Osteosarcopenic obesity: the role of bone, muscle, and fat on health

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Abstract Osteopenia/osteoporosis, sarcopenia, and obesity are commonly observed in the process of aging, and recent evidence suggests a potential interconnection of these syndromes with common pathophysiology. The term osteosarcopenic obesity has been coined to describe the concurrent appearance of obesity in individuals with low bone and muscle mass. Although our understanding of osteosarcopenic obesity’s etiology, prevalence, and consequences is extremely limited, it is reasonable to infer its negative impact in a population that is aging in an obesogenic environment. It is likely that these individuals will present with poorer clinical outcomes caused by the cascade of metabolic abnormalities associated with these changes in body composition. Clinical outcomes include but are not limited to increased risk of fractures, impaired functional status (including activities of daily living), physical disability, insulin resistance, increased risk of infections, increased length of hospital stay, and reduced survival. These health outcomes are likely to be worse when compared to individuals with obesity, sarcopenia, or osteopenia/osteoporosis alone. Interventions that utilize resistance training exercise in conjunction with increased protein intake appear to be promising in their ability to counteract osteosarcopenic obesity.

Keywords Osteopenia/osteoporosis · Sarcopenia · Obesity · Body composition

1 Introduction

Body composition refers to the amount and distribution of fat and fat-free tissues of the body; it extends beyond body weight and body mass index (BMI) because the units of body weight are evaluated for the relative proportions and distribution of fat and fat-free tissues [1]. Body composition analysis becomes particularly important in situations or clinical conditions where body weight and BMI do not accurately depict nutritional status and when abnormalities in body composition emerge [1]. Examples include but are not limited to elderly individuals who may present with normal body weight and BMI but have significant depletion in both muscle strength and mass (dynapenia/sarcopenia). These individuals may also present with deteriorated bone, undetected by assessment of body weight alone [2, 3]. Likewise, marked increases in visceral adipose tissue may occur regardless of changes in total body weight. In clinical situations such as cancer, muscle wasting with or without changes in adipose tissue also occurs regardless of BMI. In fact, obese individuals may present with depleted muscle mass and strength, similar to emaciated or cachectic patients [1].

Whether abnormalities in body composition are related to losses of bone and muscle or increases in adipose tissue, these unfavorable changes are likely to impact health. We use the term “osteosarcopenic obesity” to describe the concurrent appearance of obesity in individuals with low bone and muscle mass. We hypothesize that this phenotype may be associated with poorer functional and metabolic outcomes than each of these conditions alone, ultimately affecting quality of life, morbidity risk, and survival (Fig. 1). In this paper, we discuss potential mechanisms, populations at risk, health outcomes, and countermeasures to osteosarcopenic obesity.
2.1 Osteopenia/osteoporosis

Osteopenia/osteoporosis is a skeletal disorder characterized by compromised bone strength leading to increased risk of fractures. Osteoporosis affects approximately 12 million adults over the age of 50 years in the USA [4]. In 2005, more than 2 million incident fractures were reported in the USA alone, with a total cost of $17 billion. Even if rates stay the same, the aging of the world population is expected to increase the number of fractures and costs in the USA by 48% to greater than 3 million fractures associated with a cost of $25.3 billion [5].

Although osteoporosis is a complex entity, we can measure areal bone mineral density (BMD), which is used as a proxy to define bone strength and to diagnose osteopenia/osteoporosis [6, 7]. Dual-energy X-ray absorptiometry (DXA) is the most common diagnostic imaging technique for assessing BMD. DXA uses low-radiation X-rays of two different photon energy levels that pass through the body and are identified by a photon detector that measures the amount of energy absorbed by soft tissue and bone at each pixel [8]. This method measures both bone and soft tissue [8]. Soft tissue is further subdivided into fat and lean [also called lean body mass (LBM), Table 1] based on the empiric attenuation of both pure fat and bone-free soft tissue [9]. Therefore, bone mineral content and BMD, as well as fat and fat-free soft tissues at the whole-body and regional levels can be assessed by DXA [8, 10]. Uniform standards for diagnosing osteopenia and osteoporosis by DXA do exist. According to the World Health Organization (WHO), the operational definition of osteopenia is a BMD that lies from 1.1 to 2.4 standard deviations below (a T-score of 1.1–2.4) and osteoporosis is a BMD that lies 2.5 standard deviations or more below the average value for young healthy women (a T-score of <−2.5). Increased BMD augments the strength of bone. On the contrary, significant losses in BMD predispose an individual for increased risk of fracture.

2.2 Sarcopenia

Muscle and bone mass, as well as their strength/quality, are both lost during aging starting in the late 20s and accelerating in the 50s [11–13]. In the presence of chronic disease, drug therapy, environmental factors, poor nutrition, and physical inactivity, this loss can be accelerated.

One important advantage of using DXA is its ability to estimate appendicular skeletal muscle (ASM) mass which is of particular interest for the assessment of sarcopenia. ASM corresponds to the amount of LBM in the arms and legs, which is mainly muscle (except for a small amount of connective tissue and skin) [14].

Sarcopenia is a term originally used to describe age-related decreases in muscle mass [15]. The term has evolved to indicate a point where skeletal muscle mass and/or strength has declined past a threshold in which health is affected. The European Consensus [16] has recently defined sarcopenia as a progressive, generalized loss of muscle mass and strength
which will increase the risk for physical disability, diminished physical performance, and poor quality of life. Although losses of both muscle mass and strength can occur simultaneously, this relationship is not linear [16–18].

Although there are several working definitions of sarcopenia, one of the most commonly used criteria is a level of skeletal muscle mass (ASM index, Table 1) lower than 2 SD below the expected mean for healthy young adults, as established by DXA. This sex-specific definition corresponds to ≤7.26 kg/m² for men and ≤5.45 kg/m² for women [19]. Importantly, individuals below this cut point have a significantly increased risk of adverse functional status, such as higher risk of disability, falls, and fractures [20].

It is important to highlight that establishing the threshold to define sarcopenia has been a challenge for the past several years. A variety of cut points in the literature have been reported, which were developed using different body composition techniques such as DXA, bioelectrical impedance, skinfold thickness measurements, and computerized tomography (CT images) [21]. Although most cut points are based on measurements of muscle mass, muscle quality has also been used as a criterion to identify sarcopenia. Measurements of muscle strength (handgrip, hip, or knee strength) are popular for this purpose because of their cost-effectiveness and availability in clinical settings [22]. In summary, definitions of sarcopenia are somewhat arbitrary and are limited to the availability of large clinical and epidemiological studies (population-representative cut points) using gold-standard body composition assessment tools [23]. The reader is referred to an extensive review on the topic for an in-depth discussion [24].

3 Osteosarcoenic obesity: a new face of an old problem

Although osteopenia/osteoporosis, sarcopenia, and obesity have been recognized and assessed for decades, the concurrent appearance of these problems has just begun to be discussed. From a historical perspective, the combination of sarcopenia and obesity termed sarcopenic obesity, was the first term to be introduced [33] and is extensively studied [21].

Sarcopenic obesity is an emerging health problem characterized by the simultaneous manifestation of excess body fat and low muscle mass/strength, and it has been described by Roubenoff as the confluence of two epidemics: the aging and the obesity epidemics [34]. Since there are no standard definitions for combined sarcopenia and obesity, a variety of indices has been used, and we refer the reader to an extensive review [21]. Regardless of indices used to define this condition, the majority of studies have found sarcopenic obesity to predict worse clinical outcomes when compared to sarcopenia or obesity in isolation [21, 34, 35].

The term “sarco-osteopenia” or “sarco-osteoporosis” was first introduced by Binkley and Buehring [36]. The authors proposed that patients with both low bone and muscle mass/performance would be diagnosed with this condition. Therefore, sarco-osteopenia or sarco-osteoporosis is an interconnected syndrome which should be combined into a single term. Individuals presenting with sarco-osteopenia or sarco-osteoporosis would be at higher risk for falls and fractures and, hence, increased morbidity, reduced quality of life, and increased mortality [36].

Although the term has only recently been proposed, the association of muscle and bone mass has been extensively studied [37–41]. Specifically, the dominant role of muscle on BMD of various skeletal sites in younger and older women was reported earlier [3]. Furthermore, when there is a lack of weight training, muscle mass begins to decline during the third decade of life, and bone loss follows due to the lack of strain [42]. Even the various modes of habitual and low-impact physical activity (gardening, stair climbing, heavy housework) had a positive influence on bone in postmenopausal women [2].

As the prevalence of elderly individuals increases in the USA and throughout the world, so does the prevalence of sarcopenia and osteopenia/osteoporosis. The addition of obesity to these existing conditions exacerbates the metabolic abnormalities likely leading to reduced physical function and
quality of life. Osteosarcopenic obesity represents a change in paradigm that has gone unrecognized until recently, due to the lack of accurate technology to assess human body composition, as sophisticated tools are needed to accurately assess fat, lean, and bone tissue compartments. Furthermore, as suggested by Stenholm et al. [43], although in healthy young and older individuals bone and muscle change concurrently with changes in body weight, this process may be impaired in some individuals when the excess of body weight occurs without concurrent increases in bone and muscle mass [43].

The association among bone, muscle, and fat mass was explored by Sowers et al. [37] in adult women. The authors categorized fat and lean tissue mass into tertiles, reporting a linear increase in mean femoral neck BMD for each tertile of muscle mass. Conversely, there was a nonlinear increase in BMD for each tertile of fat mass. BMD was similarly and equally greater in the high-muscle/low-fat and high-muscle/high-fat body composition types, suggesting that greater weight alone was not associated with increased BMD. Hence, if muscle does not grow in parallel with increased body weight, BMD is not optimized [37]. The authors concluded that low muscle mass was a risk factor for low BMD in young adult women, while higher fat mass was only protective when muscle mass was adequate.

Finally, as bone and muscle loss can appear concurrently with obesity, it is reasonable to propose a new term encompassing these three conditions. The acknowledgment of osteosarcopenic obesity as an emerging public health problem increases not only scientific but also public awareness for the identification, prognostic significance, public health costs, and ultimately the development of behavioral, nutritional, and possibly pharmacological interventions to prevent or reverse this condition.

3.1 Challenges of operationalization and applicability

Unfortunately, the advantage of proposing this new abnormal body composition phenotype introduces challenges to future research endeavors. Primarily, it leads to additional debate on the diagnosis of osteosarcopenic obesity, which in turn can impact risk prediction and treatment strategies. Although the definition of osteopenia/osteoporosis has been quite widely accepted, substantial debate still exists regarding the definition of sarcopenia and even obesity [21]. Likewise, the expected prevalence of osteosarcopenic obesity in the general population is uncertain. The combination of three diagnostic criteria (for abnormal bone, muscle, and fat) may limit the number of individuals presenting with this condition, which will impact the identification of this phenotype in non-epidemiological studies in healthy populations. On the contrary, we hypothesize that the prevalence of osteosarcopenic obesity will be pronounced in those presenting with clinical conditions (e.g., cancer, diabetes, etc.).

Additional opportunities exist to identify the onset, cause, and effect of this condition. Although osteosarcopenic obesity leads to health complications (Fig. 1), it is unclear if the health implications are a cause or consequence of osteosarcopenic obesity (Fig. 2). In fact, further studies are needed to investigate the occurrence of potential reverse causality. Importantly, although future studies are needed, we anticipate that this combined phenotype will represent an advantage for risk prediction and preventive/treatment strategies in primary and secondary/tertiary care.

4 Osteosarcopenic obesity: hypothesized mechanisms

Although the etiology of osteosarcopenic obesity can only be hypothesized at this time, Fig. 2 illustrates potential mechanisms leading to progressive losses of bone and muscle mass and an increase in adipose tissue. Regardless of the initiating metabolic abnormalities, an increase in total and/or abdominal adipose tissue causes an increase in pro-inflammatory cytokines, as well as some hormonal disturbances leading to losses of both muscle and bone tissues through a variety of mechanisms which ultimately affects clinical outcomes such as increase in risk for falls and fractures and potentially a variety of other problems (discussed below). The decreases in muscle and bone are associated with decreases in physical activity; once losses hit a threshold, physical activity becomes even more limited, leading to a vicious cycle of progressive loss of muscle and bone and gain in fat, of unveiled complexity (Fig. 2).

While obesity is clearly a multifactorial condition, the primary causes appear to be related to an excess energy consumption, low levels of physical activity, and high genetic susceptibility [45]. An increase in body fat from a lack of physical activity is primarily due to the low level of energy expenditure compared to a higher level of energy intake. Interestingly, this resultant increase in adiposity is highly correlated with excess inflammation that leads to impairments in skeletal muscle function and size [46, 47]. Furthermore, while further research is needed to clarify potential mechanisms, a loss of skeletal muscle mass and function is also associated with a sedentary lifestyle [48]. Therefore, lack of activity further exacerbates the loss of muscle mass and function resulting from obesity-derived inflammation. Adding to this problem is that loss of muscle mass also accounts for a reduced level of physical activity [48]. It is clear that a sedentary lifestyle contributes to sarcopenic obesity [48, 49] and, unfortunately, leads to both disability and mobility issues greater than those with only one of these conditions [50]. The reader is referred to a comprehensive review on the topic [51].
5 Osteosarcopenic obesity: potential clinical implications

The financial burden of each representative component of osteosarcopenic obesity is substantial. For instance, in 2008, direct costs of obesity were estimated to total almost 14 billion US dollars [52], with even more capital lost in indirect costs such as absenteeism, disability, and premature mortality [53]. Direct medical expenditure related to sarcopenia was estimated in 2000 to be around 18.5 billion dollars per year [54]. Those with osteoporosis with a concurrent hip fracture may contribute more than 6 billion dollars on health-care costs per year in order to treat the fracture and underlying osteoporosis; those with osteoporosis without a fracture may contribute to 3.79 billion dollars of health-care costs [55], though both of these estimates are conservative compared to an alternative 13.7–20.3 billion-dollar estimate [5]. Clearly, these three conditions substantially augment the direct cost of the US health-care expenditure with extensive presumed indirect costs. A disease state such as osteosarcopenic obesity would therefore prove to be a considerable economic encumbrance.

Obesity alone and its related consequences is perhaps one of the most comprehensively studied and debated modern epidemics. The prevalence of obesity across a multitude of countries has accelerated in the last decade [56]. In the USA, 32.2 % of men and 35.5 % of women are classified as obese according the WHO cut points [57]. Though both of these estimates are conservative compared to an alternative 13.7–20.3 billion-dollar estimate [5], these three conditions substantially augment the direct cost of the US health-care expenditure with extensive presumed indirect costs. A disease state such as osteosarcopenic obesity would therefore prove to be a considerable economic encumbrance.

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have an increased risk of premature entrance into nursing facilities [71].

In addition to each component’s individual implications, combined disorders can influence the development of even more adverse outcomes, and one disorder may cause another. For example, in addition to the separate side effects of sarcopenia and obesity, sarcopenic obese patients have a higher incidence of impaired function [72], diminished quality of life [43], knee osteoarthritis [73], falls, disability [29], and chemotherapy toxicity [1, 74] and shorter survival in cancer patients [75] in comparison to individuals with normal body composition; this is most likely due to the dual affliction of both low muscle mass and excess adiposity. Though obesity may have a protective role on osteoporosis [76], some research has suggested that a high body weight may actually perpetuate the development of osteoporosis [77]. A large examination of over 60,000 women reported that high body weight is not protective against fracture incidence, but may in fact be associated with ankle and upper leg fractures [78]. Furthermore, those with the most muscle wasting and lowest grip strength have much higher odds of having osteoporosis, fractures, or falls than those who have more muscle mass and strength [79]. Clearly, these conditions are interrelated, and the occurrence of one may aid in the development of another and thus lead to compounded clinical implications.

Importantly, osteosarcopenic obesity is not a syndrome of elderly individuals. There are a variety of disease states and conditions where the disease itself or its treatment is associated with losses of skeletal muscle and bone alongside gains in adipose tissue. For instance, low BMD in adulthood can be caused by type I diabetes mellitus (DM), though the association between type II DM and osteoporosis is less clear [80]. Diabetes treated with insulin therapy can lead to weight gain [81], and insulin resistance can lead to accelerated muscle loss mainly due to metabolic and hormonal factors [82]. Therefore, those with diabetes are likely to present with osteosarcopenic obesity. Sarcopenia has been found to occur independently of BMI in patients diagnosed with respiratory and gastrointestinal cancers and can precipitate the loss of functional status [75]. Patients undergoing cancer therapies (especially victims of breast cancer) may be at risk for bone loss, as some treatments may suppress estrogen production (which has a protective effect on bone) as well as directly adversely affect bone metabolism [83]. Yet another clinical manifestation, chronic obstructive pulmonary disease (COPD), is associated with muscle wasting and weakness which can make even daily tasks difficult, leading to decreased activity that further intensifies sarcopenia development [84]. COPD patients display numerous risk factors for osteoporosis including smoking, physical inactivity, vitamin D deficiency, low body weight, and hypogonadism. Of particular concern is glucocorticoid use which may directly adversely affect BMD, leading to secondary osteoporosis [85]. In HIV patients, antiretroviral interventions are associated with weight gain [86] along with bone loss through multiple mechanisms; the disease itself is associated with a loss in lean mass [87], suggesting that these patients commonly suffer from osteosarcopenic obesity.

Clearly, the direct impact of osteosarcopenic obesity is a potential threat to clinical and public health. Considering the effects of low muscle and bone tissues combined with the influence of obesity, it is likely that these individuals will present with poorer clinical outcomes caused by the cascade of metabolic abnormalities associated with these changes in body composition. Regardless of the specific diagnosis cut points for muscle, bone, and adipose tissue that have yet to be determined, there is no doubt that future research is needed to explore the clinical outcomes and appropriate interventions associated with the concurrent appearance of all three conditions.

6 Countermeasures and future directions

Future research is needed to identify the countermeasures to osteosarcopenic obesity. As this is a complex condition, it is very likely that a multifactorial approach would be the best strategy. An option for clinical practice may be non-pharmacological approaches that may play a vital therapeutic role in ameliorating potential negative consequences of osteosarcopenic obesity.

Substantial evidence exists to suggest that long-term resistance training (RT) alone can promote favorable changes in body composition, muscular strength and endurance, and lipid metabolism thereby having a positive impact on obesity [88]. Other research has demonstrated increases in FFM with resistance training [89].

Resistance exercise can also be used as an effective intervention to improve BMD; however, the precise physiological actions that modulate bone remodeling are not clearly understood. Although beyond the scope of this review, some potential mechanism of action involve mechanical mechanotransduction [90, 91], production of nitric oxide (NO) as a result of mechanical loading [92–94], and prostaglandin release [92, 95].

Additionally, resistance exercise improves muscle strength and quality through a variety of different mechanisms that include satellite cell recruitment [96] and stimulation of the mammalian target of rapamycin (mTOR) pathway (which regulates skeletal muscle growth) [96]. Certain hormones (e.g., growth hormone, insulin-like growth factor I, and testosterone) are also implicated in promoting anabolism [97–99]. Finally, resistance exercise has been shown to increase lipolysis and fat oxidation [100] in overweight and obese individuals, and the combination of resistance and aerobic exercise has been shown to favorably alter body adiposity [101, 102]. Recently, the combination of aerobic
and resistance training was also shown to improve weight loss and physical function among elderly obese individuals (potentially susceptible to osteosarcopenic obesity) [103].

Nutrition also plays an important role in the development of obesity and sarcopenia. Protein intake is important for both preventing loss of muscle mass and promoting increased muscular strength and endurance [104]. In fact, evidence is mounting to suggest that manipulation of the protein/carbohydrate ratio in the diet may improve muscle mass, fat mass, and BMD in overweight and obese individuals [101, 105]. In a study of 90 free-living overweight and obese adults, it was demonstrated that a whey protein supplement providing 56 g per day of protein (with no other dietary alterations) resulted in a significantly lower body weight (~1.8 kg; p<0.006) and fat mass (~2.3 kg; p<0.005) over 23 weeks compared to an isocaloric carbohydrate supplement [106]. This higher protein intake is thought to best manage body composition via its influence on metabolism, satiety, and muscle mass [48, 107, 108].

Resistance training and protein supplementation combined together are possible therapies to attenuate many of the previously mentioned side effects that are associated with osteosarcopenic obesity due to lack of physical activity. A high-protein dietary intake combined with exercise training has been shown to effectively reduce both body weight and body fat in obese men and women [101] while also helping to maintain or even improve muscle mass in overweight or obese men and women [101, 105] and in sarcopenic individuals [109]. Data indicate that exercise training (six times per week) combined with a higher protein intake (40 % of total energy intake) over a period of 12 weeks improves body weight (~6.2 %), percent total body fat (~15.8 %), percent abdominal body fat (~26.4 %), and BMI (~6.0 %) in healthy but overweight and obese men and women [101]. Likewise, it was reported [105] that moderate protein intake (25 % of total daily energy intake) and exercise training (6 days per week) resulted in significant decreases in body weight (90.8±4.9 to 85.3±4.7 kg), percent total body fat (36.8±3.0 to 32.5±3.2 %), percent abdominal fat (39.4±2.8 to 36.6±3.0 %), and BMI (32.1±1.0 to 30.1±1.1 kg/m²) in overweight/obese men and women both with exercise (6 days/week) and without exercise. Interestingly, high-protein intake (40 %) in the non-exercising group had significant improvements over 12 weeks in body composition marked by decreases in body weight (94.5±6.5 to 89.3±5.9 kg), percent body fat (40.3±2.4 to 38.3±2.6 %), and waist circumference (102.2±5.8 to 94.3±4.8 cm). These improvements in body composition were made without the addition of an exercise program.

Taken together, increased physical activity and protein intake (likely above the current recommended reference intakes) appear to be useful for reducing adiposity and maintaining muscle and bone mass in an effort to stave of osteosarcopenic obesity. This holds true for the oldest of the old and in a variety of clinical populations, although more clinical trials are needed.

As part of the multifactorial concept of osteosarcopenic obesity, future studies on the relationship between both psychological and physical fatigue in the development and exacerbation of this syndrome must be explored. Fatigue is a behavioral marker for reduced ability to adapt to stressors, leading to reduced physical function and poorer quality of life. Reductions in fatigue by using holistic measures may be proven beneficial as a potential countermeasure for osteosarcopenic obesity [110].

Finally, given the novelty of the identification of osteosarcopenic obesity, the development of animal models will be helpful to identify the pathophysiology of this syndrome. Ultimately, experimental animal models may provide insight in how to apply these mechanisms to the human condition.

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