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Sarcopenia

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ABSTRACT

Sarcopenia is the progressive and involuntary loss of muscle mass and strength that occurs with elderly age. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP1) characterised the condition primarily by low muscle mass. The definition of sarcopenia that has been most widely adopted is that proposed by the EWGSOP1, which was updated in 2019 to become the EWGSOP2. Acute and chronic sarcopenia was included in the EWGSOP2 guideline for the first time. Although there is no consensus on the exact aetiology of sarcopenia, it is widely accepted that the condition is related to the natural ageing process. There are many chronic diseases associated with sarcopenia, including: cancer, chronic obstructive pulmonary disease, chronic heart failure, Parkinson, cognitive impairment, depression, chronic kidney disease, diabetes mellitus, human immunodeficiency virus (HIV), anorexia and osteoporosis. The assessment of sarcopenia includes a variety of methods and screening tools that are easily accessible and practical. The EWGSOP2 algorithm is delineated as "find-assess-confirm-severity," or F-A-C-S. A multidisciplinary approach is imperative for the early diagnosis and treatment of this condition. Given the multifactorial pathogenesis of sarcopenia, no definitive pharmacological therapy currently exists. Enhanced patient education and adherence to clinical recommendations are pivotal. The most effective strategies for combating sarcopenia involve a combination of nutritional support and resistance-aerobic exercise programs. Further research is needed to explore new pharmacological treatment approaches.

Keywords: Sarcopenia, EWGSOP, acute sarcopenia, chronic sarcopenia, muscle strength

INTRODUCTION

Sarcopenia is the progressive and involuntary loss of muscle mass and strength that occurs with elderly age. This condition has been linked to several adverse health outcomes, including disability and mortality.[1] Skeletal muscle mass loss has been observed to commence around the age of 35, with a rate of loss of 1-2% per year. After the age of 65, this rate typically increases to approximately 3% per year.[2] Sarcopenia is generally considered to be a geriatric syndrome; however, it can also manifest in individuals under the age of 60 years due to a number of factors, including obesity, diabetes mellitus (DM), cardiovascular diseases, renal and hepatobiliary diseases, cancer.[3-6]

DEFINITION

The definition of sarcopenia was first made by Rosenberg et al.[7] in 1989. In the 36 years under review, a range of research communities have proposed divergent definitions. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP1) characterised the condition primarily by low muscle mass.[8] This definition was inadequate to describe the decrease in muscle mass. Consequently, in 2011, the International Working Group on Sarcopenia (IWGS) advanced a revised definition, characterising sarcopenia as a condition of low muscle mass accompanied by slow gait speed.[9] In 2014, the Foundation for the National Institutes of Health (FNIH) defined sarcopenia as a condition characterised by low muscle mass and low grip strength (FNIH, 2014).[10]

The definition of sarcopenia that has been most widely adopted is that proposed by the EWGSOP, which was updated in 2019 to become the EWGSOP2.[11] Diagnosis of sarcopenia according to EWGSOP2 guidelines is shown in **Table 1**.

Table 1. Criteria for the diagnosis of sarcopenia

Diagnosis is based on documentation of criterion 1 plus (criterion 2 or criterion 3)
1. Low muscle mass
2. Low muscle strength
3. Low physical performance

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PATHOPHYSIOLOGY

Sarcopenia is characterised by a significant reduction in type II muscle fibres.[12] Mechanisms explaining the pathophysiology of sarcopenia;

Neurodegeneration

As people get older, there is a decrease in the number of alpha motor neurons in the spinal cord and a loss of peripheral nerve fibers. The subsequent insufficiency in muscle fiber activation secondary to this suggests that neurodegeneration is a major pathophysiological factor contributing to the loss of muscle mass.[13]

Decrease in Anabolic Hormones

It has been demonstrated that anabolic hormones such as human growth hormone (HGH), insulin-like growth factor-1 (IGF-1), and testosterone play a crucial role in muscle tissue development. In geriatric patients, a decline in these hormones has been observed with advancing age.[14]

Sarcopenic Obesity Associated with Insulin Resistance

As human survival has increased, the proportion of individuals with low muscle activity and high fat content has increased.[15] High body fat percentage increases the risk of insulin resistance. Insulin resistance has been shown to be inversely proportional to skeletal muscle mass.[16] Current guidelines from the European Society of Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) define the combination of sarcopenia and obesity as "sarcopenic obesity".[17] Research showing that sarcopenic obesity is a risk for cardiometabolic and physical function remains topical.[18,19]

High Cytokine Levels

Inflammatory cytokines such as tumor necrosis factor-alpha (TNF), C-reactive protein (CRP), interleukin (IL)-1 and IL-6 increase in chronic diseases and elderly. High levels of cytokines cause a decrease in protein synthesis in the muscle cell and a catabolic effect on skeletal muscle.[20]

STAGING AND CLASSIFICATION

Muscle strength and mass can change throughout a person's life. After age 50, there is an approximate 1-2% annual decline in leg muscle mass and a 1.5-5% annual decline in muscle strength. Staging and classification of sarcopenia are shown in Table 2 and 3.[8]

Table 2. Sarcopenia staging according to the European Working Group on Sarcopenia in Older People-2

Pre-sarcopenic stage	Muscle mass is decreased, while muscle strength and physical performance remain unaffected
Sarcopenic stage	Muscle mass is reduced, accompanied by a decline in either muscle strength or physical performance
Severe sarcopenia	All three criteria-muscle mass, muscle strength, and physical performance-are reduced

ACUTE AND CHRONIC SARCOPENIA

In EWGSOP2, new subgroups were updated as acute and chronic sarcopenia. Sarcopenia lasting less than 6 months is acute sarcopenia, if it lasts longer than 6 months, it is defined as chronic sarcopenia. Acute sarcopenia is usually an acute disease, whereas chronic sarcopenia is associated with chronic and progressive conditions and may increase the risk of death. This distinction was made to emphasise the importance of periodic control in patients at risk of sarcopenia. Acute sarcopenia is typically associated with an acute illness, while chronic sarcopenia is linked to ongoing and progressive conditions that may increase the risk of mortality. This distinction underscores the necessity for periodic evaluations in patients deemed to be at risk of sarcopenia.[11]

Table 3. Sarcopenia classification according to the European Working Group on Sarcopenia in Older People-2

Primary sarcopenia	
Age-related sarcopenia	No other cause evident except ageing
Secondary sarcopenia	
Activity-related sarcopenia	Physical inactivity, sedentary lifestyle
Disease-related sarcopenia	Advanced organ failure (cardiac, hepatic, renal etc.), inflammatory diseases, malignancies, endocrine disorders, osteoarthritis, and neurological disorders
Nutrition-related sarcopenia	Inadequate dietary protein and energy intake, as well as diseases and medications causing anorexia

ETIOLOGY

A study of adults aged 70 years and over reported the prevalence of sarcopenia to be 20.1% in men and 29.2% in women.[21] Another study, conducted in accordance with the 2019 diagnostic criteria of the Asian Working Group (AWGS), found the prevalence of sarcopenia among older adults to be 22.2% (24.1% in men, 21.3% in women).[22]

Although there is no consensus on the exact aetiology of sarcopenia, it is widely accepted that the condition is related to the natural ageing process.[23] A number of factors must be considered when investigating the issue of contributing factors in elderly. Such factors include reductions in type II muscle fibres, immobilisation and decreased physical activity, insulin resistance, obesity, an inadequate muscle protein synthesis response to resistance exercise, decreased serum concentrations of growth factors, and insufficient protein intake.[9,24]

There are many chronic diseases associated with sarcopenia, including; cancer, COPD, chronic heart failure, Parkinson, cognitive impairment, depression, chronic kidney disease, DM, HIV, anorexia and osteoporosis.[25-29] It is suggested that these diseases may affect muscle function in ways that limit physical activity or restrict calorie intake, leading to sarcopenia.[30]

A meta-analysis has shown that smoking increases the risk of sarcopenia.[27] Another systematic review found no evidence of a link between alcohol and the risk of sarcopenia.[31] Many studies have been conducted to determine the relationship between sleep duration and sarcopenia. However, the results of these studies are contradictory.[32] The relationship between sleep quality and sarcopenia needs further long-term research.

IDENTIFYING SARCOPENIA IN CLINICAL PRACTICE AND RESEARCH

The assessment of sarcopenia includes a variety of methods and screening tools that are easily accessible and practical. The EWGSOP2 algorithm is delineated as "find-assess-confirm-severity," or F-A-C-S (F-A-C-S; Figure).[11]

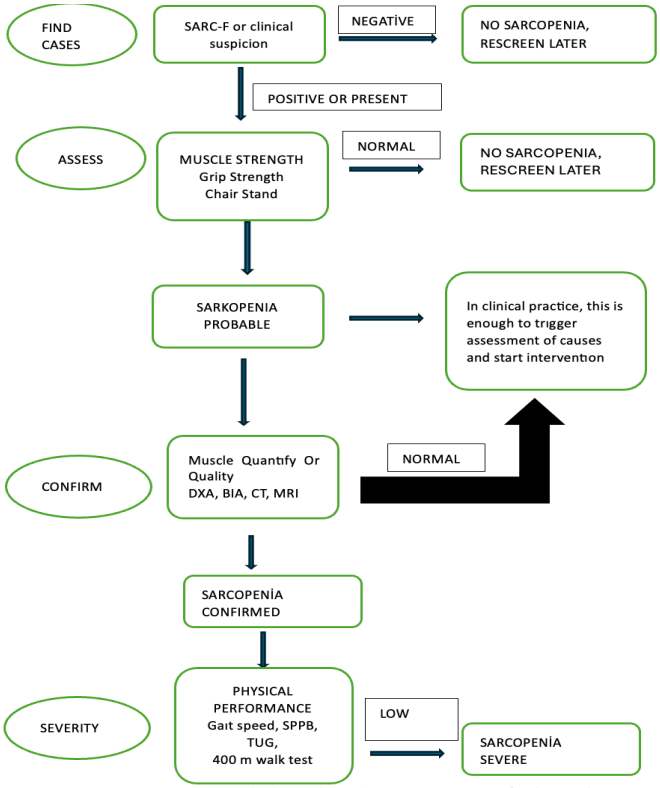

Figure. EWGSOP-2 practical algorithm (sarcopenia case finding, diagnosis and severity)

EWGSOP-2: European Working Group on Sarcopenia in Older People

SARC-F Questionnaire

The SARC-F questionnaire is a practical screening tool for sarcopenia that evaluates five categories: strength, walking, rising from a chair, stair climbing and experiences with falls.[33] The questionnaire shows low to moderate sensitivity but high specificity for predicting low muscle strength.[34] Each parameter is scored on a scale from 0 to 2, with a maximum total score of 10. A total SARC-F score of 4 or more indicates the need for further assessment of sarcopenia.[35] A project is underway to translate the SARC-F into multiple languages.[36]

MEASURING SARCOPENIA PARAMETERS

Muscle Strength

Handgrip Test: Grip strength has been shown to be an indirect measure of overall muscle strength, given its relationship to the strength of muscle groups in other parts of the body.[37] Reduced grip strength has been demonstrated to be associated with prolonged hospitalisation, diminished quality of life and functional impairment.[38] The Jamar dynamometer is a validated instrument for measuring grip strength. The recommended cutoffs for grip strength are <27 kg for males and <16 kg for females.[39]

Chair Stand Test: This practical test is used to assess quadriceps strength in the lower extremities. It measures how many times a patient can stand up and sit down from a chair without using their arms in 30 seconds.[40] The recommended threshold value for the chair stand test is five times for more than 15 seconds to stand up.[41]

Muscle Quantity or Quality

Numerous technical studies have been conducted to assess muscle mass. However, there is still no consensus on the most effective method for confirming sarcopenia. Each method has its strengths and weaknesses.[42]

Muscle quantity: The total body skeletal muscle mass (SMM), appendicular skeletal muscle mass (ASM), and the ratios of these masses to the associated height or body-mass index (BMI) value are calculated. Ratios such as (ASM/height^2), (ASM/weight), or (ASM/BMI) are then obtained.[43]

Magnetic resonance imaging (MRI) and computed tomography (CT): MRI and CT are non-invasive 'gold standard' methods for assessing muscle mass. However, due to their high cost, they are rarely used in routine practice. A definitive cut-off point for MRI and CT has not yet been established.[44]

Dual-energy X-Ray absorptiometry (DEXA): DEXA is a method that is frequently preferred by researchers and clinicians for the diagnosis of sarcopenia on account of the fact that it is both faster and more practical.[45] Adjustment is made for body size to calculate muscle mass (e.g., ASM/height^2, ASM/weight, ASM/BMI). However, there is no consensus on the most appropriate correction method or cut-off values.[46]

Bioelectrical impedance analysis: BIA is probably the most common method used to quantify SMM and ASM.[11] BIA employs a conversion equation that has been calibrated against the lean body mass measured by DEXA.[47]

Measuring Physical Performance

The physical performance tests used to determine the severity of sarcopenia recommended in the EWGSOP2 guideline are as follows:

Gait Speed Test: The 4-meter walk test, in which the time taken to complete the distance is measured using a hand-held stopwatch, is a practical assessment.[48] EWGSOP2 recommends the implementation of a single cutoff of ≤0.8 m/s as an indicator of severe sarcopenia.[11]

Short Physical Performance Battery (SPPB): The SPPB is a comprehensive evaluation test that encompasses chair-stand test, balance test, and gait speed. A total score of ≤8 has been shown to be indicative of poor physical performance and potentially more severe sarcopenia.[49]

Timed-up and Go (TUG) Test: The TUG test evaluates physical function. The patient getting up from the chair, walking 3 meters forward and 3 meters back again and sitting on the chair. The completion of this task within a time frame exceeding 20 seconds is indicative of a physical limitation.[50]

400-Meter Walk Test: Patients are instructed to complete 20 laps of a 20-metre track as expeditiously as possible, with up to two rest periods permitted. A total time exceeding six minutes is indicative of a potentially more severe degree of sarcopenia.[51]

Alternative Tests and Tools

Lumbar 3rd vertebra imaging by computed tomography: CT scans performed at the L3 vertebra level have been demonstrated to exhibit a strong correlation with total body muscle mass. This method is frequently employed, particularly in cancer patients, for early detection of sarcopenia.[52]

Ultrasonography: Ultrasonography is a rapid, practical, and reliable means of evaluating both muscle quantity and quality. The Sarcopenia Group of the European Geriatric Medicine Society (EuGMS) has proposed a consensus protocol for

the utilisation of ultrasound in muscle assessment.[53] The evaluation of muscles, such as the quadriceps femoris, has the capacity to provide information regarding muscle thickness and cross-sectional area in a relatively short timeframe.[54]

Creatine Dilution Test: The primary application of this technique is within the domain of clinical research. Following the administration of a loading dose of D3-creatine, the total body creatine pool and muscle mass can be calculated.[55]

Self-Administrated Quality of Life Questionnaire for Sarcopenia (SarQol): This is a self-administered questionnaire for individuals diagnosed with sarcopenia. Its purpose is twofold: firstly, it identifies complications that may arise from sarcopenia over time and secondly, it predicts the potential impact of these complications on the quality of life.[56]

TREATMENT

The management of sarcopenia is a multifactorial process that encompasses a combination of pharmacological and non-pharmacological approaches. Early diagnosis and treatment are important for preventing the progression of sarcopenia. A substantial body of research has demonstrated that the most efficacious treatment for sarcopenia is a combination of resistance and aerobic exercise, in conjunction with sufficient protein and energy intake.[57] Evidence has demonstrated that resistance training in sarcopenia can lead to a number of notable biological changes. These include an increase in muscle strength and mass, enhanced anabolic hormone production, a reduction in catabolic cytokine activity, and an improvement in bone density. Concurrently, the risk of fractures associated with osteoporosis can be reduced.[58] In geriatric patients, low-speed resistance exercises (2-3 seconds in the concentric phase followed by 2-3 seconds in the eccentric phase for each muscle) have been demonstrated to be the most effective way to improve muscle strength.[59] The impact of aerobic exercise on skeletal muscle has been a subject of considerable research interest, with numerous studies highlighting its beneficial effects on various physiological parameters. The exercise-induced increase in the number and function of mitochondria has been a notable finding, with research indicating that this contributes to reduced insulin resistance, enhanced exercise capacity, and a reduction in oxidative stress. A substantial body of research has demonstrated that aerobic exercise is the most efficacious approach for enhancing muscle strength and physical performance in sarcopenic individuals.[60] In order to achieve a significant clinical improvement in sarcopenia, it is essential that resistance and aerobic exercise programmes are continued for a minimum period of three months.[61]

The efficacy of exercise programmes in the treatment of sarcopenia should be enhanced through nutritional interventions. The impact of resistance exercise has been shown to be augmented by protein supplementation (1-1.2-1.6 g/kg/day, with 25-30 g of protein at each meal) taken after exercise, as well as improving muscle strength and function.[62] The efficacy of protein supplements rich in leucine (present in peanuts, soybeans, lentils, chickpeas, beef, fish, and chicken) or whey protein in increasing muscle mass is well-documented, although the effect on physical performance remains controversial.[63]

The ingestion of minimally processed natural foods (a diet in the style of the Mediterranean) once or twice per day has been demonstrated to be advantageous for muscle and bone health. The ingestion of natural dairy products has been demonstrated to reduce the risk of falls by 11% and fractures by 33%.[64] It has been demonstrated that the natural intake of calcium in excess of 1000 mg and protein levels ranging from 1.2 to 1.5 g/kg/day offers a protective effect against sarcopenia in older adults.[65]

Omega-3 polyunsaturated fatty acids (PUFA) supplementation has been found to increase lean body mass and skeletal muscle mass. Its long-term (beyond six months) use has been shown to be effective in the prevention of sarcopenia and the improvement of physical performance.[66] Evidence suggests that omega-3 supports and improves neuromuscular function, exerting a neuroprotective effect on the motor cortex with long-term supplementation.[67]

The administration of daily doses of 1-3 g of β-hydroxy-β-methylbutyrate (HMB) over a period of 8-24 weeks has been demonstrated to exert a positive influence on muscle strength and body composition. Nevertheless, the effect on muscle mass is comparatively negligible.[68]

Creatine supplementation (3-5 g/day) when combined with resistance exercise has been demonstrated to exert a positive effect on muscle and bone strength, bone and fat mass, and physical performance.[64] However, the efficacy of creatinine in the treatment of sarcopenia and chronic disease is controversial.[69]

Sarcopenia has a reduced gut flora. The administration of oral probiotic therapy, comprising *Lactobacillus roche* and *Lactobacillus galaei*, has been shown to reduce proinflammatory cytokines and potentially enhance muscle mass in cases of sarcopenia.[70]

The evidence suggests that a lack of vitamin D has a detrimental effect on muscle and bone health. The impact of vitamin D supplementation alone on sarcopenia has been demonstrated to be only mildly effective in enhancing muscle strength.[71] However, the combination of vitamin D supplementation with other nutritional interventions (e.g. leucine, probiotics, whey protein) and resistance exercise has been demonstrated to enhance muscle mass and improve physical performance in sarcopenia.[72]

Testosterone supplements have the potential to increase muscle strength in both men and women.[73] However, testosterone can cause complications such as prostate cancer, cardiovascular diseases and polycythemia vera.[74] Patient choice is important in testosterone treatment.

The influence of herbal supplements containing alkaloids, catechins, proanthocyanidins, gingerols, curcumin, and shogaols on skeletal muscle function appears to be minimal. Conversely, appetite-enhancing drugs such as ghrelin and megestrol acetate have been observed to potentially facilitate an increase in body weight and muscle mass.[75,76]

Myostatin, a hormone secreted by skeletal muscle, has been shown to inhibit muscle anabolism. Concurrent utilisation of myostatin inhibitors and resistance exercise regimens has been demonstrated to exert a positive influence on muscle mass.[77] It has been demonstrated that angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and troponin activators can also result in advantageous outcomes with regard to muscle mass and handgrip strength.[78,79] It has been

demonstrated that Bimagrumab, a monoclonal antibody that targets the activin II receptor, has the capacity to increase fat-free muscle mass and muscle volume.[80]

CONCLUSION

Sarcopenia imposes a substantial financial burden on healthcare systems, resulting in diminished quality of life for patients. A multidisciplinary approach is imperative for the early diagnosis and treatment of this condition. Given the multifactorial pathogenesis of sarcopenia, no definitive pharmacological therapy currently exists. Enhanced patient education and adherence to clinical recommendations are pivotal. The most effective strategies for combating sarcopenia involve a combination of nutritional support and resistance-aerobic exercise programs. Further research is needed to explore new pharmacological treatment approaches.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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