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Recent Progress in Sarcopenia Research: a Focus on Operationalizing a Definition of Sarcopenia

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Abstract
Purpose of Review To discuss recent progress in sarcopenia research and to highlight controversies in the field particularly around reaching consensus on a definition of sarcopenia.
Recent Findings Accordingly, this review begins with a discussion of the increasing awareness of this condition; briefly describes evolving definitions of sarcopenia; suggests a framework for consistent terminology for sarcopenia; discusses outstanding issues in the definition of sarcopenia; and reviews the association between sarcopenia and adverse outcome in older adults. In addition, the role of sarcopenia in other diseases is discussed.
Summary The field of sarcopenia continues to hold considerable promise and work continues to resolve outstanding concerns in this field with a unifying consensus definition on the horizon.

Keywords Sarcopenia · Physical function · Gait speed · Grip strength · Muscle · Lean mass

Introduction

Sarcopenia, or the age-related loss of muscle mass and its accompanying decline in strength and physical performance, has been gaining attention in recent years. The purpose of this review is to discuss recent progress in sarcopenia research and to highlight controversies in the field, particularly surrounding the operationalization of a definition of sarcopenia. The review begins with a discussion of the increasing awareness of this condition, describes evolving definitions of sarcopenia, suggests a framework for consistent terminology for sarcopenia, discusses outstanding issues in the definition of sarcopenia, and reviews the association between sarcopenia and adverse outcome in older adults. In addition, the emerging role of sarcopenia in specific diseases is discussed. The role of adiposity, sarcopenic obesity, and fat infiltration into muscle is omitted from this discussion, as those topics cover a vast literature that is outside the scope of this focused review.

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Increasing Awareness

Since the introduction of term sarcopenia nearly 30 years ago, research interest and public attention to this condition have steadily increased [1•]. The availability of a new ICD code [2, 3], progress towards a single consensus definition [4•] and recognition of the importance of muscle in other disease conditions are all likely reasons for this increased awareness.

In October 2016, an ICD-10 code (M62.84) was assigned for sarcopenia. Generated by a committee comprised of representatives from Centers for Medicare and Medicaid Services, the Centers for Disease Control and Prevention and the National Center for Health Statistics, ICD codes are intended to remove barriers to diagnosing diseases and conditions and are used for billing for care. The availability of an ICD-10 code allows for physicians to diagnose this condition and for sarcopenia to be studied in outcomes research using data from health systems. However, as the definition of sarcopenia is currently evolving, it is not clear whether an ICD-10 code for sarcopenia will have such immediate effects.

As the definition is solidified, more consistent and increased use of the ICD-10 code should occur.

Evolving Definitions

Several definitions of sarcopenia have been proposed [4•, 5–7, 8•, 9–11]. Early definitions included only lean mass [7, 8•, 10], while more recent definitions have considered sarcopenia a syndrome with several components including weakness (measured by grip strength) and/or slowness (measured by gait speed over a short distance) in addition to lean mass deficit (Table 1) [4•, 5, 6, 9]. However, substantial operational differences exist between definitions, including nomenclature, the method of assessment of lean mass (as an approximation of muscle mass), the method of standardization of lean mass to body size, cut-points for weakness, and cut-points for slowness. Since there are racial and ethnic differences in body composition and grip strength [13••, 14••], definitions for specific race and ethnic groups have also been proposed [11]. Given these differences in definitions, it is not surprising that prevalence estimates for sarcopenia vary widely and depend on the definition invoked [15, 16]. Progress continues with additional analyses and further work towards an evidence-based definition; outstanding issues in defining sarcopenia are discussed below.

Clarifying Terminology and Nomenclature in Sarcopenia

The nomenclature used in sarcopenia is often a source of confusion. For example, dual X-ray absorptiometry (DXA) measures lean soft tissue which includes muscle as well as water and all other non-fat, non-bone tissue. Often the amount of lean soft-tissue in the arms and legs (appendicular lean mass) is described as "muscle mass" when this is not the case. In addition, bioimpedance analysis (BIA) measures fat-free mass and is also often described as "muscle mass," which is not correct. At best, both are *approximations* of muscle mass. Thus, the literature is often confusing, as scientific text often refers to DXA-based measures of lean mass as "muscle mass" when it is not actually muscle alone per se. In addition, some reports consider "sarcopenia" to mean only low lean mass without regard to strength or gait speed, while others consider sarcopenia to be a syndrome that includes all of these components. Thus, for clarity, scientists should endeavor to use precise terminology whenever discussing concepts surrounding sarcopenia. Suggested nomenclature is listed in Table 2. Since the definition of sarcopenia is still evolving, it is likely that the terminology will continue to evolve as progress towards a consensus definition continues. Other researchers have suggested leaving the term "sarcopenia" to refer only to loss of muscle mass [17•]; however, the literature appears to have already evolved with most newer reports of studies in older adults now considering sarcopenia as a syndrome rather than the presence of low lean mass alone.

Outstanding Issues in Operationalizing a Definition of Sarcopenia

There remains controversy about how to define sarcopenia. The most vexing issue is the role of DXA-based measurement of lean mass in the definition. There are less critical but important issues regarding how to operationalize the components of slowness and weakness.

Mixed Associations between DXA Lean Mass and Outcomes

DXA has been recommend as a "reference standard for measuring muscle lean body mass" by an expert panel [12]. This declaration may have been misguided, for two reasons. First, as discussed above, DXA measures of lean mass are only approximations of muscle mass. Since there is no "gold standard" for the measurement of muscle mass, the accuracy of using DXA to estimate muscle mass is difficult to assess. Secondly, the relation between DXA-based measures of lean mass and subsequent adverse outcomes in older adults is not clear, with many reports demonstrating no association between lean mass and important outcomes [21••, 22, 23].

The initial paper that operationalized a definition of sarcopenia was published by Baumgartner et al. in 1998. This report defined sarcopenia as a relatively low value amount of appendicular lean mass (ALM, the non-fat, non-bone tissue of the arms and legs) divided by height squared (relative to a young reference population). This paper reported that those with relatively lower values of ALM/ht^2 had an increased likelihood of disability; balance and gait abnormalities; and a history of falls. This landmark paper helped establish the field of sarcopenia by operationalizing a definition that could be derived from a widely available device. However, the limitations of these analyses must also be considered. First, in the analyses of the association of ALM/ht^2 with prevalent disability, gait and balance problems, and falls, only 25% of the participants ($N = 199$ of 808 participants) had lean mass measured by DXA; the rest had values for ALM imputed from an equation that relied on height, weight, hip circumference, grip strength, and sex. Since each of these measures is independently associated with disability and falls [24–27], it is possible that the associations reported in the paper were induced by inclusion of these known risk factors in the prediction equation rather than because of a direct casual association of DXA-based ALM with such outcomes. Further, the authors

Table 1 Criteria for commonly used definitions of sarcopenia

	Slowness	Weakness	Low lean mass	Summary definition
International Working Group (IWG) [5]	Gait speed < 1.0 m/s	Not included	ALM/ht^2 ≤ 7.23 kg/m^2 for men and ≤ 5.67 kg/m^2 for women	Sarcopenia: both slowness and low lean mass
European Working Group on Sarcopenia Older Persons (EWGSOP) [4•]	Gait speed ≤ 0.8 m/s	Grip strength < 30 kg for men and < 20 kg for women	ALM/ht^2 ≤ 7.26 kg/m^2 for men and ≤ 5.45 kg/m^2 for women	"Sarcopenia" low lean mass plus either slowness or weakness "Severe sarcopenia" all three criteria
Foundation for the NIH (FNIH) Sarcopenia Project primary definition [6]	Gait speed ≤ 0.8 m/s	Grip strength < 26 kg for men and < 16 kg for women	ALM/BMI < 0.789 for men and < 0.512 for women[1]	"Weakness and low lean mass" is the presence of low grip strength and low lean mass "Slowness with weakness and low lean mass" is the presence of low grip strength, low lean mass, and slow gait speed
Baumgartner [7, 8•][2]	Not included	Not included	ALM/ht^2 ≤ 7.26 kg/m^2 for men and ≤ 5.45 kg/m^2 for women	"Sarcopenia": Presence of low lean mass
Newman [7, 10]	Not included	Not included	Residual of actual ALM - predicted ALM from equation[3]	"Sarcopenia": Presence of low lean mass
Society of Sarcopenia, Cachexia and Wasting Disorders (SCWD) [9, 11]	Gait speed ≤ 1.0 m/s	Not included	ALM/ht^2 ≤ 7.26 kg/m^2 for men and ≤ 5.67 kg/m^2 for women[4]	"Sarcopenia with limited mobility": Presence of low lean mass plus slow gait speed

ALM appendicular lean mass, *NIH* National Institute of Health

[1] The FNIH Sarcopenia Project also proposed an alternative definition using ALM low lean mass of < 19.75 kg for men and < 15.02 kg for women

[2] A similar cut-point of ≤ 7.25 kg/m^2 for men and ≤ 5.67 kg/m^2 for women (derived from Health ABC data) was proposed by Delmonico

[3] The equation used to calculate residuals was ALM (kg) = − 22.48 + 24.14*height(m) + 0.21 ∗ total fat mass (kg) as derived for men in the Health ABC study [12]; the cut-point for the residual was ≤ − 0.204 kg/m^2; a similar but slightly different version was proposed by Delmonico

[4] The SCWD definition suggests use of ethnic/race specific cut-points; the cut-points for whites are reported here; see Chen 2014 for cut-points for Asians

Table 2 Terminology for sarcopenia

Domain	Suggested terminology	Comments
Muscle mass	*Low lean mass* when measures are derived from DXA	Since none of these methods directly measures total muscle mass, language should be precise regarding the body composition component measured
	Low fat-free mass when derived from BIA or two-compartment models	For regional measure of specific muscles (such as CT and MRI) the muscle group should be included in the terminology (e.g., "small thigh muscle CSA")
	Small cross-sectional area (CSA) when derived from CT	
	Small muscle volume when derived from MRI	
Strength	Weakness or dynapenia [17•, 18]	Most operational definitions of sarcopenia use grip strength; reports that use other measures of strength should repeatedly clarify that grip strength was not used
Physical performance	Slowness or bradypedia [19]	Refers to gait speed over a short distance (usually < 20 m); performance on longer distance walks should be reported with other terminology (e.g., mobility disability for inability to complete the 400 m walk) [20••]
Composite condition	Presence of at least two of the above domains	Given variation in the definitions of sarcopenia, authors should explicitly state what is meant by their use of the term sarcopenia in reports

note that the prediction equation tended to overestimate ALM in those with higher levels of lean mass. Since lean mass is correlated to overall body size, and body size is a risk factor for disability, this prediction equation may have introduced differential measurement error (where the amount of error in the exposure varies across values of the outcome.) Such differential measurement error is particularly problematic in epidemiology. Unlike non-differential measurement error which generally biases effect estimates towards the null, differential error can introduce bias that is difficult to quantify, including bias away from the null, potentially resulting in spurious associations [28].

Subsequent reports of the association between lean mass (and other approximations of muscle size) and outcomes have been mixed and are summarized as having no overall association with functional limitations in a meta-analysis [21••]. A subsequent review noted that studies identified from a literature search showed a significant association between weakness and subsequent poor physical performance or disability 90% of the time, while studies examining the association between low lean mass (or muscle cross-sectional area) were only significant 35% of the time, with a much smaller summary effect estimate for low lean mass than for weakness for predicting disability or poor performance [17•]. Given the limited predictive ability of measures of lean mass by DXA, it is not clear if the data support inclusion of low lean mass in a composite definition of sarcopenia. However, this highlights a major conundrum of defining sarcopenia: how can a condition that is described as the age-related loss of muscle mass not include at least an approximation of muscle size? Future work to further solidify the definition of sarcopenia must address this issue to move the field forward. Alternatives to DXA, such as CT, MRI, or D3-creatine dilution for assessment of muscle cross-sectional area, muscle volume, or muscle mass exist [29], but have not been as widely used as DXA for the approximation of muscle mass. Thus, relatively few studies in representative populations have been completed with these measures. Further work in this area is critical to overcoming this barrier in the field of sarcopenia.

Cut-points for Defining Low Grip Strength (Weakness) and Low Gait Speed (Slowness)

Low grip strength and slow gait speed are established risk factors for mortality and disability [21••, 24, 30••, 31–33]. While both are measures of performance, grip strength measures upper body muscle function and gait speed measures lower boy mobility (of which muscle function is one important determinant). Grip strength only explains a relatively small proportion of the variance in walking speed in older adults (between 3 and 17% of the variance depending on the mode of assessment) [34]. Thus, it is possible that someone with as slow walking speed can have high grip strength and vice versa.

The specific cut-points used to classify individuals as slow or weak is not as straightforward as it may seem. For example, cut-points in grip strength for defining weakness were initially developed by expert opinion [5] and have been refined through data-driven approaches [35], but whether cut-points should differ by race and ethnicity remains an open question [36]. Several cut-points have been proposed to define slowness based on gait speed, including speed of 0.6 m/s [37], 0.8 m/s [6], and 1.0 m/s [5]. Since gait speed declines dramatically as age increases [30••], any cut-point used will demonstrate increasing prevalence of slowness as age increases. In fact, based on data from NHANES, the 1.0 m/s cut-point would classify ~90% of those over age 85 years as slow [37]. Unless it is believed that an "epidemic of slowness" exists amongst the oldest-old, the near universal presence of slowness in the oldest-old suggests that a cut-point in gait speed below 1.0 m/s (such as 0.6 m/s) may be more

appropriate for defining slowness. The cut-point for defining slowness will impact the prevalence of sarcopenia substantially. This has important implications: for example, the composition of a clinical trial could vary dramatically based on which cut-point is used to define slowness. In addition, the competing sarcopenia definitions vary regarding whether weakness and slowness and low lean mass must be present concurrently to constitute sarcopenia, or whether the presence of each component alone determines sarcopenia. Thus, how the components are combined also varies by definition and substantially changes prevalence estimates. In addition, while grip strength and gait speed have been used in many sarcopenia definitions, other measures of performance such as repeat chair stands (which can be considered a composite measure of lower extremity power and strength), the timed up and go test (rising from a chair, walking a short distance, turning, and returning to the chair) have been suggested as alternative metrics for incorporating performance into a sarcopenia definition [4•].

In addition, there may be some barriers to operationalizing the measure of grip strength or gait speed in clinical settings, although these are not insurmountable. While hand dynamometry is relatively inexpensive (units can typically be purchased for less than $500USD), the measure does require specialized equipment. Both assessment of grip strength and gait speed require some training and standardization that is not widely available outside of research settings. Many of the issues regarding the definition of sarcopenia will be discussed at a Position Development Conference organized by the Sarcopenia Definitions and Outcomes Consortium in November, 2018, in Boston, Massachusetts. The positions put forth by this meeting of international experts should address (and hopefully resolve) several of the controversies surrounding the definition of sarcopenia reported herein.

Sarcopenia as a Risk Factor for Adverse Outcomes

The association between sarcopenia and a variety of adverse outcomes in older adults has been has been reported numerous times. The vast literature means that several meta-analyses have now been conducted for the relation between sarcopenia and a number of different outcomes including mortality [38–40], disability [40, 41], falls [40], metabolic syndrome [42], fractures [43], cognitive impairment [44], hospitalization, and hospitalization-related outcomes [40, 45]. Most of these studies used a composite definition of sarcopenia that included both a measure of low lean mass plus weakness and/or slowness, such as the European Working Group on Sarcopenia in Older People (EWGSOP) definition. While sarcopenia (particularly as a composite measure) was often found to be associated with risk of these outcomes, there was some evidence of publication bias particular for mortality [39], and the associations were not always consistent across genders [43] or across various methods to assess body composition [44]. For example, in one meta-analysis, association between sarcopenia and fractures was only found for men [43]. In addition, several meta-analysis did not account for potentially confounding factors, including age [40], so it cannot be ruled out that other confounding factors explain the association between sarcopenia and adverse outcomes in older adults. This is particularly important given the associations between sarcopenia with age and co-morbid conditions [46] which may then confound any reported associations between sarcopenia and outcomes. Future meta-analyses of the role of sarcopenia in health outcomes in older adults should endeavor to include analyses that have adjusted for potentially confounding factors. In addition, none of these meta-analyses considered the relative importance of each of the components of sarcopenia, for example, whether low lean mass, weakness, and grip strength, each predicted adverse outcomes. This is important because of the evidence presented above that suggests differential effects of slowness, weakness, and low lean mass on adverse health outcomes in older people. Thus, it is not clear if the relationship between composite sarcopenia definitions and outcomes exist because of an underlying association between low lean mass and such outcomes, or if this relationship is explained by the strong association between gait speed and grip strength with mortality and disability. This issue must be resolved for a single consensus definition of sarcopenia to emerge.

Sarcopenia in Other Diseases

As noted above, in research in older adults, more recent reports rarely use the term sarcopenia to indicate low muscle mass alone (without consideration of strength or performance). This is not the case in other research areas. The role of sarcopenia in many other conditions (not limited to older adults) has also been widely reported. The literature is particularly rich in reports from diseases or conditions where computed tomography scans of the abdomen or chest are required for diagnosis or monitoring of progression, for example, in cancer, liver diseases and gastric procedures. Use of already obtained CT imaging for the diagnosis of other conditions or prognosis based on other non-disease specific factors in the image has considerable appeal, as CT scans are routinely performed in older adults. It is estimated that > 10% of the medicare population had abdominal or pelvic CT scans in 2007 [47]. In most reports of populations of individuals with specific disease (e.g., a cohort of liver transplantation), sarcopenia is usually defined as a relatively low level of muscle cross-sectional area (for example, total skeletal muscle cross-sectional area in the abdomen) [48]. This is in contrast to the

more recent definitions in older adults, which incorporate a measure of both strength and physical performance. Many reports in disease-specific populations, allow for many meta-analyses to be completed. These meta-analyses suggest that sarcopenia (again, in this context usually meaning relatively small muscle cross sectional area) is related to poor outcomes following treatment of solid tumors [49], liver transplantation [50, 51], gastrointestinal surgery [52], hepatic malignancies [53], liver cirrhosis [54], gastrectomy [55], and abdominal surgery [56]. However, whether weakness or slowness add to these measures of muscle cross-sectional area are unclear. These measures must be collected prospectively from patients; most of the published studies rely on retrospective cohort studies of patients included based on availability of images. If measures of grip strength or gait speed are substantially more predictive of poor outcomes in these populations (as is seen with these measures in studies of older adults), then such measures have the potential to greatly impact clinical care by identifying those at greatest risk of adverse outcomes. Future studies should complement measurement of muscle cross-sectional area with assessment of strength and gait speed whenever possible.

Finally, while muscle CSA by CT may be a more direct measure of muscle than DXA, there are limitations. Muscle CSA by CT is usually only based on a single CT slice at a given muscle or anatomical site. Data from Health ABC show that thigh muscle CSA by CT is highly correlated to lean mass from DXA ($r = 0.7–0.8$ depending on the lean mass measure) [57], but whether this is true in all populations or for CT CSA at all muscle sites is not clear. In addition, changes in both DXA lean mass (appendicular and total) and CT CSA of the thigh are correlated with loss of strength in Health ABC [58], but strength is lost much more quickly than lean mass or CT CSA.

Conclusion

In summary, this review has highlighted recent advances in sarcopenia research particularly surrounding how to operationalize the definition of sarcopenia. Perhaps the most pressing and controversial issue is the role of DXA measures of low lean mass as an approximation of muscle mass in the definition of sarcopenia. Other concerns include the need for standardization of nomenclature, the nature of precise cut-points for grip strength and gait speed, (including whether cut-points should vary across race and ethnicity groups), and the feasibility of such measures in clinical settings. The presence of sarcopenia (when considered as a multicomponent syndrome) has been shown generally to predict adverse outcomes in older adults, but the role of each component and whether these associations are independent of potential confounders is not clear. Finally, in a variety of disease-specific populations, sarcopenia (usually narrowly defined as cross-sectional muscle area) has also generally been shown to predict disease progression or functional status. However, most of these disease-specific population studies have not included measures of strength or gait speed, so sarcopenia as a multi-component syndrome has been largely unevaluated in these populations. The field of sarcopenia continues to hold considerable promise, and work continues to resolve outstanding concerns in this field.

Compliance with Ethical Standards

Conflict of Interest Peggy Cawthon reports non-financial support from GSK outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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