

TOWARDS A DEFINITION OF SARCOPENIA – RESULTS FROM EPIDEMIOLOGIC STUDIES

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Abstract: The age-related loss of muscle mass, also called sarcopenia, is receiving increasing attention in aging research. While the concept is frequently being used in research settings and introduced to clinical settings, thus far no consensus on its definition has been established. This article provides an overview of the history of sarcopenia definitions proposed in the literature thus far. It will describe the methodology used to develop the cutpoints for low muscle mass (or strength) in large epidemiological studies, how sarcopenia based on these cutpoints relates to functional outcomes, and the advantages and disadvantages of the different definitions. This overview will contribute to the current need to develop a consensus definition of sarcopenia which can be used in all relevant settings.

Introduction

The term sarcopenia, indicating the age-related loss of muscle mass, was first introduced by Dr. I.H. Rosenberg (1). This loss of muscle mass with aging is hypothesized to have negative consequences for health and physical functioning in old age (2). To investigate the prevalence of sarcopenia and its impact on health and functioning in old age, and to diagnose sarcopenia in clinical practice, a definition should be available. Several definitions have been developed and described in the literature. The usefulness of these definitions is generally tested by investigating the association between sarcopenia and (change in) physical functioning. It is important to realize that most of these definitions include a cutpoint for low muscle mass, not loss of muscle mass. Currently, there is no consensus on the definition of sarcopenia. In this brief review several proposed definitions of sarcopenia will be described and potential advantages and disadvantages will be discussed.

Definitions of sarcopenia

Baumgartner and colleagues were the first to develop a definition of sarcopenia (3). Based on studies showing that the amount of appendicular skeletal muscle mass (ASMM) could be estimated by using the bone-free, fat-free mass of the arms and legs as assessed with whole body dual-photon absorptiometry or dual-energy x-ray absorptiometry (DXA, 4, 5), the definition was created using ASMM. Furthermore, analogous to the body mass index, the ASMM was divided by height squared to adjust for the strong association between body height and ASMM. To define the cutpoints for low ASMM an approach similar to that of osteoporosis was taken. Older persons with a ASMM less than two standard deviations from the mean of a young reference population were considered sarcopenic. DXA data from a young (aged 18-40 years) volunteer sample of 229 non-Hispanic white men and women participating in the Rosetta Stone study (6) were used to

determine the sarcopenia cutpoints. The developed cutpoints were 7.26 kg/m² for men and 5.45 kg/m² for women (3). Although these cutpoints are limited by the fact that the young reference group was a volunteer sample and might not have been representative for young US men and women (it was actually the first young sample with available DXA measurements) they are widely being used in sarcopenia research. Using the same approach, sarcopenia cutpoints have recently been developed for Asian persons (7).

The Baumgartner cutpoints for sarcopenia were first applied to the New Mexico Elder Health Survey in which ASMM was predicted using an equation including sex, body weight, body height, hip circumference and grip strength (3). After adjustment for age, income, ethnicity, obesity, comorbidity, current smoking, physical activity and alcohol intake, sarcopenic men and women were more likely to have 3 physical disabilities. In men, but not in women, sarcopenia was also associated with >1 balance abnormality, the use of a cane or walker, and falling in the past year.

A second definition of sarcopenia was developed by Janssen and colleagues (8). Whole body skeletal muscle mass was estimated using a prediction equation including impedance and reactance as assessed with bioelectrical impedance, body height squared, sex and age. The predicted amount of muscle mass was then expressed as the percentage of total body weight to adjust for stature and the mass of nonskeletal muscle tissues (fat, organ, bone). Again, analogous to the osteoporosis definition, an index less than two standard deviations from the sex-specific mean value of a young reference group was considered to indicate class II sarcopenia. An index within one to two standard deviations from the young reference group was considered class I sarcopenia. Bioelectrical impedance data from a nationally representative sample of young adults (aged 18-39 years) participating in the Third National Health and Nutrition Examination Survey (NHANES III) were used to develop the cutpoints. A potential disadvantage of the used index is that the ratio of whole body skeletal muscle mass

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divided by total body weight is largely dependent on the amount of body fat since the between-person variation in total body fat is much larger compared to the between-person variation in skeletal muscle.

In the same cross-sectional study (8), class II sarcopenia based on the skeletal muscle index was associated with functional impairment and disability in men and women. However, after adjustment for age, race, body mass index, health behaviors, and comorbidity some of the associations disappeared. Of the 12 items, class II sarcopenia in men was only related to the tandem stand performance and self-reported limitations stooping/crouching/kneeling. In women, class II sarcopenia was associated with five items.

A third approach to define sarcopenia is the use of receiver operating characteristic curves when examining the association of different skeletal muscle cutpoints with physical disability in older persons (9). Data from 4,449 men and women aged 60 years and older who participated in the NHANES III were used. Whole body skeletal muscle mass was predicted using bioelectrical impedance measurements and divided by height squared. A skeletal muscle mass 5.75 kg/m^2 indicated high disability risk and a skeletal muscle mass between $5.76\text{-}6.75 \text{ kg/m}^2$ indicated a moderate disability risk in women. The corresponding values in men were 8.50 kg/m^2 and $8.51\text{-}10.75 \text{ kg/m}^2$. After adjustment for age, race, smoking status, alcohol intake, comorbidity and body fat, class II sarcopenic men and women showed a three to five-fold risk of having disability. In men, class I sarcopenia also showed an increased risk.

These developed cutpoints have recently been applied to another large cohort study of older persons (Cardiovascular Health Study) in which whole body skeletal muscle mass was predicted based on bioelectrical impedance measurements (10). The association of sarcopenia with disability at baseline and with incident disability during an 8 year follow-up were investigated. The prospective associations were generally weaker compared to the baseline associations. With adjustment for a large set of baseline variables and incident cardiovascular disease, class I sarcopenia was not associated with incident disability. Class II sarcopenia was associated with incident disability in women (Odds ratio 1.37 (95% confidence interval 1.10-1.72) versus those with normal muscle mass) but not in men.

Although DXA scanners have become widely available, effort has been made in examining the use of anthropometric measurements to define sarcopenia. The main advantage of this approach is the greater feasibility in clinical practice. In 1,458 French women aged 70 years and older the calf circumference was most strongly associated with predicted ASMM ($r=0.63$). However, a calf circumference value below 31 cm was not a good screening tool to detect sarcopenia based on the Baumgartner definition (sensitivity 44.3%, specificity 91.4%) (11).

In 2003, an alternative method was proposed to potentially derive sarcopenia cutpoints (12). Based on the finding in the

Health, Aging and Body Composition Study that the prevalence of sarcopenia using the original Baumgartner sarcopenia cutpoints was very high in normal weight older persons (>50%) but zero in obese older persons, a method was developed that incorporated both body height and total body fat. The lowest 20th percentile of the residuals of the regression of total body height and body fat on ASMM derived in the older men and women separately was used to define sarcopenia. The percentile cutpoint was chosen arbitrarily. This new definition was compared with the lowest 20th percentile of the ratio of ASMM divided by height squared (7.23 kg/m^2 in men, 5.67 kg/m^2 in women). These cutpoints turned out to be very similar to the original Baumgartner cutpoints (3). In men, sarcopenia according to both definitions increased the risk of having a low function. The risk of a low function score almost doubled in women with sarcopenia based on the residuals. In contrast, women with sarcopenia based on the ratio had a lower risk for having a low function. Probably, when using this definition the non-sarcopenic group includes obese women who have a low function score because of their excess body fat.

The association between sarcopenia using both these definitions and 5-year change in physical function was also examined in the Health Aging and Body Composition Study (13). Again, sarcopenia based on the residual method was better for predicting incident lower-extremity mobility limitations compared to the ratio ASMM/height² method. In fact, men and women with sarcopenia based on the ratio method had a lower risk of developing incident mobility limitations which was attenuated after adjustment for total body fat.

Recently, an international working group was established to work on a definition for sarcopenia. Different definitions for sarcopenia were applied to several large aging cohorts that include accurate, repeated measurements of ASMM by DXA (Women Health Initiative, MrOs, Health Aging and Body Composition Study, and the Longitudinal Aging Study Amsterdam). New cutpoints following the Baumgartner approach and using DXA data from young participants from the NHANES IV study were developed and applied. Moreover, previously established cutpoints were investigated. Preliminary data recently presented at several scientific meetings suggest that sarcopenia definitions based on the ratio of ASMM and height squared are of limited value to predict future decline in mobility function in older persons (unpublished).

Thus far, most of the developed definitions of sarcopenia are based on a cutpoint for low total body skeletal muscle mass or appendicular skeletal muscle mass. Several researchers have started to include measures of muscle quality to determine sarcopenia. For example, Lauretani et al. (14) investigated knee extension isometric torque, handgrip, lower extremity muscle power, and calf muscle area in relationship to poor mobility in the InCHIANTI study. Sarcopenia cutpoints were developed in the participants aged 20-29 years. Persons were considered sarcopenic when their values were less than 2 SD of the mean of the young reference group. Lower extremity muscle power

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was no better than knee-extension torque or handgrip in the early identification of poor mobility. In a second set of analyses, optimal sarcopenia cutpoints were developed using receiver operating characteristic (ROC) curves. The areas under the curve for handgrip, knee-extension torque, and lower extremity muscle power were similar and not statistically different. The area under the curve for calf muscle area was substantially smaller. These cross-sectional results could suggest that poor muscle strength should be preferred above low muscle mass to assess sarcopenia. This is supported by the findings of other epidemiological studies showing that muscle strength measures in older persons are more strongly associated with (change in) functional limitations and disability (15-18) and mortality (19-20) compared to muscle mass measures.

Other studies have examined cutpoints for poor muscle strength. In a recent study (21) cutpoints for low knee extensor strength were developed in relationship to incident mobility limitations. Data on 2,784 men and women aged 70-79 years, participants of the Health, Aging and Body Composition Study were used. Cutpoints of the ratio of knee extensor strength (Nm) divided by body weight were 1.13 Nm/kg and 1.71 Nm/kg for high and low risk of incident severe mobility limitations in men, and 1.01 Nm/kg and 1.34 Nm/kg in women. Apart from the higher risk of incident mobility limitations, persons in the high risk group also turned out to have a higher risk for incident low gait speed (<1.22 m/sec) and 7-year mortality. An earlier cross-sectional study in 192 older men and women proposed a knee extensor strength cutpoint of 2.5 Nm/kg.m(-1) in relationship to functional performance tests (22). A cutpoint of 0.80 Nm/kg.m(-1) has also been proposed (23). A point where low leg strength starts to impair gait speed cannot be easily identified since gait speed is influenced by other performance factors as well (24). Finally, a potential disadvantage for a clinical application of these proposed cutpoints is the use of an isokinetic strength measurement.

It has been questioned whether muscle strength should also be used to assess sarcopenia, since it implies that muscle mass and muscle strength are causally linked while it is now known that changes in muscle mass are not fully responsible for changes in muscle strength. Perhaps a different terminology for the loss of muscle strength or low muscle strength should be used. Recently, the term dynapenia was proposed to indicate the age-related loss of muscle strength (25).

Epidemiologic studies have shown that body fat in older persons, and especially in older women, is often a more important determinant of (deline in) physical function compared to muscle mass (16, 26-29). Moreover, in some studies the association of body fat with physical function is even stronger than the association of muscle strength (16, 30). The presence of high body fat as well as low muscle mass is called sarcopenic obesity. Recently, different definitions of sarcopenic obesity using muscle mass or muscle strength to indicate sarcopenia have been proposed and have been shown to be associated with incident disability (31, 32).

In conclusion, sarcopenia definitions based on the ratio of ASMM and height squared should be interpreted carefully because the important role of body fat is not incorporated. Moreover, although cross-sectionally associated with physical function, only weak or even inverse associations have been observed with future decline in physical function. Apart from low muscle mass, a sarcopenia definition should at least incorporate body height and body fat since they both are important determinants of the amount of muscle mass. For functional outcomes a definition based on muscle strength seems more relevant. However, it cannot be excluded that sarcopenia definitions based on low muscle mass might be relevant change in other health outcomes, such as glucose homeostasis. Furthermore, thus far no studies have investigated whether loss of muscle mass is an important determinant of functional decline, although a definition based on change in muscle mass would be less clinically useful. The concept 'sarcopenic obesity' deserves more attention in future studies, as well as the role of other muscle quality aspects, such as fat infiltration into the muscle.

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