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## REVIEW

# SARCOPENIA: AGAIN AND UPDATED

## ABSTRACT

Sarcopenia is defined as, skeletal muscle dysfunction associated with age, chronic diseases, cancer, nutrition problems and physical inactivity. The pathophysiology of sarcopenia seems to involve degeneration of neurogenic, musculogenic, synaptogenic and vasculogenic systems, mitochondrial dysfunction, metabolic factors and inflammatory mechanisms. Early detection of sarcopenia in older adults and patients is important to prevent morbidity, functional decline and death and the diagnosis requires assessment of muscle mass, muscle strength and physical performance. The strongest evidences in the treatment of sarcopenia are probably associated with the positive effects of resistance exercises on muscle strength, muscle mass and physical performance. Also protein intake needs to be increased. Positive results have been reported on supplementation with leucine,  $\beta$ -hydroxy  $\beta$ -methylbutyrate, Omega 3 and Vitamin D. Antioxidant intake naturally from food is recommended. There are promising studies related to angiotensin receptor blockers, oral anti-diabetic drugs. Interventions to prevent sarcopenia, treatment of the primarily responsible disease, suppression of inflammation, and treatment of metabolic syndromes constitute the basic components of a successful treatment.

**Keywords:** Sarcopenia; Physical Functional Performance; Muscle Strength; Aged.

## INTRODUCTION

Derived from Greek "sarx" for flesh and "penia" for loss/poverty, sarcopenia was first discovered by Leonardo da Vinci as seen in his drawings (1,2). Although three decades have passed since, it was first defined in 1989 and its clinical details and diagnosis are still controversial. While its first definition was age-related loss of muscle mass, it was agreed later, to be a skeletal muscle dysfunction associated with age, chronic diseases, cancer, nutrition problems and physical inactivity (2, 3). Recently, this clinical situation is being mentioned to exist even in the paediatric group (4).

And based on these facts, the definition was updated by Cruz Jentoft and Sayer as: sarcopenia is a progressive and generalised skeletal muscle disorder involving the accelerated loss of muscle mass and function that is associated with increased adverse outcomes including falls, functional decline, frailty, and mortality (3).

While the prevalence of sarcopenia is approximately 25% in those under 70 years of age, it goes up to 50% in the elderly aged 80 years and over (5). Its prevalence was found to be 46 % in geriatric care units and it is also prevalent in patients with hip fracture (71%), or long term hospitalizations (6-8). However, it should be noted that, the prevalence of sarcopenia may differ depending on the diagnostic criteria, cut-off values and measurement method chosen.

The reason underlying the fact that a new study on sarcopenia has been published almost every day in the last 30 years and it has become such a trend is that sarcopenia is associated with mortality, morbidity and quality of life (9, 10).

## PATHOPHYSIOLOGICAL MECHANISMS

The point we have arrived today based on research is that, sarcopenia is a result of a combination of complex multifactorial processes. The pathophysiology of sarcopenia seems to involve degenera-

tion of neurogenic, musculogenic, synaptogenic and vasculogenic systems, mitochondrial dysfunction, metabolic factors and inflammatory mechanisms. All these mechanisms have impacts on sarcopenia, but it is still difficult to establish a causal relationship between these mechanisms and their impacts on the muscle (11-13).

Although it is mostly associated with old age, there are many comorbidities that contribute to the development of sarcopenia (14). The relationship between diseases and sarcopenia gains a new dimension with a new study being conducted every day. It has been found to be associated with nutritional deficiencies, hormonal alterations, metabolic dysfunctions, inactivity (immobilization, sedentary life style), bone-joint diseases (osteoarthritis, osteoporosis, etc.), endocrine diseases (thyroid diseases, androgen deprivation, etc.), neurological diseases, kidney and liver diseases, cardiovascular and respiratory diseases, cancer, inflammatory diseases, cognitive impairment, and drug side effects as well as genetic and environmental factors (15,16). When such factors result in a loss of muscle mass and strength, patients are faced with weakness and a decline in mobility and physiologic functions. Sarcopenia is also associated with frailty and an increased incidence of falls (17, 18). Thus, it is a major challenge in rehabilitation clinics and should be addressed diligently (14,18).

## DIAGNOSTIC CRITERIA

It should be kept in mind that, the core of the sarcopenia condition involves quantitative and qualitative losses of skeletal muscle (19).

Since the time it was first identified, various study groups have tried to establish new definitions and diagnostic steps. Criteria for sarcopenia has been a matter of debate for a long time, and there are more than 6 criteria for diagnosis (20). The criteria developed by the European Working Group on Sarcopenia in Older People (EWGSOP)



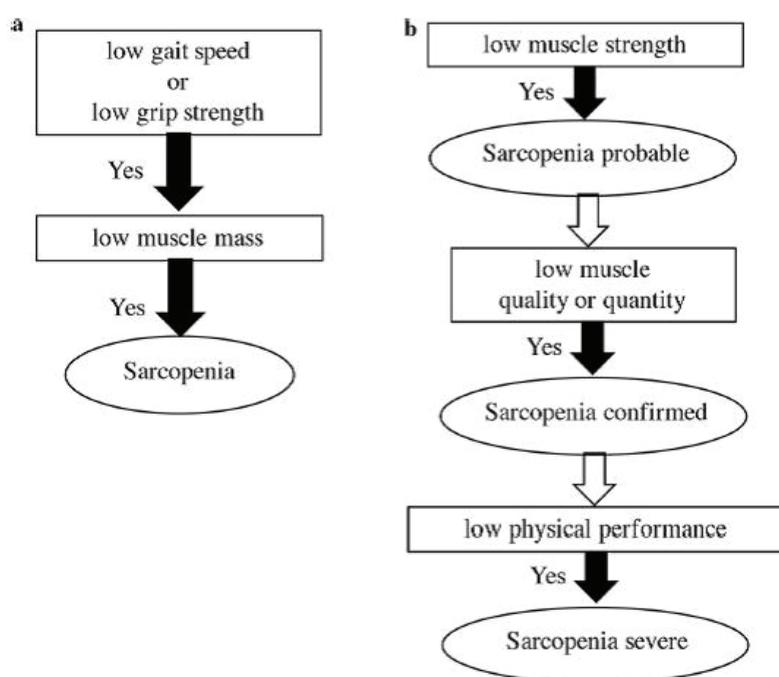
(15) and the Foundation for the National Institutes of Health - Sarcopenia Project (21) are the most widely used ones. Studies being conducted in Asia also use the criteria of the Asian Working Group for Sarcopenia (AWGS) for diagnosis besides the others (22). These criteria are still being improved and updated, the most recent update being in 2019 (15). This process will obviously continue and working groups will keep coming up with new definitions and criteria (23). Based on the information currently available, the diagnosis of sarcopenia requires assessment of muscle mass, muscle strength and physical performance. Although a low muscle mass was initially considered essential for diagnosis by EWGSOP, later studies have shown that a change in muscle strength is more predictive of adverse outcomes. Therefore, a need has arisen to issue EWGSOP2, a new version updated based on clinical and scientific evidences (Figure 1) (13).

Early detection of sarcopenia in older adults and patients is important to prevent morbidity, functional decline and death (24, 25). Although

it was given the code M62.84 in the International Classification of Diseases system very recently, the criteria proposed for the diagnosis of sarcopenia are still not widely used and can easily escape the attention in clinical practice (11, 26).

The symptoms and signs of general weakness, loss of muscle mass (visual), low walking speed, weight loss, muscle strength depletion in the arms/legs, fatigue, falls, mobility disorder, loss of energy, and difficulties in activities of daily living need to be considered red flags, raising alerts for a sarcopenia screening. If these symptoms are present, the guidelines of EWGSOP (15) recommend screening of patients for sarcopenia using SARC-F. If the SARC-F score turns out 4 and over, a muscle strength test is recommended and if there is a problem in muscle strength, then a "probable sarcopenia" diagnosis can be made. If probable sarcopenia is detected, treatment is recommended. In case there is a problem in muscle strength, a muscle quality and quantity assessment is suggested, and if a problem is found, a diagnosis of "sarcopenia" can be made. In case a physical

**Figure 1.** Sarcopenia assessment algorithm.



performance disorder is also present in the above algorithm, then a diagnosis of "severe sarcopenia" can be made. A hand grip strength or chair stand test is recommended for muscle strength assessment and a gait speed, short physical performance battery, timed up and go test, 400 mt walk or long distance corridor walk test for physical performance measurement (15).

Currently there have been some methods for evaluation of sarcopenia focusing on body composition imaging modalities such as, whole-body dual-energy X-ray absorptiometry, computed tomography (CT), and magnetic resonance imaging (MRG). But there are controversial issues, including the lack of consensus and standardization of the disease definition, imaging modality, measurement methods, and diagnostic cutoff points (27).

Recent revised European consensus on definition was as follows (Figure 1) (13, 15):

Probable sarcopenia is identified by Criterion 1.

Diagnosis is confirmed by additional documentation of Criterion 2.

If Criteria 1, 2 and 3 are all met, sarcopenia is considered severe.

- (1) Low muscle strength
- (2) Low muscle quantity or quality
- (3) Low physical performance.

Unfortunately, one can say that, there is not adequate data for muscle quality assessment although it is a very important parameter. However, recent studies suggest that early assessment of muscle quality will be of crucial importance to prevent sarcopenia in the future (13).

Validated tests and tools for current use are listed by the European consensus as; SARC-F for screening sarcopenia risk, calibrated handheld dynamometer for muscle strength, chair rise test, body mass index (BMI) for muscle quantity, MRG, CT and also Dual-energy X-ray absorptiometry (DXA) for muscle quantity/mass, Bioelectrical im-

pedance analysis (BIA) for Appendicular Skeletal Muscle Mass. Gait speed, Short Physical Performance Battery (SPPB), the Timed-Up and Go test (TUG) for the evaluation of physical performance are recommended (15).

New methods are being tested for validity, reliability and accuracy and may play a relevant role in the future. Such as; lumbar 3rd vertebra imaging by computed tomography, mid-thigh muscle measurement, psoas muscle measurement with CT, muscle quality measurement (MRI and CT), creatine dilution test, ultrasound assessment of muscle, specific biomarkers or panels of biomarkers. Since quality of life is a very considerable issue, "Sarcopenia and Quality of Life (SarQoL)" identifies and predicts sarcopenia complications that may later impact the patient's quality of life (15).

## TREATMENT OPTIONS

Treatment of advanced PC has improved recently. As the diagnostic criteria to identify patients with sarcopenia are debatable, potential treatment options also become obscure. The options in the literature are unfortunately unable to meet our needs due to their side effects and lack of evidences. Data on the mechanisms, efficacy and safety of pharmacological therapies are not satisfactory.

The strongest evidences in the treatment of sarcopenia are probably associated with the positive effects of resistance exercises on muscle strength, muscle mass and physical performance (13). An individual's general physical activity level is also important (28). An hour of increase in daily sitting time is reported to increase the risk of sarcopenia by 33% (29). Therefore, it is of utmost importance for protection to increase the level of daily physical activity as much as possible. Weekly physical activity for 150 minutes at a moderate level or for 75 minutes at an intense level is recommended (30). Rehabilitation physicians need to put their effort into planning tailor-made exercise programs, either community-based or home-based as appro-



priate.

According to general consensus reports and evidences at a lower level, protein intake needs to be increased to 1-1.5 g/kg/day to achieve an optimal health condition in the elderly. Daily protein amount should be proportioned between meals and particularly taken within the first 2-3 hours following an exercise (for muscle protein synthesis stimulation). Reports suggest that daily intake can be increased up to 2 g/kg in the cases of an injury, a severe disease, or a proinflammatory/catabolic process.

Positive results have been reported on supplementation with leucine and its metabolite  $\beta$ -hydroxy  $\beta$ -methylbutyrate (HMB) due to their contribution to protein synthesis (13, 31). HMB has been shown to improve muscle mass and to preserve muscle strength and function in older people with sarcopenia or frailty (17, 18, 32). Positive results have also been obtained with Omega 3 support but without sufficient evidence. A combination of resistance exercises and nutritional supplements is reported to have more apparent protective and healing effects (28). Vitamin D supplementation specifically for sarcopenia was found to have insufficient evidence, though there is evidence that persons with low vitamin D levels may improve their strength with vitamin D supplementation (33). Since oxidative stress is also in the aetiology of sarcopenia, use of antioxidants (vitamin E, Selenium, vitamin C, etc.) can also be considered. However, antioxidant intake naturally from food is recommended more. Specific or popular diet regimens have not produced a significant outcome. There are very promising studies related to angiotensin receptor blockers in the literature. Some oral anti-diabetic drugs are also reported to be helpful in preventing sarcopenia. Interventions to prevent sarcopenia, treatment of the primarily responsible disease, suppression of inflammation, and treatment of metabolic syndromes constitute the basic components of a successful treatment (13, 14, 34, 35).

High-dose testosterone increases muscle power and function, but has a number of potentially limiting side effects. Other drugs in clinical development include selective androgen receptor molecules, ghrelin agonists, myostatin antibodies, activin type 2 receptor antagonists, angiotensin converting enzyme inhibitors, beta antagonists, and fast skeletal muscle troponin activators (34, 35). At present, there is insufficient evidence that anabolic steroids or newer pharmacological agents (ghrelin, anti-myostatin antibodies) should be used to treat sarcopenia.

However, promising results still cannot be obtained due to side effects of some therapies and inefficacy of some others. An effective pharmacological treatment is still not available due to the quality of the studies in the literature, heterogeneous groups involved and a large amount of factors affecting sarcopenia.

## CONCLUSION

It is well shown that, sarcopenia is associated with multiple adverse outcomes such as comorbidities, poor physical performance, physical disability, depression, hospitalisation, functional decline and falls, causing the patients having worse quality of life. Indicating the importance of preventative and interventional management strategies for managing sarcopenic individuals (36).

Unavailability of distinct diagnostic criteria for sarcopenia leads to confusion in selecting a treatment option. The point that needs to be stressed is that it often escapes the attention in clinical practice and successful treatment results cannot be achieved due to its complex nature. Data on the mechanisms, efficacy and safety of pharmacological therapies are not satisfactory. But nowadays diagnosis, treatment, and prevention of sarcopenia is likely to become part of routine clinical practice. And designing effective preventive strategies that people can apply during their lifetime is of primary concern today (3).

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