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Pathogenesis and Management of Sarcopenia

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SYNOPSIS

Sarcopenia represents a loss of muscle strength and mass in older individuals and is a major determinant of fall risk and impaired ability to perform activities of daily living, often leading to disability, loss of independence and death. Sarcopenia in the elderly has now become a major focus of research and public policy debate due to its impact on morbidity, mortality and healthcare 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. The management of sarcopenia is primarily focused on physical therapy for muscle strengthening and gait training. There are no pharmacological agents currently approved for the treatment of sarcopenia.

Keywords

Sarcopenia; Muscle Strength; Muscle Atrophy; Frailty; Aging; Senescence; Fall Risk; Skeletal Muscle Mass Loss

INTRODUCTION

The term Sarcopenia (Greek, *Sarx* for “flesh” and *Penia* for “loss”) refers to the phenomenon of reduction of both muscular mass 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 outcome.(3) As the number and proportion of older persons in the population continues to rise,

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sarcopenia-related morbidity will become an increasing area of health care resource utilization.

Initial descriptions of sarcopenia focused on loss of muscle mass and did not consider inclusion of muscle strength or physical impairment as part of the disease process.(3) The 2010 European Working Group on Sarcopenia in Older People (EWGSOP) recognized that muscle strength and muscle mass are significant components of sarcopenia. The group defined sarcopenia as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with risk of adverse outcomes such as physical disability, poor quality of life and death.(4-6) Early recognition and intervention can mitigate some of these deleterious outcomes.

EPIDEMIOLOGY

There is a significant variability in the reported prevalence of sarcopenia. A recent study of community dwelling older adults (average age of 67 years) in UK found the Sarcopenia prevalence to be 4.6% in men and 7.9% in women using the EWGSOP criteria (7). A study from the USA, conducted among older adults with an average age of 70.1 years, reported the prevalence of Sarcopenia to be as high as 36.5%(8). 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 (using dual-energy X-ray absorptiometry for measuring lean body mass), and 7.1-98.0% in men and 19.8-88.0% in women (measured by bioelectrical impedance analysis) (9). In a large cohort of 2867 community-dwelling older adults (age >65 years) in Taiwan, the prevalence of sarcopenia varied from 3.9% to 7.3% with prevalence reaching 13.6% among older men aged 75 years and older(10). Much of the difference in these estimates may be due to the lack of uniform criteria to diagnose 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 presence of certain risk factors (as discussed below).

A. LIFESTYLE LACKING EXERCISE:

Lack of exercise is believed to be the foremost risk factor for sarcopenia.(11) A gradual decline in muscle fiber numbers begins around 50 years of age. (12) The decline in muscle fiber and strength is more pronounced in patients with sedentary lifestyle as compared to patients who are physically more active. Even professional athletes such as marathon runners and weight lifters show a gradual albeit more slower decline in their speed and strength with aging. (12)

B. HORMONE AND CYTOKINE IMBALANCE:

Age-related decreases in 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 (TNF-α) and interleukin-6 (IL-6).(13) Elevated levels of both TNF-α and IL-6 have been shown to be present in skeletal muscles of older individuals.

C. 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.(14)

D. MOTOR UNIT REMODELLING:

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(13).

E. EVOLUTIONARY BASIS:

Evolutionary theories implicate the failure of the body to maintain muscle mass and function with aging on genes that governing 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.(15)

F. EARLY DEVELOPMENTAL INFLUENCES:

Epidemiological 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, a marker of a poor early environment, is associated with reduced muscle

mass and strength in adult life. (16, 17) 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 (18).

DIAGNOSING SARCOPENIA

The evaluation of sarcopenia requires objective measurements of muscle strength and muscle mass. Several methods of evaluating sarcopenia currently used include walking speed, calf circumference (CC), bio-impedance analysis (BIA), handgrip strength, dual-energy X-ray absorptiometry and imaging methods (computerized tomography and magnetic resonance imaging). None of these measures are very sensitive or specific for evaluating sarcopenia. (19, 20)

In 1998, Baumgartner et al proposed using lean body mass, as determined by dual energy X-ray absorptiometry (DEXA), compared to a normal reference population as a standard measure for sarcopenia. His working definition used a cut-off point of 2 standard deviations below the mean of lean mass for gender specific healthy young adults.(2)

This methodology showed promise, being both practical and predictive for negative outcomes. (2) Moreover, given its similarity to the 1996 WHO DEXA methodology for diagnosing osteoporosis, the same scan used in osteoporosis screening may be used to estimate the degree of sarcopenia with no added cost or radiation exposure to the patient. However, this method has several limitations such as the ability of DEXA to distinguish water retention or fat infiltration within muscle or the muscle mass in relation to total body mass. Subsequently other researchers have proposed various methods to account for these limitations; but to date there is no universally accepted method to diagnose sarcopenia.

This initial definition of sarcopenia was further modified by the European Society on Clinician Nutrition and Metabolism (ESPEN) Special Interest Groups (SIG) on geriatric nutrition and on cachexia-anorexia in chronic wasting diseases. (21) Sarcopenia was defined as the following (consensus statement):

1) A low muscle mass, >2 standard deviations below that mean measured in young adults (aged 18–39 years in the 3rd NHANES population) of the same sex and ethnic background, and

2) Low gait speed (e.g. a walking speed below 0.8 m/s in the 4-m walking test).

More recently the European Working Group on Sarcopenia in Older People (EWGSOP), proposed the following diagnostic criteria for sarcopenia (6):

1) Low Muscle Mass (LMM) assessed by skeletal muscle mass index ≤ 8.90kg/m^2 (men) and ≤ 6.37kg/m^2 (women);

2) Low muscle strength (LMS) assessed by handgrip strength < 30kg (men) and < 20kg (women); and

3) Low physical performance (LPP) assessed by gait speed ≤ 0.8m/s.

A detailed description of methods to determine LMM, LMS and LPP are well described in the literature.(22) The diagnosis of sarcopenia required the presence of LMM plus LMS or LPP.

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 (6) (Table1).

These progressive stages of sarcopenia have a dose-response relationship with functional limitations.

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.(13)

Studies looking at the histological changes in muscle fibers, reveal that sarcopenia predominantly effects the type II (fast twitch) muscle fibers, whereas type I (slow twitch) fibers are much less affected.(23) The size of type II fibers can be reduced by up to 50% in sarcopenia. However, such reductions are only moderate when compared to 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. Histological 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. (24) Results from anatomic and electrophysiological studies demonstrate loss of anterior horn cells and ventral root fibers with aging. (25, 26) The mechanism of these histological changes may suggest that a chronic neuropathic process contributes to a loss of motor neurons that leads to reduced muscle mass. Other factors such as life style, hormones, inflammatory cytokines and genetic factors also influence these histological changes.

MANAGEMENT

Early recognition and intervention is the key to improved outcomes in patients with sarcopenia. Screening patients for impairment in their physical function and activities of daily living (ADLs) should be a routine part of healthcare visits for the elderly. Patients with impaired ADLs should undergo more specific testing for sarcopenia (as described above). Assessment of patients' environments for fall hazards and implementation of precautionary safety measures should be part of the treatment strategy.

NON-PHARMACOLOGIC TREATMENT

Physical inactivity is linked to loss of muscle strength and mass. Therefore an exercise regimen is considered a cornerstone in the treatment of sarcopenia. Short-term resistance exercise has been demonstrated to increase ability and capacity of skeletal muscle to

synthesize proteins.(27) Both resistance training (RT) and strength training (ST) of muscles have been shown to be somewhat successful interventions in the prevention and treatment of sarcopenia. RT has been reported to positively influence the neuromuscular system as well as increase hormone concentrations and the rate of protein synthesis. (28) A recent meta-analysis revealed some benefit of using a combined approach of dietary supplements and exercise but the findings were inconsistent among various populations. (29)

PHARMACOLOGICAL THERAPIES

Currently, there are no agents for the treatment of sarcopenia that have been FDA approved. DHEA and human growth hormone have little to no effect. Growth hormone increases muscle protein synthesis and increases muscle mass but does not lead to gains in strength and function. This, and the similar lack of efficacy of its effector, insulin-like growth factor 1 (IGF-1), may be due to local resistance to IGF-1 in aging muscle that results from inflammation and other age-related changes. (30)

Testosterone or other anabolic steroids have also been investigated. These agents have a modest positive effect on muscle strength and mass but are of limited use due to adverse effects, such as increased risk of prostate cancer in men, virilization in women, and an overall increased risk of cardiovascular events. (30, 31)

New therapies for sarcopenia are in clinical development. 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. (32) Other compounds under investigation as treatments for sarcopenia include myostatin, vitamin D, angiotensin converting enzyme inhibitors, eicosapentaenoic acid, (30, 31) thalidomide, OHR/AVR118, celecoxib, VT-122, omega-3 supplements, and anabolic agents such as ghrelin and its analogues, MT-102, BYM338 and ruxolotinib. (33) MT-102, the first-in-class anabolic catabolic transforming agent (ACTA), 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 to significant decrease in body weight in patients receiving placebo treatment.(34) In aged animal models, MT-102 has shown to reverse sarcopenia. (35) Further studies of MT-102 as a treatment of sarcopenia are currently underway. Another clinical trial using intravenous BYM338 (bimagrumab) in patients with sarcopenia is currently enrolling subjects. (36)

HERBAL SUPPLEMENTS and NUTRITION

There is a great deal of interest in using herbal supplements to promote muscular mass and health in patients with sarcopenia. A recent review reported a large number of herbal compounds with effects on skeletal muscles.(37) Some of the herbal compounds showed modest effects on skeletal muscle in human studies. These include curcumin from *Curcuma longa*, alkaloids and steroidal lactones from *Withania somnifera* (Solanaceae), catechins from *Camellia sinensis*, proanthocyanidin of *grape seeds*, and gingerols and shogaols from Zingiber *officinale*.(37) The data supporting use of these supplements in humans is limited

as pertains to efficacy as well as potential drug interactions and side effects. Hence, support for the use of herbal supplements for treatment and prevention of sarcopenia is limited until further research proves their safety and efficacy in humans.

Malnutrition also contributes to the development of 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.(38) 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 .(39) Finally, high protein intake above the Recommended Daily Allowance (in the range of 1.2 to 1.6 g/ kg per day) has been suggested to prevent age-related sarcopenia.(40)

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 above.

A. **Cachexia** is characterized by severe muscle wasting usually accompanying severe systemic diseases such as cancer, cardiomyopathy and end-stage renal disease.(41) 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.(42) Cachexia is frequently associated with inflammation, insulin resistance, anorexia and increased breakdown of muscle proteins. (43, 44) Thus, most cachectic individuals are also sarcopenic but most sarcopenic individuals are not considered cachectic. Sarcopenia is one of the elements of the proposed definition for cachexia.(42) Recently, a consensus definition to differentiate between cachexia and other conditions associated with sarcopenia have been developed by the Special Interest Group on cachexia-anorexia in chronic wasting diseases of the European Society for Clinical Nutrition and Metabolism (ESPEN-SIG).(21)

B. **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. (45) Frailty is based upon readily identifiable physical impairments with the presence of three or more of the following characteristics: unintended weight loss, exhaustion, weakness, slow gait speed and low physical activity.(45, 46) 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 as well. This

may include cognitive decline, lack of social support and the impact of the local environment. (46)

C. **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. (47) 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 healthcare providers, and differences in genetics, nutrition and lifestyle.(48) In conditions such as malignancy and rheumatoid arthritis, lean body mass may be lost while fat mass is preserved or increased.(47) Low muscle mass along with high fat mass may also be characteristic of the aging process. However, the presence of SO in older individuals poses a diagnostic challenge because the age-related reduction of muscle mass and strength may be independent of body mass index.

It has long been thought that the age-related loss of weight, along with a loss of muscle mass, was largely responsible for muscle weakness in older people. (49) However, studies in patients with SO reveal that changes in muscle composition are also important. 'Marbling', or fat infiltration into muscle, lowers muscle quality and work performance.(50) Studies to understand the pathogenesis of SO observed certain patterns of age-related changes in body muscle and fat composition. In aging men, the percentage of fat mass increases initially and later levels off or decreases.(50). There is a redistribution of fat that occurs with aging as well, characterized by an increase in intramuscular and visceral fat with a reduction in subcutaneous fat. (51, 52) Such changes may play a role in the development of SO.

CONCLUSION AND FUTURE DIRECTION

Sarcopenia is a growing global health concern. Sarcopenia has been reported to affect 5-13% of persons aged 60 to 70 years and up to 50% of people over 80 years of age. (53) In 2000, the number of people ≥ 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. (54) Even with a conservative estimate of prevalence, sarcopenia affects >50 million people today and will affect >200 million 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 healthcare 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 is recommended. (55, 56)

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 healthcare providers, early screening, and a multi-disciplinary approach to treatment is the best current practice to minimize the overall adverse impact of sarcopenia. (57)

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KEY POINTS

- Sarcopenia is a prevalent but under recognized problem in the elderly population causing limitation of activities of daily living and increases the risk of fall and mortality.
- To date a common clinical definition and diagnostic criteria for sarcopenia is lacking. The most commonly used screening tool developed by the European Working Group on Sarcopenia in Older People (EWGSOP) has several limitations but is endorsed by many professional medical societies.
- Our aim in this review is to promote awareness among physicians of early recognition of sarcopenia and its management in the geriatric patient population.

Table 1

Staging of sarcopenia

STAGE	MUSCLE MASS	MUSCLE STRENGTH	PERFORMANCE
Pre-sarcopenia	Low	Normal	Normal
Sarcopenia	Low	Low	Normal or Low
Severe Sarcopenia	Low	Low	Low

From Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age and ageing. 2010;39(4):412-23; with permission.