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Sarcopenia With Limited Mobility: An International Consensus

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Abstract

A consensus conference convened by the Society of Sarcopenia, Cachexia and Wasting Disorders has concluded that “Sarcopenia, ie, reduced muscle mass, with limited mobility” should be considered an important clinical entity and that most older persons should be screened for this condition. “Sarcopenia with limited mobility” is defined as a person with muscle loss whose walking speed is equal to or less than 1 m/s or who walks less than 400 m during a 6-minute walk, and who has a lean appendicular mass corrected for height squared of 2 standard deviations or more below the mean of healthy persons between 20 and 30 years of age of the same ethnic group. The limitation in mobility should not clearly be a result of otherwise defined specific diseases of muscle, peripheral vascular disease with intermittent claudication, central and peripheral nervous system disorders, or cachexia. Clinically significant interventions are defined as an increase in the 6-minute walk of at least 50 meters or an increase of walking speed of at least 0.1 m/s.

> “A word is not a crystal, transparent and unchanged; it is the skin of a living thought and may vary greatly in color and content according to the circumstances and the time when it is used.”
>
> —Oliver Wendell Holmes

The loss of muscle mass with aging was first recognized by MacDonald Critchley. Rosenberg felt that “no decline with age is more dramatic or potentially more functionally significant than the decline in muscle mass” and suggested that it needed a name derived from the Greek—sarcopenia (ie, flesh loss).[1,2] Baumgartner et al[3] provided an operational definition using a definition based on muscle mass corrected for height, and defined, similarly to osteoporosis, as being 2 standard deviations below the level of healthy young persons. With the advent of an operational definition, consensus began to be lost. Generally it is recognized that sarcopenia is reduced muscle mass that leads to negative effects on function and clinical outcome.

Muscle mass declines at approximately 1% per year after the age of 30 years. Severe muscle loss (ie, 2 standard deviations below healthy young) is present in 5% to 13% of 60- to 70-year-olds and 11% to 50% of those 80 and older.[4–6] This loss of muscle mass has been shown to be associated with disability in some studies. However, the development of

disability is a complex area and is almost always multifactorial in older persons. At the end of 2010, more than 1000 publications had appeared in PubMed using the definition of sarcopenia, as age-related muscle loss below 2 standard deviations of the mean for young persons. Multiple factors leading to sarcopenia have been identified[7–17] (Figure 1).

Although the definition of sarcopenia based on loss of muscle mass alone has served the scientific community fairly well, it has been less satisfying for clinicians, the pharmaceutical industry, and regulatory agencies. Unlike the measurements of bone mineral density, the measurement of muscle mass has not been widely adopted by clinicians. Regulatory agencies have failed to accept that restoration of muscle mass is, of itself, a sufficient reason to allow a drug to be approved for use. It should be noted that this is not different from the situation with osteoporosis wherein reduced bone mineral density is recognized as a legitimate indication for treatment, but for regulatory considerations, drugs have had to show a reduction in fracture incidence before approval.[18–20] These factors/impediments have led to groups, originally from the European Union, and then from the European Union and the United States with industry support, to question the clinical feasibility of the original definition, and efforts to redefine sarcopenia have been advanced.[4,21,22]

In an attempt to find a consensus, the Society for Sarcopenia, Cachexia and Wasting Disorders convened a meeting in Washington, DC, in December 2010, with participants with multiple viewpoints. The purpose of the meeting was to find a definition or set of definitions that is universally acceptable and can lead to easily definable end points for clinical trials. It was hoped that the definition developed would

- Be a meaningful surrogate for clinically useful end points, eg, decline in activities of daily living, hospitalization, nursing home residence, injurious falls, or mortality.
- Allow for treatments that worked in ways different from increasing muscle mass.
- Include only measurements that have been demonstrated to lead longitudinally to clinically meaningful outcomes and have definable cut points based on data.
- Be independent of the molecular target(s) for drug development.

THE POWER-STRENGTH-MASS CONUNDRUM

Muscle mass is the primary determinant of strength. Males are generally stronger than females primarily because they have larger muscle mass. Loss of strength tends to track with loss of muscle mass with aging in physiological studies, although the decline in muscle strength is steeper than the decline in muscle mass.[23,24] However, interventions that increase muscle mass do not necessarily increase strength.[25] Conversely, changes in strength that occur with resistance training precede measurable changes in muscle mass temporally and exceed them in size.[26] Loss in strength is not necessarily present with voluntary weight loss despite the associated loss of skeletal muscle.[27] Correlations between change in muscle mass and change in strength in older adults are inconsistent and not very robust.[28]

One reason for this inconsistency is the infiltration into muscle by fat, which is a powerful predictor of future disability and mortality.[29] This has been designated as sarcopenic obesity, myosteatosis, or the "fat frail." [30–34] Infiltration of collagen into muscle with aging can also lead to a dichotomy in the relationship between muscle mass and strength.[35] Age-associated changes in neuromuscular activation that are superimposed on changes in muscle mass may further explain the dichotomy between mass and strength/power losses.[36,37] Finally, alterations in the angle of pennation by which tendons insert into muscle can markedly alter power.[38–40] Other changes in muscle leading to a loss of strength include deposition of abnormal proteins; contractile and structural protein misfolding; and mitochondrial, neuromuscular, and plaque dysfunction.

There is a logical series of classics-derived descriptions of muscle changes that result in loss of muscle mass (sarcopenia), loss of muscle strength (kratopenia, named for the Greek god of strength, Kratos), loss of power (dynopenia), and frailty (Table 1). Like sarcopenia, a number of different definitions for frailty have been developed (Table 2).[41–49] With the exception of the Rockwood et al[46] definition, all the definitions include both strength and weight loss.

A final problem with the definition of sarcopenia is the variety of measures available to measure muscle mass. Each of these leads to slightly different cutoffs for muscle mass and are indirect measures. As such, they can be influenced by adiposity and total body water.[50–52] These different measures are compared in Table 3. Newer mechanisms such as the ^{13}C-creatine dilution method may solve some of these problems.

VALIDITY OF END POINTS

A number of studies have shown that muscle mass less than 2 standard deviations of that of a healthy young adult is predictive of disability and mortality.[9,34,53–60] At present there is no clear consensus pertaining to the magnitude of change in muscle mass that is predictive of clinically meaningful outcomes. To determine appropriate appendicular muscle mass values to predict outcomes requires a standardization using each of the instruments used to measure muscle mass. Standardization against healthy young controls 20 to 30 years of age needs to be developed for individual ethnic groups, similar to those developed for osteoporosis in the FRAX Index (www.shef.ac.uk/FRAX). A minimum of 100 control individuals needs to be included in each cohort. Development of cut points needs to exclude persons with limb pain or substantial balance problems.

Usual gait speed over a variety of distances from 4 to 6 meters has been shown to be predictive for the onset of disability, severe mobility limitation, hospitalization, and mortality.[61–65] Gait speeds equal to or less than 1 m/s appear to be equally predictive of poor outcomes. A clinically significant improvement in gait speed is at least 0.1 m/s.[65–68]

The 6-minute walking test has been used as a measure for drug approval by several regulatory agencies for the assessment of drugs for the treatment of peripheral vascular disease and pulmonary hypertension. The 6-minute walk test is highly predictive of hospitalization and mortality in medically ill persons.[69–73] A cutoff of 400 m has been

established.[69,74,75] In persons who can walk at least 100 m, a clinically significant change has been found to be more than 50 meters.[69,76,77] (There was a viewpoint among the panel that this may be better expressed as a percentage of baseline.) There is evidence that the 400-m walking test may be equally valid.[78,79]

DEFINITION

It was decided that "sarcopenia with limited mobility" would be an acceptable term to define persons with a need for therapeutic interventions. This is a specific condition with clear loss of muscle mass and a clear target for intervention. As such, it differs from the more general concept of frailty. The definition is based on consensus and may change as additional data come available. "Sarcopenia with limited mobility" is a syndrome not a disease.

Sarcopenia with limited mobility is defined as a person with muscle loss whose walking speed is equal to or less than 1 m/s or who walks less than 400 m during a 6-minute walk. The person should also have a lean appendicular mass corrected for height squared of more than 2 standard deviations below that of healthy persons between 20 and 30 years of age of the same ethnic group. The cutoffs determined are arbitrary, as the associations with mass and gait speed with disability are continuous. The limitation in mobility should not be clearly attributable to the direct effect of specific disease, such as peripheral vascular disease with intermittent claudication, or central or peripheral nervous system disorders (such as stroke, Parkinson's disease, spinal cord disease, or motor neuron disease), dementia, or cachexia.[80–83] Interventions that are considered clinically significant are an increase in the 6-minute walk of 50 meters or an increase of gait speed of 0.1 m/s. Sarcopenia is generally believed to be age-associated and its prevalence increases with aging. Research needs to establish that change in gait speed owing to therapy aimed at sarcopenia will reduce disability and that the amount of change in gait speed will predict the improvement in outcome.

It is important to recognize that sarcopenia can overlap with many of the specifically excluded conditions; and that exercise, nutrition, and other treatments that decrease sarcopenia may be useful in these conditions.[84–86] There was no consensus among the panel of whether sarcopenia as a term should be limited to use in older persons (60+ years of age) or used as a general term for adults of any age. A minority support the use of the term "myopenia" to indicate the presence of clinically relevant muscle wasting owing to any illness at any age,[87,88] with "sarcopenia" being limited to use for older persons. Sarcopenia has been generally recognized as an age-related process of multiple etiologies; however, nephrologists tend to use the term for persons with chronic kidney disease and dialysis patients with protein energy wasting and muscle wasting regardless of age. Thus, although emphasizing that this is a common condition in older age, the panel was not comfortable in limiting the definition to only older persons. There is a need to determine the role of executive function decline in the development of sarcopenia with limited mobility.[89–91] At present, fast gait speed and inability to carry out "dual tasking" appear to separate executive function mobility disorders.

We recommend that all patients older than 60 years who are falling, who feel that their walking speed has decreased, who have had a recent hospitalization, who have been on prolonged bed rest, who have problems arising from a chair, or who need to use an assistive device for walking are screened for sarcopenia with mobility impairment. As has been previously suggested, gait speed or distance traveled during a 6-minute walk should be measured in all these patients, and this mobility measure should be separately reimbursed from the regular physician visit.[92] The decision about whether to treat should be based on absolute risk of an adverse clinical outcome, such as mobility disability, and the absolute decrease in risk from treatment. Sarcopenia may be only one of several risk factors to be used in treatment decisions. Although recognizing that clinical trials in older persons with "sarcopenia with limited mobility" are challenging, there is a wonderful opportunity to develop new drugs that may greatly enhance the quality of life of older persons.[93]

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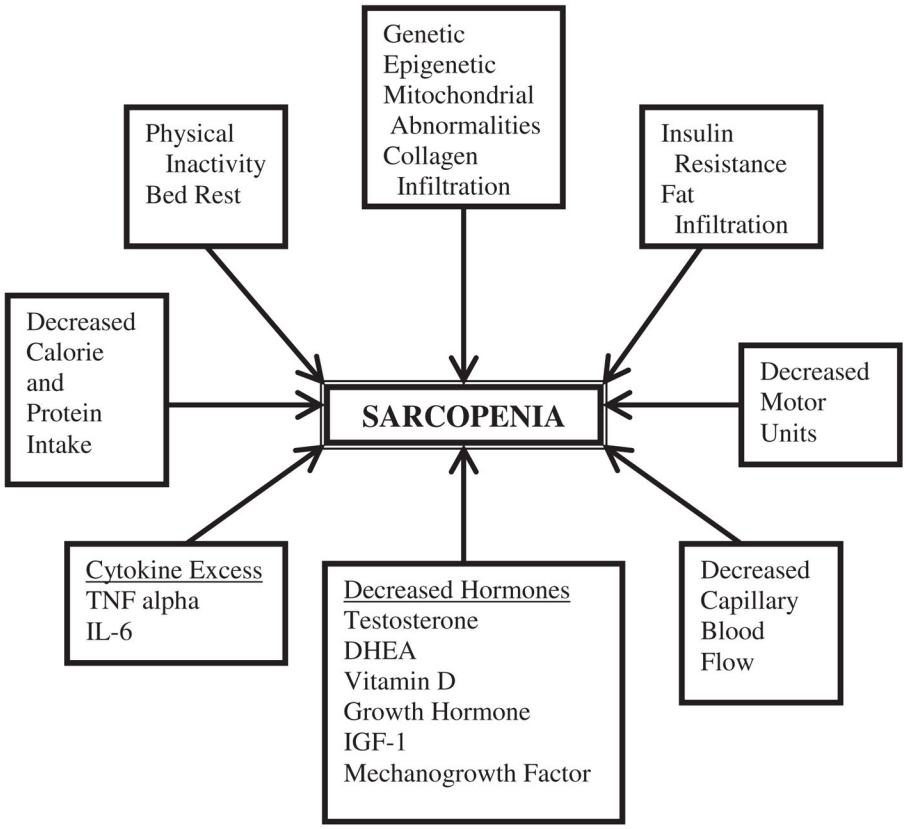

Fig. 1.
Factors involved in the pathophysiology of sarcopenia.

Table 1

Cascade Relationship between Loss of Muscle Mass and Disability

Condition	Definition	Measurements
Sarcopenia	Loss of muscle mass	DEXA MRI Computed tomography MAMC/Calf circumference Ultrasound Bioelectrical impedance * 13C-creatine dilution †
Kratopenia	Loss of force, ie, strength	Dynamometry (isometric) Isotonic or isokinetic strength tests
Dynapenia	Loss of power (Force 3 Velocity)	Walking speed Walking distance Stair climbing
Frailty	Increased risk of disability when stressed	CHS (Fried) criteria SOF criteria IANA criteria
Disability	Loss of function	Instrumental activities of daily living Activities of daily living Barthel Index Functional Index Measure

CHS, Cardiovascular Health Study; DEXA, dual-energy x-ray absorptiomety; IANA, International Academy on Nutrition and Aging; MRI, magnetic resonance imaging; MAMC, mean arm muscle circumference; SOF, Study of Osteoporotic Fractures.

*The panel did not feel this measurement should be used in clinical trials.

†Other epidemiologically valid serum measurements of muscle mass are being explored.

Table 2

Comparison of 3 Definitions of Frailty

Cardiovascular Health Study	Study of Osteoporotic Fractures	International Association of Nutrition and Aging
• Unintentional Weight loss	• Weight loss	• Fatigue
• Poor grip strength	• Inability to raise from a chair 5 times without using arms	• Resistance (climb 1 flight of stairs)
• Reduced energy level	• Reduced energy level	• Aerobic (walk 1 block)
• Slow walking speed		• Illnesses (>5)
• Low level of physical activity		• Loss of weight

Table 3

Comparison of Methods Available to Assess Muscle Mass

	Dual Energy X-ray Absorptiometry	Computed Tomography	Magnetic Resonance Imagery	Ultrasound	Bioelectrical Impedance*
Method	Measures attenuation of free muscle mass	Density of muscle area	Density of muscle area	Visualization of cross-sectional area	Indirect measure of muscle mass
Precision	1%–4%	1%–3%	1%–3%	2%	2%–4%
Radiation exposure	1 mrem (10 μSv)	15 mrem (150 μSv)	None	None	None
Availability	Readily available	Readily available	Readily available	Readily available	Available
Cost	Low	Medium	High	Low	Low
Technical difficulty	Minimum but needs standardization	Moderate	High	Moderate	Minimum
Examples of possible reference values for sarcopenia¶	Males <7.26 kg/m^2 Females <5.45 kg/m^2	Males <55 cm^2/m^2† Females <39 cm^2/m^2	Males <176 cm^3 Females <93 cm^3	Males <11 mm‡ Females M10 mm	Males <14.6kg/m^2§ Females M11.4 kg/m^2

*Bioelectrical impedance was not recommended for use by the panel.

†Lumbar skeletal mass index.

‡Musculotendon torque for gastrocnemius medialis.

§Fat-free mass index without bone.

¶It is important to recognize these are limited studies often only in one ethnic group and are given purely as examples.