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Sarcopenia: A Rheumatic Disease?

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INTRODUCTION

The term Sarcopenia (Greek, *sarx* for: “flesh” and *penia* for “loss”) refers to the phenomenon of reduction of both muscular mass, strength and function with aging.[1] Muscle strength is a critical component of walking, and its decrease in the elderly contributes to a high prevalence of falls. Sarcopenia is significantly associated with self-reported physical disability in both men and women, independent of ethnicity, age, morbidity, obesity, income, or health behaviors.[2] Reduced muscle strength with aging leads to loss of functional capacity and is a major cause of disability, mortality, and other adverse health outcomes.[3]

As the number and proportion of elderly in the population continue to rise, sarcopenia-related morbidity will become an increasing area of health care resource utilization. Increased awareness of the condition amongst clinicians and researchers specially rheumatologists is paramount to recognize and manage this condition as early recognition and intervention can mitigate its deleterious outcomes. This review highlights the major aspects of sarcopenia including definition, prevalence, pathophysiology, diagnosis and management. We also discuss the causes and impact of secondary sarcopenia.

DEFINITION

Development of a universally applicable and acceptable definition of sarcopenia has been a major limitation in the advancement of the field. Since Rosenberg first coined the term sarcopenia in 1988[1], multiple definitions of sarcopenia have been proposed, but to date there is no unanimously accepted method to define and diagnose sarcopenia. In 1998, Baumgartner and colleagues[2] proposed using lean skeletal muscle mass index (SMI) defined as appendicular (four limbs) skeletal muscle mass (ASM) as determined by dual X-ray

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absorptiometry (DEXA) divided by height (kg/m2) and compared with a normal reference population as a standard measure for sarcopenia. This methodology showed promise. It is predictive for negative outcomes and the same DEXA scan used in osteoporosis screening may be used to estimate the degree of sarcopenia, all with no added cost or radiation exposure to the patient.[2] However, muscle quantity or mass does not reflect quality and function of muscle[4].

To account for these limitations, newer definitions of sarcopenia from the European Society on Clinician Nutrition and Metabolism (ESPEN) special interest groups (SIGs)[5], International Working Group on Sarcopenia (IWGS)[6], European Working Group on Sarcopenia in Older People (EWGSOP)[7], and the Foundation of the National Institute of Health (FNIH)[8] have proposed slightly differing definitions of sarcopenia that include muscle mass and function (Table 1). In addition, the EWGSOP suggested staging of sarcopenia into 3 different categories based upon the presence of LMM and the presence or absence of functional impairment[7] (Table 2). These progressive stages of sarcopenia have a dose–response relationship with functional limitations.

EPIDEMIOLOGY

There is a significant variability in the reported prevalence of sarcopenia due to differing definitions, tools of diagnosis and patient populations. A recent study of community-dwelling older adults (average age of 67 years) in the United Kingdom found the prevalence of sarcopenia to be 4.6% in men and 7.9% in women using the EWGSOP criteria.[9] A study from the United States, conducted among adults with an average age of 70.1 years, reported the prevalence of sarcopenia to be as high as 36.5%.[10] In a Japanese population of community-dwelling elderly adults, the prevalence of sarcopenia ranged from 2.5% to 28.0% in men and 2.3% to 11.7% in women.[11]

Much of the difference in these estimates may be due to the lack of uniform criteria to diagnose sarcopenia. In fact, when assessing prevalence of sarcopenia in the same cohort using different definitions, it appears the FNIH criteria give a more conservative estimate (men=1.3%, women=2.3%), compared to IWGS (men=5.1%, women=11.8%) or EWGSOP criteria (men=5.3%, women=13.3%).[12] Interestingly the criteria agreed in exclusion of sarcopenia but not for establishing a diagnosis. This underscores the critical need for a uniform, universally applicable operating definition of sarcopenia.

RISK FACTORS

Sarcopenia is considered by most to be an inevitable part of aging. However, the degree of sarcopenia is highly variable and is dependent upon the presence of certain risk factors.

Lifestyle Lacking Exercise

Lack of exercise is believed to be the foremost risk factor for sarcopenia.[13] A gradual decline in muscle fiber numbers begins around 50 years of age.[14] Even professional athletes such as marathon runners and weight lifters show a gradual, albeit slower decline in their speed and strength with aging.[14] The decline in muscle fiber and strength is more

pronounced in patients with sedentary lifestyle as compared to patients who are physically more active.

Hormone and Cytokine Imbalance

Age-related decreases in anabolic hormone concentrations, including growth hormone, testosterone, thyroid hormone, and insulin-like growth factor, lead to loss of muscle mass and strength. Extreme muscle loss often results from a combination of diminishing hormonal anabolic signals and promotion of catabolic signals mediated through pro-inflammatory cytokines such as tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6).[15] Elevated levels of both TNFα and IL-6 have been shown to be present in skeletal muscles of older individuals.

Protein Synthesis and Regeneration

A decrease in the body's ability to synthesize protein, coupled with inadequate intake of calories and/or protein to sustain muscle mass, is common in sarcopenia. Oxidized proteins increase in skeletal muscle with aging and lead to a buildup of lipofuscin and cross-linked proteins that are inadequately removed via the proteolysis system. This leads to an accumulation of non-contractile dysfunctional protein in skeletal muscles, and is part of the reason muscle strength decreases severely in sarcopenia.[16]

Motor Unit Remodeling

Age-related reduction in motor nerve cells responsible for sending signals from the brain to the muscles to initiate movement also occurs. Satellite cells are small mononuclear cells that abut muscle fibers and are normally activated upon injury or exercise. In response to these signals, satellite cells differentiate and fuse into the muscle fiber, helping to maintain muscle function. One current hypothesis is that sarcopenia is caused, in part, by a failure in satellite cell activation.[15]

Evolutionary Basis

Evolutionary theories implicate the failure of the body to maintain muscle mass and function with aging on genes that govern these traits. This hypothesis suggests that genes suited for high levels of obligatory muscular effort required for survival in the Late Paleolithic epoch are ill-matched to a modern lifestyle characterized by high levels of lifelong sedentary behavior.[17]

Early Developmental Influences

Epidemiologic research into the developmental origins of health and disease has shown that early environmental influences on growth and development may have long-term consequences for human health. Low birth weight, considered a marker of a poor early environment, is associated with reduced muscle mass and strength in adult life.[18] One study has shown that lower birth weight is associated with a significant decrease in muscle fiber score, suggesting that developmental influences on muscle morphology may explain the association between low birth weight and sarcopenia.[19]

SARCOPENIA HISTOPATHOLOGY

Early sarcopenia is characterized by a decrease in the size of muscle. Over time, a reduction in muscle tissue quality also occurs. This is characterized by replacement of muscle fibers with fat, an increase in fibrosis, changes in muscle metabolism, oxidative stress, and degeneration of the neuromuscular junction. This ultimately leads to progressive loss of muscle function and to frailty.[15]

Studies looking at the histologic changes in muscle fibers reveal that sarcopenia predominantly affects the type II (fast-twitch) muscle fibers, whereas type I (slow-twitch) fibers are much less affected.[20] The size of type II fibers can be reduced by up to 50% in sarcopenia. However, such reductions are only moderate when compared with overall reductions in muscle mass. This raises the possibility that sarcopenia represents both a reduction in muscle fiber number as well as reduced fiber size. Histologic studies comparing muscle cross-sections of elderly with those of younger individuals reveal at least 50% fewer type I and type II fibers by the ninth decade.[21] Multiple factors have been implicated to contribute to these histological changes such as chronic neuropathy due to loss of anterior horn cells and ventral root fibers associated with aging[22,23], lifestyle, hormones, inflammatory cytokines, and genetic factors.

SCREENING AND DIAGNOSIS

Although, various consensus groups have different recommendations for screening, in general, elderly patients and/or patients with a history or recurrent falls, unintentional weight loss or other chronic conditions such as heart disease should be assessed for impairment in their activities of daily living (ADLs). Those with impaired ADLs should undergo more specific testing for sarcopenia. Most consensus groups recommend initial testing of mobility impairment with gait speed that involves assessing time taken to walk 4m at normal pace. If gait speed falls below 0.8m/s (1m/s under IWGS criterion) then assessment of muscle mass or strength should be performed. Other assessment of physical performance includes assessment of balance, climbing stairs and rising from a chair.

Body composition can be assessed by DEXA, anthropometry, bioelectrical impedance, MRI or CT scan. DEXA is the most widely accepted method of assessing appendicular muscle mass, however it is limited by its inability to differentiate intra-muscular fat or water.[24] Another method used to assess for muscle mass is bio-impedance analysis, which calculates electrical resistance using sensors to measure muscle mass. This has been shown to overestimate muscle mass and underestimate fat mass.[24,25]

Grip strength is the preferred and most widely used method to assess muscle strength. It involves using hydraulic dynamometer, where the participant is asked to squeeze as hard as they can for 3 seconds. This is repeated three times on each side, alternating between left and right and the highest reading is recorded. For patients with hand deformity, pain or stiffness, a rubber-ball model dynamometer is more acceptable.

MANAGEMENT

Early recognition and intervention are key to improved outcomes in patients with sarcopenia. Assessment of patients' environments for fall hazards and implementation of precautionary safety measures should be part of the treatment strategy.

Current Treatment Options

Resistance Training Exercise and Vibration Therapy—Physical inactivity is linked to loss of muscle strength and mass. Therefore, an exercise regimen is considered a cornerstone in the treatment of sarcopenia. Both resistance training and strength training of muscles are successful interventions in the prevention and treatment of sarcopenia by virtue of their positive influence on, 1) the neuromuscular system, 2) an increase in anabolic hormone concentrations, and 3) an increase in the ability and capacity of the muscles to synthesize proteins.[26,27] Whole Body Vibration Therapy, which involves using specialized equipment with or without aerobic exercises has also been reported to improve muscle strength and function.[28,29]

Nutritional Supplementation—Malnutrition also contributes to sarcopenia. Nutritional screening and implementation of nutrition care plans similar to the approach to cachexia should be part of a multidisciplinary approach to manage sarcopenia. A validated tool for nutritional needs assessment developed by The British Association for Parenteral and Enteral Nutrition is available online at www.bapen.org.uk.[30] Protein and amino acid supplementations like leucine enriched whey protein in combination with resistance training have shown benefits to muscle mass, strength and physical performance.[31–33] High protein intake above the recommended daily allowance (in the range of 1.2–1.6 g/ kg/d) has been suggested to prevent age-related sarcopenia.[34] Vitamin D supplementation (with or without whey protein) also appears to help improve muscle strength, especially in patients >65 years and with a serum concentration below 30 nmol/L.[32,35]

Pharmacological Treatment Directions

Currently, there are no agents for the treatment of sarcopenia that have been approved by the US Food and Drug Administration. Anabolic agents to increase muscle building and agents that decrease muscle catabolism are being explored in sarcopenia.[36]

Androgen/androgen receptor modulators—Testosterone has been used as a therapeutic intervention for sarcopenia for many years. It has a positive effect on muscle mass, it increases muscle strength and it improves functional measures such as gait speed. However, treatment with testosterone is limited due to adverse effects such as increased risk of prostate cancer in men, virilization in women, and an overall increased risk of cardiovascular events.[37–39] Selective androgen receptor modulators (SARMs) are of particular interest because of their tissue selectivity. It is hoped that androgenic signaling with these agents can achieve gains in skeletal muscle mass and strength without dose-limiting adverse events.[40,41] One agent, MT-102, has recently been tested in a phase II clinical study for treating cachexia in late-stage cancer patients. The study data show significant increases in body weight in patients treated with 10 mg of MT-102 twice daily

over the study period of 16 weeks, compared with a significant decrease in body weight in patients receiving placebo treatment.[42] Another SARM, MK-0773, showed increase in muscle mass, however did not show any difference in strength or function in women with sarcopenia.[43]

Myostatin Inhibition—Myostatin is highly expressed in skeletal muscle cells and prevents muscle growth. Inhibitors targeting myostatin or its receptor (ActRIIB) have been developed to help improve muscle mass and strength. A humanized monoclonal antibody, LY2495655, has shown increase in muscle mass and improvement in functional measures of muscle power in elderly patients with increased falls in a phase II clinical trial.[44] Bimagrumab (BYM338) is an anti-myostatin receptor antibody that has shown promising results with increase in muscle mass, strength and gait speed in a phase II clinical trial in patients with sarcopenia.[45] Further studies with these and other myostatin inhibitors are under way and will provide further information on their efficacy and safety.

Other therapies in development—Other compounds under investigation as treatments for sarcopenia include growth hormone, angiotensin-converting enzyme inhibitors, beta1-antagonists like epindolol, eicosapentaenoic acid, thalidomide, OHR/AVR118 (a novel peptide-nucleic acid immunomodulator), celecoxib (COX-2 inhibitor), VT-122 (combination beta-antagonist and COX-2 inhibitor), omega-3 supplements, and anabolic agents such as ghrelin and its analogues, and ruxolotinib.[46]

Herbal Supplements—There is a considerable interest in using herbal supplements in sarcopenia. A recent review reported a large number of herbal compounds with effects on skeletal muscles.[47] Some of the herbal compounds like curcumin from *Curcuma longa*, alkaloids and steroidal lactones from *Withania somnifera*, catechins from *Camellia sinensis*, proanthocyanidin of grape seeds, and gingerols and shogaols from *Zingiber officinale* showed modest effects on skeletal muscle in human studies.[47] However, the data supporting use of these supplements in people are limited with regards to efficacy, potential drug interactions and adverse effects and thus, recommendations for their use in sarcopenia is limited pending further research.

SECONDARY SARCOPENIA

Sarcopenia is often related to other underlying medical conditions. The pathogenic mechanisms that cause muscle wasting in secondary sarcopenia can provide useful insights into age-related sarcopenia. The management of secondary sarcopenia should focus on treating the underlying primary condition, with the same strategies to improve skeletal muscle strength and mass outlined previously.

Cachexia

Cachexia is characterized by severe muscle wasting usually accompanying severe systemic diseases such as cancer, cardiomyopathy, and end-stage renal disease. Cachexia has recently been defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass.[48] Cachexia is frequently associated with inflammation, insulin resistance, anorexia, and increased breakdown of

muscle proteins. Thus, most cachectic individuals are also sarcopenic, but most sarcopenic individuals are not considered cachectic. Sarcopenia is among the elements of the proposed definition for cachexia.[48]

Frailty

Frailty is a geriatric syndrome resulting from age-related cumulative declines across multiple physiologic systems, with impaired homeostatic reserve and a reduced capacity of the organism to withstand stress. The syndrome encompasses increased vulnerability to adverse health outcomes such as falls, hospitalization, institutionalization, and mortality.[49] Frailty is based upon readily identifiable physical impairments, with the presence of 3 or more of the following characteristics: unintended weight loss, exhaustion, weakness, slow gait speed, and low physical activity.[49,50] There exists significant overlap between frailty and sarcopenia; most frail older people have sarcopenia, which suggests a common pathogenic mechanism. The general concept of frailty, however, goes beyond physical factors to encompass psychological and social dimensions such as cognitive decline, lack of social support, and the impact of the local environment.[50]

Sarcopenic Obesity

Sarcopenic obesity (SO) is a medical condition in which low lean body mass seen in sarcopenia is coupled with high fat mass. It is associated with impaired functional capacity, disability, metabolic complications, and mortality.[51] The reported prevalence of SO is between 2% to 21.7%. The likely explanation for wide variability in reported prevalence is due to factors such as lack of awareness of SO among health care providers and differences in genetics, nutrition, and lifestyle. In conditions such as malignancy, lean body mass may be lost while fat mass is preserved or increased.[51] Studies in patients with SO reveal that changes in muscle composition like marbling, or fat infiltration into muscle, lowers muscle quality and work performance thereby contributing to weakness.[52] Studies to understand the pathogenesis of SO have also observed certain age-related patterns of fat composition like an initial increase and then leveling off of fat mass as well as redistribution of fat from subcutaneous tissue to muscle and viscera that may play a role in development of SO.[52]

Sarcopenia in Systemic Autoimmune Diseases

Patients with systemic autoimmune diseases like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), spondyloarthritides and systemic sclerosis are especially predisposed to developing sarcopenia in light of the underlying pro-inflammatory state and the decrease in muscle use due to inactivity and pain. Nearly 10% of SLE patients have been reported to have sarcopenia.[53] Loss of muscle mass and function is 2–3 times more common in RA patients.[53–55] Patients with RA have also been reported to have more rapid decline in their hand grip strength which is inversely related to the duration of their disease, regardless of their age.[56] Similarly patients with spondyloarthritis and systemic sclerosis have been reported to have higher prevalence of sarcopenia.[57–59] Inflammatory burden of the disease and treatment may influence the prevalence and extent of sarcopenia and its limitation on activities of daily living. Early treatment and control of disease along with physical therapy focusing on resistance training may help in prevention of sarcopenia in these patients.

SUMMARY AND FUTURE DIRECTION

Sarcopenia is a growing global health concern. Sarcopenia has been reported to affect 5% to 13% of persons aged 60 to 70 years and up to 50% of people over 80 years of age.[60] In 2000, the number of people at least 60 years old around the world was estimated to be 600 million. This population is expected to rise to 1.2 billion by 2025 and 2 billion by 2050. Even with a conservative estimate of prevalence, sarcopenia affects more than 50 million people today and will affect more than 200 million people in the next 40 years.

The diagnosis of sarcopenia can be difficult to affirm. The comprehensive measurements used in research are not always practical in health care settings and do not typically influence care planning. Exercise remains the intervention of choice for managing sarcopenia, but implementing an exercise program may be challenging for many reasons. The role of nutrition in preventing and treating sarcopenia is less clear. Although there is vigorous debate about what level of protein intake is optimal, ensuring adequate protein intake and replacing deficient nutrients and vitamins are recommended.

Future research should focus on exploring the biological pathways that lead to sarcopenia, along with the search for improved diagnostic biomarkers. Increased awareness among patients and health care providers, early screening, and a multidisciplinary approach to treatment are the best current practices to minimize the overall adverse impact of sarcopenia.

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KEY POINTS

- Sarcopenia involves the loss of muscle mass, muscle strength and physical function with ageing.
- It is a prevalent but under-recognized problem in the elderly population, causing limitation of activities of daily living and increasing the risk of fall and mortality.
- To date, a common clinical definition and diagnostic criteria for sarcopenia are lacking. Many commonly used screening tools use parameters to assess for muscle mass, strength and function to define sarcopenia.
- The goal of this article is to promote awareness among physicians of early recognition and management of sarcopenia.

SYNOPSIS

Sarcopenia refers to the age-related loss of muscle mass, muscle strength and physical function. With an increase in the number and proportion of elderly in the population, sarcopenia is a growing global health concern due to its impact on morbidity, mortality, and health care expenditure. Despite its clinical importance, sarcopenia remains under-recognized and poorly managed in routine clinical practice. This is, in part, due to a lack of available diagnostic testing and uniform diagnostic criteria. This article provides the general practitioner or rheumatologist an overview of the pathophysiology, diagnosis and management of this complex and critical entity.

Table 1

Sarcopenia Definitions from Various Consensus Groups

Consensus Group	Muscle Mass	Muscle Strength	Physical Performance
ESPEN SIG[5]	>2SD below mean muscle mass in adults 18–39yo in NHANES III cohort	N/A	Gait speed <0.8 m/s
IWGS[6]	SMI - Men ≤7.23 kg/m^2 - Women ≤5.67 kg/m^2	N/A	Gait speed <1m/s
EWGSOP[7]	SMI - Men ≤7.23 kg/m^2 - Women ≤5.67 kg/m^2	Hand Grip Strength - Men <30kg - Women <20kg	Gait speed <0.8m/s
FNIH[8]	Muscle mass/BMI - Men ≤0.789 - Women ≤0.512	Hand Grip Strength - Men <26kg - Women <16kg	Gait speed <0.8m/s

ESPEN SIG: European Society on Clinician Nutrition and Metabolism special interest groups; IWGS: International Working Group on Sarcopenia; EWGSOP: European Working Group on Sarcopenia in Older People; FNIH: Foundation of the National Institute of Health; NHANES III: 3rd National Health and Nutrition Examination Survey; SMI: Skeletal Muscle Index by dual X-ray absorptiometry (DEXA); BMI: body mass index

Table 2

Sarcopenia Staging

Stage	Muscle Mass	Muscle Strength	Performance
Presarcopenia	Low	Normal	Normal
Sarcopenia	Low	Low	Normal or low
Severe sarcopenia	Low	Low	Low

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