Review

Defining and diagnosing sarcopenia: Is the glass now half full?

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A B S T R A C T

Low muscle mass and function exert a substantial negative impact on quality of life, health and ultimately survival, but their definition, identification and combination to define sarcopenia have suffered from lack of universal consensus. Methodological issues have also contributed to incomplete agreement, as different approaches, techniques and potential surrogate measures inevitably lead to partly different conclusions. As a consequence: 1) awareness of sarcopenia and implementation of diagnostic procedures in clinical practice have been limited; 2) patient identification and evaluation of therapeutic strategies is largely incomplete. Significant progress has however recently occurred after major diagnostic algorithms have been developed, with common features and promising perspectives for growing consensus. At the same time, the need for further refinement of the sarcopenia concept has emerged, to address its increasingly recognized clinical heterogeneity. This includes potential differential underlying mechanisms and clinical features for age- and disease-driven sarcopenia, and the emerging challenge of sarcopenia in persons with obesity. Here, we will review existing algorithms to diagnose sarcopenia, and major open methodological issues to assess skeletal muscle mass and function under different clinical conditions, in order to highlight similarities and differences. Potential for consensus on sarcopenia diagnosis as well as emerging new challenges will be discussed.

1. Introduction: skeletal muscle organ failure

Most organs and tissues allow for prolonged functional adaptation in the presence of damage and disease with loss of cell mass and functional impairment. Loss of as much as 10 % of skeletal muscle mass is however associated with higher risk of clinically relevant complications, including immune function impairment and higher risk of infection, particularly in the presence of other disease conditions [1,2]. Loss of approximately one third of skeletal muscle total mass is virtually incompatible with survival [1,2]. Changes in muscle function are not superimposable to those in mass, but these variables are commonly generally associated [3–8], potentially leading to impaired physical activity, disabilities, risk of falls and trauma and reduced autonomy. Most importantly, impaired skeletal muscle mass and function are very common in the general population and in most clinical conditions [9–11]. Indeed, decline of muscle mass and function may be a common and to some extent inevitable feature of the aging process, thereby affecting to different extent each aging individual. Age-associated loss of skeletal muscle mass and function are due to complex, synergistic age-associated derangements that will not be discussed in detail in this paper. They however include lifestyle modifications with low physical activity, low or inadequate calorie and protein intake, protein-catabolic systemic and muscle derangements including oxidative stress, pro-inflammatory cytokine profile and insulin resistance, as well as endocrine and neuro-muscular derangements [9]. Similar muscle-catabolic changes, as well as loss of appetite and low physical activity, most importantly virtually characterize any acute and chronic disease condition, that may therefore be also associated with muscle derangements independently of age [12–17]. Age-associated comorbidities may conversely further enhance the risk of muscle changes caused by both aging and disease, with higher risk for muscle loss and disabilities in older individuals with polymorbidity [3,18–20].

The term sarcopenia currently defines loss of skeletal muscle mass and function [4,9,10,18,21–23]. The term was introduced in 1989 by Rosenberg [24,25] and initially selectively indicated the age-related decline in lean body mass. Different diagnostic criteria and to some extent different definitions of sarcopenia have been used in clinical research, but despite discrepancies a strong negative impact of low

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muscle mass and function have clearly emerged. Negative clinical consequences indeed include frailty, disabilities and loss of autonomy with institutionalization [3,20,23] and increased mortality [26]. Low skeletal muscle mass may directly favor the onset of metabolic diseases by reducing glucose utilization, with higher risk of insulin resistance and type 2 diabetes [1,15,27]. Skeletal muscle is also a key, direct contributor to fitness and exercise capacity, and it plays an obvious role in respiratory function [16]. Sarcopenia may therefore be also associated with impaired fitness and functional parameters with direct negative impact on prognosis in cardiorespiratory conditions [16,28–30]. In addition and importantly, sarcopenia has been associated with higher morbidity and lower survival in the aging population and in a number of disease conditions and clinical settings at all ages [10,31].

From the above considerations, sarcopenia has emerged as a major

Table 1
Main sarcopenia definitions and diagnostic criteria. ALM: appendicular lean mass; ASM: appendicular skeletal muscle mass; BIA: bioelectrical impedance analysis; BMI: body mass index; BW: body weight; CfC: calf circumference; ChS: chair stands; DXA: dual energy X-ray absorptiometry; GtS: gait speed; h: height; HGS: hand grip strength; F: female; M: male; MM: muscle mass; SARC-F: Strength, Ambulation, Rising from a chair, Stair climbing and history of Falling screening test; SARC-CalF: SARC-F with CfC assessment; SPPB: Short Physical Performance Battery; TUGT: Timed Up-and-Go Test; WkT: Walk Test.

Panel	Definition of sarcopenia	Algorithm/diagnosis	Strength/functional tests cutoffs	Muscle mass tests cutoffs
ESPEN 2010	Condition characterized by loss of muscle mass and muscle strength	Combined presence of: 1) ↓Muscle mass 2) ↓Function (GtS or other well-established test)	4 m GtS < 0.8 m/s	MM/BW < 2 SD below the mean measured in young (18–39 years) subjects of the same sex and ethnicity
SCWD 2011	Syndrome characterized by reduction in muscle mass associated with limitation in walking, not resulting from specific pathologic conditions or cachexia	Combined presence of: 1) ↓Function (WkS)[a] 2) ↓Muscle mass (ALM/h2)	GtS ≤ 1 m/s or 400 m WkT ≥ 6 min	ALM/h^2 < 2 SD below the mean measured in healthy young (20–30 years) subjects of the same ethnicity
IWGS 2011	Age-related loss of muscle and function. Is a complex syndrome that is associated with isolated loss of muscle mass or associated with increased fat mass	Diagnostic steps: 1) Case finding: specifically consider patients who are bedridden, cannot independently rise from a chair, or ↓GtS 2) Assessment: perform DXA 3) Diagnosis: ↓muscle mass + ↓GtS	GtS < 1 m/s	by DXA, using currently validated definitions, e.g.: ASM/h^2 ≤ 7.23 kg/m^2 M, ≤5.67 kg/m^2 F
FNIH 2014	Functional limitation in the presence of reduced weakness (reduced strength) as a consequence of reduced muscle mass	Diagnostic steps: 1) Suspect: poor physical function 2) Assessment: ↓strength (HGS) 3) Diagnosis: ↓strength + ↓lean body mass (ALM/BMI)	HGS (recommended) <26 kg M, <16 kg F HGS/BMI (alternate) <1.0 M, <0.512 F	ALM/BMI (recommended) < 0.789 M, <0.512 F ALM (alternate) < 19.75 kg M< 15.02 kg F
AWGS 2019	Age related loss of muscle mass, plus low muscle strength, and/or low physical performance	Diagnostic steps: 1) Suspicion/assessment Primary healthcare/community setting: a) Case finding: ↓muscle mass (CfC) or ↑SARC or SARC-CalF b) Assessment (possible sarcopenia): ↓strength (HGS) or ↓physical performance (ChS, WkSp, SPPB) Acute to chronic healthcare/clinical research setting: Case finding: clinical condition[b] or ↓muscle mass (CfC) or ↑SARC or SARC-CalF; proceed to diagnosis 2) Diagnosis (all settings): combined presence (consecutive diagnostic steps) of: ↓ strength (HGS), then ↓ Physical performance (WkSp, ChS, SPPB), then ↓ASM 3) Staging Sarcopenia: ↓muscle mass + ↓strength OR ↓performance Severe Sarcopenia: ↓muscle mass + ↓strength AND ↓performance	CfC <34 cm M, <33 F SARC-F ≥ 4 SARC-CalF ≥ 11 HGS <28 kg M, <18 kg F ChS (5-rises) ≥ 12 s 6m GtS < 1.0 m/s SPPB: ≤9	ASM < 7 kg/m^2 M, <5.4 kg/m^2 F (DXA); <7 kg/m^2 M, <5.7 kg/m^2 F (BIA)
EWGSOP 2019	Progressive and generalised skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality	Diagnostic steps: 1) Case finding: SARC-F or clinical suspicion 2) Assessment (probable sarcopenia): ↓strength (HGS, ChS) 3) Diagnosis: ↓strength + ↓muscle quantity or quality (ASM, ASM/h^2) 4) Severity: diagnosis + ↓physical performance (GtS, SPPB, TUGT, WkT)	HGS < 27 kg M, <16 kg F ChS (5-rises) > 15 s GtS ≤ 0.8 m/s SPPB ≤ 8 TUGT ≥ 20s 400m WkT ≥ 6 min	ASM < 20 kg M, <15 kg F ASM/h^2 < 7.0 kg/m^2 M ASM/h^2 < 5.5 kg/m^2 F

[a] The person should also have a limitation in mobility should not be clearly attributable to the direct effect of specific disease.
[b] Any of the following: functional decline or limitation, unintentional weight loss, depressive mood, cognitive impairment, repeated falls, malnutrition, chronic conditions/diseases.

and common clinical threat, and it has been appropriately included in the International Classification of Disease in 2016 [32]. Awareness of the importance of routinely assessing skeletal muscle mass and function in at risk individuals in clinical practice has been however, unfortunately, generally low. Patient identification and treatment of sarcopenia should be relevant clinical priorities, but they are not commonly and systematically implemented. To this regard, lack of universally accepted sarcopenia definition and diagnostic criteria represent obvious major hurdles, since different approaches are currently proposed, with different methodologies and resulting in confusing discrepancies. In the current review, we will summarize existing tools to diagnose sarcopenia, focusing on their similarities and differences as well as the potential for current and future implementation. We will also comment on major open methodological issues in assessment of skeletal muscle mass and function based on the existing diagnostic tools. Finally, we will discuss potential areas for further refinement of the sarcopenia concept.

2. Sarcopenia definition and diagnosis: are we filling the glass?

Several sarcopenia definitions and diagnostic criteria are currently available. Approaches introduced at the time of appearance of the sarcopenia concept, that focused on muscle mass, are still compared to more recent ones that have been mainly proposed by international consensus groups or scientific societies. These include the European Working Group on Sarcopenia in Older People (EWGSOP), the Asian Working Group on Sarcopenia (AWGS), the International Working Group on Sarcopenia (IWGS), the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project and the subsequent Sarcopenia Definition and Outcome Consortium (SDOC), the Society on Sarcopenia Cachexia and Wasting Disorders (SCWD) and the ESPEN Special Interest Groups on cachexia-anorexia in chronic wasting diseases and nutrition in geriatrics (Table 1). Whereas different available tools are a potential source of misunderstanding and potentially confusion, development of several proposals reflects increasing interest in the concept of sarcopenia and has led to undeniable enhancement of attention, awareness and clinical research. Common features and differential approaches will be described and discussed here. Since EWGSOP and AWGS updated their algorithm in 2019 [21,23], for the purpose of the current paper we will analyze the more recent versions which will be defined as EWGSOP2 and AWGS2019, with comparisons with previous versions when considered useful.

2.1. Muscle mass

The original definition of sarcopenia explicitly referred to an age-related decline of lean body mass, and sarcopenia has been initially identified in clinical research through low skeletal muscle mass in affected individuals. Different surrogates of whole-body skeletal muscle mass have been however proposed, due to inability of available methodologies to routinely selectively measure whole-body skeletal muscle tissue. Surrogates include lean body or fat-free mass, with skeletal muscle tissue included with other non-muscle components. More direct or approximate measures of specific muscle areas or muscle groups could conversely be obtained by various methods, but assumptions are needed to use their changes as a marker of altered muscle mass at whole-body level. Availability of methodologies and technical approaches have largely influenced selected muscle indexes in research. Clinical and pathophysiological considerations also affected selection and interpretation; in particular, lower limb muscle has been considered to be particularly relevant due to its key role in locomotion and therefore in preserving physical performance and autonomy, key clinical parameters affected by sarcopenia. Due to the above considerations, appendicular skeletal muscle mass (ASMM), and its surrogates appendicular lean mass (ALM) or the more recently defined appendicular soft lean tissue by DXA, has been introduced as reference surrogate of whole-body skeletal muscle mass in most diagnostic algorithms [4,18,22,23,33]. Muscle mass is included in all major definitions, albeit with different priority in diagnostic algorithms. Notably, SDOC questioned the validity of available methods and did not reach consensus on a gold standard methodology to assess lean mass, and therefore represents an exception by not including muscle mass in its current sarcopenia definition [34].

2.2. Muscle function

All structured proposals for sarcopenia definition and diagnosis recommend association of low skeletal muscle mass with indexes of muscle function or physical performance, which also includes muscle function but is influenced by neurological and cardio-respiratory components. EWGSOP2 and AWGS2019 as well as FNIH and SDOC propose inclusion of muscle function, with handgrip strength as functional parameter [4,21,23,34]. EWGSOP2 and AWGS2019 also include physical performance at various stages of sarcopenia diagnosis, while IWGS, SCWD and the ESPEN SIG only include physical performance without muscle strength. The shift to include and in some cases prioritize skeletal muscle function parameters in sarcopenia diagnosis, along with muscle mass, has several reasons. It has clearly emerged over the years that low skeletal muscle mass is associated with function, but this relationship may be altered in various conditions, including the aging process [35]. Systematic reviews have interestingly reported higher prevalence of sarcopenia using low muscle mass as only diagnostic criterion, compared to those observed when both low mass and function are required [36], potentially suggesting earlier appearance of muscle mass decline, which could only later lead to functional impairment. It is also possible that methodological issues contribute to discrepancies since, as discussed above, only indirect methods for muscle mass assessment are currently available, and they may not directly measure muscle groups involved in functional assessment [37,38]. Finally and importantly, introducing low muscle function in sarcopenia diagnosis allows for direct evaluation of clinically significant health outcomes with significant prognostic value. Indeed low muscle function has overall emerged as a better predictor of negative outcomes than muscle mass assessed by different methods [39–42].

2.2.1. Low muscle strength as preliminary diagnostic criterion – cause for probable-possible sarcopenia

Due to its clinical relevance, two major consensus diagnostic proposals (EWGSOP2 and AWGS2019) have not only included muscle strength in the diagnostic process, but they also recommended it as a preliminary first step. In this algorithm, assessment of muscle mass is therefore only recommended if low muscle strength is first confirmed. Moreover, both EWGSOP2 and AWGS2019 indicate low muscle strength as sufficient reason to trigger investigation into potential causes of muscle functional impairment (such as lifestyle, disease and potentially follow-up reassessment) and to start intervention [23,33]. In particular, EWGSOP2 proposes that low muscle strength per se is defined as “probable sarcopenia”, while AWGS2019 proposes the definition of “possible sarcopenia”. Notably, the proposed sequence of measurements implies that low muscle mass per se is not sufficient for sarcopenia diagnosis. No hierarchy between function and mass criteria is proposed by other consensus initiatives.

2.3. Physical performance

Different definitions are available for physical performance. A most pertinent description in the context of sarcopenia may be an “objectively measured whole-body function related to locomotion” [23]. In practice, physical performance involves skeletal muscle function but may be significantly influenced by other functional domains including neurological ones and potentially cardio-respiratory function for prolonged walking tests, which are however not commonly recommended. There is good agreement on accepting different tools to assess physical performance, which include gait speed, chair-stand test or the Short Physical

Performance Battery (SPPB) [10,18,21–23]. Physical performance tests have been included in all consensus sarcopenia diagnostic proposals, although with different roles and significance. IWGS, SCWD, SDOC and the ESPEN SIG approaches recommend slowness detected at walking tests associated with low muscle mass as one of two diagnostic criteria [10,18,22,34]. The 4- or 6-meter walking test (EWGSOP2010, IWGS) [22,43] or the 5 time chair stand test (AWGS2014) [33], have been also considered as potential screening, suspicion or assessment tools. They are still included for preliminary assessment before confirming diagnosis with body composition techniques by the AWGS (AWGS2019) [21], and were recommended by the guidelines developed in 2018 by the task force of the International Conference on Sarcopenia and Frailty Research ICFSR [44]. An alternative concept seems to also emerge from revisions of EWGSOP and AWGS, with physical performance proposed in EWGSOP2 as a determinant of sarcopenia severity to be assessed after diagnosis through gait speed and SPPB [23], and not for early steps of the diagnostic algorithm [23]. Notably the EWGSOP2 proposal included the chair-stand test as a proxy of leg strength as an alternative to handgrip strength [23]. The AWGS2019 proposal also introduced a potential role of impaired performance in assessing disease severity, with severe sarcopenia resulting from simultaneous presence of low muscle mass, strength and performance, as opposed to sarcopenia with low muscle mass and either low strength or low performance [21].

Overall, low physical performance appears to be an important component of the sarcopenia phenotype, with a potential debate on whether it should be considered a marker of more advanced clinical conditions where sarcopenia has already compromised whole-body functions, or still a component of initial screening and assessment.

2.4. Sarcopenia screening

In the context of the diagnostic process, most consensus proposals describe conditions for suspicion of sarcopenia that should trigger the full diagnostic procedure. They could emerge from the clinical setting or as patient complaint, but they should be also actively investigated in the context of a systematic sarcopenia screening process. Sarcopenia suspicion factors from clinical history include weakness or general functional decline and history of falls (EWGSOP2, AWGS2, IWGS, SCWD) [18,21–23]. Negative health events including acute and chronic disease and hospitalizations are also considered as risk and suspicion factors (AWGS2, IWGS) [21,22], and specific conditions such as cancer are explicitly mentioned in other consensus documents (SCWD) [18]. The latter disease-based approach is relevant in expanding the concept of sarcopenia from geriatric syndrome to potential consequence of many disease conditions at any age. Besides clinical history, several tools have been proposed to assess potential risk for sarcopenia. Most common ones are questionnaires focusing on functional status, with SARC-F included in most current algorithms [21,23], based on five scored items including history of falls and four subjectively assessed parameters [45]. SARC-F has been validated as predictor of functional outcomes and sarcopenia per se in large cohorts [45–47] with good specificity although its sensitivity has been inevitably low [48,49]. An additional approach includes anthropometric assessment of calf muscle mass with calf circumference, as well as mixed approaches combining questionnaires and calf circumference. Calf circumference alone has been demonstrated to predict important clinical outcomes in large cohorts [50], as well as diagnosis of sarcopenia [51–53]. Mixed tools with association of calf circumference and questionnaires include SARC-calf [54–56] and Ishii test [56–58], and combination tools appear to yield more accurate prediction of sarcopenia at least in specific settings [55,57,59–61].

2.4.1. "Screening" or "case finding"?

Early suspicion factors leading to the full diagnostic process have generally been reported to have good specificity, but almost inevitably low sensitivity, with a variable but generally large proportion of individuals identified as non-sarcopenic at the end of the diagnostic process [49,62]. Improving sensitivity without reducing specificity is a challenge which should be addressed by future clinical research. Given the clinical, personal and socio-economic burden of sarcopenia, a wide screening approach has however the potential to remain cost-effective, particularly in the presence of relatively simple early stages of sarcopenia assessment through functional tests. To further define this concept, EWGSOP2 and AWGS have strongly supported the expression "case finding" to replace "screening", thereby underscoring the primary goal to elicit awareness of sarcopenia and self-reported suspicion factors among at-risk individuals and involved healthcare professionals, with priority on specificity rather than sensitivity.

2.5. Summary (Table 1)

Various proposals for translation of the sarcopenia concept in clinical practice have become available in the last 15 years. Differences in constructs and components of the diagnostic algorithm have led to inevitable discrepancies, whose detailed analysis is beyond the scope of the current paper. Nevertheless, similarities are also substantial and have contributed to build an important foundation for enhancement of awareness of sarcopenia, as an important organ failure characterized by reduced skeletal muscle mass and function, leading to impaired physical performance with substantial impact on patient outcomes in most disease conditions. EWGSOP2 and AWGS2019 also aimed at proposing a structured stepwise approach for implementation in clinical practice, emphasizing and proposing criteria for case finding, preliminary assessment of muscle function, final diagnosis with muscle mass followed by severity staging involving physical performance (Fig. 1). Several scientific Societies have endorsed these approaches [9,23], and their use in clinical research appears to be growing. On the other hand, relevant issues remain to be defined and require further consensus efforts.

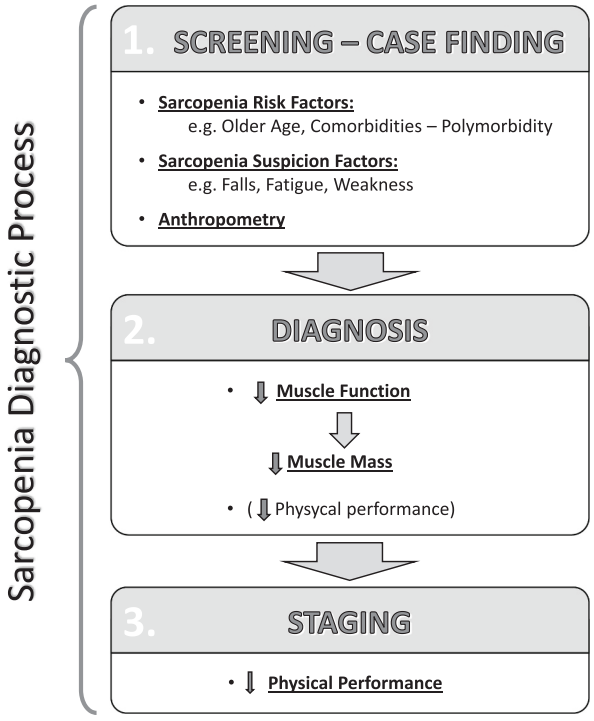

Fig. 1. Summary of potential consensus features for sarcopenia diagnosis from existing algorithms, with particular regard to EWGSOP2 and AWGS2019 structured indications for the screening-case finding, diagnostic and staging steps. Physical performance is included in both the Diagnosis and Staging sections, due to remaining discrepancies on this topic.

3. Sarcopenia diagnosis: methodology and open questions

As mentioned above, different constructs and algorithms make it inevitable that relevant discrepancies emerge when comparing different approaches for sarcopenia diagnosis. Constructs only including skeletal muscle mass may lead to higher estimates of sarcopenia prevalence [63,64]. Constructs including both mass and function however also show significant variability when compared for sarcopenia prevalence [64]. The current review does not aim at quantitative comparisons between diagnostic approaches, also considering that no construct is currently considered as gold-standard benchmark. It should be however pointed out that despite quantitative discrepancies, different criteria may show very good agreement in ruling out sarcopenia [64,65]. Diagnosing sarcopenia through different approaches is conversely generally associated with good ability to predict negative outcomes including disabilities, morbidity and mortality in different clinical settings [26,66]. Increasing consensus on sarcopenia definition and diagnostic algorithms has of course strong potential to reduce discrepancies and variability, and consensus initiatives involving experts and scientific societies should be sought and may indeed be underway [67].

Fundamental methodological hurdles however also contribute to variability, and should be considered for parallel work to progress towards accurate assessment of sarcopenia. Whereas tools for measuring muscle strength (handgrip strength) or assessing physical performance (gait speed, SPPB, TUG) are accepted with good agreement by the major diagnostic approaches, various alternatives are proposed for muscle mass, reflecting methodological problems and uncertainties.

3.1. Measurement and assessment of skeletal muscle mass

As also introduced above, measurement of total skeletal muscle mass is inherently complex with available techniques, and it has been a limiting factor in implementation of sarcopenia diagnostic algorithms in clinical practice. There is currently no agreement on gold-standard methodologies among those available for reasonable implementation in routine clinical settings, and balancing methodological accuracy and availability for clinical practice has been difficult [68]. Whole-body approaches are inherently unable to directly measure skeletal muscle mass, and surrogates including lean body mass, fat-free mass, lean soft tissue are commonly used, requiring various assumptions [68]. The D3-creatine dilution method has been proposed to isotopically identify muscle tissue and could represent a potentially accurate method to measure total muscle mass [69,70] but its routine, large-scale implementation in clinical practice appears to be problematic. Specific muscle sections may be more directly measured, for instance by computerized tomography or ultra sound for psoas muscle area, or indirectly assessed, for instance by anthropometry for calf and arm muscles [68], but such "pars for all" methods imply assumptions for extrapolation to whole-body muscle mass.

Sarcopenia diagnostic algorithms that explicitly recommend methodologies for muscle mass assessment focus on DXA, BIA and CT scans [18,21–23]. Dual-energy X-ray absorptiometry (DXA) is considered to provide the best approximate for muscle mass, and to be appropriate for clinical implementation, due to its ability to dissect bone tissue, to measure regional body composition, and its being already available for bone density measurement in clinical practice. DXA is however also unable to directly measure muscle tissue, and its results are currently referred to as "lean soft tissue". Appendicular skeletal muscle mass, assessed by DXA-measured appendicular lean mass or appendicular lean soft tissue [71,72], is well validated for predicting poor clinical outcomes [29,73], and for the above combined reasons it has been considered in some studies a semi-gold standard to compare alternative assessment methods [23,71,74], although its results may be affected by body thickness, position, and hydration status. Bioelectrical impedance analysis (BIA) relies on equations and assumptions for measuring fat mass and estimating fat-free mass (FFM) [23,72]; equations may also differ in different devices. Clinical limitations also need to be considered, including the presence of hyper- or hypo-hydration, but several studies supports predictive value of BIA outcomes [75,76], and its availability for routine clinical practice also in outpatient settings makes it likely to help large-scale implementation [72]. Multi-frequency BIA is less limited by fluid balance and is explicitly recommended by the AWGS2019 [21]. CT scans may provide accurate direct measurement of selected muscle areas with appropriate standardization, at the level of the L3 vertebra, at mid-thigh, or focusing on psoas muscle [72], generally associated with strong prediction of clinical outcomes [77,78]. In addition, and at variance with DXA and BIA, CT may provide direct information on muscle density which mainly reflects lipid deposition and therefore may be a marker of muscle quality [68,79]. CT is however limited to patients undergoing examination for reasons other than sarcopenia diagnosis, making it unfit for large scale utilization, for instance in the general aging population. Ultrasound is an emerging methodology with potential for large availability in various clinical settings, and it has been considered in the more recent EWGSOP and AWGS papers [21,23], but deemed still in need of standardization before recommendation for sarcopenia diagnosis.

3.2. Anthropometry: screening or diagnosing?

Surrogates of skeletal muscle mass can be also derived from anthropometry, particularly from mid-arm and calf circumferences [72,80]. Their simplicity makes them particularly attractive for clinical use, where they could be implemented with minimal training also by non-specialized personnel [72]. For these reasons anthropometry has been included in sarcopenia diagnostic proposals for screening and case-finding [21,53]. However, muscle mass assessment by anthropometry and particularly calf circumference has been also shown to be associated with more refined, semi-gold standard methodologies. Good correlations have been reported indeed between calf circumference and DXA-measured appendicular lean mass in the NHANES 1999–2006 cohort, with related good prediction of clinical outcomes [50]. Among available diagnostic approaches, however, calf circumference remains included only in screening and case-finding steps, and it has been only introduced as muscle mass proxy by EWGSOP2 when no other assessment is available [23]. However and importantly, more recent guidance papers for muscle mass assessment in the context of malnutrition diagnosis reached global consensus in recommending that anthropometry be considered and encouraged for assessing skeletal muscle mass in the absence of technical devices, or when expertise to use them and interpret their results is missing [68]. Further evaluation of the potential role of anthropometry and calf circumference in sarcopenia diagnosis could be included in future refinement of consensus initiatives.

3.3. Standardization of results and cut-offs

Besides methodological issues, lack of consensus also involves standardization of results. Firstly, muscle mass is correlated with body size, and the issue of adjustment of SMM or ASM for body mass or height needs to be addressed. Among major available proposals, most include adjustment for height squared [64,72,81]. However adjustment for body mass index (BMI) is presented by FNIH, and EWGSOP2 does not recommend adjusted- over non-adjusted measurements [4,23]. An additional fundamental issue is definition of cut-offs for parameters to be recognized in the sarcopenia range as opposed to normality. Whereas the latter represents a key step in defining any disease condition, cut-offs for sarcopenia diagnosis have been a source of debate and remain to some extent uncertain [9]. Methodological complexity makes muscle mass cut-offs more difficult to standardize, although proposed sex-dependent cut-offs for ASM/height2 from commonly endorsed techniques DXA and BIA seem remarkably similar, with differences well within the 10 % or even 5 % range [22,23,64]. Also remarkably, variability in cut-offs from relevant Asian studies summarized by the recent

AWGS paper was mostly <5 % with DXA and BIA [21], and quite comparable to values suggested by EWGSOP2 from the European perspective, and previously by IWGS [22,23]. Indeed cut-offs for strength and performance tools such as handgrip strength and gait speed during a 4-meter walking test are less numerous. Most proposals indicate 0.8 m/s for speed [10,23] with alternatives including 1 m/s [18,21,22]. Grip strength cut-offs for HGS were 28, 27 or 26 kg for men in AWGS, EWGSOP2 or FNIH respectively, and 18 or 16 kg for women in AWGS or EWGSOP2-FNIH.

The above considerations and results may justify a fundamental question on whether seeking further improvements in accuracy and reduction of error size may be cost-effective, against the risk of delaying implementation of sarcopenia diagnosis in clinical practice due to potential confusion from different recommendations. This issue becomes even more relevant when considering that samples and cohorts to determine normality are also inherently subject to variability, and may never provide a universally valid normality cut-off [82]. A proposal to simplify cut-off approaches has been made by EWGSOP2 that suggested rounded numbers for simplicity, indicating that losses in accuracy could be balanced by enhanced implementation and therefore identification and potential treatment of more and more affected individuals [23]. It should also be pointed out that finalizing consensus on well-tested methodologies should not exclude, but rather should allow to focus research and resources on standardization and cut-off definition for more novel methods, thereby expanding available tools and further promoting clinical implementation, such as ultrasound [23,72,83]. In addition and importantly, simplified universal consensus approaches could be more appropriate for better investigated areas such as aging, whereas assuming validity of cut-offs generated in aging populations in the context of acute and chronic disease-induced sarcopenia at earlier ages could be risky, and further investigation should be in well-selected disease-specific cohorts.

3.4. Muscle quality: future fourth criterion?

As discussed, accepted criteria for diagnosing sarcopenia in clinical practice are muscle mass, muscle function and physical performance. The sarcopenia concept however also includes low muscle quality, whose inclusion is more clearly recommended by EWGSOP2 [23]. Indeed EWGSOP2 stated that sarcopenia may be diagnosed by either low muscle mass or muscle quality after detection of low strength, but current limitations in clinical assessment of muscle quality prevent its clinical definition and routine assessment [84–86]. Muscle quality may be defined as a reduced muscle strength per unit of muscle mass. This approach may be intuitive in implying impaired functional ability of muscle tissue units, which may be theoretically due to metabolic derangements, with particular regard to energy metabolism and energy production [87], altered protein quality [88] or altered composition, with lower contractile mass and enhanced connective or fat deposition tissue [7,89,90]; i.e. fibrosis and myosteatosis. Calculation of the strength-mass ratio is however not recommended by any algorithm and may be still limited by uncertainties in strength and particularly mass measurement, which could enhance variability of a combined index. Direct assessment of muscle tissue composition could be an alternative parameter for skeletal muscle quality; the more commonly proposed approach is through CT imaging to measure muscle density as a marker of fat infiltration [91]. Although this approach has been implemented and low density was shown to be associated with relevant clinical outcomes [90], its standardization and validation appears incomplete for clinical recommendation in sarcopenia diagnosis.

4. Sarcopenia: the challenge of clinical complexity

Improved sarcopenia definition and availability of diagnostic algorithms has undoubtedly allowed to invigorate sarcopenia research in the last one-two decades despite remaining uncertainties and incomplete consensus. It seems almost inevitable that increasing awareness and data availability has brought forward new clinical questions and complexity. It is therefore possible that desirable growing agreement on fundamental sarcopenia diagnosis may be paralleled by additional debate to address emerging features of muscle failure. Main issues appear to be: 1) the epidemiologically alarming clinical challenge of the association between sarcopenia and obesity (defined as sarcopenic obesity); 2) the extension of the sarcopenia phenotype well beyond the older adult population, particularly in the presence of acute or chronic disease-driven muscle catabolism; 3) the rate of sarcopenia onset over time, with the proposed categories of acute and chronic sarcopenia. These issues have been more explicitly discussed in the EWGSOP2 consensus paper, but sarcopenic obesity appears to be a growing clinical problem addressed also by nutrition and obesity societies [92–95], whereas disease-associated sarcopenia has been previously recognized by other groups including IWGS and SCWD [18,22].

4.1. Sarcopenic obesity

Obesity is defined by excess fat accumulation with negative health consequences [96], but it is increasingly clear that persons with obesity are at risk of losing muscle mass and strength, thereby developing sarcopenia, under several common conditions [92,94,97]. Whereas high body mass may be associated with parallel increments of skeletal muscle mass in the general population [98], obesity and excess adipose tissue may be associated with muscle-catabolic derangements, including but not limited to low-grade systemic and muscle inflammation, oxidative stress and insulin resistance [99], further exacerbated by the onset of metabolic complications such as metabolic syndrome and type 2 diabetes. Poor nutritional habits and sedentary lifestyle may further enhance muscle catabolism [100,101]. Also similar to non-obesity related sarcopenia, the aging process and the onset of acute and chronic comorbidities that are extremely common in obesity may lead to accelerated loss of muscle mass and function [101–103]. Finally, persons with obesity undergo weight-losing treatments that are well-known to inherently involve lean body mass and skeletal muscle [104,105].

Sarcopenic obesity has been until recently only defined and detected in clinical research through existing definition and tools for sarcopenia or obesity, in the absence of a unifying pathophysiological or clinical approach [97]. Importantly, ability of tools conceived for sarcopenia diagnosis in the absence of obesity may have sub-optimal ability to detect the condition in obesity patients [94,97], with even higher variability reported than observed in non-obese cohorts [97]. It is indeed generally conceivable that specific pathophysiological, epidemiological and clinical features in obesity require specific tools and approaches. An international consensus document has been recently proposed by experts summoned by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO), and its validity is expected to be tested in future studies.

4.2. Primary and secondary sarcopenia

The concept of sarcopenia has been developed in the geriatric medical community [9,24,25]. Sarcopenia has been indeed initially defined as “age-related” loss of skeletal muscle mass [24,25] and function [4,21,33,43,48], and for many years it has been overwhelmingly studied in older adults [9,43]. It is however well recognized that skeletal muscle failure with weakness, slowness and disabilities may occur at any age in the presence of several medical conditions and risk factors. In particular, virtually any acute or chronic disease may affect muscle mass and function independently of age, through synergistic negative impacts on muscle protein anabolism, appetite and physical activity [12–17]. Indeed it is well recognized that loss of muscle mass occurs in disease, with independent negative clinical consequences [14,15,17,26], also in the context of related conditions such as malnutrition [106]. The term sarcopenia has been therefore more recently proposed to also define

disease-related loss of muscle mass and function at any age, particularly in the EWGSOP2 and SCWD definitions, under the category of "secondary sarcopenia" as opposed to "primary sarcopenia" that should continue to define the age-related syndrome. Similar to the overwhelming majority of diseases that occur at any age with the same definition, unifying disease- and age-related sarcopenia under the same definition appears to be conceptually sound and potentially useful for clinical practice. In addition, it should be pointed out that age-related sarcopenia is also commonly associated or accelerated by the onset of disease, which of course is most frequent in older patients [3,18–20]. Categorizing age- and disease-related sarcopenia as primary and secondary, respectively, may conversely be useful, for both pathophysiological and clinical reasons. Indeed it is well possible that higher intensity and rate of muscle loss in accelerated disease conditions, different age background, differential lifestyle and nutritional state conditions, disease-specific pathophysiological and clinical features, including hospitalizations and treatments, may all interact and lead to specific features in secondary sarcopenia. Specific derangements in different muscle protein pools, including for instance mitochondrial-energy metabolism components or myofibrillar proteins defining fiber type and composition, might be also clinically important and respond to different therapeutic approaches. These might require different diagnostic tools and criteria, as well as different therapeutic approaches (see below). Also relevant, this terminology further aligns to how osteoporosis is described and defined. Indeed, osteoporosis and sarcopenia are often concomitantly appearing; this topic falls beyond the scope of the current review but it may also warrant further consideration for systematic sarcopenia definition and assessment [107].

4.3. Obesity- and disease-related sarcopenia: specific tools and standardization?

As mentioned above, sarcopenia has been studied and diagnostic criteria were developed mainly in the context of geriatrics, and in cohorts of non-obese older adults. Effectiveness of currently proposed tools for sarcopenia screening and diagnosis in the context of obesity and in younger individuals with acute or chronic diseases could therefore be sub-optimal. For instance, normalization of skeletal muscle mass for body mass, rather than body height, seems to be more relevant or indeed necessary in persons with obesity, compared to non-obese individuals. Use of calf circumference and in general anthropometry could be misleading in obesity, although adjustments have been recently proposed that could improve its predictive value also in the presence of higher body mass [50]. Also relevant, limitations of devices for muscle mass assessment should be kept in mind for obese individuals [68]. In general, the relationship between muscle mass and function could be modified in obesity or under conditions of accelerated sarcopenia due to aggressive catabolic diseases. On the other hand, the sensitivity of case finding tools such as the SARC-F questionnaire in younger individuals with disease-related secondary sarcopenia could be lower than in older more frail individuals. The recent ESPEN-EASO algorithm for sarcopenic obesity screening and diagnosis has started to address these issues for persons with obesity, and future studies and consensus may be needed for potential optimization of tools specifically addressing secondary sarcopenia in different disease conditions.

5. Conclusions

In the last 15 years, the sarcopenia concept has been developed with several diagnostic algorithms that enhanced awareness, with rapid increase of clinical research. More than 17k papers are found in PubMed, with yearly growth and >3k papers per year since 2021. All algorithms have contributed to advance the field, although EWGSOP and AWGS showed the ambition to propose more detailed guidance for clinical implementation in routine practice, including primary care; indeed they have been employed in the majority of available studies [26] and have been endorsed by several scientific societies [9,23]. With the growth of the aging population worldwide and the steep increase in prevalence of non-communicable diseases and their complications, making sarcopenia diagnosis possible in clinical practice seems an urgent priority for the healthcare community, and a responsibility for experts. Consensus on main issues addressed by the existing diagnostic algorithms seems possible, and indeed a global consensus initiative has been recently launched and named Global Leadership Initiative on Sarcopenia or GLIS [67]. The discussion could help overcome existing discrepancies to launch a consensus algorithm with advancement on several practical aspects described in this review. Further research could be needed to further optimize sarcopenia screening, diagnosis and ultimately treatment in specific conditions, such as obesity and disease-related muscle loss.

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CRediT authorship contribution statement

Rocco Barazzoni: Conceptualization, Writing – original draft. **Tommy Cederholm:** Writing – review & editing. **Michela Zanetti:** Writing – review & editing. **Gianluca Gortan Cappellari:** Conceptualization, Writing – review & editing.

Competing interest

The authors have no conflict of interest to declare with regard to the content of this paper.

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