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Sarcopenic Obesity: Epidemiologic Evidence, Pathophysiology, and Therapeutic Perspectives

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Abstract

Purpose of Review

This review provides a comprehensive update on the definition, assessment, epidemiology, pathophysiology, clinical implications, and therapeutic approach of sarcopenic obesity (SO) and highlights the challenges, limitations, and knowledge gaps in SO research.

Recent Findings

The confluence of a rapidly aging population with rising obesity rates has led to the phenotype of SO, defined as the concurrent presence of sarcopenia and obesity. Despite efforts, a standardized definition of SO is still lacking. Its prevalence varies widely between studies, depending on population characteristics and different definitions. The major pathogenetic mechanisms include age-related changes in body composition and hormonal milieu, positive energy balance, pro-inflammatory pathways, and insulin resistance. Lifestyle interventions, including caloric restriction and physical activity, are the cornerstones of SO treatment.

Summary

SO is a multifaceted syndrome with serious clinical implications. The development and implementation of effective prevention and treatment strategies is a top priority based on its dramatically increasing health impact.

Keywords Aging · Body composition · Obesity · Sarcopenia · Sarcopenic obesity · Skeletal muscle tissue

Introduction

Adults over the age of 65 constitute at present 13% of the global population and are the fastest growing demographic group, expected to reach 2 billion people by the year 2050 [1]. The proportion of people > 80 years is also projected to increase dramatically in the next decades [2••]. The aging process is associated with a progressive and generalized loss of skeletal muscle mass (SMM) and function, which is termed sarcopenia. In parallel with the development and progression of sarcopenia in older adults, the prevalence of obesity is also rising within the aging population as a result of unhealthy diet and a sedentary lifestyle and is expected to reach 50% in older adults by the year 2030 [3, 4]. The confluence of these two conditions, a rapidly aging population and rising obesity rates, has led to the phenotype of sarcopenic obesity (SO), defined as the concurrent presence of both sarcopenia and obesity in the same individual [5]. SO is estimated to affect 100–200 million people in the next 35 years globally [6•].

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In healthy individuals, skeletal muscle grows in harmony with changes in body weight. This physiological response may be impaired in some older subjects who can become obese without a parallel growth of their SMM, ending up having low muscle mass and strength relative to their body size. This progressive mismatch between muscle mass and strength is the result of poor muscle quality, including reduced fiber size and number, intrinsic reduction of fiber contractility, muscle fat infiltration, modification of motor units, and impaired neuromuscular integrity [7]. The major pathogenetic mechanisms underlying SO include age-related hormonal changes, a positive energy balance, chronic low-grade inflammation, and insulin resistance [2••, 8].

Both sarcopenia and obesity may independently pose increased risks for adverse health outcomes. When these two conditions are combined, the health risks may be synergistically amplified [2••, 9]. Epidemiologic studies have shown that SO is a better predictor of physical disability in older age than sarcopenia or obesity alone [9]. Furthermore, accumulating evidence suggests that SO is associated with an increased risk of disability, frailty, cardiometabolic disease, hospitalization, loss of independence, impaired quality of life, and mortality, thereby imposing a heavy burden upon individuals, societies, and health care systems [2••]. In view of the substantial negative impact of SO upon morbidity and mortality, its accurate diagnosis, effective prevention, and treatment are highlighted as an ultimate priority among researchers and clinicians [10].

The present review provides a comprehensive update on the current definitions, methods of assessment, epidemiologic trends, pathophysiologic mechanisms, clinical implications, and conventional and emerging therapeutic approaches of SO and highlights the unresolved challenges, limitations, and knowledge gaps in the field.

Definitions and Methods of Assessment

Defining SO is based on the individual definitions of sarcopenia and obesity. Although defining obesity has been fairly consistent in different studies, the definition of sarcopenia has been largely heterogeneous, incorporating several variations of SMM, muscle strength, and physical function measures. Despite efforts to reach a consensus on appropriate diagnostic criteria and cut-off points, a standardized definition for SO is still lacking. This lack is a major constraint in advancing our knowledge in the field. It also makes the accurate diagnosis of SO challenging and impedes the comparability of findings of different studies [2••, 6•, 11•].

In order to accurately diagnose SO, a body composition analysis is warranted to obtain a quantitative assessment of SMM and fat mass (FM) [12]. Crude anthropometric indices such as body weight or body mass index (BMI) cannot capture changes in SMM and FM and have therefore no place in the algorithms of SO evaluation [2••]. Dual-energy X-ray absorptiometry (DXA) is highly recommended for use in research and clinical practice due to its availability, affordability, diagnostic accuracy, and adequate reproducibility for the assessment of total and regional SMM and FM [13]. Bioimpedance analysis (BIA) represents a simple, inexpensive, rapid, and portable alternative to DXA, which allows for assessment of SMM. Its utility is limited by a lack of validation for individuals aged > 80 or severely obese patients, a vulnerability to standard errors and lack of population specificity and the impact of hydration status on its accuracy [14, 15]. The use of computed tomography (CT) and magnetic resonance imaging (MRI), although considered gold standard methods for accurate body composition analysis, is primarily limited to research settings due to high costs, limited availability, and radiation exposure in the case of CT [16].

Sarcopenia Component

The term sarcopenia was first proposed by Irwin Rosenberg in 1989 [17]. Although it was originally applied to denote the age-related decline in SMM, the definition of sarcopenia has evolved and now integrates both quantitative and qualitative aspects of skeletal muscle tissue. Sarcopenia is currently recognized as an acute or chronic muscle disease with a specific ICD-10 Diagnosis Code since 2016 (M62.84) [18], characterized by low SMM and poor muscle quality, expressed as either weak muscle strength or impaired physical performance [19]. Primary sarcopenia refers to age-related sarcopenia and is common among older adults, while the term secondary sarcopenia is used regardless of age to indicate sarcopenia which is causally related to lack of physical activity (bedrest, immobility), poor nutrition (inadequate protein intake, malnourishment), or chronic diseases (advanced organ failure, malignancy, chronic inflammatory disorders) [19]. Sarcopenia may begin in early adulthood with limited atrophy of muscle fibers and progress as a result of complex interactions between genetic and environmental factors [20]. The related concepts of frailty and cachexia can be components of sarcopenia. Frailty is defined as having three out of unintentional weight loss, self-reported exhaustion, muscle weakness, slow walking speed, and low physical activity [21]. Although it was originally believed that low muscle strength in sarcopenic individuals is the direct inevitable result of low SMM, it is now clear that muscle mass and strength are not linearly associated. It has been suggested that muscle strength declines faster and is more important than SMM in determining functional capacity and overall health in older age [22, 23]. Low muscle strength is termed dynapenia [24] and has been recognized as a potent predictor of functional disability, metabolic derangement, and mortality among older adults [25–27].

Table 1 Operational definitions of sarcopenia by different working groups and scientific societies

Working group	Definition of sarcopenia	Cut-off points for muscle indices	Prevalence of sarcopenia (%)[a]
EWGSOP 2010 [19]	Low SMM + low muscle strength OR low physical performance	SMM (DXA): ASM/height^2 ≤ 7.23 kg/m^2 (men), ≤ 5.67 kg/m^2 (women) Strength: Handgrip strength < 30 kg (men), < 20 kg (women) Performance: Habitual gait speed ≤ 0.8 m/s in both sexes	5.3% (men) 13.3% (women)
EWGSOP2 2019 [28••]	Sarcopenia -probable, if low muscle strength -confirmed, if low muscle strength + low SMM -severe, if low SMM + low muscle strength + low physical performance	SMM (DXA): ASM/height^2 ≤ 7.23 kg/m^2 (men), ≤ 5.67 kg/m^2 (women) Strength: Handgrip strength < 30 kg (men), < 20 kg (women) Performance: Habitual gait speed ≤ 0.8 m/s in both sexes	NA
IWGS 2011 [29]	Low SMM + low physical performance	SMM (DXA): ASM/height^2 ≤ 7.23 kg/m^2 (men), ≤ 5.67 kg/m^2 (women) Performance: Habitual gait speed < 1 m/s in both sexes	5.1% (men) 11.8% (women)
AWGS 2014 [30]	Low SMM + low muscle strength OR low physical performance	SMM (DXA): ASM/height^2 ≤ 7.0 kg/m^2 (men), ≤ 5.4 kg/m^2 (women) Strength: Handgrip strength < 26 kg (men), < 18 kg (women) Performance: Habitual gait speed ≤ 0.8 m/s in both sexes	NA
FNIH Sarcopenia Project 2014 [31]	Low SMM + low muscle strength + low physical performance	SMM (DXA): ASM/BMI ≤ 0.789 (men), ≤ 0.512 (women) Strength: Handgrip strength < 26 kg (men), < 16 kg (women) Performance: Habitual gait speed ≤ 0.8 m/s in both sexes	1.3% (men) 2.3% (women)

[a] Data on prevalence rates of sarcopenia are derived from reference [32]

NA not available, *ASM* appendicular skeletal muscle mass, *AWGS* Asian Working Group for Sarcopenia, *BMI* body mass index, *DXA* dual-energy X-ray absorptiometry, *EWGSOP2* European Working Group for Sarcopenia in Older People 2 (revised consensus report), *FNIH* Foundation for the National Institutes of Health, *IWGS* International Working Group for the study of Sarcopenia, *SMM* skeletal muscle mass

Several working groups and scientific societies worldwide have tried to provide evidence-based guidance on the most suitable diagnostic criteria and thresholds for defining sarcopenia, as shown in Table 1 [19, 28••, 29, 30–32]. The European Working Group for Sarcopenia in Older People (EWGSOP) integrated low SMM and function (strength or performance) in their definition, suggested a clinical algorithm for sarcopenia detection using gait speed before proceeding to SMM or strength measurements, and recommended measuring SMM by DXA or BIA using mathematical thresholds [19]. In the 2019 revised consensus report of EWGSOP2, skeletal muscle strength dominates over SMM in defining sarcopenia. According to this report, sarcopenia should be clinically suspected when muscle strength is low. The diagnosis of sarcopenia is further confirmed by measuring low SMM with DXA or BIA, and sarcopenia is classified as severe, if there is concomitant impairment of physical performance [28••]. The International Working Group for the study of Sarcopenia (IWGS) defined sarcopenia as the combination of low SMM and poor physical function (measured as gait speed < 1 m/s) [29]. The Asian Working Group for Sarcopenia provided guidelines for individuals of Asian descent and suggested using muscle strength and physical function for initial screening, followed by the EWGSOP approach using lower thresholds [30]. Finally, the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project

defined sarcopenia as fulfilling all three diagnostic criteria (low SMM + low muscle strength + poor physical performance), recommended using DXA for assessing SMM, and identified sex-specific cut-off points for low SMM adjusted for BMI [31].

In sarcopenia definitions, SMM can be assessed using one of the following methods: appendicular SMM defined as the sum of SMM in the upper and lower extremities divided by height in meters squared (ASM/height^2) [9, 19, 30, 33–35]; ASM adjusted for height and total FM using the residual method based on linear regression analysis [35, 36]; ASM adjusted for BMI [31]; unadjusted or absolute ASM [31]; and whole-body SMM unadjusted or adjusted for weight, height, or BMI [19, 28••]. As obese subjects tend to have increased SMM, defining sarcopenia based solely on absolute SMM without accounting for body mass may lead to substantial underestimation of its prevalence in the obese [37]. Hence, it is generally recommended to adjust SMM for measures of body size. Skeletal muscle strength can be assessed as handgrip strength in kg measured by a calibrated handheld dynamometer, and less often as knee extension strength [38]. Physical performance can be assessed via objective physical function tests such as the Short Physical Performance Battery (SPPB), which assesses composite functional outcomes related to lower extremity function such as gait speed, chair stands, and standing balance [39].

The exact numerical cut-off points for muscle indices in specific populations are reviewed in detail elsewhere [2••, 6•, 28••].

Obesity Component

Obesity can be addressed either as overall or central adiposity in the definitions of SO. For overall obesity, the most commonly applied indices include BMI and FM% derived by whole-body DXA or alternatively BIA. It has been suggested that FM has better predictive validity for the development of cardiometabolic disease than BMI [40] and should thus be preferred. For central adiposity, indices such as waist circumference or CT-derived visceral fat mass can be used. Anthropometric indices such as BMI and waist circumference have poor sensitivity, especially in the elderly. In one study, BMI classified correctly only 41% of elderly men and 45.1% of elderly women as obese, while the respective percentages with waist circumference were 64.2% and 81% [41]. Thus, anthropometric measures should be used with caution in SO studies, only if other body composition assessment methods are unavailable.

In studies with SO participants, the obesity component has been defined as either BMI ≥ 30 kg/m^2 [35], elevated FM% based on sex-specific thresholds (≥ 27 or 28% for men, ≥ 35, 38, or 40% for women) [9, 34, 42], or elevated waist circumference based on population-specific tertiles [43] or established thresholds (≥ 88 cm for women and 102 cm for men, according to the World Health Organization WHO) [44]. The American Association of Clinical Endocrinologists (AACE) recommends using the WHO fat thresholds for defining obesity, namely FM% > 25% for men and > 35% for women [45]. To date, no separate cut-off values for BMI, FM%, and waist circumference defining obesity have been proposed in older adults [46].

Epidemiologic Trends in the Prevalence of SO

The prevalence of SO varies broadly between studies depending on population characteristics (age, gender, race, ethnicity) and different definitions. Considering all studies together, its average prevalence in older adults ranges between 5 and 10%, is similar between men and women, higher in Hispanics, lower in non-Hispanic blacks, and higher in subjects aged > 80 [6•, 47••]. It is also higher when more arbitrary definitions are used such as the lowest two SMM quintiles for sarcopenia or the highest two FM% quintiles for obesity [48]. Of note, the overlap in SO diagnosis using different diagnostic criteria is less than 50% [49].

A review of 8 different definitions reported a 19- to 26-fold variation in sex-specific prevalence rates. According to this analysis, sarcopenia definitions depended on different thresholds, reference populations, and SMM measurement techniques [50]. A comparison of SO rates using BIA to define sarcopenia and DXA-derived FM% to define obesity demonstrated an increasing prevalence with advancing age [51]. In another study, rates ranged from 0 to 84.5% in women and 0 to 100% in men, depending on definition [37]. In a population-based cohort analysis using NHANES (National Health And Nutrition Examination Survey) data applying FNIH diagnostic criteria for sarcopenia, the prevalence of SO was 12.6% in men and 33.5% in women. These rates increased significantly with age, reaching 27.5% in males and 48% in females aged over 80 [52]. In South Korean SO Study, the estimated prevalence of SO ranged between 1.3 and 15.4% in men and between 0.8 and 22.3% in women [53].

The prevalence of dynapenic obesity, the combination of obesity with poor muscle strength, is even less clear. Data from the InCHIANTI study reported rates of 3.2–8.7%, using low knee extensor strength for dynapenia and high BMI or waist circumference for obesity [54]. In the Cardiovascular Health Study, using low handgrip strength and high waist circumference to define dynapenic obesity, prevalence rates approached 11% [55], while data from the FNIH classified 4.1% of men and 14% of women as dynapenic obese based on low grip strength and elevated BMI [56].

Underlying Pathophysiologic Mechanisms Contributing to SO

In both aging and obesity, skeletal muscle becomes intrinsically weak. The major features of aging skeletal muscle, especially in the context of concomitant obesity, comprise selective type II muscle fiber atrophy (reduced number and size of fast glycolytic type II fibers), fiber denervation due to loss of motor neurons in the context of age-associated neurodegeneration, ectopic fat infiltration within or between muscle fibers (myosteatosis), and altered mechanical properties of the muscle-tendon system [8, 57]. A prominent functional aspect is the dysregulated muscle protein balance with reduced muscle protein synthesis and increased protein breakdown [58]. This abnormality is related to the so-called anabolic resistance, defined as the blunted response of muscle to various anabolic stimuli including insulin, growth factors, amino acids (AAs), and resistance exercise [59]. The major factors contributing to anabolic resistance in SO are skeletal muscle insulin resistance, reduced muscle perfusion and nutrient delivery as a result of obesity-related atherosclerotic vascular alterations, and reduced postprandial AA bioavailability [60, 61].

SO may occur as a result of the following complex interrelated mechanisms:

(i) *Age-related changes in body composition*: Body composition undergoes significant changes with aging in both sexes under the potent influence of lifestyle and hormonal factors. Major such changes are a gradual increase in total FM, preferential fat accumulation in visceral depots, reduction in peripheral subcutaneous fat, ectopic pattern of peri-organ or intra-organ fat deposition and progressive decline in SMM so that body weight is mostly gained as fat rather than lean mass [2••, 62]. Over the age span from 20 to 80 years, there is approximately 30% reduction of total SMM [63].

(ii) *Hormonal changes*: Aging is associated with several hormonal alterations including insulin resistance, reduced thyroid hormone responsiveness, increased cortisol levels, reduced levels of growth hormone (GH), insulin-like growth factor 1 (IGF-1), sex steroids, and DHEA-S (dehydroepiandrosterone-sulfate). All these changes exert adverse effects on body composition, favoring the SO phenotype [2••, 57]. In women, menopause is associated with increased FM, visceral fat accumulation, and decreased SMM [64]. In men, testosterone deficiency associated with aging may negatively affect SMM and body fat distribution [65].

(iii) *Pro-inflammatory pathways*: In aging, circulating levels of pro-inflammatory cytokines such as tumor necrosis factor a (TNF-a), interleukin-6 (IL-6), and interleukin-1 (IL-1) are elevated [66]. These inflammatory mediators, produced mainly by hypertrophic adipocytes and immune cells infiltrating adipose tissue, may act directly upon skeletal muscle and promote muscle catabolism through accelerated muscle protein degradation and myocyte apoptosis via mechanisms related to inflammation and oxidative stress [2••, 11•, 57, 66]. The catabolic actions of pro-inflammatory cytokines are mainly responsible for sarcopenia-promoting effects associated with aging and obesity.

(iv) *Myocellular mechanisms*: The most important myocellular biological pathways mediating the pathophysiology of SO involve intramyocellular deposition of lipids (IMCLs) promoting lipotoxicity, inflammation, muscle insulin resistance, and mitochondrial dysfunction [67], augmented skeletal muscle oxidative stress as a result of mitochondrial dysfunction promoting oxidative damage and degradation of vital skeletal muscle proteins leading to compromised protein turnover and impaired muscle fiber contractility [68], upregulation of myostatin expression, being a fundamental negative regulator of skeletal muscle growth, resulting in impaired muscle genesis [69], and reduced numbers of satellite mesenchymal progenitor cells, undergoing adipocyte differentiation in the setting of obesity and IMCL deposition, leading to impaired muscle regeneration capacity [70].

Sarcopenic Obesity or Obese Sarcopenia?

There is a bidirectional association between sarcopenia and obesity in the pathogenesis of SO. On the one hand, low SMM can lead to reduced resting metabolic rates and total energy expenditure, promoting fat gain. On the other hand, obesity may favor the development and progression of sarcopenia through a multifactorial network of clustered alterations [11•]. It has been proposed that SO should be rather renamed into obese sarcopenia, to reflect the dominant direction of the pathogenetic pathway and capture the notion that the pathogenetic cascade of SO mainly originates from adipose tissue dysfunction and inflammation [71••].

Adipose tissue and skeletal muscle tissue are strongly interconnected through a dynamic cross-talk [72] (Fig. 1). Dysregulated adipokine and cytokine secretion as a result of an expanded, inflamed, and dysfunctional adipose tissue (increased leptin, TNF-a and IL-6, decreased adiponectin) may elicit adverse effects upon skeletal muscle, including impaired insulin sensitivity, reduced fat oxidation, IMCL deposition, induction of catabolism and inflammation, and downregulation of muscle interleukin-15 (IL-15) [66]. Intramyocellular lipids and their derivatives, mainly diacylglycerols and ceramides, induce mitochondrial dysfunction, oxidative stress, lipotoxicity, and insulin resistance and

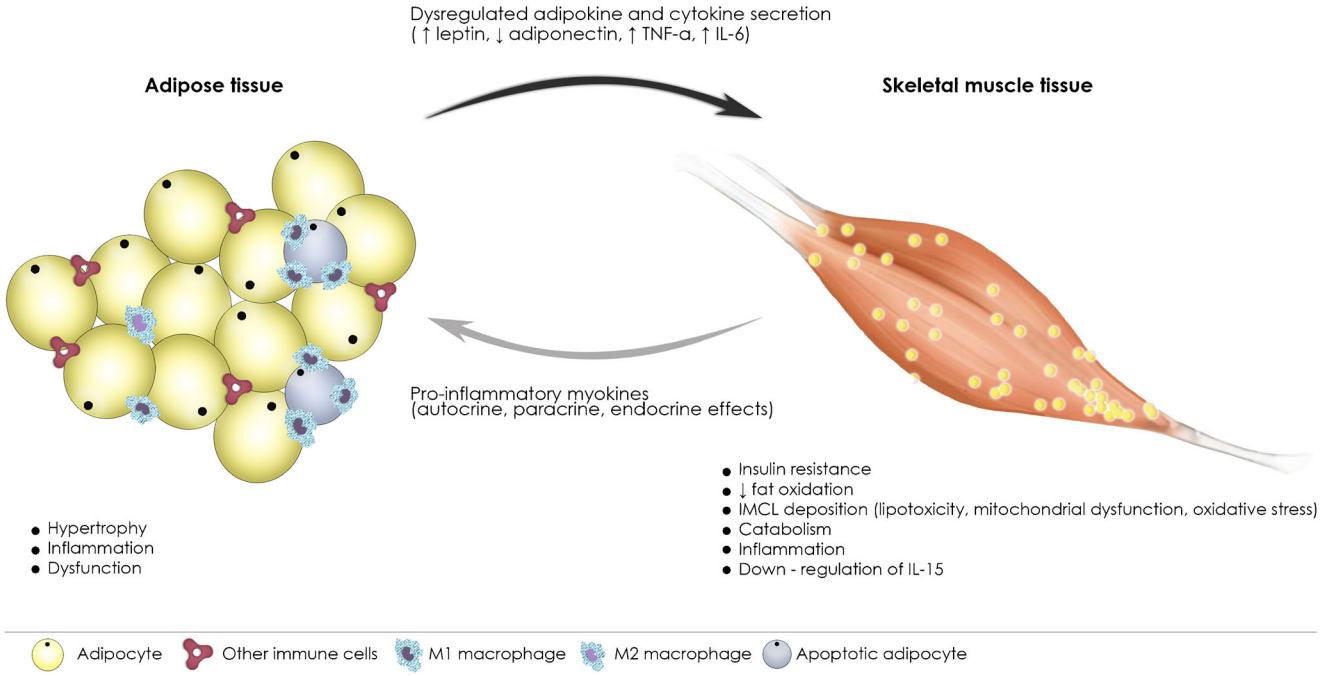

Fig. 1 The core biological pathway mediating the pathophysiology of sarcopenic obesity (SO) is the strong interconnection between adipose and skeletal muscle tissue. The dominant direction of this pathway is from adipose tissue to muscle, as indicated by the thicker arrow. In obesity, adipose tissue becomes expanded, inflamed, and dysfunctional and is characterized by a dysregulated secretion of adipokines and cytokines. These chemokines act upon skeletal muscle tissue and impair insulin sensitivity, reduce fat oxidation, promote IMCL deposition, induce catabolism and inflammation, down-regulate muscle IL-15, and enhance the secretion of pro-inflammatory myokines. These myokines may induce muscle dysfunction by autocrine and paracrine effects, but they may also exert endocrine effects and exacerbate adipose tissue inflammation, establishing a vicious cycle of mutual adipose and skeletal muscle tissue inflammation, which is the prominent pathogenetic hallmark of SO. IL-6: interleukin-6; IL-15: interleukin-15; IMCL: intramyocellular lipid; TNF-a: tumor necrosis factor a

promote an increased secretion of pro-inflammatory myokines capable of inducing muscle dysfunction via autocrine and paracrine effects. These myokines may also exert endocrine effects and exacerbate adipose tissue inflammation, establishing a vicious cycle maintaining the mutual muscle and adipose tissue inflammation and triggering the pathogenetic cascade of SO [71••] (Fig. 1).

Beyond the interplay between adipokines and myokines, several other mechanisms may also explain how obesity can lead to skeletal muscle impairment: (i) physical inactivity as a result of obesity-associated musculoskeletal complications may have a direct negative impact upon skeletal muscle protein turnover and oxidative capacity [73]. (ii) Obese subjects, although overfed, may also be undernourished. They mostly consume energy-dense nutrient-poor diets, and they often display micronutrient deficiencies which may negatively affect SMM and function [11]. (iii) Obesity-related cardiometabolic abnormalities such as type 2 diabetes (associated with oxidative stress, inflammation, and mitochondrial dysfunction) and atherosclerosis (altering muscle tissue perfusion) may promote muscle catabolic pathways and impair muscle quality and metabolism [74]. (iv) Obesity is directly associated with chronic conditions such as heart failure, obstructive pulmonary disease, kidney disease, and cancer [75]. All these may contribute heterogeneous sources of inflammation and oxidative stress and impair spontaneous physical activity, thereby synergistically enhancing muscle loss and dysfunction. (v) Therapeutic interventions in obese individuals such as bariatric surgery and hypocaloric diets may lead to muscle catabolism in the initial rapid weight loss phase as a result of profound energy deficits [76].

Skeletal muscle derangements associated with obesity are more likely in patients with longer obesity duration, obesity-related comorbidities, and older individuals who are prone to adverse muscle changes due to aging *per se* [11•].

Adverse Health Consequences of SO

SO has been associated with major clinical implications: increased risk of disability; mobility limitations and overall impaired physical capacity [9, 77]; elevated risk of cardiometabolic abnormalities such as insulin resistance, dyslipidemia, hypertension, type 2 diabetes, and low-grade inflammation [43, 54, 78]; increased risk of fractures [79]; depression and compromised overall psychological health [80]; poor outcomes in cancer [81]; increased mortality risk [82]; reduced health-related quality

Table 2 A summary of established and novel treatment modalities for SO

Treatment modality	Aims and mechanisms	Comments
Well-established therapeutic strategies		
• Caloric restriction	Lose predominantly body fat and improve physical function, moderate energy deficit of 200–750 kcal/day, target ~ 10% weight loss in 6 months and then weight loss maintenance	No specific diets have been tested in SO, adherence to diet may predict success, challenges in limiting calories in older adults should be acknowledged
• Protein supplementation	Mitigate loss of SMM and strength during weight loss, 1–1.2 g/kg/day protein in divided doses, daily enrichment with 2.5–2.8 g leucine	A one size fits all protein recommendation is inappropriate, further evidence is needed to support supplemental protein for improved functional outcomes in SO
• Calcium supplementation	Prevent impaired bone metabolism during energy restriction, 1200 mg/day supplemental calcium preferably through dietary modification	Coupled (with vitamin D) supplementation
• Vitamin D supplementation	Same goals as with calcium, may improve muscle function in SO, 1000 IU/day, target blood 25-OH-D3 levels > 30 ng/mL	Coupled (with calcium) supplementation
• Aerobic exercise	Improve cardiorespiratory fitness, 150 min/week moderate to vigorous training	Begin at a low to moderate intensity, duration and frequency to maximize tolerance and promote adaptation, individualized approach is necessary
• Resistance training	Improve SMM/strength and attenuate muscle and bone loss during weight loss interventions, 60–75 min per session, 3 non-consecutive sessions per week, combining strength, balance and flexibility	Begin at a low to moderate intensity, duration and frequency to maximize tolerance and promote adaptation, individualized approach is necessary
Novel therapeutic strategies under investigation		
• Testosterone and SARMs	Increase muscle and bone mass by increasing IGF-1 and decreasing inflammatory markers, enobosarm (non-steroidal SARM) targets selectively androgen receptors on muscle and bone and is deprived of androgenic effects elsewhere in the body	Conflicting data on impact on muscle strength and function, early efficacy studies show improved SMM in patients with cancer
• Myostatin inhibitors	Enhance skeletal muscle growth and improve physical function, directly inhibit SMM loss	Promising data in patients with cancer-related cachexia
• Mesenchymal stem cells	Regenerate skeletal muscle tissue, common precursors of muscle, bone and cartilage	Future treatment of sarcopenia, an early study suggests a role for treating frailty in humans, cost, regulatory constraints and ethical barriers need to be considered
• Anamorelin (oral ghrelin analog)	Promote appetite and enhance SMM through anabolic and anti-inflammatory properties	Safe, well-tolerated, used in cancer cachexia, potentially beneficial for SO patients with low SMM and intact muscle strength
• Vitamin K	Inhibit bone resorption and osteoclast formation, mitigate bone loss during weight loss	Conflicting data regarding effects on bone mineral density and fractures
• Anti-obesity medications	Promote weight loss (liraglutide, lorcaserin, phentermine/tomiramate, naltrexone/bupropion), most of them promote fat loss with minimal effects on SMM	Approved for non-geriatric populations, unknown safety/efficacy in older adults, off-label use
• Bariatric surgery	Promote weight loss	Unknown safety/efficacy in the elderly population, may exacerbate weight loss-induced sarcopenia and osteoporosis
• Neuromuscular activation	Enhance muscle contraction efficiency and function, whole-body vibration therapy using electric stimuli (person standing on vibration platform) or tai chi	Mixed data on efficacy, safe and convenient alternative to conventional exercise
• Periodization strategies	Achieve peak physical performance, systematic variation in training specificity, intensity and volume within periods	Used in sports programs, may be feasible in sedentary frail older adults, no effect on muscle strength, power or physical performance in patients with SO, still premature to endorse

IGF-1 insulin-like growth factor 1, *SARMs* selective androgen receptor modulators, *SMM* skeletal muscle mass, *SO* sarcopenic obesity

of life [83]; institutionalization and expanded health care costs [84]. 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.

Therapeutic Approaches for SO Prevention and Treatment

Lifestyle interventions, including caloric restriction and physical activity, are considered the cornerstones for counteracting SO. Two approaches have 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 not be measured as changes of body weight alone. If the treatment strategy is limited to weight loss interventions, there can be inevitable health risks for elderly individuals, mainly related to the concomitant loss of bone and skeletal muscle mass and exacerbation of osteosarcopenia. Table 2 provides an updated summary of currently established and novel treatment strategies.

Rationale and General Principles of Dietary Strategies

The major dietary strategies for SO treatment comprise caloric restriction, protein and micronutrient supplementation. It is important to note that the quality of evidence for dietary recommendations in SO is currently poor and the existing guidelines are mainly derived from expert opinion statements rather than properly designed randomized clinical trials.

Weight management in older adults can be challenging. Energy restriction with a hypocaloric diet may result in the loss of approximately 25% of SMM, exacerbating sarcopenia [12]. The energy deficits induced by acute caloric restriction may downregulate skeletal muscle protein synthesis and enhance proteolysis, contributing to reduced SMM and strength [85]. Very low calorie diets or protein-sparing diets aiming at rapid weight loss are strongly discouraged in older adults, due to potential loss of SMM and risks of dramatic fluid and electrolyte imbalances [2••, 33]. A moderate energy restriction of 200–750 kcal/day, targeted at a moderate weight loss of 0.5–1 kg/week or 8–10% of initial body weight after 6 months, while assuring adequate protein and micronutrient intake, is recommended both in the general population and in older adults with SO [33, 46, 86]. Strategies aimed at optimizing muscle protein anabolism during weight loss interventions such as combining diets with resistance training, consuming food just before exercise, or distributing protein intake throughout the day may prevent weight loss-induced sarcopenic effects [87••, 88••].

An increased dietary protein intake is mandatory during weight loss in order to stimulate skeletal muscle protein synthesis [61]. Older adults need a higher protein intake to stimulate protein synthesis due to underlying anabolic resistance [89]. To assure optimal muscle function with aging, a dietary protein intake of 1–1.2 g/kg/day is recommended and an even higher intake for older patients suffering from sarcopenia or other chronic diseases [61]. The supply of essential AAs with a high proportion of leucine is important for increasing muscle protein synthetic rate [90]. Leucine strongly increases insulin release, a potent anabolic stimulus inhibiting muscle proteolysis, promoting net postprandial muscle protein accumulation, and optimizing anabolic stimulation by essential AAs [91]. Beyond the total amount of ingested protein, its source and biological quality, the timing of intake and the specific AA composition may be also relevant for SMM and strength preservation [92]. Overall, animal protein is thought to be more effective in muscle protein anabolism than plant-derived protein, although this has not been explicitly addressed in the setting of SO [93]. Furthermore, spreading out daily protein intake every 3–4 h rather than pulse feeding at specific meals may be beneficial for patients with SO in further augmenting the effects of protein intake [94].

Conventional strategies to minimize the adverse effects of weight loss on bone metabolism include calcium and vitamin D3 supplementation [95]. Vitamin D deficiency has been associated with sarcopenia and an increased risk of falls and fractures, independently of concurrent obesity [96]. Furthermore, vitamin D may improve muscle function in patients with SO through beneficial effects of its bioactive metabolites [97]. The Society for Sarcopenia, Cachexia and Wasting Disease recommends a total protein intake of 1–1.5 g/kg/day, a leucine-enriched balanced essential AA mix and an adequate supply of vitamin D for the management of sarcopenia [98].

Rationale and General Principles of Exercise Strategies

Physical activity (aerobic, resistance, or both combined) is considered a powerful tool to counteract SO given its potential to mediate one or more of the following biological effects: ameliorate hormonal milieu [6•], reduce oxidative stress [99], induce mitochondrial biogenesis and improve skeletal muscle oxidative capacity [99], increase skeletal muscle capillary density [100], increase the number and size of type II fast twitching muscle fibers [101], activate satellite cells to regenerate injured muscle by releasing a number of growth factors able to stimulate the proliferation and differentiation of muscle satellite cells [70], mitigate muscle inflammation and downregulate circulating inflammatory biomarkers [102], abrogate myocyte apoptosis and interfere with mechanisms of cellular quality control such as autophagy and mitophagy [103].

Various professional societies recommend that all older adults, even frail ones, engage in at least 150 min per week of moderate to vigorous aerobic activity, combined with two non-consecutive sessions of resistance training, focusing on strength, flexibility, and balance [45, 104]. Aerobic activity can improve cardiorespiratory fitness, counteract obesity, and reduce mortality [105], while resistance training has proven efficacy in muscle hypertrophy and strengthening in older adults [106]. Alternative exercise modalities such as yoga, tai chi, and aquatic training could be theoretically beneficial, but their effects in SO have not been validated [107, 108].

The main goal of exercise in SO is to improve mobility and autonomy by enhancing elasticity, strength, and physical endurance [109•]. Individualized regimens are recommended

due to the associated comorbidities and physical limitations of older individuals. They should begin at a low to moderate intensity, duration and frequency, to minimize injuries, maximize compliance, and progressively promote exercise adaptations [88••]. Aerobic activity should initially target ~ 65% of peak heart rate, aiming to reach 70–85% over the duration of the regimen. Resistance activities should originally focus on 1–2 sets of 8–12 repetitions at ~ 65% of one repetition maximum (maximal force generated in a single repetition), with the aim to proceed to 2–3 sets of 75% of one repetition maximum over time. These recommendations are also valid for frail older adults [88••]. Exercise until fatigue rather than failure is recommended to prevent musculoskeletal injuries [109•].

Resistance Training The majority of studies suggest that resistance exercise is an effective strategy to improve body composition and physical performance in SO [109•]. A study comparing different exercise interventions in older adults with SO reported that subjects in the resistance group displayed the most significant improvements in muscle strength, and also that resistance training for 8 weeks resulted in maintenance of SMM, decreased FM, and increased handgrip strength [106]. Furthermore, recent intervention studies with elastic band resistance training in SO older women for 12 weeks have demonstrated significant improvements in SMM, muscle quality and physical capacity, as well as reductions in FM [110].

Aerobic Activity Although there is limited evidence regarding the effects of aerobic activity in SO, it appears to be effective for losing excess FM and improving muscle function in older adults with SO, especially when combined with other strategies such as resistance training or nutritional interventions. A randomized controlled trial in SO older adults showed that aerobic activity for 8 weeks reduces total and visceral FM and maintains SMM [106].

Concurrent Exercise Concurrent exercise, namely the combination of resistance and aerobic training, has shown better effects on the functional status of obese older adults than either intervention alone [88••]. In a study testing the effects of concurrent exercise in SO, 3 months of biweekly concurrent exercise of 60 min duration resulted in increased knee extension strength, increased arm and leg SMM, and decreased total FM [111].

All things considered, exercise seems to be the most powerful tool against sarcopenia in the elderly, with robust evidence backing its efficacy. Apart from exercise, all other interventions, mainly dietary, proposed by various guidelines, are not strongly supported by well conducted and large studies and are thus mostly the result of expert opinion.

Rationale for Multicomponent Interventions

Complex or multimodal strategies encompass both nutritional and exercise interventions. In patients with SO, combining diet-induced weight loss and regular exercise can improve physical function and ameliorate frailty more than either intervention alone [112]. Furthermore, a large number of studies emphasize the need for exercise training during hypocaloric dietary interventions in order to partly mitigate SMM loss and prevent an exacerbation of osteosarcopenia, maintaining musculoskeletal health [2••]. It is generally accepted that a combination of a moderate weight loss diet with concurrent exercise and a high protein intake, mainly derived from animal sources and evenly distributed throughout the day, is the most effective strategy to improve body composition in SO [109•]. Despite the solid rationale for combined interventions to counteract SO, there are only few relevant studies. The differences in study protocols, durations of intervention, and target populations make it difficult to provide state-of-the-art recommendations. Therefore, more studies addressing the potential benefits of combining several exercise modalities with dietary interventions in SO populations are needed.

High Protein Intake + Exercise The combined effects of high dietary protein intake or protein supplementation with exercise in SO have been scarcely addressed. In one randomized controlled trial testing the combination of aerobic and resistance exercise with essential AA supplementation, no significant effects were found on SMM or physical function in SO older adults [111].

Emerging Treatment Modalities for SO

A number of novel investigational therapies may independently hold promise or could be considered adjunctively for treating SO (Table 2).

Testosterone supplementation has been shown to promote IGF-1 expression and enhance SMM through increased muscle protein synthesis [113]. In hypogonadal older men, gains in SMM after testosterone supplementation have been reported to range between 1.6 and 6.2 kg [114]. In older frail men with testosterone deficiency, supplementation has positive effects on body composition and quality of life [115]. Data on testosterone effects on muscle strength and function are less encouraging, and it has been suggested that improvements in SMM do not directly result in improved function [115]. Future research should identify responders to androgen supplementation among those with reduced SMM or reduced strength, and also evaluate whether testosterone therapy may help preserve muscle and bone mass during weight loss in patients with SO. Adverse events, especially cardiovascular complications, merit consideration. To date, the AACE [45], the

Endocrine Society [116], and The Obesity Society [33] do not recommend testosterone supplementation as a treatment for either sarcopenia or obesity.

Selective androgen receptor modulators (SARMs) have been associated with increased SMM without parallel improvements in muscle strength or physical performance in older sarcopenic adults [117]. Due to their selectivity, SARMs developed in the past 5 years have an excellent safety profile, while transdermal SARMs are expected to emerge in the future [118]. These agents could be theoretically beneficial for patients with SO who require predominantly SMM rather than strength improvement.

Myostatin inhibitors increase in vitro SMM and strength, downregulate inflammatory pathways, and improve insulin resistance [119]. They directly reduce the expression of myostatin in muscle and adipose tissue and might be beneficial for patients with sarcopenia, SO, and their associated metabolic perturbations.

Whole-body vibration therapy has emerged as a safe and convenient technique, which applies the transmission of mechanical stimuli to activate the primary endings of muscle spindles, simulating skeletal muscle contraction and leading to neuromuscular activation [120]. In a review of 13 trials in older adults, there were significant effects on knee extension strength and functional measures [121]. The combination of vibration therapy with resistance training [122] or vitamin D supplementation [120] has shown mixed results. In SO, this alternative type of exercise is well-tolerated and has led to reductions in FM and increments in skeletal muscle strength [123], although evidence is still limited.

Unmet Needs, Challenges, and Knowledge Gaps

To further advance our current understanding of the unique phenotype of SO, the scientific community needs to address the following needs:

(i) To establish a robust definition for SO, since the most important barrier in SO research is the lack of uniform diagnostic criteria. Progress is especially needed in the definition of sarcopenia. Although diagnostic criteria for primary sarcopenia have been proposed, relevant methodological issues are still under debate and specific thresholds for use in clinical practice remain inconsistent.

(ii) To integrate reliable body composition assessment techniques such as DXA, CT, or MRI into routine clinical practice. Assessing SMM with DXA or BIA, and muscle strength with handgrip dynamometry, can be helpful in identifying subjects with SO. Future studies should develop strategies for dissemination and implementation of these diagnostic tools.

(iii) To further elucidate the descriptive epidemiology of SO with regard to outcomes beyond weight loss, morbidity, and mortality, focusing on patient-centered outcomes such as physical functionality and quality of life. Properly powered clinical trials studying functional and disease-specific outcomes are urgently needed.

(iv) To refine understanding regarding optimal dietary interventions. At present, the optimal macronutrient composition of diets recommended in SO remains poorly defined, and no specific diets have been tested in this population. Aspects like type of protein, timing of protein intake in relation to exercise and optimal composition of essential AAs need to be specified.

(v) To determine the optimal frequency, intensity, and duration of aerobic and resistance training, which are the core physical activity components of SO treatment. Longitudinal studies should verify whether diet-induced weight loss, in conjunction with combined aerobic and resistance exercise, may prolong independence in SO, and assess the efficacy of alternative modalities. Whether diet and physical activity should be combined with pharmacotherapy such as testosterone supplementation requires further investigation.

Summary and Conclusions

The confluence of two conditions, a rapidly aging population and rising obesity rates, has led to the extreme phenotype of SO, defined as the concurrent presence of sarcopenia and obesity in the same individual. SO is associated with an increased risk of disability, cardiometabolic dysregulation, hospitalization, impaired quality of life, and mortality, thereby imposing a heavy burden upon individuals, societies, and health care systems. In view of the substantial negative impact of SO, its accurate diagnosis, effective prevention, and treatment emerge as a top priority among researchers and clinicians.

To further advance current understanding of this unique phenotype, the scientific community should try to establish a universally applicable definition, integrate reliable body composition assessment techniques into routine clinical practice, focus on patient-centered outcomes such as physical function and quality of life, explore the optimal characteristics of dietary interventions, and finally determine the optimal frequency, intensity, and duration of aerobic and resistance training, which are the core physical activity components of SO treatment.

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Compliance with Ethical Standards

Conflict of Interest C.K., S.L., M.D., and A.K. declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with humans or animals performed by any of the authors.

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- • Of importance
- •• Of major importance

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