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Chapter 2

# Sarcopenia in the Context of Skeletal Muscle Function Deficit (SMFD)[1]

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**Abstract**

Evidence shows that not only changes in skeletal muscle mass but changes in strength and other factors underpinning muscle quality play a role in muscle function decline and impaired mobility associated with aging. Changes in both strength and quality may precede loss of muscle mass. Skeletal muscle function deficit (SMFD) is a terminology that embraces this evolving conceptualization of sarcopenia and age-related muscle dysfunctions. This chapter provides a discussion on sarcopenia in the context of SMFD, including operational definitions and methodological challenges associated with their establishment; integration of muscle quality into SMFD; efforts to identify diagnostic cutoff values for low muscle mass and weakness and their predictive validity to mobility disability; need for standardized muscle quality assessment; clinical and public health relevance and research opportunities. Changes in muscle composition, based on excessive levels of inter- and intramuscular or intramyocellular fat are striking features increasingly addressed in the literature, found to affect muscle metabolism and peak force generation. Methods to easily and rapidly assess muscle composition in multiple clinical settings and with minimal patient burden are needed. Further characterization of SMFD should emphasize integration of muscle quality and factors behind changes in quality, as well as associated clinical and research implications.

**Keywords:** skeletal muscle function deficit, sarcopenia, reduced muscle mass, low muscle mass, low muscle strength, muscle quality, biomarkers, outcomes

[1]The views expressed in this chapter are those of the author and do not necessarily represent the views of the National Institute of Health, National Institute on Aging, the U.S. Department of Health and Human Services (HHS), or the U.S. Federal Government.

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## 1. Introduction

Numerous efforts around the definition of sarcopenia and its better characterization through biomarkers including cutoff values for muscle mass, muscle strength (weakness), and performance measures, as well as the identification of outcomes of clinical and investigational significance have evolved in the past many years and continue to be heavily investigated. Since 1989, when sarcopenia was first defined as an age-related reduction in muscle mass [1] and the association of low muscle mass and functional impairment was demonstrated [2], scientific and technological advances have helped us improve our understanding of the mechanisms underlying age-related alterations in muscle mass, muscle strength, and muscle quality. Substantial attention has also been given to investigate the relationships of these alterations to mobility impairment, disability, fatigue, risk of metabolic disorders, falls, and mortality in older adults [3]. This ongoing work responds to the need to identify preventive and therapeutic interventions that can delay, improve, revert, or eliminate the changes in muscle mass, strength, and quality. The scientific community, including regulatory scientists, and practicing health care professionals recognize that "a more specific definition of sarcopenia may not only be necessary to align it with new scientific advances, but it is highly desirable on practical grounds because specific criteria are critical for identifying candidate patients for clinical trials that test therapies aimed at reversing or alleviating the complications of sarcopenia and its associated manifestations [4]."

It is estimated that by 2050, 2 billion people worldwide will be age ≥65 years. Preserving mobility and quality of life into old age will be a challenge because impaired mobility is often a precursor of functional decline, disability, and loss of independence. Evidence now shows that not only changes in muscle mass, but other factors underpinning muscle quality also play a role in the decline in muscle function and impaired mobility associated with aging. Changes in muscle quality may precede loss of muscle mass. This provides new opportunities for the assessment of muscle mass, strength, and quality particularly to detect who could benefit from interventions to prevent decline or improve muscle function [5].

The purpose of this chapter is to provide basic science, clinical researchers and expert clinicians with a review of the literature on key efforts to establish clinically meaningful diagnostic cutoff values for low muscle mass and low muscle strength, integrate muscle quality into these efforts, discuss the clinical and public health relevance, and highlight research opportunities for sarcopenia in the context of skeletal muscle function deficit. The new terminology "skeletal muscle function deficit" was coined in 2014 to embrace the evolving concepts of sarcopenia and other aging-related muscle dysfunctions that contribute to clinically meaningful mobility impairments [6].

### 1.1. Terminology and nosology issues: sarcopenia in the context of skeletal muscle function deficit

Sarcopenia is a condition with a complex multifactorial etiology, which is summarized in **Table 1** [7]. Age-related decreases in muscle performance associated with physical impairment are only partially explained by reduction in muscle mass, with many other pathophysiologic

factors contributing to age-related impairments in muscle performance. Based on these facts, decreases in muscle performance and in muscle mass require independent evaluation. The importance of assessing muscle quality, currently defined as strength per unit of appendicular skeletal muscle mass, also continues to be highly emphasized.

Although consensus groups noted below have incorporated the criterion of impaired physical and/or muscle performance into their recommended definitions of sarcopenia, they have not addressed the issue of specific diagnostic terminologies. The lack of sufficient specificity resulting from the use of "sarcopenia," an anatomic term currently used to define a functional condition with which it is imperfectly correlated, and for which nonanatomic contributory factors have been identified, generates confusion. Some of this confusion originates from the fact that reduced muscle mass *per se* is a feature of several other conditions in both older and younger people. Adopting a nosology that accommodates the literal concept of sarcopenia—reduced muscle mass—while applying other diagnostic terms for other age-related muscular conditions that contribute to impaired physical performance seems to hold a valuable clinical approach. "Skeletal muscle function deficit" (SMFD) fits this purpose well. The term indicates a shortfall in function that can evolve to more significant impairment and mobility-disability. The diagnostic criteria for "SMFD" can, then, include: (A) Measures of muscle performance and strength that provide effective cutoff values for identifying those whose mobility disability is related to impairments. Muscle performance is the capacity of a muscle or a group of muscles to generate forces to produce, maintain, sustain, and modify postures and movements that are required for functional activity. Strength is the muscle force exerted to overcome resistance under a specific set of circumstances. Power is the work produced per unit of time or the product of strength and speed. (B) Measures of muscle mass (e.g., "sarcopenic SMFD"), and (C) Measures of muscle quality. Factors impacting muscle quality can be described using measures of muscle composition or myosteatosis (fat infiltration of muscles) as these are very relevant to mobility outcomes and to the identification of effective preventative and therapeutic interventions in older adults. Muscle quality is also largely impacted by intricate intramuscular ultrastructure and morphology of contractile tissue, as well as the relationship between structure and function [6, 8].

A variety of known and putative muscular pathologies can be evaluated as their contribution to SMFD, including newly identified contributory pathologies. This approach also specifies other already recognized conditions that can lead to "SMFD" (e.g., diabetic polyneuropathy or secondary malnutrition), which can be distinguished from age-related conditions contributing to "SMFD" with etiology not yet well established. Further, it accommodates future knowledge in diagnostic specificity based on improved understanding of the mechanisms of aging and disease. Specific neurogenic factors, intrinsic muscle factors, or systemic factors may lead to the characterization of specific subtypes of age-related sarcopenia, to methods for diagnosing them, and to the identification of new therapeutic targets. In sum, the broad concept of "SMFD" comprising a variety of contributory etiologies provides a framework for developing diagnostic categories that are useful for both clinical practice and research. This approach has been successfully implemented with conditions that are clinically manifested as impaired physiologic functions (e.g., congestive heart failure, chronic obstructive pulmonary disease) and have multiple contributory factors [6].

| |
|---|
| **Age-related** |
| • Reduced physical activity |
| • Mitochondrial dysfunction |
| • Anorexia of aging |
| • Apoptosis |
| • Hormones |
| • Low levels of testosterone |
| • Low levels of growth hormone |
| • Low levels of insulin-like growth factor (IGF)-1 |
| • Elevated levels of cortisol |
| • Low levels of vitamin D |
| **Proinflammatory cytokines** |
| • Interleukin-1 |
| • Interleukin-6 |
| • Tumor necrosis factor (TNF)-alpha |
| • Neuronal |
| • Loss of motor endplates |
| • Peripheral neuropathy |
| **Vascular** |
| • Peripheral vascular disease |
| • Reduced capillary function |
| **Weight loss** |
| • Dieting |
| • Malabsorption |
| • Disease-related |
| **Hormones** |
| • Low levels of testosterone |
| • Low levels of growth hormone |
| • Low levels of insulin-like growth factor (IGF)-1 |
| • Elevated levels of cortisol |
| • Low levels of vitamin D |
| **Neuronal** |
| • Loss of motor endplates |
| • Peripheral neuropathy |

**Table 1.** Multifactorial etiology for sarcopenia [7].

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## 2. Operational definitions for sarcopenia

Several operational definitions have emphasized that sarcopenia should now be defined as a loss of muscle function associated with a loss of muscle mass [9–18]. This change in definition from the original meaning of sarcopenia [1] is justified by some experts as necessary due to current knowledge that muscle quality and muscle performance do not directly relate to muscle mass [19, 20]. Two very important factors are thought to be responsible for this knowledge: the compromise of neuromuscular junctions in sarcopenia and the myosteatosis accompanying the aging process [21–24]. Below is a brief description of these operational definitions published by key consensus groups. It should be highlighted that a quantitative definition of sarcopenia that characterizes this condition in terms of rationally-defined cutoff values for lean body mass and muscle strength is comparable to the evolution of the operational definition of osteoporosis in terms of bone mineral density to detect individuals at increased risk for fractures. Efforts to identify an operational definition for sarcopenia include those:

- Based on muscle mass in relationship to the range of muscle mass within a reference population;
- Essentially based on expert opinion, but considering muscle mass and performance criteria;
- Essentially based on expert opinion, but considering muscle mass, muscle strength and physical performance; and
- Evidence-based, data-driven, considering muscle mass, muscle strength, and their predictive validity to mobility disability.

**Table 2** summarizes in a comparative way, the currently available operational definitions for sarcopenia. While they might involve similar criteria, marked variations in cutoff values exist as alluded below.

| **Working group/target population** | **Screening** | **Operational definition** | |
|---|---|---|---|
| | | **Muscle mass** | **Muscle strength/ function** |
| EWGSOP – European Working Group on Sarcopenia in Older People [9]*All person ≥ 65 years* | Gait speed. If gait speed is ≤0.8 m/s, proceed to body composition evaluation. If gait speed >0.8 m/s, measure hand grip strength; if low muscle strength (weakness) is detected, proceed to body composition evaluation | Low muscle mass in patients with gait speed ≤0.8 m/s or normal gait speed but low muscle strength.DXA ASM/height$^2$ ≤7.23 kg/m$^2$ for men; ≤5.67 kg/m$^2$ for women | Low grip strength <30 kg for men; <20 kg for womenorgait speed <0.8 m/s |
| IWGS/IANA - International Working Group on Sarcopenia Task Force/ International Academy on Nutrition and Aging [11] *Persons with clinical declines in physical function, strength, or health status* | Physical function (4-m gait speed). If gait speed < 1.0 m/s, proceed to body composition evaluation | Low appendicular lean mass/height$^2$ (assessed by DXA):≤7.23 kg/m$^2$ for men; ≤5.67 kg/m$^2$ for women | Poor functioning, gait speed |

| Working group/target population | Screening | Operational definition | |
|---|---|---|---|
| | | Muscle mass | Muscle strength/ function |
| SIG- Special Interest Group: Cachexia-Anorexia in Chronic Wasting Diseases [12]*Older persons* | – | Low muscle mass (≥2 standard deviations below the mean measured in young adults of same sex and ethnic background) | Low usual gait speed (<0.8 m/s in the 4-m walking speed).Gait speed test can be replaced by other physical performance measures |
| SCWD - Sarcopenia with Limited Mobility [10]*Persons >60 years with clinical declines in physical function, strength, or health status. Exclude specific muscle diseases, peripheral vascular disease with intermittent claudication, central and peripheral nervous system disorders and cachexia* | Distance walked during a 6-min walk test (cutoff value 400 m) or gait speed <1.0 m/s (4- to 6-m track length) | Low appendicular lean mass/height$^2$ (≥2 standard deviations below the mean measured in healthy persons aged 20–30 years old from the same ethnic group) | Poor functioning, 6-m walk or gait speed |
| AWGS -Asian Working Group for Sarcopenia [15]*Community-dwelling persons 60 or ≥ 65 years, according to the definitions of elderly in each individual country.Persons with specific clinical conditions in all health care settings.* | Screening in community settings—people aged 60 or ≥65 years (according to definitions of elderly in each individual country) living in communities.Specific clinical conditions in all health care settings—presence of recent functional decline or functional impairment; unintentional body weight loss for over 5% in a month; depressive mood or cognitive impairment; repeated falls; undernutrition; chronic conditions (e.g., chronic heart failure; chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease, connective tissue disease, tuberculosis infection, and other chronic wasting conditions) | 2-standard deviations below the mean muscle mass of young reference group or the lower quintile as the cutoff value determination.Low appendicular lean mass/ height$^2$:<7.0 kg/m$^2$ for men and <5.4 kg/m$^2$ for women, using DXA.<7.0 kg/m$^2$ for men and <5.7kg/m$^2$ for women, using BIA | Gait speed ≤ 0.8 m/s as the cutoff value for low physical performance.Lower 20th percentile of handgrip as strength as cutoff value for low muscle strength before outcome-based data are available.Low handgrip strength is suggested to be defined as < 26 kg for men and < 18 kg for women. |
| FNIH - Foundation for the National Institutes of Health, Sarcopenia Project [14] | Patient presents with poor physical function. If weakness is present, proceed to evaluate for low muscle mass; if low muscle mass is detected, it is possible it might be the cause of weakness. If weakness is not present or if low muscle mass is not detected, proceed to investigate for other causes of poor physical performance. | Recommended cutoff value:Appendicular lean mass adjusted to BMI ($ALM_{BMI}$) <0.789 for men and <0.512 for women.Alternate cutoff value:ALM <19.75 kg for men and <15.02 kg for women. | Gait speed < 0.8 m/ sRecommended cutoff value:Grip strength (GS Max) <26 kg for men and <16 kg for women.Alternate cutoff value:GS adjusted to BMI ($GSMax_{BMI}$) <1.0 for men and <0.56 for women. |

**Table 2.** Comparative summary of sarcopenia definitions.

*Muscle mass in relationship to the range of muscle mass within a reference population*. The first definition of sarcopenia included the relative muscle mass 2 standard deviations (SDs) below the mean of a large sex-specific reference population 18–40 years old [2]. This definition used a measure of relative muscle mass obtained by dividing absolute muscle mass estimated by dual energy x-ray absorptiometry (DXA) by height squared. Following, sarcopenia was classified per its severity as: (1) Class I sarcopenia (skeletal muscle index between 1 and 2 SDs below the young adult values) and (2) Class II sarcopenia (skeletal muscle index above 2 SDs below the young adult reference). Skeletal muscle index was calculated by dividing total muscle mass by total body mass, with muscle mass evaluated by bioelectrical impedance analysis (BIA) [25].

*Essentially expert opinion, but considering muscle mass and performance criteria*. Numerous recommendations for a definition of sarcopenia consider muscle mass and performance criteria. The European Working Group on Sarcopenia in Older People (EWGSOP) proposed a diagnosis for sarcopenia that requires low muscle mass (estimated by the ratio of appendicular lean mass (ALM) over height squared, ≤7.23 kg/ht$^2$ for men and ≤5.67 kg/ht$^2$ for women) accompanied by either low muscle strength (measured by grip strength <30 kg for men and <20 kg for women) or low physical performance (measured by gait speed <0.8 m/s). The group defined three stages for the condition: (1) Presarcopenia (loss of muscle mass); (2) sarcopenia (loss of muscle mass accompanied by either loss of strength or physical performance); and (3) severe sarcopenia, with all three aspects present [9]. The definition of sarcopenia by the International Working Group on Sarcopenia (IWGS)/International Academy on Nutrition and Aging (IANA) [11], the European Society for Clinical Nutrition and Metabolism Special Interest Group on cachexia-anorexia in chronic wasting diseases and nutrition in geriatrics [12], and the Society of Sarcopenia, Cachexia, and Wasting Disorders (SCWA) [10], require that both lean mass and gait speed be included in the diagnostic criteria for the condition.

*Essentially expert opinion, but considering muscle mass, muscle strength, and physical performance*. The Asian Working Group for Sarcopenia (AWGS) decided to take a similar approach for the diagnosis of sarcopenia, but unlike the EWGSOP, it recommends measuring both muscle strength (handgrip strength) and physical performance (usual gait speed) as the screening test [15]. The group also recommends using 60 or 65 years as the age for sarcopenia diagnosis per the definitions of older adults in each Asian country. The group, though, supports using BIA for sarcopenia diagnosis and evaluation of effects. It recommends: (A) Using 2 standard deviations below the mean muscle mass of young reference groups or lower quintile as the cutoff value determination; height-adjusted skeletal muscle mass; for using DXA, cutoff values include 7kg/m$^2$ in men and 5.4 kg/m$^2$ in women; for BIA, cutoff values include 7kg/m$^2$ in men and 5.7 kg/m$^2$ in women, defined by appendicular skeletal muscle mass/height$^2$. (B) Using the lower 20$^{th}$ percentile of handgrip strength of a study population before outcomes data are available; low handgrip strength defined as <26 kg for men and <18kg for women. (C) Using ≤0.8m/s as the cutoff value for low physical performance.

*Evidence-based, data-driven, considering muscle mass, muscle strength, and predictive validity to mobility disability*. The studies supported by the National Institute on Aging and the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project utilized a data-driven analysis

of a large pool of data (>26,000) from studies on aging (epidemiologic and clinical trials) to identify criteria for clinically relevant low muscle strength (weakness) and low lean mass [17]. By addressing the relationship between mobility impairment (defined as gait speed ≤0.8 m/s) and muscle strength (measured by handgrip strength), strength cutoff values (<26 kg for men and <16 kg for women) were determined below where low strength (weakness) is likely to contribute to slow gait [26]. By relating these strength cutoff values to muscle mass (estimated by appendicular lean mass adjusted to body mass index [ALM/BMI]), additional cutoff values were determined (<0.789 for men, <0.512 for women), below which low lean mass is likely to contribute to low muscle strength [27]. The cutoff values resulting from these analyses were also found to have a predictive significance on incident mobility impairment over 3 years of follow-up. This two-step analyses that links a clinical condition (mobility impairment) to a functional test result (weakness), which is in turn linked to a potential therapeutic target (muscle atrophy) is useful for establishing participant selection criteria and outcome measures for trials of pharmaceutical or other interventions [14, 17, 28]. These studies, however, were conducted in relatively heathy community-dwelling older adults. In addition, harmonization of DXA data was not conducted prior to pooling data from all studies for analysis. Therefore, additional research is ongoing to validate the findings above by analysing harmonized pooled data from well-designed observational and interventional studies from populations of older adults with high prevalence of mobility disability (see RFA-AG-15-013 http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-15-013.html). The main goal is to develop and assess differing diagnostic cutoff values with regard to properties such as sensitivity, specificity, and positive predictive value. Because the populations involved display a variety of chronic conditions, it is possible that differing criteria might be needed to identify population subgroups. The extent to which lack of harmonization of DXA data significantly compromised the reliability of previously established cutoff values is to be seen.

### 2.1. Validation of the different definitions of sarcopenia

Validation of the different definitions of sarcopenia is ongoing. Using the criteria recommended by the IWGS/IANA, the prevalence of sarcopenia was slightly less compared to the EWGSOP criteria [29]. Using the EWGSOP criteria, 4.6% of males and 7.9% of females in Hertfordshire were found to have sarcopenia [30]; Japanese men and women age 65–80 years were found to have sarcopenia at a rate of 21.8 and 22.99%, respectively [31]; among people 80 years and older, sarcopenia was present in 12.5% [32]; and in nursing homes, 32.8% of the residents had sarcopenia [33]. Still using the EWGSOP criteria, sarcopenia was found to be highly predictive of earlier mortality in nursing home residents [34], in community-dwelling older Korean men [35], and in older adults admitted to acute care [36]. Sarcopenia assessed with the EWGSOP criteria has also been associated with a greater increase in falls [37, 38] and has been shown to predict mobility and instrumental activities of daily living disability [39]. Similarly, the SCWD criteria have been found to predict ADL and IADL difficulties, frailty and mortality in a longitudinal study [40].

Because the FNIH criteria were based on developing cutoffs using a variety of large epidemiological studies [14], these criteria are more restrictive with only 1.3% of men and 2.3% of women being defined as having sarcopenia. While a strong negative percent agreement has

been reported with EWGSOP, the positive percent concurrences are generally low (5–32%). Additional comparative studies are needed, particularly to evaluate best predictive ability.

### 2.2. Methodological challenges in establishing diagnostic cutoff values

Analyses of pooled data from large studies on aging with measures of muscle mass, and strength still face numerous challenges including different follow-up intervals, use of more than one brand and/or generation of devices to measure body composition, use of more than one type of handgrip dynamometer, use of more than one distance to calculate gait speed, and data harmonization issues [17]. Cutoff values for measurements of muscle mass, muscle strength, and physical performance for the diagnosis of sarcopenia may also differ across populations due to a series of factors including race and ethnicity, body size, lifestyle, and cultural backgrounds. Cutoff values established for Caucasians may not be applicable to Africans, Asians, or Hispanics. For example, as acknowledged by the AWGS, the Asian continent has a rapidly growing population with a wide range of ethnicities, cultural, social, religious backgrounds, and lifestyles [15]. In addition, Asia's aging population status and economic development varies significantly across Asian countries. Moreover, the age cutoff that defines the population of older adults may differ not only among Asian countries, but also around the world. The lack or paucity of outcomes-based studies is another factor presenting a challenge to the assessment of sarcopenia.

The discussion in this section focuses on key methodological issues associated with the body composition assessment and the need to establish a standardized approach to develop and apply diagnostic cutoff values. Assessments of body composition vary in precision and in the target tissue. The use of anthropometric methods does not allow tissue-specific inferences. BMI, a descriptive index encompassing both the lean and fat mass, is expressed as weight divided by stature squared ($kg/m^2$). The availability of extensive national reference data and their established relationships with levels of body fat, morbidity, and mortality in adults is an advantage to the use of BMI. However, the use of BMI alone to evaluate athletes and persons with conditions such as sarcopenia where body weight may be altered considerably by changing proportions of muscle and fat masses is cautioned [41].

BIA produces estimates of total body water, fat-free mass, and fat mass by measuring the resistance of the body as a conductor to a very small alternating electrical current. This is not a direct measure of skeletal muscle. Measurements can be easily altered by fluid retention and health status, providing inaccurate results that limit considerably the clinical application. BIA was developed to mainly determine the volume of body fat and muscle mass, but not specific appendicular muscle mass. While validation studies have been reported on BIA's accuracy in the diagnosis of sarcopenia, results also strongly depend on the accuracy of the equation of the equipment and the conditions associated with the assessment (e.g., temperature, humidity, skin condition, and others) [42–45]. New BIA equipment models will likely provide more precise measurements of appendicular muscle mass [24, 46]. Portability, reasonable cost, fast processing, noninvasiveness, radiation-free functions, and convenience of use are advantages to BIA suitability for sarcopenia assessment in the community. Despite recommendations by EWGSOP on the use of BIA validated equations in sarcopenia research, its use has been

discouraged by others [10, 47]. Moreover, BIA equipment in Western countries is not derived from populations from other regions of the world and, therefore, results are unlikely to be able to be extrapolated to particular populations [15].

Currently, the precision of devices to measure body composition such as DXA, computed tomography (CT), and magnetic resonance imaging (MRI) has been well recognized [47]. DXA is currently the most widely employed method for muscle mass measurement in sarcopenia research. It is commonly available in both clinical and research settings, is relatively inexpensive, and provides sufficiently precise results [41, 47, 48]. DXA is considered a suitable alternative to distinguish between fat, bone mineral, and lean tissues, it leads to minimal radiation exposure. However, its use in community screening is still challenging. In 2008, the Center for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS) released a DXA whole body dataset from the National Health and Nutrition Examination Survey (NHANES) population-based sample acquired with modern fan bean scanners in 15 counties across the United States from 1999 through 2004 [49]. The reference dataset was partitioned by gender and ethnicity and DXA whole body measures of %fat, fat mass/height$^2$, lean mass/height$^2$, appendicular lean mass/height$^2$, %fat trunk/%fat legs ratio, trunk/limb fat mass ratio of fat, bone mineral content (BMC), and bone mineral density (BMD) were analysed to provide reference values for subjects 8–85 years old. DXA reference values for adults were normalized to age; reference values for children included total and subtotal whole body results and were normalized to age, height, or lean mass.

The estimation of fat and lean tissue by DXA is based on assumptions regarding levels of hydration, potassium content, or tissue density, and these assumptions vary with manufacturer. Some analytical differences across manufacturers and models, and the risk of generating biased results due to the low differentiation between water and bone-free lean tissue are among limitations with DXA [48]. Estimates of body composition are also affected by differences in software employed, methodological issues, and intra- and intermachine differences. Testing of specific manufacturers and models revealed that overestimations of fat-free mass may occur. DXA systems are currently capable of scanning a very broad range of weights (neonates to morbidly obese). Repeatability is also very high for all reported total body measures, with the percent fat measures typically better than 1% (standard deviation) and 2% (coefficient of variation) for total fat and lean mass measures. Whole-body DXA scans can be subdivided into arms, legs, trunk, head, and android/gynoid soft tissue regions to report all bone and soft tissue measures within a region. While work is ongoing, there is not yet a reliable phantom that can be used to cross-calibrate DXA systems between manufacturers or a standard of accuracy of percent fat. Some success at representing muscle mass as appendicular lean mass in just the legs and arms has been achieved, but it has yet to be shown as a reasonable surrogate of muscle strength or function. Further work with DXA machines will lead to the development of more refined models of visceral and muscle fat [47].

Despite being considered gold standards for the evaluation of body composition, the use of computed tomography (CT) and magnetic resonance imaging/spectroscopy (MRI)/(MRS) has been impacted by their high cost, CT-generated radiation exposure, and inconvenience for use in community screening. Both are techniques relevant to body composition assessment

requiring additional time and software to provide whole body quantities of fat and lean tissue. CT can distinguish body tissues based on a technique helpful to assess nonfat tissue or the fatty infiltration of skeletal muscles. It accurately measures a direct physical property of the muscle (e.g., cross-sectional area and volume). It allows the evaluation of muscle density (a parameter related to intramyocellular adipose tissue deposit) as well as subcutaneous and intramuscular adipose tissue deposition [48].

MRI/MRS has been increasingly used to study body composition in related physiological and pathological conditions. MRI can be used for whole body assessment in normal or moderately overweight people (limitations exist in accommodating very obese people) and measure the volume of body components (e.g., fat tissue, skeletal muscle, organs, and bone). Recent advances suggest that fat tissue is not a homogeneous depot but contains distinct components with different metabolic activities. MRI provides similar measures as CT, with the additional capacity of multiple slice acquisition and 3D volumetric estimates, and no radiation exposure. Quantification of subregions of fat depots such as visceral (i.e., omental, mesenteric, and extraperitoneal), intermuscular, and bone marrow is possible with DXA. A single slice in the upper abdomen has been shown not only to provide the best representation of total volume of visceral fat, but also to correlate with health risks even more closely than the traditionally used slice located at the L4–L5 level. When fat infiltration is increased, MRS imaging allows a more accurate measurement of intramyocellular fat [41, 47]. High technical complexity and costs, as well as inapplicability to persons with older models of implanted medical devices (e.g., joint prostheses) are among the limitations associated with MRI.

#### *2.2.1. Harmonization of DXA data from multiple studies*

Studies focusing on the development of cutoff values for low muscle mass and low muscle strength frequently use appendicular lean mass (ALM) as a primary independent variable, obtained by DXA. Because these studies generally combine data from many different cohorts to measure ALM, it is critical that DXA measurements be compatible across studies. Owing to the variation between the manufacturers' (Hologic and GE Lunar) designs and systematic improvements in hardware and software instituted over time within each machine type, DXA values obtained for a given individual may vary across machines. It is necessary, therefore, to implement a quantitative adjustment to harmonize or put all measurements on the same theoretical scaling. This harmonization process may require a few steps including the harmonization of DXA values within manufacturer's systems and harmonization between different manufacturers. Studies have been conducted to address standardization and cross-calibration of body composition using GE Healthcare Lunar and Hologic DXA systems. Equations developed are facilitating the combination of results in clinical and epidemiological studies [50–52].

### 2.3. Sarcopenia diagnosed without measurements

Fracture risk can be determined almost accurately by FRAX questions as by measuring bone mineral density [53]. Because muscle function is more noticeable than bone function, the idea of developing and adopting a simple questionnaire to identify individuals with sarcopenia was realized with the development of the SARC-F scale. This simple and rapid questionnaire

to assess the presence of sarcopenia is illustrated in **Table 3** [54]. Robust validation, indicating that SARC-F performed at similar level to the EWSGSOP and AWGS definitions of sarcopenia has been reported, with suggestions that sarcopenia can be screened for without a need to measure muscle mass or to directly measure muscle function [55].

### 2.4. Sarcopenia and the FY2017 United States Update of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modifications (ICD-10-CM)

Effective October 1, 2016, the U.S. Department of Health and Human Services (HHS) Centers for Disease Control and Prevention (CDC) has established an ICD-10-CM code for "sarcopenia" (M62.84) for use by the medical community in the United States [56]. For that purpose, sarcopenia is defined as a combination of low muscle mass and weakness in older adults that leads to functional deficits. The new code designation for the condition has the potential to affect the clinical assessment and management of sarcopenia, as well as facilitate data collection and impact sarcopenia research. Because sarcopenia is a condition that can lead to serious adverse outcomes (e.g., mobility impairment, falls, disability, and death) [25, 57–61], the creation of an ICD10-CM code emphasizes the importance of recognizing and treating the condition. The availability of an ICD-10-CM code for sarcopenia has the potential to facilitate recognition of the condition and the future establishment of guidelines for the clinical diagnosis and management of sarcopenia; support requests for tests and referrals, and the development of educational materials targeting potential prevention and management of sarcopenia. It can serve as a stimulus to advance research including new drug development and new indications by the HHS Food and Drug Administration (FDA) for the treatment of sarcopenia. It can certainly contribute to easier access to more reliable data collection on the condition by a variety of system data sources (e.g., electronic medical records, death certificates). Despite these potential advantages, challenges are faced with the need to increase awareness of the availability of such code and, most importantly, how to use it in face of the current lack of a standardized clinical/diagnostic assessment of sarcopenia.

| Evaluation component | Questions | Scoring |
|---|---|---|
| Strength | How much difficulty do you have in lifting and carrying 10 pounds? | None = 0Some = 1A lot or unable = 2 |
| Assistance with walking | How much difficulty do you have walking across a room? | None = 0Some = 1A lot, use aids, or unable = 2 |
| Rising from a chair | How much difficulty do you have transferring from a chair or bed? | None = 0Some = 1A lot or unable without help = 2 |
| Climbing stairs | How much difficulty do you have climbing a flight of 10 stairs? | None = 0Some = 1A lot or unable = 2 |
| Falls | How many times have you fallen in the past year? | None = 01 to 3 falls = 14 or more falls = 2 |

**Table 3.** SARC-F scale: scores of 4 or more indicate sarcopenia [54].

### 2.5. Biomarkers and outcomes for sarcopenia

The most basic biomarkers (functional, biological, or imaging-related) that can be utilized in clinical trials of sarcopenia and considered the most reliable and promising to evaluate age-related changes of skeletal muscle have been discussed and recommended. **Table 4** summarizes information on these proposed biomarkers for sarcopenia research. In addition, the measurement of motor unit number index, which can be used to assess the number and the size of the motor units is a very important biomarker as loss of motor unit input to muscle is a significant cause of sarcopenia in at least half of older individuals [22, 48, 62].

In view of the molecular mechanisms involved in the pathogenesis of sarcopenia, potential emerging sarcopenia biomarkers have been discussed. Normal muscle mass and function maintenance are thought to be dependent on the dynamic balance between the positive regulators of muscle growth such as bone morphogenetic proteins (BMPs), brain-derived neurotrophic factor (BDNF), follistatin (FST) and irisin, and negative regulators including TGFβ, myostatin, activins A and B, and growth and differentiation factor-15 (GDF-15). The authors hypothesized that the shift in this balance to muscle growth inhibitors, along with increased expression of the C-terminal agrin fragment (CAF) associated with age-dependent neuromuscular junction (NMJ) dysfunction, as well as skeletal muscle-specific troponin T (sTnT), a key component of contractile structure, is a main mechanism underlying sarcopenia pathogenesis. Based on these facts, the molecular elements mentioned above are proposed as emerging sarcopenia biomarkers [63].

As indicated previously the EWGSOP recommends the use of physical performance, muscle strength, and muscle mass as the primary treatment outcome indicators for sarcopenia intervention trials. Activities of daily living, quality of life, metabolic and biochemical markers, inflammatory markers, global impression of change by subject or physician, falls, admission to nursing home or hospital, social support, and mortality are recommended by that group as secondary outcome indicators [9].

The AWGS recommends the following approach in outcome indicators assessment for sarcopenia research. This approach targets the measurement of changes in two ways over a period. The AWGS also recommends the use of fear of falling and incontinence as outcome indicators for sarcopenia research [15]:

**a.** Static approach: Activities of daily living, quality of life, inflammatory markers, falls, frailty issues, mobility disorders, admission to hospitals, admission to long-term care facilities, and mortality.

**b.** Dynamic approach: Changes in muscle mass, muscle strength, physical performance, frailty status, instrumental activities of daily living, and activities of daily living.

Finally, the importance of tapping into the patient experience, identifying the linkage between clinical measures and patient reports, and building self-report into submissions for drug

| | | Inclusion-exclusion criteria | Baseline evaluation | Endpoint assessment |
|---|---|---|---|---|
| Muscle function | Physical performance measures | +++ | +++ | +++ |
| | Muscle strength measures | +++ | +++ | +++ |
| | Disability | +++ | +++ | +++ |
| Muscle mass | Anthropometry | + | - | - |
| | Bioelectrical impedance analysis | + | - | - |
| | Dual energy X-ray absorptiometry | +++ | ++ | ++ |
| | Computerized tomography | ++ | +++ | +++ |
| | Magnetic resonance imaging | ++ | +++ | +++ |
| | Echography | ++ | ++ | ++ |
| | Electrical impedance myography | + | ++ | ++ |
| Biological confounders (mechanisms) | Inflammation | ++ | ++ | ++ |
| | Oxidative damage | ++ | ++ | ++ |
| Note: | Antioxidants | ++ | ++ | ++ |
| The importance of all these | Apoptosis | + | ++ | ++ |
| biomarkers in the evaluation of sarcopenia will largely depend on the study | Nutritional parameters (albumin, hemoglobin, urinary creatinine, others) | +++ | ++ | ++ |
| hypotheses, the specific aims, and/or the target population | Hormones (dehydroepiandrosterone, testosterone, insulin-like growth factor-1, others) | ++ | ++ | ++ |

- not recommended for this use; + may be of use; but severely limited; ++ suitable for this use; +++ recommended for this use.

**Table 4.** Potential biomarkers for clinical trials on sarcopenia [48].

approval to the HHS FDA have been a matter of discussion among experts. Work is ongoing with questionnaires focusing on patient-reported outcome measures in sarcopenia, but validation is pending [64]. In addition, the HHS FDA conducted on April 06, 2017, a public meeting on patient-focused drug development for sarcopenia. The HHS FDA is interested in obtaining patient perspectives on the impact of sarcopenia on daily life and patient views on treatment approaches.

## 3. Integrating muscle quality in efforts to define sarcopenia and muscle quality in the context of skeletal muscle function deficit

Aging is associated with significant changes in body composition, gradual increase in total body fat during adulthood followed by a loss later in life, and remodeling of fat distribution. The latter involves an increase in inter/intramuscular and visceral fat, and a gradual loss of subcutaneous fat. Weight gain and weight loss overtime have been linked with preserved muscle mass and accelerated muscle atrophy, respectively. Both, however, are associated with increased fat infiltration of muscles. Adverse health and functional outcomes including the development of insulin resistance and impaired mechanical muscle function seem to be concurrently or independently associated with the aging changes mentioned above. Evidence suggests that the correlation between "muscle quantity" and "muscle function" (e.g., muscle strength) is relatively weak, and in contrast to muscle strength, muscle mass has been demonstrated to be a poor predictor of functional limitation, gait speed, and even mortality. It is, in fact, becoming increasingly clear that muscle quality (force per unit of muscle mass) and neural function play a key role in the development of mobility disability and that a new endpoint incorporating these aspects in addition to muscle mass and strength might be useful.

### 3.1. Defining muscle quality: the need for a standardized assessment

Multiple factors are known to underpin muscle quality and determine the changes in muscle function and mobility later in life. Those who conduct sarcopenia-related research have usually used relative force production (ratio of peak force and a measure of body size, regional lean body mass, or cross-sectional area) as the favored approach to characterizing muscle quality [65, 66]. Emerging definitions of muscle quality, however, call for its expansion to include muscle composition, metabolism, aerobic capacity, insulin resistance, fat infiltration, fibrosis, and neural activation [67], all of which easily correlate with the concept of SMFD. The term muscle quality allows investigators to explore aspects of SMFD beyond the construct of age-related decline of lean body mass [6]. While the meaning of muscle quality is linked to the primary functions of the skeletal muscle, it can be expanded to include both physiology and pathophysiology [8]. There is also a need to develop and adopt a standardized assessment of muscle quality. In doing so, it is essential to consider the complexity of the skeletal muscle tissue and its physiologic roles that include not only movement via force production, but also metabolism through its maintenance of glucose/insulin homeostasis and amino acid storage, thermoregulation, and autocrine/paracrine/endocrine signaling via myokine production. This expanded view of muscle quality is essential to improve our understanding of SMFD [8].

A preliminary conceptual model for the assessment of muscle quality has been proposed, built on skeletal muscle primary physiologic functions. This conceptual model is categorized in domains that have both clinical and research applications. The domains are the following: (A) force production; (B) metabolism (endocrine, neurologic, orthopedic); (C) thermoregulation; and (D) signalling/myokine production. No endpoint(s) have been identified as best to establish the quantitative profile of muscle quality. Similarly, no standardized approaches to endpoint measures have been recommended that can be linked to any of the domains above. None have been identified as the most strongly associated with mechanisms controlling muscle function or with predicting mobility status and mortality in older adults. Muscle quality seen under this perspective provides the advantage of going beyond the strict lean body mass-driven assessment approach to sarcopenia research. Ongoing research focusing on the local and systemic effects of fat infiltration of muscles and on the emerging methods to quantify changes in muscle composition and function is reflecting this perspective [8].

### 3.2. Factors underpinning muscle quality

Below is a brief discussion on the multiple factors underpinning muscle quality, all of which fall under the proposed domains for assessing muscle quality. The concept of muscle quality cannot be represented by a single endpoint measure, but the factors that affect muscle quality are frequent targets of measurement used to characterize skeletal muscle. The discussion provided in this section does not enclose every assessment target, but addresses common examples of factors that may serve as measures for basic, translational, and clinical trials related to muscle quality and sarcopenia or muscle quality in the context of SMFD. Factors intrinsic to skeletal muscles are crucial for function and homeostasis. Factors extrinsic to skeletal muscles considerably impact muscle activity and muscle mass building and maintenance. Both intrinsic and extrinsic factors affect net force production.

#### *3.2.1. Muscle characteristics/architecture*

Muscle characteristics include size, fiber type, and contractile components. Fiber type and number determine muscle size. Muscle cross-sectional area has a positive relationship with muscle strength in young lean individuals, while smaller and weaker muscles are usually seen in older adults. Muscle cross-sectional area and lower limb skeletal muscle volume are associated with greater fat mass in both men and women [68], likely due to intermuscular lipid or noncontractile components. There are three types of muscle fibers as identified in **Table 5** [68]. The loss of types I and IIb muscle fibers associated with aging is attributed to changes in activity and consequent disuse and denervation. Conflicting literature demonstrates no link at all or a link between advanced age and changes in muscle fiber composition with gradual loss of type IIb muscle fibers [69]. Conflicting limited evidence is also seen in older adults in relation to changes in muscle fiber type, muscle cross-sectional area, and strength. Contractile properties of types I and II muscle fibers at the single fiber level seem to be maintained independent of the presence of mobility limitation [70], but again, evidence is conflicting. It has been suggested that maximal shortening velocity is lower in single fibers from older adults because of changes in myosin heavy chain isoform distribution to a more hybrid pattern. A

| Type I | Type IIa | Type IIb |
|---|---|---|
| Predominantly generate energy via oxidative pathways for prolonged low force production.Relatively small cross-sectional area compared to type IIb fibers, but have greater oxidative capacity.Recruited during low intensity activities of daily living (e.g., walking) | Capable of generating energy via oxidative and nonoxidative pathways | Predominantly generate energy via nonoxidative pathways for rapid high force production.Recruited during high intensity activity |

**Table 5.** Types and functions of skeletal muscle fibers [68].

lower maximal shortening velocity in myosin heavy chain has been observed in types I and IIa fiber of older adults including those who are very active. The evidence, however, is debatable because of limitations with study power and potential confounding with physical activity. Preservation of single muscle fiber contractile properties with age is thought to imply that differences in skeletal muscle function are related to quantitative changes in muscle fiber size or number rather than qualitative changes in the muscle's contractile properties [68].

Fiber arrangement within a muscle (e.g., parallel or pennation pattern) will determine fascicle length, pennation angle, and cross-sectional area, all of which can change with age. Older adults 70–81 years of age are reported to have smaller fascicle length and pennation angle (compared to younger adults 27–42 years) of the gastrocnemius medialis [71], but several weeks of bed rest have not resulted in changes in the pennation angle of the vastus lateralis muscle. Nevertheless, modest improvements in muscle architecture are reported to be possible with 4–5 weeks of resistance training. Changes in muscle architecture also appear to precede changes in muscle size in young healthy adults.

Cross-sectional assessment of skeletal muscles provides relevant information on muscle function because both individual muscle fiber diameter and cross-sectional diameter of the whole muscle are associated with strength. Force production is related to the architectural characteristics of the skeletal muscle including muscle fiber length and arrangement in relation to the direction of the force produced by the whole muscle. Thus, both cross-sectional and longitudinal orientation of measures of skeletal muscles are valuable in the assessment of the size-strength relationship and the identification of age-related differences in muscle strength per size. Sarcomeric changes in myofibrillar disorder, Z-line streaming, and dilatation in aged skeletal muscle have been observed in electron microscopic analysis. The characteristics/architectural changes highlighted above have been combined in a composite measure—physiological cross-sectional area (PCSA)—to reflect both strength and change in strength in leg extension [8].

Muscle weakness is attributed to changes in muscle composition, muscle contractile quality, and neural activation [72]. However, measures of muscle composition, size, and architecture generally do not consider the neural input into fibers, which dictate contraction potential and force production. Strength measures are an important indicator of muscle performance and show the ability to change in response to a variety of interventions to tackle sarcopenia and frailty

in older women with clinically relevant muscle weakness independent of the presence of low muscle mass [73]. Muscle strength and size have been used as a single measure of muscle quality known as "relative strength," reflecting the expression of muscle force production relative to muscle or body size. It has been suggested that strength per unit of muscle tissue may serve as a better indicator of age-related differences in muscle quality prior to changes in lean tissue mass [74]. A novel functional metric—muscle quality index—estimates muscle power from body anthropometrics and timed chair raises; it has been found to have higher reliability and greater responsiveness following a resistance exercise regimen in older adults, compared to other functional measures (e.g., gait speed, grip strength, the get-up and go test, etc.) [75].

*3.2.2. Muscle aerobic capacity*

Muscle quality and function in both middle-aged and older adults are determined by metabolic characteristics of the muscle. Aerobic capacity reflects the maximal ability to use oxygen (cardiovascular adaptation to transport oxygen; within skeletal muscle adaptation to use oxygen) in response to energy demands of physical activity. Evidence shows that aerobic capacity declines at an accelerated rate after age 50, and is a strong predictor of mobility assessed by gait speed in older adults. Evidence from cross-sectional muscle analyses from healthy men and women (18–90 years) reveals that mitochondrial DNA, mRNA abundance, and energy (ATP) production diminishes with age. Both skeletal muscle mitochondrial capacity and efficiency, and whole body peak aerobic capacity have been linked to gait speed [68, 76, 77].

The progressive decline in mitochondrial function observed in aging results in the accumulation of reactive oxygen species (ROS) generated by the incorporation of a single electron to the oxygen molecule. Specifically, ROS negatively impact muscle quality, playing an extremely important role in all muscle functions, muscle aging, contraction, fatigue, dystrophy or waste [78–80]. Mitochondria are the major producers of ROS, which damage DNA, proteins, and lipids. Animal and human studies have typically shown that aging changes in mitochondria can be reflected by increased mutations in mitochondrial DNA, decreased activity of some mitochondrial enzymes, altered respiration with reduced maximal capacity at least in sedentary individuals, and reduced total mitochondrial content with increased morphological changes. With mitochondrial dynamics altered (e.g., fusion and fission rates, mitochondrially induced apoptosis), net muscle fiber loss and age-related sarcopenia may ensue. Strategies such as exercise and caloric restriction that reduce oxidative damage can improve mitochondrial function. While these strategies may not completely prevent the primary effects of aging, they may help to attenuate the rate of decline [81, 82].

It is also well established that contracting muscles produce both ROS and nitrogen species. Although the sources of oxidant production during exercise continue to be debated, growing evidence suggests that mitochondria are not the dominant source [83]. Regardless of the sources of oxidants in contracting muscles, intense and prolonged exercise can result in oxidative damage to both proteins and lipids in the contracting myocytes. Further, oxidants regulate numerous cell signaling pathways and modulate the expression of many genes. There has been much controversy about measurements of mitochondrial energy production. These controversies may be explained by differences in methodological approaches and whether physical activity is controlled for.

Age-related changes in skeletal muscle mass and composition can result in increased insulin resistance and later to reduced capacity for insulin-mediated glucose disposal. Relative muscle mass in healthy nondiabetic older adults is inversely linked to glucose tolerance and insulin resistance [84]. Muscle strength adjusted for BMI, however, has been reported to be negatively associated with insulin resistance in a large population based study of older women, but not men, after adjustment for confounders. No association between muscle leg strength and insulin resistance in men or women >50 years has been observed in an analysis of the National Health and Nutrition Examination Survey (NHANES) [85]. In some studies, gait speed assessments are found to be inversely associated with insulin resistance, suggesting that insulin resistance may serve as an indicator of poor muscle quality underpinning low levels of physical fitness and poor scores on gait speed tests. Improvement in glucose disposal and skeletal muscle metabolism in older overweight or obese men has been observed over 6 months of both regular aerobic and resistance exercise. Fat infiltration of muscles is also associated with insulin resistance.

### *3.2.3. Myosteatosis*

Myosteatosis refers to fat infiltration in skeletal muscle that can lead to large negative clinical effects including poor metabolic and skeletal muscle health, accelerated aging, and impaired longevity. This ectopic fat tissue has become an important factor behind muscle quality and may serve as a predictor of muscle function in older adults. Two modalities of myosteatosis are identified: (1) intermuscular fat, which represents the visible extracellular adipose tissue located beneath the muscle and between and within muscle groups; (2) intramuscular fat or intramyocellular lipids, which represents infiltration within myocytes, i.e., the presence of microscopic lipid droplets used as energy within the muscle. This ectopic fat infiltration increases with aging, seems to act synergistically with sarcopenia and is also present in muscular dystrophies. The biological mechanism underlying increases in myosteatosis with aging in humans remain largely under investigated, with the need to identify and better understand regulatory factors including evidence of senescent cells and cultured cells developing into preadipocytes and fat cells. This is an opportunity for future development of therapies to preserve skeletal muscle health [8, 86, 87].

Individuals with comparable thigh circumference may have distinct muscle function due to the proportion of fat infiltration to contractile elements. In older adults with multimorbidity, intermuscular adipose tissue evaluated by MRI was reported as the strongest predictor of mobility, but strength and quadriceps lean tissue explicated some of the variation in mobility in this study [88]. Increased mobility loss, reflected by decreased six-minute walk distance, decreased gait speed, decreased physical performance, difficulty with repeated chair stands, and slower stair descent and timed get-up and go tests have been reported as the result of myosteatosis effects on muscle metabolism and function [8]. In young healthy persons with 30 days of leg disuse by suspension, myosteatosis was found to increase by 15–20% and exceeded the loss of lean muscles (calf and thigh) [89]. Myosteatosis is also known to lead to the transition of muscle fibers from type II to type I, which result in muscles with impaired contractile capacity and decreased power [90, 91]. It is also suggested that myostetatosis may harm muscle and mobility because fat infiltration leads to changes in muscle fiber orientation.

Proinflammatory cytokines secreted by fat tissue in the skeletal muscle microenvironment may also lead to proteolysis and muscle catabolism [8].

Fat storage and infiltration into muscle may be a marker of metabolic profile. In older adults, intermuscular adipose tissue was found to positively correlate with higher fasting plasma glucose and lower glucose tolerance [92]. Myosteatosis has been linked to insulin resistance and an increased risk of developing type-2 diabetes, hypertension, and dyslipidemia, independent of total body adiposity (measured by BMI or DXA whole body fat). Further investigation, however is still needed on the association of myosteatosis and metabolic disease independent of visceral fat. The metabolic consequences of myosteatosis depend on age, race/ethnicity, aerobic conditioning, sensitivity to insulin, amount of physical activity, and anatomic region. Further investigations are necessary to verify whether myosteatosis acts as a marker of metabolic dysfunction or may have an intermediary modifying role in insulin resistance [8].

Physical activity seems to be able to revert intermuscular fat infiltration. In men 60 years old, six months of aerobic exercise and weight loss decreased intermuscular adipose tissue of the leg and improved fasting plasma glucose and glucose tolerance. Four weeks of an imposed decrease in physical activity due to unilateral lower limb suspension resulted in 15–20% increase in the intermuscular adipose tissue in the thigh and calf, respectively. Strength loss was associated with the increase in the intermuscular adipose tissue, after adjustment for loss of muscle mass and considering initial baseline values.

#### *3.2.4. Muscle fibrosis*

Impairment in the muscle repair process can lead to muscle fibrosis, which involves the deposition of collagen and extracellular matrix proteins instead of proteins necessary to repair and restore tissue function. Fibrosis is also seen in different tissues because of extra fat accumulation. The presence of fibrosis in the skeletal muscle of older adults is hypothetical at this point, and further studies are needed to investigate how or whether fibrosis is a factor in muscle quality. Evidence, however, is available indicating that progressive intermuscular adipose tissue infiltration in middle aged or older adults may lead to fibrosis and impairment of muscle function and mobility [68].

#### *3.2.5. Motor units and neuromuscular activation*

Other potential factors related to muscle quality in middle and old age include components of the neuromuscular system and neuromuscular activation. Skeletal muscle fibers are organized in bundles of motor units. Each motor unit is innervated by a motor nerve, which connects to an alpha motor-neuron in the spinal cord. Across the lifespan, motor units go through remodeling, denervation and reinnervation. These units are reported to be decreased in the tibialis anterior muscle of men 65 years old and those >80 years compared to younger men (25 years), but the reduced motor unit number was only related to strength in men >80 years [93].

Neuromuscular activation has been proposed as another measure of muscle quality. Impairments in neuromuscular activation affect the rate of force development and muscle power needed for dynamic movements. Improvements in neuromuscular activation generally precede increases in muscle mass in response to resistance training. Neuromuscular activity and acceleration was

impaired during dynamic leg extensions in mobility-limited older adults compared to mobile older adults [94]. The rate of neuromuscular activation was significantly associated with physical function scores. Among middle-aged and older adults without mobility limitations, no significant differences in measures of neuromuscular activation were detected. However, whether neuromuscular impairment precedes the development of mobility limitations is still unclear.

### 3.3. Emerging alternative clinical imaging and other measures of muscle quality

Relatively high costs, limitations with access, and the testing burden associated with invasive techniques are barriers to standardized assessment of muscle quality. The use of routine tissue composition analysis is hampered by the need for further demonstration of its diagnostic value and contribution to both diagnostic and therapeutic decision making. The emerging literature on the effects of age-related increases in intramuscular adipose tissue on muscle performance and metabolism, has led to the development of alternative assessment. Methodological approaches ranging from multifrequency electrical impedance analysis to quantitative diagnostic sonography have been used to characterize skeletal muscle mass and quality in older adults and in those with muscle disease [95]. Noninvasive, high precision, imaging modalities such as MRI has been used to diagnose and assess progression of a number of neuromuscular conditions. Quantitative musculoskeletal diagnostic ultrasound has been proposed as a clinically feasible means of characterizing muscle structure. Ultrasound has been shown to be highly reliable for assessing cross-sectional areas of large individual human muscle and particularly useful in mobility-impaired individuals who cannot be easily transported to scanners (CT, MRI) [48].

Electrical impedance myography (EIM) is another promising technique based on the surface application and measurement of a high frequency, low intensity electrical current applied to specific muscles. It detects changes in the conductivity and permittivity of skeletal muscles caused by alterations in muscle composition and structure. It has been found repeatable and sensitive to skeletal muscle changes in persons with amyotrophic lateral sclerosis. Mass isopotomer distribution analysis based on the evaluation of protein and proteome synthesis rate is obtained by heavy water labelling; it is a very promising approach due to the wide spectrum of proteins analysed [48].

The success of emerging alternative imaging measures of muscle quality relies on their easy-to-use in diverse clinical settings and ability to discriminate between older adults with and without sarcopenia, identify those at risk for impaired muscle performance, and those who can benefit from preventive and therapeutic interventions. A symposium report on "The Need for Standardized Assessment of Muscle Quality in Skeletal Muscle Function Deficit and Other Aging-Related Muscle Dysfunctions" provides a good insight on these emerging approaches [8].

## 4. Conclusion: clinical relevance and research opportunities

Aging muscles and other aging-related muscle dysfunctions present with a functional deficit in one or more elements or components of SMFD involving muscle mass, muscle strength

or muscle quality. To further characterize SMFD, additional investigation and understanding of the factors behind changes in muscle quality with aging are needed. The concept of muscle quality is critical and should be expanded beyond muscle strength or power per unit of muscle mass, to encompass muscle aerobic capacity and other key factors which closely relate to mobility and other important activities of daily living. Assessment or diagnostics tools sensitive to small changes within skeletal muscle that precede a decline in mass, strength and function can enable preventative steps to maintain healthy muscles. Diagnostic ultrasound and other assessment methods continue to be developed for characterizing muscle pathology, and enhanced sonography using sensors to provide user feedback and improve reliability is currently the subject of ongoing investigation and development. Measures of relative muscle force (e.g., specific force or grip strength adjusted for body size) have been proposed as methods to assess changes in muscle quality. Performance-based assessments of muscle power via timed tests of function and body size estimates are associated with lower extremity muscle strength and may be responsive to age-related changes in muscle quality. The challenge remains to reach a consensus on diagnostic criteria, tools, and consistent methodological approaches for assessing or measuring components of SMFD that are practical in a community or clinical setting. These should be considered priority for the scientific community and health care providers.

To date, no studies have assessed exclusively and concurrently aging-related changes in muscle mass, muscle strength, muscle function, and muscle quality. Analyses of pooled data from large studies on aging with measures of muscle mass and strength still face numerous methodological challenges. As highlighted by experts in the field, future well-designed large prospective studies of interventions to improve muscle mass, muscle strength, muscle function, and muscle quality can observe age-related changes in skeletal muscles over time and generate the evidence to help identify individuals that will benefit from interventions to prevent or treat these changes.

From the public health perspective, further characterization of SMFD is very relevant to several ongoing therapeutic developments. For example, we already know that resistance exercise is the primary therapeutic strategy to prevent and reverse sarcopenia; aerobic exercise also has a therapeutic role, as demonstrated by the Lifestyle Interventions and Independence for Elders (LIFE); vitamin D has been shown to enhance muscle function in persons with low muscle function; and evidence that leucine-enriched essential amino acid supplementation will increase muscle mass and potentially function. Limited evidence, however, suggests that testosterone increases muscle mass and strength, and potentially function in older adults with hypogonadism, but its safety remains unclear. Drug development efforts with selective androgen receptor modulators (SARMs) are promising in increasing muscle mass and stair climbing. Ongoing research is also investigating numerous antibodies that modulate myostatin and the activin II receptor, as well as ghrelin agonists, which increase food intake and release growth hormone [7].

The potential impact of clearly addressing SMFD and properly integrating muscle mass, muscle strength, and muscle quality is critical to future therapeutic development to help older adults with muscle dysfunctions maintain independence and quality of life.

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