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Considerations concerning the definition of sarcopenia

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Abstract

In this commentary, we describe the sarcopenia spectrum that results in frailty and consider the impact of several components of the frailty definition on its global prevalence. We review proposed operational definitions of sarcopenia and the extent to which they have been shown to predict hard clinical outcomes, such as hip fracture, falls, and mortality. A head-to-head comparison of nine proposed operational definitions of sarcopenia as predictors of falls revealed that the definition involving appendicular lean mass (ALM)/ht² alone was a significant predictor; the prevalence of sarcopenia by this definition was 11 %. We consider the strengths and limitations of definitions that include functional measurements, such as gait speed and grip strength, along with measures of lean tissue mass. The functional assessments are harder to standardize than the more objective ALM measurements. The prevalence of sarcopenia by definitions that include functional and lean mass measurements tends to be lower than the prevalence by definitions that include lean mass alone. A low prevalence limits opportunity for early identification and application of prevention strategies. For these and other reasons, it seems advantageous to base the operational definition of sarcopenia on ALM/ht² alone. This commentary addresses the importance of a globally applicable operational definition of sarcopenia and both desirable and undesirable features of such a definition.

Keywords

Falls; Fractures; Frailty; Mortality; Sarcopenia; Sarcopenia definition

Introduction

Fractures are the result of the combination of falling and osteoporosis, and sarcopenia is a leading cause of falls. Currently, there is no generally accepted operational definition of sarcopenia, but there is wide recognition that a definition is needed.

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Compliance with ethical standards

Conflicts of interest None.

Because there are conceptual parallels between osteoporosis and sarcopenia, it may be useful to consider the *general* and *operational* definitions of osteoporosis. Osteoporosis has a general definition that is essentially reduced bone mass and strength and an operational definition that specifies ranges of bone mineral density (BMD) as normal, low bone mass, and osteoporosis [1]. These ranges are expressed as the number of standard deviations above or below the mean of a single young reference population. The operational definition is used to compare the prevalence of osteoporosis across nations, to select patients for intervention trials, etc. Apart from the operational definition, there is also an algorithm (FRAX®) that is used to determine a 10-year fracture risk of individual patients (www.shef.ac.uk/FRAX/). The FRAX® algorithm is adapted to specific countries by incorporation of their fracture rates and death rates; the FRAX® risk score is used in conjunction with local economic considerations (i.e., willingness/ability to pay for fracture prevention) to set country-specific treatment thresholds. There is uniformity in the operational definition of osteoporosis globally, whereas FRAX-based treatment thresholds vary around the globe.

The purpose of this commentary is to (1) describe the sarcopenia spectrum that results in frailty, falls, fractures and mortality; (2) consider the impact of several components of the frailty definition on its global prevalence; (3) review evidence that several candidate definitions of sarcopenia predict important clinical outcomes, hip fractures, and falls; and 4) conclude by discussing attractive features of an effective definition of sarcopenia¹.

The sarcopenia spectrum and frailty

The term sarcopenia or “paucity of flesh” was coined by Irwin Rosenberg, who thought that the muscle wasting that had such important consequences in older adults would gain more attention in the medical community if it had a name [2]. Muscle changes that occur over time result in a spectrum that includes normal, pre-sarcopenia, and sarcopenia; these changes lead to frailty (Fig. 1) and ultimately to disability. Not all sarcopenic individuals are frail, but the risk of frailty is greatly increased among sarcopenic elders. Several components of the definition of frailty and their impact on its prevalence around the world are considered next because they may provide insights into desirable (and undesirable) features of potential definitions of sarcopenia.

Frailty

A general definition of frailty is a biologic syndrome of decreased reserve and resistance to stressors, leading to vulnerability to adverse outcomes [3]. The *operational* definition of frailty by the widely used Fried definition consists of any three of the following five components: (1) unintentional weight loss (>10 lb in the last year), (2) exhaustion, (3) weakness (grip strength in the lowest quintile for age and sex), (4) slow gait (walking speed in the lowest quintile for age and sex), and (5) low physical activity (<383 kcal/week for males and <270 kcal/week for females) [4]. The presence of two of these components defines “pre-frail” subjects [4]. In the 5317 adults aged 65 years and older in the US

¹This commentary describes the content of an invited presentation by B D-H at the 2016 IOF-ESCEO congress in Malaga, Spain entitled: “Defining Sarcopenia”.

Cardiovascular Health Study, 6 % of men and 6 % of women were frail by the Fried definition and 15 % of men and 14 % of women were pre-frail [4]. Selected components of the frailty definition, slow gait speed [5] and low grip strength [6], have been shown to predict mortality. Moreover, survival with advancing age declined increasingly rapidly in normal, pre-frail, and frail elders [4].

The global prevalence of frailty and pre-frailty has been described by Choi et al. [7] based on nationally representative populations [4, 8–12]. These authors compared the prevalence of frailty by the Fried definition in community-dwelling adults, age 65 years and older in studies published in 2001–2014 (Table 1). The prevalence of frailty varied more than fivefold, from 4.9 to 27.3 % [7]. It was the lowest in Taiwan (4.9 %), Switzerland (5.8 %), Ireland (6.0 %), and the USA (6.9 %) and the highest in southern European countries, Spain (27.3 %), Italy (23.0 %), France (15.0 %), and Greece (14.7 %). Choi et al. speculated that a potential contributing factor to the high prevalence in these Mediterranean countries may be their lower rates of institutionalization [7]. Other cultural differences may also have played a role in the subjective portions of the frailty assessment, particularly the “exhaustion” component. Other factors contributing to the variable prevalence may have been the use of different study populations and different cut points in the definitions of weakness and slow gait (i.e., cut points were based on the lowest quintile of the individual studies rather than a common reference population). The physical assessments may also have been influenced by differences in the degree to which individuals administering the tests motivated the subjects. Finally, the dynamometers used to measure grip strength and their calibrations likely differed across the studies.

Sarcopenia

There is agreement on the general definition of sarcopenia as meaning loss of muscle mass and function. Several working groups have proposed *operational* definitions of sarcopenia, but at this time, there is no universally accepted definition. Proposed definitions include the presence of low skeletal muscle mass either alone or with the addition of low grip strength and/or slow gait speed. Most of the definitions include appendicular lean mass (ALM) determined by dual-energy X-ray absorptiometry (DXA). Nine proposed operational definitions are summarized in Table 2 [13–20]. These definitions differ in the ALM reference populations used, in the approaches used to adjust ALM for body size, in the cut points used to define low ALM, and in the inclusion or exclusion of the functional measures, gait speed and grip strength. Most but not all groups adjusted lean mass for body size by using ALM/ht^2 .

Relationship to hip fracture and mortality

Part of the process of developing an operational definition for sarcopenia includes demonstrating that the subjects meeting the definition have an increased risk of an important clinical outcome. To date, there is evidence from the Health ABC study in 3075 adults aged 70–79 that ALM/ht^2 alone is associated with a reduced risk of hip fracture in men (HR (95 % CI) = 0.58 (0.36, 0.91)) but not in women (HR = 1.04 (0.66, 1.63)) [21]. In a large cohort of 22,482 elderly Chinese men and women, ALM/ht^2 alone was inversely associated

with hip fracture in both men (OR = 0.240 (0.138, 0.4180)) and women (OR = 0.479 (0.278, 0.823)) [22]. In the Amsterdam Longitudinal Aging Study, ALM/ht² was inversely associated with mortality in the men but not in the women [23]. In Health ABC, however, muscle strength but not mass was associated with mortality [24].

Relationship to falls

Muscle weakness has been identified as the strongest risk factor for falls, followed by a history of a prior fall, gait deficit, and balance deficit [25]. Falls are frequent occurrences, and they have significant consequences. One in three community-dwelling people over age 65 and one in two over age 80 fall at least once each year [26]. Falls result in serious injuries in 10 to 15 %, fractures in 5 %, and hip fractures in 1 to 2 %. Over 90 % of fractures occur as a result of a fall. The healthcare cost of falls in the USA was estimated in the year 2000 to be \$18.5 billion [27].

We recently compared the extent to which the operational definitions of sarcopenia shown in Table 2 predict falls in a single cohort [28]. The Boston STOP/IT study was used in this analysis [29]. Briefly, 445 community-dwelling adults (199 men and 246 women) aged 65 years and older were enrolled in a 3-year trial to determine the effect of supplementation with calcium and vitamin D₃ (500 mg/700 IU) versus placebo on rates of bone loss. Fall information was gathered on each 6-month visit. Additionally, after each fall, participants were instructed to send a postcard to staff which prompted a call to document the details of the fall. The subjects had a mean age of 71 years. The mean ALM/ht² was 8.19 kg/m² in the men, and 6.24 kg/m² in the women. Mean grip strength was 1.0 m/s in the men and the women. In this 3-year study, 231 participants fell, and there was a total of 514 falls. The prevalence of sarcopenia in the STOP/IT study by the four definitions using variations in ALM alone and by the five composite definitions that also included one or more functional measures is shown in Table 3. Notably, the prevalence among the four definitions employing ALM alone varied twofold. In contrast, the prevalence among the five definitions that included one or more functional assessments varied 10-fold.

In view of the sarcopenia spectrum described in Fig. 1, it would be anticipated that the prevalence of falls would be higher in frail than in sarcopenic subjects. This was borne out in the finding that the 3-year prevalence of *first fall* in frail subjects in the Cardiovascular Health Study was 28 % [4]. The prevalence of any fall would have been considerably higher in these elderly subjects because many participants would have had multiple falls [30].

The prospective rate of falls (95 % CI) in participants considered sarcopenic versus non-sarcopenic by each operational definition in the Bischoff-Ferrari study [28] is shown in Fig. 2. The studies that considered ALM alone used different formulas (ALM/ht² vs ALM adjusted for BMI) and different cut points for ALM. Two of the nine definitions were statistically significant predictors of falls in men and women combined, the Baumgartner definition relying on ALM/ht² alone [13] and the Cruz-Jentoft definition that included ALM/ht² plus gait speed and grip strength [17]. The prevalence of sarcopenia differed in these two definitions (11.0 % in Baumgartner and 7.1 % in Cruz-Jentoft). In a sensitivity analysis, when the ALM/ht² cut off in the Cruz-Jentoft definition was adjusted to bring its prevalence close to that of Baumgartner (i.e., to 11.8 %), the Cruz-Jentoft definition was no

longer a significant predictor of falls (RR 1.41(0.97, 1.03)) [28]. Thus, in the STOP/IT study, *for a given prevalence of sarcopenia of about 11 %*, the addition of gait speed and/or grip strength to ALM/ht² did not add significantly to the predictive capability of falls. A potential reason that the functional measures did not add predictive power on fall risk is that they do not effectively capture true functional capacity related to fall risk in healthy community-dwelling older adults, even when carefully measured. Potential reasons for this, as pointed out by Bijlsma et al. [31], are that physical performance and strength are dependent on parameters other than muscle strength, such as cardiovascular fitness and joint function. Alternatively, functional measures may add a complicated signal, as greater functional capacity may give a greater opportunity to fall [32]. For mass alone, Scott et al. reported that ALM/ht² was a significant predictor of fall risk in men but not women in a younger Tasmanian cohort, mean age 61 years [33]. Fall risk was estimated in this study by performing the Physiological Profile Assessment (PPA) at the beginning and end of the 5-year observation period. The PPA includes vision, reaction time, proprioception, knee extension strength, and balance. Additional head-to-head comparisons of performance of the available definitions in predicting hard clinical outcomes in larger data sets are needed. In summary, ALM/ht² alone has been shown to predict hip fracture, falls, and mortality. In the one available head-to-head comparison [28], at a given prevalence of about 11 %, ALM/ht² was a significant predictor of falls whereas ALM/ht² with grip and/or gait speed was not.

Features of an effective global definition of sarcopenia

A standardized operational definition with specified gradations (e.g., pre-sarcopenia, sarcopenia) is needed. ALM/ht² will be an important objective component of a global definition, and it would ideally be based on standardized cut points and a single reference data base. The definition must be demonstrated to be predictive of one or more important clinical endpoints (e.g., hip fracture, falls, injurious falls, and mortality). The elements of the definition would optimally have minimal operator and cultural dependency. Functional/performance measurements are particularly vulnerable to such dependencies in a busy clinical setting. The definition would optimally result in a prevalence that is high enough to enable a substantial number of people at risk to be identified early enough to benefit from intervention(s) *before* they become frail. Available evidence discussed above suggests that definitions based on ALM/ht² have a significant gradient of risk for hip fractures and falls; definitions based on this component alone also have reasonable prevalence. Once a global operational definition has been established, it must then be demonstrated that individuals meeting this definition of sarcopenia would benefit from specific interventions.

Conclusion

Selecting a definition of sarcopenia requires balancing the potential benefit of including functional measures along with measurements of ALM against the difficulties related to their inclusion. The functional measurements are harder to standardize than DXA-based ALM measurements, and they add considerable variability for cultural and other reasons described above. The prevalence of sarcopenia by definitions that included ALM alone varied 2-fold whereas prevalence among the composite definitions that included ALM and one or more functional measures varied 10-fold. However, by most of the composite

definitions (four out of five), the prevalence of sarcopenia was quite low, ranging from 2.7 to 7.1 %. A very low prevalence limits opportunity for early identification and application of prevention strategies. It also poses challenges in developing effective global strategies to reduce sarcopenia. For example, it may discourage drug development initiatives in low-prevalence environments because the interventions would have limited application there. More studies are always needed, but at this point, the balance appears to lean in favor of use of ALM/ht² alone to define sarcopenia operationally. This is not to downplay the importance of functional assessment—it will always be a critical component of elder care because the approach to treatment of sarcopenia would depend upon functional capacity along with other factors.

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Fig. 1.
The sarcopenia spectrum

Fig. 2. Prospective rate of falls in sarcopenic versus non-sarcopenic seniors [29]. The *solid circles* are based on definitions that included ALM alone, and the *open circles* are based on definitions that included ALM and/or grip strength and gait speed [28]

Prevalence of frailty by the Fried scale in community-dwelling adults 65 years and older in nationally representative populations

Table 1

Author	Country	Number	Frail, %	Pre-frail, %
Fried et al. [4]	USA	5317	6.9	44.6
Santos-Eggmann et al. [8]	Europe	7510	17.0	42.3
	Sweden	1038	8.6	45.3
	Denmark	877	12.4	38.4
	Netherlands	1261	11.3	38.5
	Germany	1146	12.1	34.6
	Austria	849	10.8	40.7
	Switzerland	470	5.8	46.5
	France	803	15.0	43.6
	Italy	958	23.0	45.6
	Spain	733	27.3	50.9
	Greece	939	14.7	44.9
Chen et al. [9]	Taiwan	2238	4.9	40.0
Hubbard et al. [10]	UK	3055	8.1	
O'Halloran et al. [11]	Ireland	1426	6.0	43.0
Lee et al. [12]	Korea	11,844	7.8	50.4

From Choi et al. [7], with permission

Table 2

Proposed definitions of sarcopenia

Definition	ALM/ht ² (kg/m ²)	Reference population	Gait speed (m/s)	Grip strength (kg)
Baumgartner [13]				
Men	7.26	Rosetta study		
Women	5.45			
Delmonico 1 [14]				
Men	7.25	Health ABC		
Women	5.67			
Delmonico 2 [15]				
	7.26 ^a	Health ABC		
Studenski 1 [16]				
Men	<0.789 ^b	9 studies		
Women	<0.512 ^b			
Cruz-Jentoft [17]				
Men	TS ^c	NS	<0.8	<30
Women	TS ^c	NS	<0.8	<20
Fielding [18]				
Men	7.23	Health ABC	<1.0	
Women	5.67		<1.0	
Morley [19]				
Men	6.81	NHANES IV	1.0	
Women	5.18		1.0	
Muscaritoli [20]				
Men	37 % ^d	NHANES III	0.8	
Women	28 % ^d		0.8	
Studenski 2 [16]				
Men	<0.789 ^b	9 studies		<26
Women	<0.512 ^b			<16

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NS not specified
^aALM + term for fat mass in the same cohort (Health ABC)
^bALM adjusted for BMI
^cTS—two mentioned (Baumgartner or Delmonico 1), none selected
^dTotal body lean by bio impedance/body weight $\times 100$, as determined by Janssen et al. [34]

Table 3

Prevalence of sarcopenia in community-dwelling men and women age 65 years and older [29]

Definition	Prevalence %		
	Men	Women	All
Definitions based on muscle mass alone			
Baumgartner [13]	12.2	10.2	11.0
Delmonico 1 [14]	11.2	21.5	16.9
Delmonico 2 [15]	14.2	27.2	21.4
Studenski 1 [16]	9.6	13.4	11.7
Composite definitions			
Cruz-Jentoft [17]	6.6	7.4	7.1
Fielding [18]	3.6	6.2	5.0
Morley [19]	3.1	2.5	2.7
Muscaritoli [20]	20.4	26.2	23.6
Studenski 2 [16]	1.55	4.51	3.1

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