Special Article

Establishing the Link Between Lean Mass and Grip Strength Cut Points With Mobility Disability and Other Health Outcomes: Proceedings of the Sarcopenia Definition and Outcomes Consortium Conference

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Abstract

Background: Lack of consensus on how to diagnose sarcopenia has limited the ability to diagnose this condition and hindered drug development. The Sarcopenia Definitions and Outcomes Consortium (SDOC) was formed to develop evidence-based diagnostic cut points for lean mass and/or muscle strength that identify people at increased risk of mobility disability. We describe here the proceedings of a meeting of SDOC and other experts to discuss strategic considerations in the development of evidence-based sarcopenia definition.

Methods: Presentations and panel discussions reviewed the usefulness of sarcopenia as a biomarker, the analytical approach used by SDOC to establish cut points, and preliminary findings, and provided strategic direction to develop an evidence-based definition of sarcopenia.

Results: The SDOC assembled data from eight epidemiological cohorts consisting of 18,831 participants, clinical populations from 10 randomized trials and observational studies, and 2 nationally representative cohorts. In preliminary assessments, grip strength or grip strength divided by body mass index was identified as discriminators of risk for mobility disability (walking speed <0.8 m/s), whereas dual-energy X-ray absorptiometry-derived lean mass measures were not good discriminators of mobility disability. Candidate definitions based on grip strength variables were associated with increased risk of mortality, falls, mobility disability, and instrumental activities of daily living disability. The prevalence of low grip strength increased with age. The attendees recommended the establishment of an International Expert Panel to review a series of position statements on sarcopenia definition that are informed by the findings of the SDOC analyses and synthesis of literature.

Conclusions: International consensus on an evidence-based definition of sarcopenia is needed. Grip strength—absolute or adjusted for body mass index—is an important discriminator of mobility disability and other endpoints. Additional research is needed to develop a predictive risk model that takes into account sarcopenia components as well as age, sex, race, and comorbidities.

Keywords: Sarcopenia, Lean mass cut-points, Grip strength cut-points, Mobility disability, Risk factors for mobility disability.

The concept of sarcopenia as a clinical biomarker to identify older adults at risk of physical disability and poor health outcomes is appealing for older adults who are at risk for mobility disability, practicing clinicians who care for these patients, and to the pharmaceutical companies engaged in the development of function promoting therapies to prevent or treat functional limitations (1–3). Although many have proposed that the definition be based on the measurement of lean mass and/or muscle strength (3–14), the lack of consensus on how to diagnose sarcopenia has limited the ability of practicing clinicians to diagnose and treat this condition and has hindered pharmaceutical efforts to develop function promoting therapies. The powerful demographic trends toward aging of human populations across the globe have inspired large investments in the field of sarcopenia by governments, pharmaceutical companies, and professional societies across geographic boundaries. The Sarcopenia Definition and Outcomes Consortium (SDOC) was formed to address this global public health need.

In response to a funding opportunity announcement from the National Institute on Aging (NIA), several investigators representing many cohort studies and clinical populations formed the SDOC. This team has applied data-driven analytical approaches to define sarcopenia. In October 2017, the SDOC held a meeting to discuss important considerations in the development and clinical application of an evidence-based definition of sarcopenia. This meeting also included a keynote lecture to highlight similarities and differences between the definitions of sarcopenia and osteoporosis. The analytical approach used by the SDOC investigators to establish cut points for lean body mass and/ or muscle strength measures to define sarcopenia and its implications were discussed in several presentations and panel discussions. This article provides a summary of the conference proceedings including preliminary findings of the analyses and potential strategies toward the development of a consensus definition of sarcopenia. Several original manuscripts describing the methods and detailed results of these analyses are being prepared for publication.

Overview of the SDOC Goals and Analytic Approach

The primary goal of the SDOC is to develop and evaluate evidence-based diagnostic cut points for low lean mass and/or muscle strength that identify people at increased risk of objectively assessed mobility disability, defined as usual gait speed less than 0.8 m/s over 4–6 m. Secondary goals are to evaluate the identified cut points against incident clinical outcomes such as mortality, falls, fractures, and instrumental activities of daily living disability and to assess performance characteristics (sensitivity, specificity, and predictive value) in population-based studies and clinical populations. These analyses build on those of the related Foundation for the National Institutes of Health Sarcopenia project that preceded this effort and ran from 2009 to 2012. In 2015, the National Institute on Aging funded the SDOC, and the Foundation for the National Institutes of Health provided additional support in March 2016.

The SDOC project represents one of the most ambitious efforts to define sarcopenia using an evidence-based approach informed by the analyses of data from large epidemiological studies, randomized clinical trials and cohorts of clinical populations, and two nationally representative population-based cohorts. The SDOC project not only evaluated the cut points that emerged from the SDOC analyses but also evaluated other competing definitions existing in the literature (3–14).

Sources of Epidemiological Data

The data used by the SDOC came from eight epidemiological cohorts consisting of 18,831 participants (13,683 men and 5,148 women) with a mean age of 75 years (Table 1) (15–24). Of these participants, 3,143 (17%) had self-reported mobility limitation defined as any difficulty walking 2–3 blocks or climbing 10 steps. In addition, SDOC included 10 clinical populations of patients drawn from randomized trials and smaller observational studies in patients with hip fractures and HIV (25–34). Finally, the cut points derived from analyses of the epidemiological studies were applied to two nationally representative population-based cohorts, the Health and Retirement Survey (*n* = 7,370 with 3,170 men and 4,200 women) and the National Health and Aging Trends Survey (*n* = 5,614, with 2,460 men and 3,154 women) (35,36) to determine the prevalence of older adults who were below these thresholds.
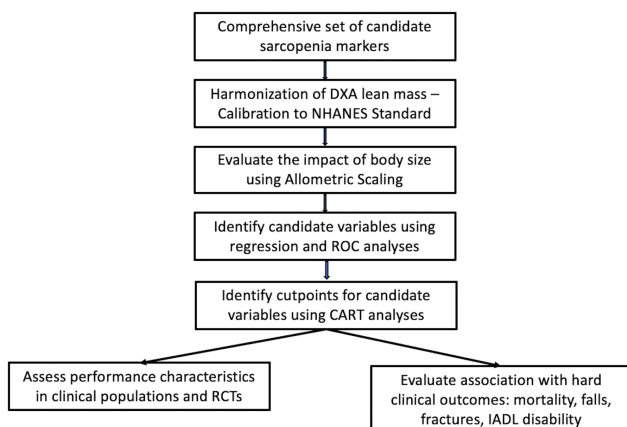
Analytical Approach

The analytic approach of the SDOC is summarized in Figure 1. As noted later, we first harmonized the measurements of body composition assessed by dual-energy X-ray absorptiometry (DXA),

Table 1. Studies Participating in the Sarcopenia Outcomes and Definitions Consortium

Study	Eligibility	N Men	N Women
Epidemiological studies			
Osteoporotic Fractures in Men (MrOS) Study[1,2]	Ambulatory community-dwelling men, aged ≥ 65 y	5,835	0
Study of Osteoporotic Fractures (SOF)[3,4]	Ambulatory community-dwelling women, aged ≥ 65 y	0	1,246
Health, Aging and Body Composition Study (Health ABC)[5]	Nondisabled black and white men and women aged 70–80	652	746
MrOS Sweden[6]	Men aged ≥ 70 y in three Swedish communities	2,876	0
Mr and MsOS Hong Kong[7,8]	Men and women aged ≥ 65 y residing in Hong Kong	2,000	2,000
Concord Health and Aging in Men Project (CHAMP)[9]	Men aged ≥ 65 y living near Concord, Australia	1,529	0
Cardiovascular Health Study[10,11]	Age ≥65 y at original study enrollment	638	871
Johnston County Arthritis Study[12]	Rural white and black residents of Johnston County, North Carolina	153	285
Epidemiological studies total		13,683	5,148
Clinical populations and randomized trials			
LIFE-Pilot Trial	Men and women aged 70–89 y	72	187
VIVE2 Trial	Community-dwelling men and women ≥ 70 y	80	64
TOM Trial	Community-dwelling men ≥ 65 y	194	—
SECRET Trial	Men and women aged > 60 y with HFPEF	16	71
PIE2 Trial	Men and women aged ≥ 60 y with HFPEF	17	40
IDEA Trial	Men and women aged ≥ 60 y with closed hip fracture	54	130
MACS Bone Strength Substudy (BOSS)	HIV-infected and HIV-uninfected men aged 50–79 y	370	—
Women's Interagency HIV Study	HIV-infected and HIV-uninfected women aged 30–55	—	187
Baltimore Hip Studies 4	Community-dwelling women ≥ 65 y	—	121
Baltimore Hip Studies 7	Men and women aged ≥ 65 y and admitted for surgical repair of hip fracture	54	71
Clinical populations and randomized trials total		857	871
Population-based studies			
Health and Retirement Survey (HRS)	Men and women aged 51+; our analyses limited to those ≥ 65 y	3,170	4,200
National Health and Aging Trends Study (NHATS)	Nationally representative sample of Medicare beneficiaries, ≥ 65 y	2,460	3,154
Population-based studies total		5,630	7,354

Note: LIFE-Pilot, Lifestyle Intervention for Elders Pilot Study; MrOS Sweden, Osteoporotic Fractures in Men Study in Sweden; MrOS Hong Kong, Osteoporotic Fractures in Men Study in Hong Kong; MsOS Hong Kong, Osteoporotic Fractures in Women Study in Hong Kong; TOM Trial, Testosterone in Older Men with Mobility Limitation Trial; VIVE2 Trial, The Vitality, Independence, and Vigor in the Elderly 2 Study; SECRET Trial, Exercise Intolerance in Elderly Patients With HFpEF (Heart Failure With Preserved Ejection Fraction); PIE2 Trial, Pharmacologic Interventions in the Elderly Study 2; IDEA Trial, Intensive Diet and Exercise for Arthritis study.

The Analytical Approach

Figure 1. A schematic depiction of the analytic approach. Full color version is available within the online issue.

and other variables across the epidemiological studies, thereby removing excess variation resulting from the use of different machines and methods in different studies. We selected candidate markers of the sarcopenia phenotype after assessing the effect of allometric scaling. We used receiver operating characteristic and area under the curve from logistic regression to screen several putative "sarcopenia" variables derived from lean mass, grip strength, body size, and their combinations against the outcome of mobility disability, defined as walking speed less than 0.8 m/s. Those variables with the highest area under the curve that were most consistently associated with mobility disability were entered into Classification and Regression Trees models to derive cut points for low muscle mass and strength as discriminators of mobility disability. Sex-stratified Classification and Regression Trees analyses were conducted with age, several measures of body size (height, weight, and body mass index), grip strength (alone or standardized to body size), and lean mass (total, appendicular, and leg lean mass alone or standardized to body size) as potential discriminators of mobility disability. Finally, we examined the ability of these cut points to predict other incident clinical endpoints (e.g. mortality, falls, mobility, and instrumental activities of daily living disability) and evaluated the performance characteristics of these cut points in clinical populations and nationally representative samples (sensitivity, specificity, predictive value, and prevalence).

Harmonization of DXA Data

Owing to the variation between the machines and software, DXA values obtained for a given individual may vary across machines. Therefore, DXA-derived estimates of lean and fat mass were harmonized across the eligible epidemiological cohorts using mathematical equations provided by scientific group at Hologic, Inc (37).

Allometric Scaling

We used allometric scaling to evaluate various coefficients to account for the influence of body size on lean mass and strength (38). For example, the measure of appendicular lean mass/height^2 (ALM/ht^2) includes the ht^2 term to remove the influence of height (as a surrogate measure for body size) from the lean mass measure. However, the squared term is arbitrary, and another power (perhaps $x^{3.1}$ or $x^{4.2}$) may more appropriately account for height. Thus, we regressed the log of height on the log of appendicular lean mass and took the intercept of this regression as the allometric coefficient. A total of 73 different measures of low lean mass or grip strength (stratified by gender) allometrically scaled to height, height^2, weight, body surface area, body mass index, fat mass, appendicular fat mass, leg lean mass, etc. were evaluated against gait speed cutoffs, using the area under the receiver operating characteristic curve. We performed both ratio-based and regression residual approach with grip strength and appendicular lean mass.

This enabled us to determine the number of subjects below each cut point and to compare the sensitivity and specificity of the cut points to those of leading definitions of sarcopenia.

The performance characteristics of various cut points for the recovery from hip fracture cohorts (Baltimore Hip Studies 4 and 7) were analyzed separately. This was necessary because the hip fracture cohorts differed from other studies in that patients with hip fracture are not ambulatory at the point of fracture and then improve over time, whereas other populations of older adults generally exhibit declining walking performance over time. Data from two cohorts in the Baltimore Hip Studies (*n* = 226) were used; mobility disability was defined as gait speeds of less than 0.6 m/s; and improvement in gait speed as an increase of at least 0.1 m/s (note: the baseline was measured at 2 months post-fracture). The Classification and Regression Trees-derived cut points were used to derive prevalence estimates and to evaluate the sensitivity and specificity of these cut points in predicting both objectively measured mobility disability 6 months post-hip fracture and improvement in gait speed from 2 to 6 months.

The performance characteristics of various cut points in the HIV cohorts were also analyzed separately. The life span of HIV+ individuals is now almost the same as that for HIV– individuals. In general, HIV+ populations have a higher prevalence of aging-related comorbidities, and older HIV+ populations may have a more rapid decline in physical function with aging and an earlier appearance of physical frailty. The cut points were applied to those with or at risk of HIV infection and their sensitivity, specificity, and predictive value in identifying low gait speed in this population were compared. The data came from the Bone Strength Sub Study of the Multicenter AIDS Cohort Study, a study of men who have sex with men; these men have been evaluated semi-annually since 1984 at four U.S. sites. The data on women were obtained from the Musculoskeletal Sub Study of the Women's Interagency HIV Study, a cohort of women with or at risk for HIV infection recruited from three Women's Interagency HIV Study sites. All participants were receiving anti-HIV therapy.

The cut points were applied to two nationally representative studies of older adults—The Health and Retirement Survey and the National Health and Aging Trends Study—to estimate the proportion of adults with values below cut points in the older U.S. population and to describe how prevalence varies by age, sex, and race/ethnicity. In addition, we determined the sensitivity and specificity of various cut points for the identification of mobility disability (<0.8 m/s gait speed). The advantage of these studies is that the sampling frame in the U.S. population is known, thus, the responses can be reweighted to account for missing data from the underlying population to provide true population level estimates for the United States.

Synthesis of the Preliminary Analytical Results

The SDOC investigators presented the conceptual framework of the analytical approach and preliminary results of the analyses. First, the DXA harmonization had little impact on high-level conclusions. This effort has important implications for clinical practice and cross-comparison with other analyses and addressed a major criticism of previous efforts to define sarcopenia. Second, the SDOC found that allometric scaling had minimal impact on the sensitivity and specificity of cut points for identifying mobility disability. Third, the SDOC's initial analyses consistently identified a small subset of variables, most often a cut point in grip strength or grip strength/body mass index as discriminators for identifying men and women at risk for mobility disability. Body composition measures (e.g. body mass index, lean mass by DXA, or body fat) did not emerge as potential discriminators of older adults with mobility disability. Fourth, many of the candidate definitions that included grip strength were associated with increased risk of mortality, hip fracture, falls, mobility disability, and instrumental activities of daily living disability. However, measures of DXA-based lean mass did not discriminate persons at risk for these outcomes. Fifth, the sensitivity, specificity, and prevalence varied in different populations (e.g. clinical populations, patients with hip fracture, and HIV+ individuals). For patients with hip fracture, the proportion of those with mobility disability at baseline was very high, so a more important outcome in this population may be the recovery of mobility. Finally, the prevalence of sarcopenia as defined by low grip strength increased with age and was high in older Americans. The sensitivity, specificity, and prevalence varied by definition, sex, and race.

Discussion

Historical Perspective From the Osteoporosis Field

Dr. Cummings' keynote lecture highlighted the similarities between osteoporosis and sarcopenia: both are defined by cut points of a continuous biomarker (39). The establishment of bone mineral density (BMD) cut points to define osteoporosis catalyzed the development and approval of drugs for the treatment of osteoporosis and made it easier for clinicians to diagnose osteoporosis and get reimbursed. The cut point for osteoporosis as a *T*-score equal to –2.5 was based on consensus of a World Health Organization's Expert Panel that was informed primarily by the prevalence of "osteoporosis" in women aged at least 50 years at candidate cut points: a prevalence of 15% at a *T*-score less than –2.5 was considered reasonable (39,40). Eventually, a *T*-score less than or equal to –2.5 at either the hip or spine became an entry criterion for clinical trials of new drugs and an Food and Drug Administration-approved indication for their prescription.

Table 2. A Summary of the Preliminary Findings and of the Recommendations of the Sarcopenia Definition and Outcomes Consortium (SDOC) Conference

Preliminary findings of the SDOC analyses
- Grip strength—either absolute or adjusted for body mass index—is an important discriminator of mobility disability, and a predictor of adverse health-related outcomes, such as falls, instrumental activities of daily living disability, and mortality.
- Lean mass, measured using dual-energy X-ray absorptiometry, is not a good discriminator of mobility disability.

Major recommendations of the SDOC Conference
- Develop a series of position statements on sarcopenia definition that are informed by the findings of the SDOC analyses and synthesis of the literature.
- Establish an independent International Expert Panel to review the position statements and the supporting analytical results and the literature synthesis.
- Convene an International Sarcopenia Definition and Outcomes Position Statement Conference to solicit a consensus on the position statements that would form the foundation of the evidence-based sarcopenia definition.
- Develop a predictive risk model that takes into account sarcopenia components as well as age, sex, race, and comorbidities.

The World Health Organization Committee defined "osteopenia" as a hip BMD *T*-score of between –1.0 and –2.5 (39,40). However, most women aged 50–60 years with "osteopenia" had a low absolute risk of fracture. Thus, the definition of "osteopenia" resulted in labeling millions of women who had a low absolute risk of fracture as having a "disease", sometimes causing anxiety and increasing the prescription of drugs to women with a low risk of fracture. To mitigate this problem, a multivariable index called FRAX (Fracture Risk Assessment Tool) that considers risk factors, such as age, sex, and history of fracture, is now commonly used to estimate a person's absolute risk of fracture (41).

Dr. Cummings cautioned that a cut point to define sarcopenia, such as that based on grip strength, should not be viewed as a disease diagnosis. Establishing a cut point would increase awareness of this condition, which could lead to recommendations of physical activity interventions or other lifestyle changes that might be beneficial; it also could lead patients to believe that they have a disease and heighten anxiety and increase use of drug therapies by people who have a low risk of mobility disability. Dr. Cummings suggested that absolute risk of an important outcome, such as mobility disability, may be a more rational basis for clinical interventions.

The attendees suggested that SDOC develop a robust risk model of mobility disability or other important clinical outcomes. When therapies become available, treatment thresholds should take into account the treatment's benefits and costs. In addition, a *clinical diagnosis* of "sarcopenia" may also include consideration of functional limitations, such as slow walking, difficulty rising from a chair without hands, or walking upstairs; and treatment would be indicated for improving these functions and enabling older individuals to remain independent.

Considerations in Implementation of Sarcopenia Definition in Clinical Practice and Drug Development

The potential hurdles in the implementation of the measures of sarcopenia in assessments of older adults and steps that can be taken to increase awareness among patients and clinicians were discussed. The reimbursement issues could be potential barriers to implementing grip strength in clinical practice. It was suggested that the initial application of cut points may be focused on identifying the most impaired. Outcome measures in health care are best adopted when a new measure adds value in helping a clinician make individual patient decisions. The cost and burden of measuring grip strength are minimal, but the consequences of the diagnosis, in addition to the cost of testing and treatment, should be weighed against potential benefits.

There is limited understanding of sarcopenia among clinicians and patients. Scientific journals can play a big role in raising awareness. Professional societies can also play an important role in maintaining outcomes registries. Patients make especially effective advocates—they can have a substantial impact on policy makers and funding agencies. The panel noted that efforts to raise awareness now are important, as it takes many years to translate knowledge into clinical practice. Some of these efforts have already been initiated by patient advocacy organizations such as the aging in motion (AIM) Coalition, which recently facilitated the approval of an *ICD-10* code for sarcopenia. To further advance this effort, the AIM Coalition has submitted an 18-month proposal to the Food and Drug Administration to begin the process of qualifying performance measures such as gait speed tests as functional measures in clinical trials. Partnering with patient organizations such as the American Association of Retired Persons may advance efforts to increase awareness of sarcopenia. Local groups can work with others at the national level to capture input of diverse populations.

The panel discussants noted that drug development for sarcopenia has been much more difficult than expected for several reasons. The lack of regulatory guidance was cited as a major impediment. In addition, sarcopenia affects a population with a lifetime of environmental exposures, multiple diseases, and unknown genetics. It has a complex biology and there are no good preclinical models in which to confirm or predict that a target intervention will have the intended effect in humans with this condition.

Recommendations

Strategies to harmonize a sarcopenia definition and to incorporate it into clinical practice, clinical trials, and treatment guidelines require continued international collaborative effort (Table 1). The attendees urged the formation of an International Expert Panel to review the analytical findings and a synthesis of the published evidence and to develop a series of position statements that would form the basis of a consensus definition of sarcopenia to be discussed at an International Consensus Conference in the Fall of 2018 (Table 2). However, sarcopenia defined by a cut point should not be viewed as a "disease" without a corresponding method for estimating a person's risk of important outcomes that are the main motivation for interventions. Anticipating a consensus definition of "sarcopenia," there also is a need to develop potential strategies for the dissemination and implementation of sarcopenia definition in clinical practice. The discussion emphasized the need to simultaneously develop predictive risk

model of adverse health outcomes, such as physical disability, that takes into account sarcopenia components as well as age, sex, race, and comorbidities.

Conflict of interest statement

None declared

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