

# Clinical definition of sarcopenia

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## Summary

**Sarcopenia is a condition characterized by loss of skeletal muscle mass and function. Although it is primarily a disease of the elderly, its development may be associated with conditions that are not exclusively seen in older persons. Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength and it is strictly correlated with physical disability, poor quality of life and death. Risk factors for sarcopenia include age, gender and level of physical activity. In conditions such as malignancy, rheumatoid arthritis and aging, lean body mass is lost while fat mass may be preserved or even increased. The loss in muscle mass may be associated with increased body fat so that despite normal weight there is marked weakness, this is a condition called sarcopenic obesity. There is an important correlation between inactivity and losses of muscle mass and strength, this suggests that physical activity should be a protective factor for the prevention but also the management of sarcopenia. Furthermore one of the first step to be taken for a person with sarcopenia or clinical frailty is to ensure that the sarcopenic patient is receiving correct and sufficient nutrition. Sarcopenia has a greater effect on survival. It should be important to prevent or postpone as much as possible the onset of this condition, to enhance survival and to reduce the demand for long-term care. Interventions for sarcopenia need to be developed with most attention on exercise and nutritional interventions.**

*KEY WORDS: sarcopenia; epidemiology; weakness; sarcopenic obesity.*

## Definition

The interest about sarcopenia, the age-related loss of skeletal muscle mass and function, is growing considerably. In 1989, Rosenberg proposed the term 'sarcopenia' (Greek 'sarx' or flesh + 'penia' or loss) to describe this age-related decrease of muscle mass (1, 2). Although sarcopenia is primarily a disease of the elderly, its development may be associated with conditions that are not exclusively seen in older persons, like disuse, malnutrition and cachexia. Like osteopenia, it can also be seen in younger patients such as those with inflammatory diseases (3). Muscle accounts for 60% of the body's protein stores. Muscle mass decrease is directly responsible for functional impairment with loss of strength, increased likelihood of falls, and loss of autonomy (4, 5). Sarcopenia still has no broadly accepted clinical definition, consensus diagnostic criteria, International Classification of Diseases 9th Revision (ICD-9) codes or treatment guidelines. One of the most important recent developments has been convergence in the operational definition of sarcopenia (6, 7). Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death (8, 9). The three consensus papers which have published a definition of sarcopenia were written under the auspices of, respectively, the European Working Group on Sarcopenia in Older People (EWGSOP) (10), the European Society for Clinical Nutrition and Metabolism Special Interest Groups (ESPEN-SIG) (11), and the International Working Group on Sarcopenia (IWGS) (12). The consensus definitions were as follows:

- The presence of low skeletal muscle mass and either low muscle strength (e.g., handgrip) or low muscle performance (e.g., walking speed or muscle power); when all three conditions are present, severe sarcopenia may be diagnosed (EWGSOP);
- The presence of low skeletal muscle mass and low muscle strength (which they advised could be assessed by walking speed) (ESPEN-SIG);
- The presence of low skeletal muscle mass and low muscle function (which they advised could be assessed by walking speed) and "that [sarcopenia] is associated with muscle mass loss alone or in conjunction with increased fat mass" (IWGS). Thus, the EWGSOP consensus, by separating muscle strength and muscle performance, allows for a slightly broader definition and provides a classification of a severe condition (13).

Moreover the diagnosis of sarcopenia can then be carried out by assessing the following parameters:

- 1) Measure walking speed in elderly (>65 years). If walking speed is below 0.8 m/s at the 4-m walking test, measure the muscle mass. A low muscle mass, i.e. a percentage of muscle mass divided by height squared is below two standard deviations of the normal young mean (<7.23 kg/m<sup>2</sup> and in women at <5.67 kg/m<sup>2</sup>) as defined using dual energy X-Ray absorptiometry.

- 2) If the walking speed at the 4-m walking test is higher than 0.8 m/s the hand-grip strength should be tested; if this value is lower than 20 Kg in women and 30 Kg in man the muscle mass must be analyzed as described previously (10-14).

The EWGSOP published guidelines in 2010 where specific parameters to identify sarcopenia have been identified. EWGSOP suggests a conceptual staging as 'presarcopenia', 'sarcopenia' and 'severe sarcopenia'. The 'presarcopenia' stage is characterized by low muscle mass without impact on muscle strength or physical performance. This stage can only be identified by techniques that measure muscle mass accurately and in reference to standard populations. The 'sarcopenia' stage is characterized by low muscle mass, plus low muscle strength or low physical performance. 'Severe sarcopenia' is the stage identified when all three criteria of the definition are met (low muscle mass, low muscle strength and low physical performance) (10). Recognizing stages of sarcopenia may help in selecting treatments and setting appropriate recovery goals. The EWGSOP consensus also discussed the frailty concept and its overlap with sarcopenia. It recognized, as others have done, that frailty is characterized by deficits in multiple organ systems, i.e., psychological, cognitive, and/or social functioning, as well as physical limitations (13).

It's also important to distinguish sarcopenia from cachexia. The term cachexia is derived from the Greek words *kakòs* (bad) and *hèxis* (condition). Cachexia may be defined as a multifactorial syndrome characterized by severe body weight, fat and muscle loss and increased protein catabolism due to underlying disease(s). Cachexia is clinically relevant since it increases patients' morbidity and mortality. Contributory factors to the onset of cachexia are anorexia and metabolic alterations, i.e. increased inflammatory status, increased muscle proteolysis, impaired carbohydrate, protein and lipid metabolism (15).

## Epidemiology

Sarcopenia increases from 14% in those aged above 65 years but below 70, to 53% in those above 80 years of age. Depending on the literature definition used for sarcopenia, the prevalence in 60-70-year-olds is reported as 5-13%, while the prevalence ranges from 11 to 50% in people >80 years. The number of people around the world aged >60 years was estimated at 600 million in the year 2000, a figure that is expected to rise to 1.2 billion by 2025 and 2 billion by 2050. Even with a conservative estimate of prevalence, sarcopenia affects >50 million people today and will affect >200 million in the next 40 years. The impact of sarcopenia on older people is far reaching; its substantial tools are measured in terms of morbidity, disability, high costs of health care and mortality (16-20). Sarcopenia is both common and associated with serious health consequences in terms of frailty, disability, morbidity and mortality. The estimated direct health-care cost attributable to sarcopenia in the USA in 2000 was £18.5 bn (17).

## Etiopathogenesis

The mechanisms of sarcopenia are not clearly defined. Well-described risk factors for sarcopenia include age, gen-

der and level of physical activity, and resistance exercise is particularly effective for slowing the age-related loss of skeletal muscle. Furthermore, sarcopenia is associated with major co-morbidity such as obesity, osteoporosis and type 2 diabetes and insulin resistance (19, 20). But perhaps the most powerful indication that the loss of skeletal muscle, in particular of its strength, is important comes from the evidence that it predicts future mortality in middle-aged as well as older adults. In some individuals, a clear and single cause of sarcopenia can be identified. In other cases, no evident cause can be isolated. Thus, the categories of primary sarcopenia and secondary sarcopenia may be useful in clinical practice. Sarcopenia can be considered 'primary' (or age-related) when no other cause is evident but aging itself, while sarcopenia can be considered 'secondary' when one or more other causes are evident (10). In many older people, the etiology of sarcopenia is multi-factorial so that it may not be possible to characterize each individual as having a primary or secondary condition. This situation is consistent with recognizing sarcopenia as a multi-faceted geriatric syndrome. Among external factors a deficient intake of energy and protein will contribute to loss of muscle and function. Reduced intake of vitamin D has been associated with low functionality in the elderly. Acute and chronic co-morbidities will also contribute to the development of sarcopenia in older persons. Co-morbidities may on one hand lead to reduced physical activity and periods of bed rest, and on the other hand to increased generation of proinflammatory cytokines that play important triggering roles for proteolysis. Individuals who have had an active lifestyle throughout their life have more lean body mass and muscle mass when aged (21, 22).

## Sarcopenic obesity

In conditions such as malignancy, rheumatoid arthritis and aging, lean body mass is lost while fat mass may be preserved or even increased. The loss in muscle mass may be associated with increased body fat so that despite normal weight there is marked weakness, this is a condition called sarcopenic obesity. The relationship between age-related reduction of muscle mass and strength is often independent of body mass. It had long been thought that age-related loss of weight, along with loss of muscle mass, was largely responsible for muscle weakness in older people. However, it is now clear that changes in muscle composition are also important, e.g. 'marbling', or fat infiltration into muscle, lowers muscle quality and work performance. With aging, lean body mass decreases, while fat mass increases preferentially in the intra-abdominal area, even in relatively weight-stable, healthy individuals. Obesity and sarcopenia may potentiate each other and act synergistically causing physical impairment, metabolic disorders and mortality. Aging is often associated with chronic inflammatory conditions such as obesity, atherosclerosis, type 2 diabetes and insulin resistance. In older individuals, skeletal muscle protein synthesis is resistant to the anabolic action of insulin. Therefore, insulin resistance may be associated with age-related muscle loss. Inversely, loss of skeletal muscle, which is the largest insulin-responsive target tissue, may produce insulin resistance that promotes cardiovascular disease and other metabolic disorders (23-25). Sayer et al. (26) reported that decreased grip strength was significantly associated with homeostasis

model assessment of insulin resistance as well as increased odds of having metabolic syndrome. Moreover, increases in visceral fat may lead to the augmented secretion of pro-inflammatory cytokines that may promote a catabolic effect on muscles, as well as insulin resistance. Recently, several studies have reported that inflammation may be directly associated with sarcopenia. Cesari et al. (27) found that C-reactive protein (CRP) and interleukin-6 (IL-6) are positively associated with total fat mass and negatively associated with fat-adjusted appendicular lean mass. Moreover, Schaap et al. (28, 29) reported that TNF- $\alpha$  and its soluble receptors showed the most consistent associations with decline in muscle mass and strength. On the other hand, several previous studies have demonstrated that serum 25-hydroxyvitamin D (25[OH]D) levels are inversely correlated with various measures of obesity, including weight, body mass index (BMI) and waist circumference. In addition, Visser et al. (30) reported that lower 25[OH]D levels increase the risk of sarcopenia in older men and women. Low 25[OH]D levels may be associated with both sarcopenia and low physical activity. It has been proposed that excess energy intake, physical inactivity, low-grade inflammation, insulin resistance and changes in hormonal homeostasis may result in the development of sarcopenic obesity. It is now established that adipose tissue is an active endocrine organ that secretes hormones and cytokines that affect systemic inflammatory status. Either adipocytes or infiltrating macrophages in adipose tissue produce adipokines and proinflammatory cytokines, such as IL-6 and tumor necrosis factor- $\alpha$ , which induce the production of CRP in the liver. Honda et al. found that protein-energy wasting is common in overweight end-stage renal disease patients and is associated with inflammation. Furthermore, Stenholm et al. (31) found that the combination of high body fat percentage and low hand grip strength is associated with increased levels of CRP. These results suggest inflammation has an important role in the development of sarcopenic obesity. Scott et al. (32) observed that 25[OH]D may be important for the maintenance of muscle function and mass. In this study was found that 25[OH]D levels were positively associated with SMI in both sexes. Moreover, lower 25[OH]D levels were significantly associated with sarcopenic obesity in men even after adjusting for confounding factors. In another cross-sectional study of 2,208 subjects (aged 55 and older), low handgrip strength and walking limitation (<1.2 m/s or difficulty walking 500 m) were correlated with increased body fat. The researchers found that the prevalence of walking limitation was much higher in persons who simultaneously had a high body fat percentage and low handgrip strength (61%) than in those with a combination of low body fat percentage and high handgrip strength (7%) (33).

### **Sarcopenia as a risk factor**

Although sarcopenia itself is an adverse health outcome, it is also a risk factor for other adverse events. Sarcopenia increases the risk of physical limitation and subsequent disability; recent researches also show that this condition increases the risk of comorbid conditions. In a systematic review and meta-analysis of published (prospective) studies that had assessed physical capability (using measures such as grip strength, walking speed, chair rises, and standing balance) and subsequent outcome (including fracture, cogni-

tion, cardiovascular disease, hospitalization, and institutionalization), Cooper (34) et al. found that those who demonstrated lower physical capability had a higher risk of negative outcomes. Furthermore, according to Fried (23) et al., the loss of the muscle mass plays an important etiologic role in the frailty process of elderly subjects, being also a key player of its latent phase and explaining many aspects of the frailty status itself. Sarcopenia is frequently associated with poor endurance, physical inactivity, slow gait speed and decreased mobility. The age-related muscle mass loss is also associated with an increased risk of incident disability, all-cause mortality and higher health-care costs in the older people (35, 36). Information on sarcopenia among community living older subjects and its relation to survival is still lacking. In a previous study, the muscle mass was demonstrated to be a predictor of overall mortality after a follow-up of 4 years. However, some recent studies suggested that muscle function may be a more powerful predictor of disability and mortality than the muscle mass (37, 38). Indeed, sarcopenia, independent of its causes, may predict negative outcomes, such as falls and/or subsequent difficulty in instrumental and basic ADL. Furthermore, it has been associated with an increased risk of death, hospitalization, need for long-term care and higher health care expenditures. The evidence that sarcopenia has a greater effect on survival than other clinical characteristics is significant for clinical practice among old and frail older persons. The traditional medical model should move from a disease-centred perspective to a functioning-centred view. In this respect, the prevention of sarcopenia is one of the major goals of public health professionals and clinicians. There is an established link between inactivity and losses of muscle mass and strength, this suggests that physical activity should be a protective factor for the prevention but also the management of sarcopenia. Furthermore one of the first step to be taken for a person with sarcopenia or clinical frailty is to ensure that he or she is receiving correct and sufficient nutrition. Greater emphasis is needed, therefore, to prevent or postpone as much as possible the onset of sarcopenia among older people, to enhance survival and to reduce the demand for long-term care (39-41).

### **Conclusion**

Sarcopenia remains an important clinical problem that impacts millions of older adults. Causes of this condition include declines in hormones and numbers of neuromuscular junctions, increased inflammation, declines in activity, and inadequate nutrition. There are a lot of conditions correlated with sarcopenia like obesity, diabetes and reduced account of VitD. It has been proposed that excess energy intake, physical inactivity, low grade inflammation, insulin resistance and changes in hormonal homeostasis may result in the development of sarcopenic obesity (19-33). The sarcopenia is highly correlated with frailty and risk of falls in elder, it also represents an important risk factor for disability and mortality. Therefore sarcopenia has a greater effect on survival (39-41). Accordingly to these evidences it should be important to prevent or postpone as much as possible the onset of sarcopenia among older people, to enhance survival and to reduce the demand for long-term care. Interventions for sarcopenia continue to be developed, the interest on the sarcopenia must be increased, in particular by analyzing the effect of exercise and nutritional interventions.

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