CHAPTER
103 Sarcopenic Obesity—The Missed Link: An Update

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INTRODUCTION

Normal aging is linked with 1% muscle loss from 30 years of age, which tends to accelerate after 70 years of age. Lean muscle mass, which is approximately 50% of the total body weight in young adults, reduces to about 25% by the age of 75–80 years. The rate of loss is up to 8% per decade after the age of 40 years, and up to 15% per decade after the age of 70 years. Loss of muscle mass is greater in people with diabetes.

Hormones such as total testosterone that improves muscle protein synthesis decrease by 1% per year and levels of dehydroepiandrosterone sulfate, a precursor to testosterone, also reduce with aging. Hyperthyroidism and chronic illness are also linked with muscle loss and reduced physical functioning. In 2016, sarcopenia was recognized as a disease and assigned an International Classification of Disease, 10th revision (ICD-10) code.

With age, apart from the development and progression of sarcopenia, the occurrence and prevalence of obesity also rise due to unhealthy diet and sedentary lifestyle. The combination of high muscle mass and low fat mass (FM) is generally considered as healthy while the reverse as unhealthy. In obese individuals, metabolic change due to sedentary lifestyle, adipose tissue derangement, comorbidities, etc., can result in a similar situation. Recently, a new body composition category—sarcopenic obesity (SO)—has emerged, which reflects the coexistence of sarcopenia and obesity. SO is increasingly recognized as a clinical entity as it significantly affects patient-centered outcomes. It has multifactorial etiology and its prevalence increase with age. SO is gaining attention because it is associated with many other age-related diseases that present as altered intercellular communication, dysregulated nutrient sensing, and mitochondrial dysfunction. Older adults identified with low muscle-to-fat ratio (MFR) have been found to have poor functional performance and high cardiometabolic risk. Higher cholecystectomy incidence is seen to be associated with low muscle mass, low muscle strength, sarcopenia, and SO. Preliminary results suggest that SO may be associated with telomere shortening and may represent an important risk factor for accelerated aging than sarcopenia and obesity alone. Four body composition phenotypes have been proposed in older populations: Normal, sarcopenic, obese, and sarcopenic obese. SO affects around 5–6% of Indian adults annually. SO is more common in older adults than in young adults. Both sarcopenia and obesity may individually cause threat for adverse health outcomes. But when combined, these two conditions can cause health threats that can be synergistically amplified. Studies have shown that SO is a better predictor of physical disability than sarcopenia or obesity alone.

Management includes optimal diet and exercise strategies to combat the adverse outcomes. There are some potential and emerging treatments for SO, for instance, pharmacological interventions (testosterone supplementation, selective androgen receptor modulators, myostatin inhibitors, and antiobesity drugs), electrical acupuncture, whole-body electromyostimulation, and A2B agonist.

SARCOPENIC OBESITY: AN EMERGING CHALLENGE

Sarcopenic obesity is a new category of obesity in older adults who have high adiposity with low muscle mass. With aging, a progressive increase in FM, which normally peaks at about the age of 65 years in men and later in women, is observed. Aging is also associated with body fat distribution changes, with visceral abdominal fat increase and subcutaneous abdominal fat decrease. Moreover, in the elderly, ectopic fat deposition within non-adipose tissue such as the skeletal and cardiac muscle, liver, and pancreas has been observed. This phenomenon occurs even without significant changes in body mass index (BMI) or body weight. However, sarcopenia may arise in individuals with obesity at any age. Obesity can independently lead to loss of muscle mass and function due to the negative impact of adipose tissue-dependent metabolic derangements such as oxidative stress (OS), inflammation, insulin resistance (IR), and high prevalence of chronic noncommunicable diseases.

DEFINITION

Body mass index does not distinguish between FM and lean mass. In 2000, Baumgartner introduced the term of SO, a condition characterized by coexistence of low muscle mass and a high body FM. But it may underestimate sarcopenia in overweight and obese subjects, thus leading to an underdiagnosis of SO. Hence, more definitions of SO have been proposed.

The European Working Group on Sarcopenia in Older People (EWGSOP) proposed a clinical definition of sarcopenia, for case finding in older adults, in 2009. This definition proposed includes the presence of both low muscle mass and low muscle function (low strength and/or low physical performance). The International Working Group on Sarcopenia proposed a similar definition in 2011, based on a low appendicular or whole-body fat-free mass combined with poor physical functioning. In 2014, the Foundation for the National Institutes of Health Sarcopenia Project recommended defining sarcopenia using specific cut points for low lean mass (appendicular lean mass adjusted for BMI, 0.789 for men and 0.512 for women) and for muscle weakness (grip strength, 26 kg for men and 16 kg for women). However, to date there is no universally accepted definition or classification for sarcopenia, or therefore for SO. Studies have shown that SO is a better predictor of physical disability than sarcopenia or obesity alone. In 2022, the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) defined SO as the coexistence of obesity and sarcopenia (includes mass and function).

ETIOLOGY AND PATHOGENESIS OF SARCOPENIC OBESITY

Sarcopenic obesity is a result of many complex interrelated mechanisms as mentioned below **(Fig. 1)**.

Aging

Many changes in body composition on aging due to lifestyle and reduced physical activity result in increased accumulation of fat, thus, leading to SO phenotype.

Hormonal Changes

Hormonal changes that occur with aging result in IR, reduced thyroid hormone, increased cortisol levels, reduced growth hormones (GH), reduced insulin growth factor 1 (IGF-1), decreased sex steroids, etc., resulting in development of SO phenotype.

Proinflammatory Pathways

Aging results in increased levels of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and IL-1. These inflammatory mediators cause muscle atrophy (increased catabolism) and adipocyte hypertrophy (infiltration of immune cells), both leading to SO.

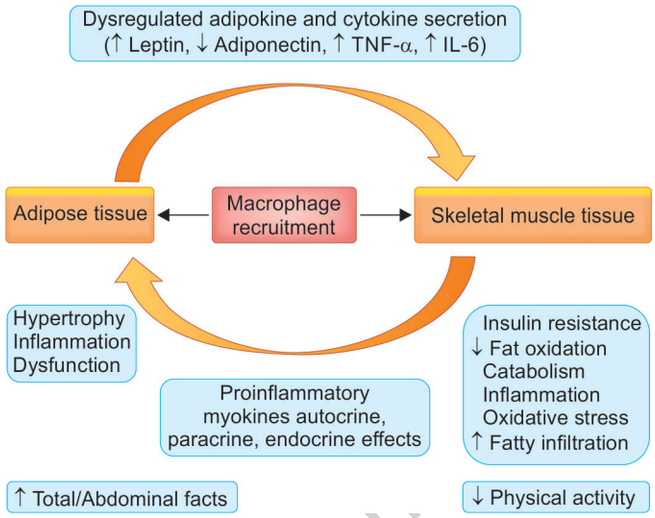

FIG. 1: Pathophysiology leading to sarcopenic obesity.
(IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha)

Myocellular Mechanisms

One of the important parameters leading to SO is intramyocellular deposition of lipids (IMCLs) that promotes lipogenesis, inflammation, muscle IR, OS, and mitochondrial dysfunction. This leads to impaired myocyte satellite cells differentiation/proliferation, leading to sarcopenia due to obesity.

Oxidative Stress

Oxidative stress leads to accumulation of reactive oxygen species (ROS)/reactive nitrogen species (RNS), accompanied by cellular damage. OS leads to infiltration of immune cells in the adipose tissue leading to obesity and IR. OS also causes damage to the myocyte/satellite cells, leading to sarcopenia. Thus, OS can lead to SO.

SARCOPENIA IN ASIAN POPULATIONS: A DISTINCT ENTITY

Asian people have been seen to have lower muscle mass, weaker grip strength, slower gait speed, and greater body FM with central distribution; however, the intensity of age-associated muscle mass decline in the older Asian population remains comparatively unaltered, but the decline rate in muscle strength or physical performance with aging was more noteworthy. Additionally, Asian people showed greater elevation in FM and higher incidence of central obesity with aging, particularly in women.

PREVALENCE OF SARCOPENIC OBESITY

The prevalence of SO varies greatly with definitions, assessment techniques, and populations. SO prevalence generally varies from 0 to 25% in older adults in different studies. The prevalence of sarcopenia in Indian population is approximately 39%. A study conducted in the Indian population in 2015 by the Indian Council of Medical

Research (ICMR) concluded that the prevalence rate of obesity and central obesity varies from 11.8 to 31.3% and 16.9 to 36.3%, respectively. SO affects around 5–6% of Indian adults annually.

SCREENING

Screening is based on the concomitant presence of an elevated BMI or waist circumference (WC) with ethnicity specific cutoff points. Validated questionnaires, e.g., SARC-F (Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls) in older subjects. The Asian Working Group for Sarcopenia (AWGS) suggests that preliminary screening of sarcopenia can be based on a measurement of calf circumference (<34 cm in men, <33 cm in women), the SARC-F scale (≥4), or SARC-Calf scale (≥11). Dual-energy X-ray absorptiometry (DEXA) or bioelectrical impedance analysis (BIA) can be used to improve skeletal muscle mass (SMM) measurements during hospitalization.

DIAGNOSIS AND METHOD OF ASSESSMENT

According to the consensus of the AWGS, the diagnosis of this ailment necessitates analysis of:

- Muscle mass
- Muscle strength
- Physical performance

Body Composition

- DEXA
- BIA
- Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI)

In fact, both DEXA and BIA, the body composition methods that are usually recommended for definition of sarcopenia, are not able to recognize either myosteatosis (MS) or myofibrosis (MF) and also does not take into account muscle function in terms of strength and performance, and it is important because both muscle strength and performance decline quicker than muscle mass with aging.

To accurately diagnose SO, quantitative assessment of SMM and FM is vital. CT and MRI are considered as gold standard for accurate diagnosis of SMM and FM, but their use is limited due to high cost, limited availability, and radiation exposure in case of CT **(Table 1)**.

Skeletal Muscle Functional Parameters

- Hand-grip strength (HGS)
- Knee extensor strength (adjusted for body mass in populations where data are available)
- Chair-stand test (five-time sit-to-stand test; 30 seconds chair-stand test)
- Gait speed test (GS) EWGSOP threshold < 0.8 m/s
- Timed up and go (TUG)
- Short physical performance battery (SPPB)

TABLE 1: Diagnosis techniques for sarcopenic obesity.

Technique	Benefits	Limitations
Dual-energy X-ray absorptiometry	• Rapid • Noninvasive • Minimal radiation • High precision • Simultaneously measures SMM and FM	• Portability • Cost • Limited access • Dependent on patient hydration • Does not distinguish between fat and lean mass
Computed axial tomography	• Identifies and quantifies myosteatosis • High precision • Differentiates between fat and lean mass	• Portability • Cost • Limited access • Radiation
Magnetic resonance imaging	• No radiation • Identifies and quantifies myosteatosis • High precision • Differentiates between fat and lean mass	• Portability • Cost • Limited access • Long duration of test
Muscle tissue ultrasound	• Low cost • No radiation • Real-time imaging • Inflammation and infiltration of muscle tissue can be differentiated	Dependent on type of ultrasound device and examiner's skill

(FM: fat mass; SMM: skeletal muscle mass)

Muscle functional cutoff points need to be validated as reference values for sex, ethnicity, and age stratum. Moreover, studies suggest the necessity to adjust HGS to body mass.

Biomarkers for Sarcopenia

Several biomarkers have been studied. Irisin, a myokine that is released by skeletal muscles, is a potential biomarker for sarcopenia. Low irisin levels (<9.49 ng/mL) in type 2 diabetes mellitus (T2DM) patients is an independent risk factor for SO.

Staging

- *Stage I*: No complications attributable to altered body composition and skeletal muscle functional parameters.
- *Stage II*: Presence of at least one complication attributable to altered body composition and skeletal muscle functional parameters [e.g., metabolic diseases, disabilities resulting from high FM and/or low muscle mass, cardiovascular (CV) and respiratory diseases].

ADVERSE HEALTH CONSEQUENCES OF SARCOPENIC OBESITY

Sarcopenic Obesity has been Associated with Major Clinical Implications

Increased risk of disability; mobility limitations and overall impaired physical capacity; elevated risk of cardiometabolic abnormalities such as IR, dyslipidemia, hypertension, T2DM and low-grade inflammation; increased risk of fractures, depression and compromised overall psychological health; poor outcomes in cancer; increased mortality risk; reduced health-related quality of life; institutionalization; and expanded healthcare costs are some clinical implications. However, the cross-sectional design of related studies fails to provide solid information on causal relationships. This highlights the need for longitudinal studies to elucidate the real impact of SO on the onset and progression of specific diseases **(Fig. 2)**.

MANAGEMENT OF SARCOPENIC OBESITY

Two approaches need to be pursued at the same time: Gaining SMM while losing FM. The effects of any intervention should focus on changes in body composition and functional parameters and should not be measured as changes of body weight alone. If the treatment strategy is limited to only weight loss interventions, there can be inevitable health risks for elderly individuals, mainly related to the concomitant loss of bone and SMM and exacerbation of osteosarcopenia.

Therefore, it is very important to focus on body fat loss and maintenance or accretion of muscle mass, so as to maintain strength, function, and resting metabolic rate (RMR). Combined therapy of nutrition along with exercise is the most accepted strategy for these goals.

Resistance Training

Resistance training is one of the most accepted training for older adults that can improve body composition without weight loss.

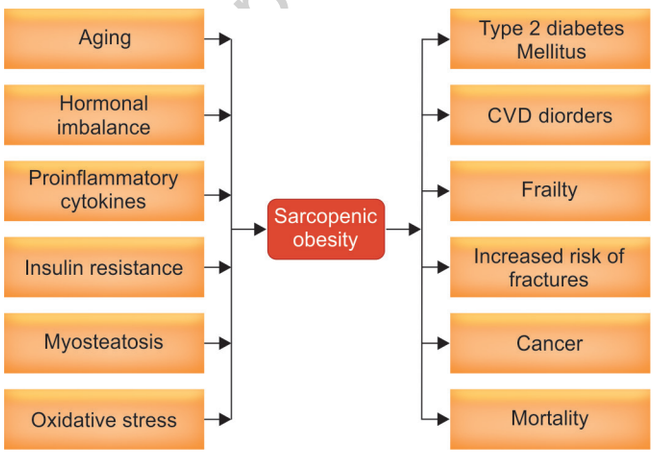

FIG. 2: Sarcopenic obesity: Causes and consequences.
(CVD: cardiovascular disease)

Fiatarone et al. showed that an 8-week training program of resistance training led to an increase in muscle mass in even frail, institutionalized 90-year-old men and women. Weight training (resistance training) for 3 days a week increases muscle mass, with a decrease in FM in healthy men and women aged 50–75 years of age, with body weight remaining unchanged.

Resistance training also induces changes in muscle fiber in healthy men and women aged 60 years or older.

Along with severe calorie restriction, resistance training is beneficial. Calorie restriction usually leads to a reduction in both fat and lean mass. Resistance exercise, when prescribed along with calorie restriction, can help prevent muscle loss. As a result, this can lead to a decrease in FM along with maintaining muscle mass.

Essential Amino Acids Supplementation

Essential amino acids (EAA) supplementation along with resistance exercise can enhance muscle protein synthesis and can improve body composition by increasing lean mass, not FM. In men and women aged 25–35 years, ingestion of EAA before intense resistance exercise resulted in a significant increase in muscle protein synthesis and an increase in lean mass. Similarly, 12 weeks of resistance training with twice-a-day consumption of protein supplement (17 g of EAA) by healthy young men stimulated greater gain in lean mass compared with resistance training alone. Administration of 15 g of EAA to healthy middle-aged men, along with resistance training program, resulted in attenuation of loss of muscle and gains in fat.

Dietary Protein

Even without resistance exercise, a high-protein diet may itself provide an anabolic environment for promoting retention or accretion of muscles over time. A study conducted by Solerte et al. concluded that in older men and women aged 64–84 years with sarcopenia, oral supplementation with 16 g/day of EAA was sufficient to increase lean mass in 8 months. This effect persisted over time and resulted in a decrease in TNF-α, which is found to be elevated in the sarcopenic process. Protein supplementation also prevents muscle loss during calorie restriction, with minimal energy deficit. Higher consumption of high-quality protein (aiming for 1–1.2 g/kg/day or even higher intake 1.2–1.5 g/kg/day) than the current recommended dietary allowance (RDA) might be advantageous for older adults and malnourished medical inpatients. It is also seen that when an individual consumes insufficient diet, the loss of protein can be lessened or even stopped by addition of carbohydrates or fats to the food and is regarded as the "protein-sparing action" of carbohydrates and fats.

TREATMENT STRATEGIES (TABLE 2)

Newer Emerging Treatments

Electrical acupuncture and whole-body electromyostimulation associated with nutritional supplementation are

TABLE 2: Novel treatment strategies.

Treatment modality	Mechanism	Comments
Testosterone and SARM	• Increase muscle mass by increasing IGF-1 • Decrease inflammatory markers	• Conflicting results • Early studies showed good results in cancer patients
Myostatin inhibitors	• Enhance skeletal muscle growth • Inhibit SMM loss	Promising results in cancer-related SMM loss
Mesenchymal stem cells	Precursors for skeletal muscle tissue	• Promising result as an early treatment for sarcopenia • Cost, regulatory and ethical constraints
Anamorelin (oral ghrelin analog)	• Anabolic effects • Anti-inflammatory properties	Safe, well tolerated in cancer patients with cachexia
Anti-obesity medications	• Promote weight loss • Minimal effects on SMM	• Approved for nongeriatric population • Not known in older adults
Bariatric surgery	Results in weight loss	• Unknown safety and efficacy in older patients • May exacerbate weight loss induced sarcopenia and osteoporosis
Neuromuscular activation	Enhances muscle contraction efficiency and functions	Mixed data on efficacy and safety

(IGF-1: insulin growth factor 1; SMM: severe maternal morbidity; SARM: selective androgen receptor modulators)

new and effective strategies to induce changes in body composition. Whole-body vibration therapy has also found to be safe and convenient technique to cause neuromuscular activation and simulate the contraction of skeletal muscle.

A recent study demonstrated that the adenosine receptor (A2B) is highly expressed in muscle tissue and brown adipose tissue (BAT) and may be a target for SO.

UNMET NEEDS, CHALLENGES, AND KNOWLEDGE GAPS

- To establish a robust and standardized definition of SO
- To establish reliable techniques to assess body composition for diagnosing SO
- Further elucidate on descriptive epidemiology of SO, beyond weight loss, morbidity, and mortality, focusing more on patient-centric outcomes such as physical functionality and quality of life
- At present, no specific dietary plans have been tested in populations suffering from SO. Several aspects such as the type of protein, optimal concentration of amino acids to be given, and specificity of the amino acids need to be established.
- To acquire more knowledge regarding optimal frequency, duration, and intensity of exercise (aerobic and resistance). Also, to evaluate if diet and exercise can be combined with pharmacotherapies such as testosterone supplements.

CONCLUSION

The convergence of two conditions—a growing aging population and increasing obesity rates have led to an increase in the prevalence of SO, which is defined as the concurrent presence of sarcopenia and obesity in the same individual. SO can lead to an increase in risk of disability, CV disorders, hospitalization, impaired quality of life, and mortality. Because of such negative effects of SO, its effective diagnosis, prevention, and treatment emerge as a top priority among researchers and clinicians.

To further advance the current knowledge, the scientific community should try to establish a robust definition and a reliable assessment/diagnostic method, conduct more patient-centric trials, and finally obtain concluding evidences with the help of trials for dietary and resistance-training interventions.

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