Role of Sarcopenia Definition and Diagnosis in Clinical Care: Moving from Risk Assessment to Mechanism-Guided Interventions

This editorial comments on the articles by Bhasin et al, Manini et al, Cawthon et al, Patel et al, and Grosicki et al. in this issue.

This issue contains a position statement from the Sarcopenia Definition and Outcomes Consortium (SDOC),[1] together with supporting original studies.[2-5] SDOC was created in 2016 by the National Institute on Aging and the Foundation for the National Institutes of Health with the main goal of identifying evidence-based and clinically relevant cutpoints for lean mass and strength.[1] Overall, the main results of the SDOC confirm the importance of slow gait speed and handgrip strength in the definition of the sarcopenia phenotype while questioning the inclusion of lean muscle mass measured by dual-energy X-ray absorptiometry (DXA).

Sarcopenia is a geriatric condition with a major impact on health, functional independence, and quality of life in older adults.[6,7] Defined as a decline in muscle mass and quality with an underlying multifactorial etiology, sarcopenia has been considered to represent a geriatric syndrome.[8] However, recent efforts to move sarcopenia diagnosis and management into the clinical setting and help guide the use of specific pharmacologic interventions[9] have followed a translational path previously pursued for bone mineral density (BMD; Figure 1). As a result, sarcopenia was somewhat reconceptualized as a novel disease[10] with the creation of a specific International Classification of Diseases, Tenth Revision (ICD-10) code in 2016.[11]

Ability to code for sarcopenia as a diagnosis has generated excitement among clinicians. Nonetheless, moving this clinical construct from that of a multifactorial geriatric syndrome with its many attendant complexities to the conceptualization of a single disease-based diagnosis poses challenges. Cutpoints are needed in medicine to provide targets for intervention and objectives for clinical management. However, clinicians still rely on many arbitrary decisions and contingent situations (ie, current knowledge about the disease, priorities in the formulation of the diagnosis, availability and access to diagnostic services). This is particularly true in geriatric medicine.[12] Geriatricians are quite used to looking at cutpoints in a flexible manner, well aware that any one single categorical variable, especially when considered in isolation from other relevant factors, is unlikely alone to make a big difference in the care of frail older adults. Heterogeneity in this population highlights the need for more flexible and less categorical approaches.

To that end, SDOC explains in the main article that "the performance characteristics of these cutpoints vary with age, race/ethnicity, comorbid conditions, and population." Therefore, sex-specific cutpoints derived in these analyses should be evaluated in additional diverse populations including clinical populations with specific conditions."[1] Furthermore, as also shown by Patel et al,[5] prevalence of muscle weakness largely depends on the construct defining each variable. In other words, every time the indicators of muscle strength are modified, different results are obtained, and therefore what we consider as sarcopenia changes. Similarly, analyses conducted by Grosicki et al also show how changes in variables and thresholds substantially modify the prevalence (and likely characteristics) of the target population.[3] It is thus evident that the choice of a standardized approach to the assessment of the critical components of sarcopenia may bring a certain dose of uncertainty, variability, and at times even arbitrariness.

Any resulting ambiguity is further enhanced by the pragmatic adaptations that have to be considered when these epidemiological findings are applied to individuals in clinical settings. For example, a person with a body mass index (BMI; a clearly suboptimal but widely used parameter to define obesity) of 29.9 kg/m^2 is unlikely to differ biologically, phenotypically, or clinically from someone with a BMI of 30 kg/m^2, yet such decimal differences place the two individuals into different categories. In the context of sarcopenia, the heterogeneous biological, clinical, and social complexities involving the individual as well as differing characteristics of the personnel and location where such evaluations are conducted will unavoidably play a role in decisions pertaining to choice of variables, cutpoints (especially during the screening phase), and final definitions of the condition of interest. For all these reasons, it might be argued that a unique "gold standard variable" and/or the "best cutpoints" may translate poorly from the worlds of epidemiology and computational modeling to real-world clinical settings.

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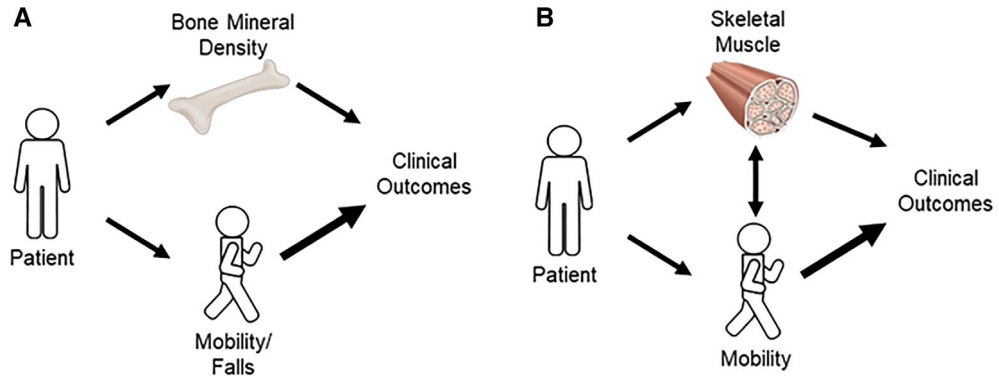

Figure 1. Complementary and contrasting roles of bone mineral density (BMD) and skeletal muscle assessments in geriatric care. (A) BMD represents an important and well-validated measurement used to define risk of hip fractures in adults of all ages while also helping to guide the use of preventive therapies. However, in many older adults, mobility and balance issues contributing to falls emerge as an important risk factor, at times eclipsing BMD as the predominant risk factor for future fractures. (B) Sarcopenia has been defined as declines in muscle mass and muscle quality with aging. Measurements of mobility performance have been validated as powerful predictors of frailty, future disability, hospitalization, and death. However, in contrast to BMD, a bidirectional relationship exists between muscle and mobility performance, and muscle mass alone without some assessment of mobility performance is a poor predictor of such risk. Future studies are needed to better define the role of varied, preferably noninvasive, measures of muscle mass and quality in specific subcategories of sarcopenia, as well as other often coexisting chronic conditions of aging.

However, rather than abandoning such efforts, we view these challenges as opportunities to help better guide our path forward. By considering every individual as a case per se with all of his or her individual peculiarities and specificities, we suggest that cutpoints of this kind not be used as part of binary decision-making algorithms, but rather that they be considered as merely one important element within a multidimensional assessment of all the varied factors that may ultimately constitute the meaning of different types and subtypes of "sarcopenia" in different individuals. Thus perhaps the identification of the so-called best cutpoint may be most useful in terms of prognostication for epidemiological, insurance, and administrative purposes as opposed to clinical care.

SDOC also suggests not including DXA in the evaluation of sarcopenia,[1] in contrast to several other consensus documents available on the topic that still include DXA in spite of its well-known limitations.[10,13,14] The classification and regression tree analyses performed by Manini et al undoubtedly demonstrate the superiority of muscle strength over the DXA results.[4] These findings are also supported by the work by Cawthon et al exploring the predictive capacity of different sarcopenia components for the onset of negative health-related outcomes.[2] These recommendations are consistent with evidence that measures of physical performance and muscle strength may be more clinically relevant than muscle quantity measures in the prediction of adverse events.[15,16]

DXA limitations are well known, yet as a result of efforts to replicate its successful use involving bone to that addressing muscle, DXA has evolved from being considered a suboptimal methodology for the assessment of skeletal muscle to one of the most recommended choices for implementing sarcopenia in the clinical setting. Although DXA has largely remained the same technique, what has changed over time includes these factors:

1. Increased awareness of sarcopenia and its consequences, highlighting the need for rapid clinical implementation, combined with growing demands for sarcopenia evaluation and broad availability of DXA devices;
2. Considerable body of knowledge regarding sarcopenia derived from DXA;
3. Absence of real alternatives, especially given expected volume of need. SDOC suggests the D3-creatine dilution method as a more accurate measure of total body muscle mass. Although we recognize the potential value of this technique for the definition of sarcopenia and even its suggested superiority over other quantitative parameters of muscle mass,[17] we need to consider that studies using D3-creatine measures in relevant populations are still rare and probably insufficient for determining the critical cutpoints desired by SDOC. Moreover, capacity and experience with this measure in the clinical setting are still very limited.

Although we realize that the statement is part of a methodologically rigorous process, saying that "Lean mass measured by DXA should not be included in the definition of sarcopenia"[1] may devalue the huge amount of evidence produced over the past decade. It may potentially leave sarcopenia as a less meaningful construct when deprived of quantitative skeletal muscle assessment. It is not possible to ignore what has been done because a suboptimal technique was used, especially in the absence of a clear alternative. At the same time, clinicians cannot suspend their activities in this field waiting for yet another sarcopenia definition, especially now that this condition is recognized as an entity of interest by public health and regulatory authorities.[11,18] Questioning the most commonly used methodology for the assessment of a critical component of its construct may hamper the process leading to the needed legitimation of sarcopenia in the clinical world. Furthermore, for

Table 1. Clinical Recommendations for Sarcopenia Diagnosis

• Consider sarcopenia in all clinical decision making involving older adults
• Share sarcopenia knowledge with trainees
• Use ICD-10-CM diagnosis code M62.84 for all patients with probable sarcopenia
• Note there is no current role for routine clinical use of DXA for skeletal muscle mass measurement
• Note that body composition assessment can be useful for giving support to clinical decisions by providing a measure of the biological background
• Use simple screening mobility tests by observing gait or the Five Times Sit to Stand Test
• Lobby local clinical and IT leaders plus EMR vendors to develop linkages from unobtrusive and standardized measures of gait velocity to current EMR systems
• Promote efforts to better reflect interindividual heterogeneity of geriatric sarcopenia in clinical care and research, leading to appropriate M62.84 diagnosis subcodes

Abbreviations: DXA, dual-energy X-ray absorptiometry; EMR, electronic medical record; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; IT, information technology.

regulatory reasons, the approval of pharmacologic interventions does require the clear identification of a specific pathophysiologic pathway, defined by a clinical phenotype (eg, muscle weakness, dysmobility), an assessment method to be used clinically (eg, dynamometer, gait speed test), a biological substratum (eg, skeletal muscle mass), and validated biomarkers.

In the meantime, what are clinicians to do in the midst of these very important research nuances and ongoing controversies? As illustrated in Figure 1A, BMD has emerged as a validated and widely accepted measure that is predictive of the risk of fracture and attendant disability, in addition to any contribution from mobility and balance contributing to the risk of falls. At the same, BMD helps guide the use of specific interventions targeting bone that have been shown to decrease the risk in older women and men. In contrast, the relationship between the muscle "counterpart" of BMD and clinical outcomes is not only much weaker but also more nuanced and complex (Figure 1B). First, skeletal muscle mass measured via DXA and mobility performance are closely related and exert a bidirectional positive influence on each other. Second, mobility performance is a much more powerful and reliable predictor of clinical outcomes than muscle mass. Third, we hope new preferably noninvasive techniques will help guide the treatment of declines involving muscle in a more targeted and mechanism-guided fashion.

Table 1 lists our recommendations to clinicians based on these rigorous and important SDOC analyses. We must include sarcopenia in all of our clinical decision making involving older adults, use every teachable moment to share our accumulated knowledge in this area with trainees, and use the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis code (M62.84) when billing. Although the use of DXA-derived measurements of muscle mass cannot be justified in routine clinical care at this time, we must not let "the perfect become the enemy of the good." The body composition measurement (in particular, via DXA given its large diffusion) may still be useful for confirming clinical evaluations as well as embracing a more biology-driven, person-tailored assessment of the aging individual.

However, given the powerful role of physical performance measures as modifiable predictors of key clinical outcomes in geriatric patients, we must strive to incorporate such measurements into everyday clinical practice. Simple screening tests such as observing usual walking speed or asking a patient to rise five times from a chair with arms crossed should be part of our clinical routine. We must also explore new ways for introducing quantitative measurements of physical performance (eg, gait velocity) into our clinical practice, so that such information may become routinely available via the electronic medical record (EMR) system.[19] Unfortunately, EMR developers have generally not given much consideration to the unique needs of older patients when designing their systems, following software developments that are largely conducted to address local needs and financial resources. To that end, we must individually and collectively lobby biomedical Informatics experts, EMR vendors, the EMR industry, and regulatory agencies about the critical importance of including such information as an additional "vital sign" for older adults of no lesser relevance than weight, blood pressure, or heart rate.[20] We see this as the missing link leading to the improved identification, monitoring, and targeted management of declines in physical performance in our older patients.[19] This will allow that therapies currently available to us (eg, exercise, anabolic steroid replacement, vitamin D replacement) and hopefully soon others will be optimally, most widely and most effectively used.

Equally important will be efforts to further develop the ICD-10-CM diagnosis code for sarcopenia to have subcodes reflecting the tremendous heterogeneity of contributing risk factors, underlying mechanisms, and ultimately optimum therapies. For example, age-related sarcopenia associated with involuntary weight loss needs to be distinguished from sarcopenia associated with obesity. Moreover, the coexistence of other chronic or acute conditions (eg, renal failure, human immunodeficiency virus, congestive heart failure, cancer, COVID-19 infection) will likely introduce novel key elements reflective of both similarities and differences from those seen in the theoretical individuals presenting with the so-called pure sarcopenia of aging.

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