular findings, demonstrating that aging impairs the Akt/mTOR/p70s6k protein synthesis pathway and induces profound mitochondrial ultrastructural damage, perfectly mirroring the functional decline seen in human sarcopenia.[6]

Nutritional and Lifestyle Interventions

The bidirectional relationship between sarcopenia and metabolic disorders emphasizes that myosteatosis and insulin resistance operate in a detrimental feedback loop with muscle atrophy.[3] Consequently, lifestyle and nutritional interventions form the cornerstone of management. High adherence to a Mediterranean dietary pattern—rich in polyphenols, antioxidants, and polyunsaturated fatty acids—is prospectively associated with mitigating age-related muscle decline and preserving walking speed and physical performance.[8]

Comparison of the 15 Included Sources

First Author	Journal	Year	Cohort / Casuistry	Criteria Used	Results	Ref.
Zhang X	Maturitas	2026	68,064 postmenopausal women	EWGSOP2, NMR metabolomics	Identified an 86-metabolite signature predicting sarcopenia risk via lipid/amino acid dysregulation.	[1]
Johri N	J Diabetes Metab Disord	2023	Literature review (T2DM focus)	AWGS / FNIH definitions	Systemic inflammation and AGEs significantly compromise muscle strength and mitochondrial function.	[2]
Mesinovic J	Diabetes Metab J	2023	Review of older adults	EWGSOP / AWGS / SDOC	Established a bidirectional link between T2DM and sarcopenia, driven by myosteatosis and inactivity.	[3]
de Luis Roman D	Nutrients	2024	991 hospitalized patients	EWGSOP2, Rectus femoris US	Determined precise ultrasound cut-off values (e.g., CSA) yielding high sensitivity for severe sarcopenia.	[4]
Quagliariello V	Cancers	2024	In vitro (AC-16 & HSKMC)	Cellular and molecular assays	Vericiguat reduced apoptosis and inflammation by modulating the NLRP-3 and MyD-88 pathways.	[5]
Aranda-Martínez P	Int J Mol Sci	2024	Zebrafish (2 to 60 months)	Histology, TEM, Gene expr.	Revealed age-dependent disruptions in muscle ultrastructure, mitochondrial dynamics, and Akt/ mTOR.	[6]
Zhang FM	Ageing Res Rev	2023	Oncology populations	SARC-F, SARC-CalF	Cancer burden heavily accelerates epigenetic aging and systemic inflammation, hastening sarcopenia.	[7]
Dominguez LJ	Nutrients	2025	15,986 participants (9 cohorts)	EWGSOP / AWGS	High adherence to the Mediterranean diet correlates with preserved muscle mass and walking speed.	[8]
Fox B	JBI Database System Rev	2015	Systematic review	EWGSOP guidelines	Highlighted methodological variability; underscored the necessity of a standardized grip strength protocol.	[9]
Cruz-Jentoft AJ	Age Ageing	2019	Consensus review	EWGSOP2	Updated definition focusing on low muscle strength as the primary indicator of sarcopenia.	[10]
Chen LK	J Am Med Dir Assoc	2020	Consensus review	AWGS 2019	Provided updated algorithms tailored for Asian populations, enhancing diagnostic accuracy.	[11]
Rosenberg IH	J Nutr	1997	Editorial / Review	Early definition	Coined the term sarcopenia, establishing its clinical relevance regarding age-related muscle mass loss.	[12]
Studenski SA	J Gerontol A Biol Sci	2014	Pooled cohort analysis	FNIH criteria	Established data-driven cut-points for weakness and low muscle mass linked to clinical outcomes.	[13]
Bhasin S	J Am Geriatr Soc	2020	Consensus review	SDOC criteria	Position statement emphasizing functional outcomes over isolated muscle mass measurements.	[14]
Dent E	J Nutr Health Aging	2018	Clinical Guidelines	ICFSR guidelines	Issued international clinical practice guidelines standardizing sarcopenia screening and management.	[15]

DISCUSSION

The diagnosis and management of sarcopenia require a highly integrated approach due to the multifaceted nature of the disease. This review highlights that relying solely on physical and anthropometric measurements is insufficient for early diagnosis. The bidirectional relationship between sarcopenia and metabolic disorders emphasizes that myosteatosis and insulin resistance operate in a detrimental feedback loop with muscle atrophy.[3] Furthermore, oncological conditions and their subsequent treatments induce profound cachexia and secondary sarcopenia by heavily accelerating epigenetic aging, heightening somatic mutation frequencies, and sustaining systemic inflammation.[7]

At the molecular level, the disruption of mitochondrial bioenergetics and the activation of proteolytic pathways underscore the biochemical manifestation of sarcopenia. Experimental models provide crucial insights into how aging blunts the Akt/ mTOR anabolic pathway while severely damaging mitochondrial ultrastructure.[6] Addressing these biochemical aberrations is paramount for therapeutic development.[5] Concurrently, lifestyle modifications remain foundational. High adherence to a Mediterranean dietary pattern—rich in polyphenols, antioxidants, and polyunsaturated fatty acids—is prospectively associated with mitigating age-related muscle decline, combating oxidative stress, and preserving physical performance.[8] Ultimately, transitioning towards a multi-domain diagnostic algorithm that merges ultrasound imaging,[4] standardized strength protocols,[9] and omics-based laboratory tests[1] will drastically improve clinical phenotyping and targeted therapeutic administration.

CONCLUSIONS

Sarcopenia is a complex syndrome necessitating comprehensive diagnostic criteria that transcend traditional clinical assessments. While grip strength and muscle ultrasound offer highly practical and effective clinical screening tools, integrating biochemical inflammatory markers, specific metabolomic signatures, and epigenetic profiles is imperative for holistically capturing the pathophysiology of muscle decline. Future clinical frameworks must embrace a multidimensional diagnostic paradigm to facilitate earlier detection and the implementation of precise, personalized interventions.

Limitations

The primary limitation identified in current sarcopenia research is the persistent heterogeneity of diagnostic definitions across major international consortia (e.g., EWGSOP[10] vs. AWGS[11] vs. SDOC[14]), which leads to discrepancies in prevalence estimates and outcomes. While initiatives such as the Global Leadership Initiative in Sarcopenia (GLIS) strive for unification, the lack of universally standardized cut-off values for novel laboratory and ultrasound parameters currently limits their routine integration into everyday clinical practice.[4,9]

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Conflict of Interest

The authors declare no conflict of interest.

Institutional Review Board Statement

The study was approved by the Scientific Review Committee of Nefrocenter Research. with protocol code no. 135, 21 January 2026.

Dataset Generation

Not applicable. No datasets were generated or analyzed during this study.

Informed Consent

Not applicable.

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AI Declaration

No AI or similar technologies were used in the drafting of this manuscript.

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