



Is There Enough Evidence for Osteosarcopenic Obesity as a Distinct Entity? A Critical Literature Review

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Abstract

The co-existence of impaired bone health (osteopenia/osteoporosis), reduced muscle mass and strength (sarcopenia), and increased adiposity (obesity) in middle-aged and older people has been identified in recent studies, leading to a proposal for the existence of “osteosarcopenic obesity” as a distinct entity. Evidence for the pathophysiological overlap of these conditions is mounting, although a causal relationship is yet to be established. Each component condition occurs frequently with increasing age, and with shared risk factors in many instances, thus, an overlap of these three conditions is not surprising. However, whether the concurrent existence of sarcopenia, osteoporosis and obesity leads to an increased risk of adverse musculoskeletal outcomes and mortality above and beyond the risks associated with the sum of the component parts remains to be proven and is a question of research interest. In this article, we review evidence for the existence of osteosarcopenic obesity including the current operational definition of osteosarcopenic obesity, prevalence, pathophysiology, outcomes and exploratory approaches to the management of components. We conclude that, there is insufficient evidence to support a discrete clinical entity of osteosarcopenic obesity at this time. To expand knowledge and understanding in this area, there is a need for consensus on a definition of osteosarcopenic obesity which will allow for identification, further epidemiological studies and comparisons between studies. Additionally, studies should assess whether the clinical outcomes associated with osteosarcopenic obesity are worse than the mere addition of those linked with its components. This will help to determine whether defining a person as having this triad will eventually result in a more effective treatment than addressing each of the three conditions separately.

Keywords Obesity · Osteoporosis · Sarcopenia · Osteosarcopenia · Sarcopenic obesity

Introduction

The rise in obesity prevalence over the last few decades poses a burdensome public health problem, with the combined overweight and obese population in many countries accounting for the majority of people, especially among the middle-age and older-age groups [1, 2]. Typically, all contributory factors to obesity, sarcopenia, and osteoporosis— increase in fat mass, decrease in lean muscle mass and muscle strength, and decrease in bone mass and function—occur

with “normal aging”. Increased body fat can be present either as an overt overweight/obesity or fat redistributed into visceral organs and/or fat infiltrated into bone and muscle, which occurs especially with age and some chronic diseases [3, 4]. While reducing body weight is the primary strategy for obese individuals, weight-reduction therapies may compromise the ability to preserve muscle function and mass [5].

Sarcopenia, is a progressive and generalized skeletal muscle disorder, which can be detected as low muscle strength and confirmed by the presence of low muscle quantity or quality [6, 7]. Sarcopenic individuals have both decreased muscle mass and increased intra- and intermuscular fat: changes that are associated with mobility limitations in older people [8]. The co-presence of sarcopenia and obesity has

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been described in the literature as sarcopenic obesity [9]. Diminished physical performance leads to frailty, increased risk of falls, and subsequent fractures, causing a loss of independence, reduced quality of life, and greater morbidity and mortality [10]. The risk of frailty and disability in obese individuals with low muscle mass and function has been reported to be higher than that observed in non-obese counterparts with similar muscle alterations [11].

Osteoporosis, a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility, occurs frequently, particularly in older women. At the age of 50 years, the remaining lifetime probability of a major osteoporotic fracture in Sweden is 22% in men and 46% in women [12].

Sarcopenia and osteoporosis have similar risk factors that include genetics, endocrine function, and mechanical factors. Additionally, bone and muscle closely interact with each other not only mechanically but also metabolically. The combination of osteoporosis/osteopenia and sarcopenia has been termed osteosarcopenia [13–15]. It is unclear whether individuals with so-called osteosarcopenia are at greater risk of adverse clinical outcomes than those with sarcopenia or osteoporosis alone. In a small study of hip fracture patients, the 1-year mortality of those with osteosarcopenia (15.1%) was higher than that of those with osteoporosis alone (5.1%) or sarcopenia alone (10.3%) [16]. Consistent with this observation, a study of patients admitted to intensive care reported that 1-year mortality was increased in individuals with sarcopenia, osteopenia or the combination compared with controls [14]. In a study of 68 pre-frail adults, osteosarcopenic individuals showed a significant reduction in physical performance compared with sarcopenic and osteopenic/osteoporotic individuals [17]. A large study of 5544 older men (mean age = 73.7 years) from the Osteoporotic Fractures in Men study showed that hazard for fracture compared with healthy controls was substantially greater for men with both low bone mineral density (BMD) and sarcopenia (3.8-fold) than for men with only one condition (1.1- to 1.7-fold) [18].

In contrast, a large cohort of community-dwelling men aged ≥ 70 years with combined osteopenia/osteoporosis and sarcopenia did not have an increased risk falls and fracture compared with those with either condition alone [19]. In a recent analysis, participants of the Women's Health Initiative (WHI) were classified into mutually exclusive groups based on BMD and sarcopenia status [20]. Whereas low BMD was associated with increased risk of hip fracture, women with sarcopenia alone were at similar risk of hip fracture to non-sarcopenic women with normal BMD, suggesting that sarcopenia alone was not predictive of this outcome. In a further WHI study, appendicular lean mass was predictive of incident hip fracture amongst 872 participants aged 65 years or older

who met Fried's criteria for frailty, but this association did not remain statistically significant after adjusting for total hip BMD [21]. These findings are consistent with those of a study of 5911 older men and women in whom sarcopenia, was not associated with incident fractures or falls after adjustment for femoral neck BMD [22]. The disparate findings from these various studies may be in part related to the definitions used for osteoporosis and sarcopenia, but these observations do lead to the question of whether sarcopenia yields any information on fracture risk additional to that obtained from BMD.

Recent studies identifying the co-existence of impaired bone health (osteopenia/osteoporosis), reduced muscle mass or strength (sarcopenia), and increased obesity in middle-aged and older women, have led to the proposal of "osteosarcopenic obesity" as a distinct entity [3]. In this classification, osteosarcopenic obesity is described as the most advanced stage in a conceptual model of bone, muscle, and fat tissues in healthy and disease states resulting from aging, or individual comorbidities [23]. Each component of osteosarcopenic obesity occurs frequently with increasing age, and with shared risk factors; thus, an overlap in prevalence is not surprising. However, whether the concurrent existence of sarcopenia, osteoporosis and obesity leads to an increased risk of adverse outcomes including mortality above and beyond the risks associated with the sum of the component parts remains to be proven and is a question of research interest. In this article we critically review evidence for the existence of osteosarcopenic obesity, including definition, prevalence, pathophysiology, outcomes and exploratory approaches to the management of components.

Methods

Articles included in this narrative, critical literature review were identified through literature searches of PubMed, Scopus, and Embase using the following MeSH items or free words: "osteoporosis", "sarcopenia", "obesity" "osteosarcopenia", "osteosarcopenic obesity"; additional terms searched for in either the title, abstract or keywords included: "definition", "epidemiology", "pathophysiology", "hormones", "exercise", "nutrition", "non-pharmacological", "pharmacological". The search strategy was limited to studies conducted in humans, publications in English language, and full-length articles published from inception until January 15, 2018. Finally, the methodological sections and reference lists of relevant articles (particularly review articles) were scrutinised (by JB, EMD, RF, JMK, FL, SM, SP, JYR, PS) for potentially interesting articles. The process for literature identification and selection of the final number of references included in this paper is outlined in Fig. 1.

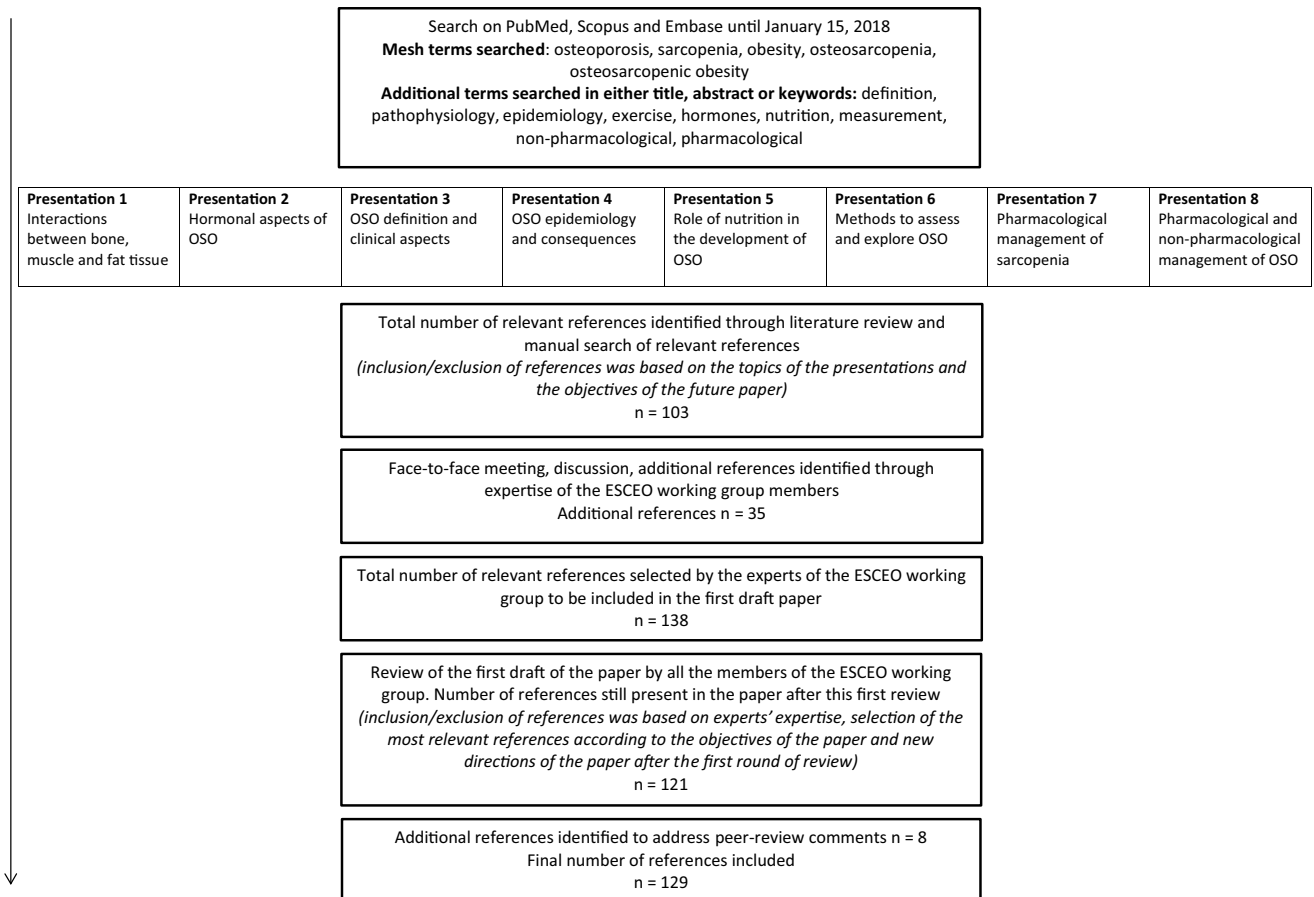


Fig. 1 Literature selection process. OSO, osteosarcopenic obesity

Epidemiology

A few studies have appeared in the literature reporting on the epidemiology of osteosarcopenic obesity. However, without a standardised definition of osteosarcopenic obesity it is difficult to make comparisons and draw conclusions on prevalence of as the published studies use multiple definitions for the osteosarcopenic obesity components (Table 1) [24–26].

Definitions

Obesity

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. Body mass index (BMI) provides a crude measure of obesity—defined as a person’s weight (in kilograms) divided by the square of his/her height in metres; the World Health Organization (WHO) defines obesity in a person with a BMI of $\geq 30 \text{ kg/m}^2$, while a person with a BMI $\geq 25 \text{ kg/m}^2$ and $< 30 \text{ kg/m}^2$ is

Table 1 Multiple definitions of osteosarcopenic obesity components used in clinical studies

Study	Osteopenia/osteoporosis	Sarcopenia	Obesity
Szlejtf et al. [24]	At least one T -score ≤ -1	FNIH criteria: $ALM_{BMI} < 0.512$ and grip strength $< 16 \text{ kg}$ in women	Fat mass: 35% body fat if < 60 years; 40% if > 60 years (females)
Chung et al. [25]	At least one T -score ≤ -1	$ALM/ht^2 < 2$ SD below sex-specific young adult mean	Fat mass $> 30\%$ in males or $> 40\%$ in females
Ilich et al. [26]	At least one T -score ≤ -1	ALM residual value of < 1.43 (20%)	Fat mass $\geq 35\%$ (females)

ALM appendicular lean mass, ALM/ht^2 appendicular lean mass index normalised for height, FNIH Foundation for the National Institutes of Health, SD standard deviation

considered as overweight [27]. An alternative definition of obesity based on body fat percentage is not well established and has arbitrary cut-off points [28]: the WHO proposes $\geq 35\%$ body fat for women < 60 years [29] and $> 40\%$ body fat for women aged ≥ 60 years and older [30].

Sarcopenia

Currently, there is no international consensus on the operational definition of sarcopenia, and several definitions of sarcopenia are used with consequent impact on the prevalence of sarcopenia [6, 31–34]. For example, a study of 445 community-dwelling seniors (mean age 71 years, 45% men) examined the prevalence of sarcopenia using seven available definitions of sarcopenia plus two related definitions. The prevalence of sarcopenia varied between 2.5 and 27.2% among women, and 3.1 and 20.4% among men [33].

The European Working Group on Sarcopenia in Older People (EWGSOP) is one of the most widely used conceptual and operational definitions of sarcopenia [6] but different cut-off points were recommended for diagnosis for muscle mass, muscle strength and gait speed. In a sample of hospital referees aged ≥ 65 years the prevalence of sarcopenia varied two-fold from 9% to 18% depending on the cut-offs applied [35]. Thus, the basis for defining variants of sarcopenia are based on questionable foundations.

Recently, the EWGSOP2 has published a revised European consensus on the definition and diagnosis of sarcopenia to delineate clear criteria and tools that define and characterize sarcopenia in clinical practice and research populations. The EWGSOP2 guidelines focus on low muscle strength as the primary parameter to detect sarcopenia; the diagnosis is confirmed by the presence of low muscle quantity or quality, and when all three qualities are detected sarcopenia is considered as severe. In addition, the EWGSOP2 provides clear cut-off points for measurements of variables that identify and characterize sarcopenia [7].

Osteoporosis

Notably, the definitions employed for the bone component of osteosarcopenic obesity have included both osteopenia and osteoporosis, and consequently may capture a very large proportion of the population of women aged over 50 years. In Sweden, for example, the prevalence of osteopenia is approximately 70% of women aged ≥ 50 years, whereas the prevalence of osteoporosis is 21% [12]. Osteopenia is measured using BMD and based on the lowest *T*-score of the posteroanterior spine, femoral neck, trochanter, or total hip (*T*-score between 1.0 and 2.5 standard deviations [SD] below the mean adult value) [36]. Osteoporosis is measured as the *T*-score for BMD assessed at the femoral neck (reference

site) and defined as BMD 2.5 SD or more below the mean adult value [36, 37].

Diagnostic Techniques

Dual-energy X-ray absorptiometry (DXA) is commonly used in clinical practice and epidemiological studies to assess body composition, in terms of bone, non-fat mass and fat mass (Table 2). Regional bone density is measured using DXA of the lumbar spine, femoral neck or total hip. Muscle mass is determined from DXA whole body scan which estimates lean mass (i.e. muscle, water, fibrous tissue and viscera) [6, 31, 32]. The composite Short Physical Performance Battery (SPPB) is the most widely used test of overall physical performance [23, 38]. Other techniques employed for exploration of the pathophysiology of the interactions between bone, muscle and fat include bioelectric impedance analysis (BIA) and magnetic resonance imaging (MRI). MRI and computed tomography are used experimentally to assess muscle fat infiltration, which may be important when considering osteosarcopenic obesity. Anthropometric measurements (e.g. mid-upper arm circumference) may be used to assess obesity, but have suboptimal correlation with other methods.

Reported Prevalence of Osteosarcopenic Obesity

Given the heterogeneous approach to the definitions of sarcopenia, osteosarcopenia and obesity, defining the prevalence of osteosarcopenic obesity is problematic. A prevalence of 12–19% of osteosarcopenic obesity has been reported in women aged over 50 years [24–26]. A Mexican study of women aged ≥ 50 years ($N=434$) found a prevalence of 19% and osteosarcopenic obesity was associated with frailty and poor physical performance [24]. Another study among postmenopausal women of mean age 63 years found a prevalence of osteosarcopenic obesity of 12.1% and an association with poorer functionality in women

Table 2 Methods to assess osteosarcopenic obesity components

	Primary measure	Secondary measure
Osteopenia/osteoporosis	DXA	
Sarcopenia	DXA Grip strength Gait speed	BIA SPPB
Obesity	DXA	BMI Waist circumference BIA

BIA bioelectric impedance analysis, *BMI* body mass index, *DXA* dual-energy X-ray absorptiometry, *SPPB* short physical performance battery

presenting with osteosarcopenic obesity, particularly compared to obese women, increasing the risk for bone fractures and immobility due to the combined decline in bone and muscle mass, and increased fat mass [26]. Investigation of the Korean National Health and Nutrition Examination Survey (including $N=3385$ men and $N=4064$ women aged >50 years) found the incidence of sarcopenia, sarcopenic obesity, and osteosarcopenic obesity as 31.5%, 5.1%, and 4.1%, respectively. Sarcopenic obesity was associated with increased odds for the development of osteoporosis among the middle-aged and older-aged Korean population [25].

Obesity at a young age may also contribute to the early development of osteosarcopenic obesity and frailty sooner than that which occurs in a lean population. Overweight/obese but otherwise healthy young adults (aged 18–21 years) exhibit ‘osteosarcopenic elements’ including: increased fat mass, and decreased muscle and bone mass compared with lean controls [39].

Pathophysiology

Recent evidence suggests a potential interconnection between osteoporosis, sarcopenia, and obesity with shared pathophysiology [40]. The changes in body composition that occur over a lifetime, and interplay between mechanisms leads to progressive losses of bone and muscle mass and an increase in adipose tissue (Fig. 2) [40]. An increase in total and/or abdominal adipose tissue causes an increase in pro-inflammatory cytokines, as well as hormonal disturbances leading to losses of both muscle and bone tissues through a variety of mechanisms which ultimately affect clinical outcomes, such as an increase in risk for falls and fractures [40].

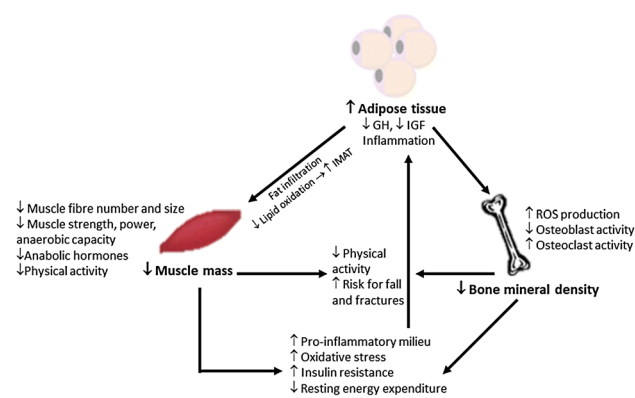


Fig. 2 The interplay between bone, muscle and adipose tissue. GH, growth hormone; IMAT, intramuscular adipose tissue; IGF, insulin-like growth factor; ROS, reactive oxygen species. Reproduced from: Ormsbee MJ et al. Osteosarcopenic obesity: the role of bone, muscle and fat on health. *J Cachexia Sarcopenia Muscle* (2014) 5:183–192. Reproduction permitted under the terms of the Creative Commons Attribution-NonCommercial License

Bone and muscle are physically and functionally coupled. Several age-related alterations of bone microenvironment and an altered bone-muscle cross-talk are proposed to be relevant contributors to loss of bone strength and mass characteristic of osteoporosis [41]. Insulin-like growth factor-I (IGF-I), myostatin, and cytokines (e.g., interleukin-6 [IL-6]), collectively referred to as myokines, are released from skeletal myocytes and exert actions on the muscle and the bone. Analogously, osteokines, including osteocalcin, osteoprotegerin and bone matrix proteins are released from bone cells and participate in the regulation of musculoskeletal homeostasis [41].

The reductions in muscle and bone tissues 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 as well as gain in fat [40]. While age-related changes may be considered of primary importance, other important factors may include endocrine disorders, inadequate nutrition, inflammation, neurodegenerative disorders, physical inactivity, and other chronic and lifestyle factors [42].

Hormonal Aspects

There are cumulative hormonal changes that occur with aging and obesity, such as a substantial decrease in levels of the main anabolic hormones. Hormonal players that are identified as having a potential role in development of the components of osteosarcopenic obesity are listed in Table 3 [42]. Changes in anabolic hormones have been associated with unfavourable changes in muscle mass, muscle function and impaired functional capacity. Testosterone has a dose-dependent impact on fat-free mass in both the young and old, with higher levels associated with reduction in fat mass and increase in skeletal muscle mass and strength [43]. Low levels of testosterone, but not oestradiol, predict frailty in older men and are associated with incident falls [44–46].

Non-androgenic anabolic hormones predict the risk of frailty in aging men, including IGF-I, dehydroepiandrosterone, parathyroid hormone, and 25-OH vitamin D [47]. Age-related decreases of serum levels of adrenal androgens are shown in healthy men and women [48, 49]. Higher levels of cortisol are detected in frail older women, with blunted diurnal variation in cortisol levels compared with non-frail individuals [50]. Increasing age is also shown to influence 24-h integrated concentration of growth hormone in normal individuals [51].

Increasing age and obesity both contribute to sarcopenia, for which a postulated mechanism involves disturbed insulin signalling and insulin resistance [9]. Frailty and sarcopenia are newly emerging and high impact complications of diabetes [52]. Both diabetes and obesity impact on muscle loss [52], and muscle mass is inversely associated with insulin

Table 3 Hormonal players identified with a potential role in the development of osteosarcopenic obesity components

Hormone class	Examples
Anabolic	Somatotropic axis, sex steroids
Adrenal cortex	Cortisol, adrenal androgens
Insulin	
Adipokines	TNF- α , IL-6, adiponectin, BMPs, IL-13, IL-15, IL-10, leptin, resistin, chimerin, myostatin
Myokines	Myostatin, irisin, BMPs, FGF-21, IL-10, MCP-1, TNF- α , IL-6, IL-1 β , IGF-I

BMP bone morphogenetic protein, *FGF* fibroblast growth factor *IGF-I* insulin-like growth factor, *IL* interleukin, *MCP-1* monocyte chemoattractant protein-1, *TNF- α* tumour necrosis factor- α

resistance and prediabetes [53]. Hyperglycaemia predicts persistently lower muscle strength with aging [54], and an excessive loss of skeletal muscle mass has been detected in older adults with type 2 diabetes [55]. In the obese state, dysregulation of adipokines that contribute to muscle maintenance in the lean state leads to sarcopenia [9].

Mechanisms responsible for the development of osteosarcopenic obesity components are complex and may include multiple factors: endocrine versus local regulation, threshold effects, hormonal implications of comorbidities, and cross-talk between endocrine-immune-neurologic factors. Bidirectional interactions between hormonal changes and altered body composition are identified but uncertainties remain as to causalities versus reverse causalities, and bidirectional interactions create conditions for self-amplifying vicious circles. While many potential and biologically plausible contributing mechanisms are postulated, indicating a likely multifactorial pathogenesis, biologically plausible hypotheses have not yet established a clinical relevance for pathophysiology, prevention, or treatment. Furthermore, there is a need for unravelling of the complex ‘local’ fat-muscle-immune system interactions and their interaction with systemic hormones and neurogenic factors.

Nutritional Aspects

The role of nutrition in the development of osteosarcopenic obesity components is significant. Middle-aged and older women who eat a healthy diet are less likely to have multiple body composition abnormalities [56]. The typical Western diet and lifestyle promotes several chronic diseases including the components of osteosarcopenic obesity, by facilitating a pro-inflammatory state, largely via the imbalance in omega-6/omega-3 polyunsaturated fatty acid (PUFA) ratio and low-fibre and high-processed food consumption [57], which is linked to a higher risk of frailty and fractures [58, 59]. A Western pattern diet is linked to a higher risk of sarcopenia in menopausal women as compared with a Mediterranean pattern diet (high in low-fat dairy, vegetable, fish, nut, olive and vegetable oil), which is associated with lower risk [60]. Greater adherence to a Mediterranean pattern diet

is associated with less loss of skeletal muscle mass and lean body mass, better physical performance [61], a significant reduction in waist circumference [62], and a lower incidence of frailty [63].

Deficiencies in macronutrients are important, specifically protein and amino acid intake (in particular the branched amino acids) in terms of quantity, quality (type of protein, essential amino acids, and absorption rate) and timing of intake. Energy imbalances in aging, excessive high glycaemic carbohydrate, lower protein intakes and low long-chain PUFA intakes may contribute to the components of osteosarcopenic obesity [64]. Dietary protein intake contributes to maintenance of lean muscle mass and may be a modifiable risk factor for sarcopenia in older adults [65]. Protein intakes of ≥ 1.0 g/kg body weight/day may be optimal for maintaining lean mass and physical function in older adults [66].

Deficiencies in multiple micronutrients may be important in osteosarcopenic obesity, in terms of intake, absorption, and bioavailability [67]. Obese adults are shown to have lower micronutrient intake and higher prevalence of micronutrient inadequacy as compared with normal weight adults [68]. Low serum vitamin D level in mid- and later-life is associated with multiple indices of adverse body composition [69].

Summarizing the above, it has to be acknowledged that very few studies have specifically addressed nutritional intake in the context of osteosarcopenic obesity. Most of the presented information has been derived from studies that focused separately on sarcopenia, osteoporosis or obesity.

Health Outcomes

Although understanding of the aetiology, prevalence, and consequences of osteosarcopenic obesity components are, so far, limited, it is reasonable to infer a negative impact in an aging, and increasingly obese population. The potential clinical consequences of osteosarcopenic obesity are linked to each of the underlying conditions, with the possibility of interaction to increase further the adverse health effects. Clinical outcomes associated with osteosarcopenic obesity

components include: increased risk of fractures, impaired functional status (including activities of daily living) [70, 71], physical disability, insulin resistance, increased risk of infections, increased length of hospital stay, and reduced survival [40]. However, there is little evidence to date on an additive or multiplicative health impact of osteoporosis in a distinct overlap with obesity and sarcopenia. The cascade of metabolic abnormalities associated with changes in body composition related to osteosarcopenic obesity components may also be important in younger populations with comorbidities such as diabetes mellitus, glucocorticoid use, or malignancy.

Frailty is a geriatric syndrome resulting from age-related declines across multiple physiological systems leading to increased risk of falls, hospitalisation, institutionalisation and mortality [72, 73]. Frailty and sarcopenia overlap in terms of physical factors [74], and osteoporosis is linked to frailty [75]. The link between obesity and frailty is less clear and complex. Osteosarcopenic obesity components occur frequently in middle-aged and older women and are independently associated with frailty and poor physical performance; women with osteosarcopenic obesity have lower functional abilities and higher frailty scores compared with their counterparts without osteosarcopenic obesity [24].

Body Fat Location: Distinguishing Between Visceral and Subcutaneous Adipose Tissue

The location of body fat may have differential impact upon health outcomes. Abdominal obesity is more closely associated with incidence of frailty than general obesity in older people [76]. Among a sample population of older people ($N=801$), the prevalence of osteosarcopenic obesity was determined as 6.8%; subjects with a visceral/subcutaneous adipose tissue ratio > 1 were classified as having visceral obesity, and subjects with values under 1 were classified as having subcutaneous obesity [77]. Visceral obesity was closely linked to a higher risk of fractures and inflammation [77].

Management of Osteosarcopenic Obesity Components

No clinical studies are currently available that have tested therapeutic approaches in individuals with osteosarcopenic obesity. The components of osteosarcopenic obesity occur as a result of sedentary behaviour and a lack of regular physical activity, among other factors. Consequently, the therapeutic approach should include a combination of tailored exercise, optimised nutrition, and pharmacotherapy targeted at the three components.

Exercise

Multidimensional treatment protocols should include a programme of multimodal exercise comprising the elements of balance, aerobic and resistance exercise. Mobility-limited older individuals have a distinct muscle phenotype of poor muscle quality and intermuscular fat accumulation. The rise in intermuscular fat found in sarcopenia may be suppressed by physical activity [78]; mobility-limited older people have a greater change in intermuscular adipose tissue over time [8]. Moderate-intensity physical activity programmes significantly improve physical functioning in mobility-limited older adults, attenuate intermuscular fat accumulation and improve muscle quality. A lifestyle intervention study of aerobic and resistance exercise versus health education in older people (aged 70–89 years) resulted in a positive improvement in physical activity (SPPB) over an average of 2.7 years follow-up [79]. A study of the effects of a 12-week program of resistance training in older women ($N=62$, mean age 68 years; mean BMI 27 kg/m²) found that performing 3 sets of each exercise 3-times weekly has beneficial effects on the risk factors for osteosarcopenic obesity including skeletal muscle mass and strength. Moreover, moderate-intense physical exercise is an important stimulus for osteoporosis prevention and treatment [80].

Nutrition

Nutritional interventions to prevent and/or alleviate osteosarcopenic obesity components include: adequate intake of protein (> 0.8 g/kg/day), calcium (1200 mg/day), magnesium (320 mg/day), and vitamin D (800 IU/day), and increasing consumption of foods containing omega-3 PUFAs (1 g/day) and fibre (25 g/day for women) [57, 81]. There is evidence for a higher protein requirement in older people (1.0–1.2 g/kg/day), due to a blunted muscle protein synthetic response to protein ingestion, and higher protein intake is recommended in those who are exercising (≥ 1.2 g/kg/day) and in older adults with acute or chronic diseases (1.2–1.5 g/kg/day) [81–83]. Dietary protein quality is also important. Leucine supplementation enhances myofibrillar protein synthesis in older men consuming lower- and higher-protein diets with and without exercise [84]. Increased protein intake (> 0.8 g/kg/day) is known to increase BMD in older people with osteoporosis [81, 85].

Vitamin D deficiency is associated with osteosarcopenic obesity components [69, 86]. The combined intervention of a vitamin D with high whey protein, leucine-enriched oral supplement has resulted in improvements in muscle mass and lower-extremity function as well as in a decrease in fat mass among sarcopenic older adults [87, 88]. Omega-3 PUFAs may influence skeletal muscle health and function [89], and correlations are found between omega-3 and

omega-6 PUFAs, protein intake, BMD and physical performance [90]. Omega-3 PUFA supplementation increases the rate of muscle protein synthesis in older adults [91].

It is as yet unclear how high protein diets impact on body weight, and how dietary intervention can improve bone, muscle and fat all together, for which further studies are warranted.

Combined Exercise and Nutrition

Older adults who exhibit osteosarcopenic obesity components may benefit from combined efforts to improve diet (as specified above) and physical activity involving aerobic, strength, flexibility and balance training, which requires further investigation [57]. Together these can positively influence intermuscular fat accumulation and improve muscle quality with equivocal effects on physical functioning. Supplementation with whey protein, essential amino acids and vitamin D, in conjunction with age-appropriate exercise, is shown to increase fat-free mass and strength, and boost nutritional status, physical function and quality of life in sarcopenic older persons (mean age 80 years) with only a 12-week program [92]. In the VIVE-2 study a combination of exercise intervention (3 times per week for 6 months) and nutritional supplementation with whey protein (20 g), vitamin D (800 IU), calcium, vitamins and minerals (150 kcal) among people aged 70+ years, led to an increase in muscle density and a reduction in intermuscular fat [78, 93, 94].

Gut Microbiota

Increasing evidence suggests a role for altered gut microbiota on inflammation, obesity, and other chronic conditions. A connection between osteosarcopenic obesity components concurrent with altered microbiota in older individuals, particularly those living in long-term care facilities, has been established [95]. The gut microbiota may be a new therapeutic target in muscle wasting [96]. The gut microbiota can modulate amino acid availability; antibiotics have been shown to increase levels of circulating amino acids, which would have been otherwise degraded by intestinal bacteria [97].

Pharmacotherapy

Research interests have focused on pharmacological agents to separately address the three components of osteosarcopenic obesity. Medications available to reduce obesity have limited effects and are yet to be properly tested in older people [98, 99]. Drugs available for the prevention and treatment of osteoporosis impact upon BMD and fracture risk, although their effect on muscle or fat mass is not well

studied [100, 101]. Multiple pathways are involved in the loss of muscle mass arising from aging, malnutrition, obesity, inflammation and inactivity, which offers many targets for therapeutic intervention [102].

Several pharmacological agents are currently under investigation to manage sarcopenia e.g., testosterone, selective androgen receptor modulators (SARMs), AMP-activated protein kinase (AMPK) agonists, activin 11R antagonists, growth hormone, IGF-I analogues, and ghrelin-modulating agents [103]. Targeting pathways that centrally regulate both bone and muscle (e.g. growth hormone, IGF-I, sex steroids), and newly emerging pathways that facilitate communications between these two tissues (e.g. activin/myostatin) might allow a greater therapeutic benefit in frail older people [104]. To aid future development of new therapeutic targets for sarcopenia, recommendations for the conduct of clinical trials have been developed, along with the proposal for a core outcome set to include the domains of activity/independence, quality of life, costs, and muscle mass, strength and performance [105, 106].

Testosterone

Pharmacological treatment effects with anabolic hormones can be demonstrated but are rather mitigated and of uncertain clinical significance alongside some safety concerns. Several trials conducted with testosterone show a direct effect on muscle mass and, in several cases, on muscle strength and performance, with a slight reduction in body fat, and some effect on bone density [107–110]. Testosterone supplementation is also shown to benefit other aspects of health, including sexual function, physical function, vitality, quality of life and improved mood [109, 111]. However, when considering testosterone replacement therapy, the potential benefits of treatment must be weighed against the possible side effects [112, 113], and the broad application of testosterone therapy in older men with low testosterone level is not recommended [114].

Selective Androgen Receptor Modulators (SARMs)

SARMs have the same anabolic effect on muscle tissue as testosterone. These new drugs may expand the clinical application of androgens in sarcopenia as they enter the clinical phase of research, although to date there are few studies. Treatment with ostarine (enobosarm) for 3 months is demonstrated to increase muscle mass and stair climbing power in healthy older men and postmenopausal women [115].

Growth Hormone

Many studies reported only marginal effects of growth hormone (GH) supplementation on skeletal muscle mass, bone

density, fat mass and physical function [116]. Most studies have documented that GH supplementation is ineffective in older subjects, by increasing muscle mass but not muscle strength [117–119]. Moreover, the majority of trials conducted on GH supplementation have reported a high incidence of adverse effects [116, 118, 119]. Consequently, GH treatment should not be considered as a safe strategy to improve body composition and functionality in older individuals.

Ghrelin Agonist

Ghrelin concentrations have been reported to be strongly correlated with the amount of skeletal muscle mass. An enhanced ghrelin blood concentration results in an increased sensation of hunger and food intake. Considering that anorexia and malnutrition are important causes of sarcopenia, it has been hypothesised that ghrelin supplementation could be effective. Very few clinical studies on synthetic ghrelin or ghrelin agonist treatment have been conducted in older subjects. In healthy older adults, without sarcopenia, 2 years of an oral ghrelin mimetic agent (ibutamoren mesylate; MK-0677) increased the GH and IGF-I blood levels and muscle mass but without significant changes in strength or physical function [120]. In other studies of ibutamoren in persons with hip fracture the increase in plasma IGF-I levels was not paralleled by improvement in most functional performance measures, and one trial was terminated early due to a safety signal of congestive heart failure [121, 122].

Myostatin Inhibitors

Myokines are involved in communication pathways from skeletal muscle to bone [123]. Myostatin (growth differentiation factor-8) is a member of the transforming growth factor- β (TGF- β) superfamily that is expressed almost exclusively in skeletal muscle. Myostatin inhibits myoblast proliferation and thus acts as a negative regulator of skeletal muscle mass.

At present, limited data is available from human studies of myostatin inhibitors [124]. Bimagrumab increased total thigh muscle volume and appendicular muscle mass in sarcopenic older persons ($N=40$) [125]. In parallel, decreases in intermuscular thigh adipose tissue of 9.5% and 3.8% in subcutaneous thigh fat were measured at 24 weeks [125]. Participants with slower walking speed at baseline receiving bimagrumab had greater improvements in gait speed (mean 0.15 m/s, $p=0.009$) and 6-min walk distance (mean 82 m; $p=0.022$) than those receiving placebo [125]. In addition, bimagrumab improved body composition and insulin sensitivity in insulin-resistant individuals [126]. This initial proof-of-concept data still needs to be confirmed in larger pivotal trials.

Angiotensin-Converting Enzyme (ACE) Inhibitors

The effects of ACE inhibitors on muscle function have been mainly attributed to positive cardiovascular effects. There is contrasting data from observational studies and RCTs for the effect of ACE inhibition on skeletal muscle. Among 95 participants that completed a 20-week trial, the mean 6-min walking test was significantly improved in subjects receiving perindopril relative to the placebo group (mean between-group difference 31 m) [127]; while another trial reported no beneficial effect on physical performance in older subjects receiving an ACE inhibitor for 6 months [128]. A combined study of leucine and ACE inhibitors as therapy for sarcopenia (LACE trial) is underway [129].

Discussion

A review of the current literature shows that while data is accumulating for the existence of osteosarcopenic obesity as a distinct entity a number of questions remain, not least the clinical relevance of identification of such a condition. A progressive loss of bone and muscle mass and increase in adipose tissue occurs with normal aging. Thus, identification of the epidemiological overlap of osteoporosis, sarcopenia, and obesity is perhaps not surprising given the common risk factors and increasing prevalence of these conditions in older age. Evidence for the pathophysiological overlap of these conditions is expanding, which may occur through an interplay of inflammatory and hormonal mechanisms. However, a causal relationship between the osteosarcopenic obesity components is yet to be identified, and more comprehensive research to understand the underlying biological phenomena linking the three conditions is needed.

Whether osteosarcopenic obesity should be distinguished as a distinct condition, separate from osteosarcopenia or sarcopenic obesity remains to be determined. Additional studies should assess whether the clinical outcomes associated with osteosarcopenic obesity are worse than the mere addition of those linked with its components. Consequently, this will help to determine whether defining a person as having this triad will result in better treatment and outcomes than addressing each of the three conditions separately.

In conclusion, we consider that there is insufficient evidence to support a discrete clinical entity of osteosarcopenic obesity at this time. To expand knowledge and understanding in this area, there is a need for consensus on a definition of osteosarcopenic obesity, which will allow for identification, further epidemiological studies and comparisons between studies. A critical first step in this process requires further research to standardise the operational definition of osteosarcopenic obesity components (sarcopenia and obesity). Furthermore, research is needed to confirm or reject the

hypothesis that the identification of osteosarcopenic obesity adds anything to the concept of osteosarcopenia plus obesity, in terms of clinical outcomes and therapeutic guidelines.

Authors' Contributions The views expressed in this article represent the outcomes of a Working Group jointly organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the World Health Organization Collaborating Center for Public Health Aspects of Musculoskeletal Health and Aging, Liège, Belgium, and held in Zurich, Switzerland, on January 16th, 2018. The working group comprised a global representation of clinicians and researchers with different specialties invited for their expertise and knowledge regarding osteoporosis, sarcopenia, and obesity: Jürgen Bauer, Cyrus Cooper, Alfonso Cruz-Jentoft, Roger Fielding, John Kanis, Jean-Yves Reginster, Olivier Bruyère, Matteo Cesari, Roland Chapurlat, Nasser Al-Daghri, Elaine Dennison, Jean-Marc Kaufman, Francesco Landi, Andrea Laslop, Médéa Locquet, Stefania Maggi, Eugene McCloskey, Simone Perna, René Rizzoli, Yves Rolland, Mariangela Rondanelli, Pawel Szulc, Bruno Vellas, and Mila Vlaskovska. Selected members of the working group (JYR, RF, JMK, SM, ED, SP, PW, FL, JB) conducted literature searches and exchanged peer-review publications with the full working group in advance of the meeting, and presented their assessment of the available data to colleagues at the meeting (including: CC, ACJ, JK, OB, RC, JMK, FL, AL, ML, SM, EMC, SP, RR, YR, PS, BV, MV). Agreement on the principles outlined in this article were based on an exchange of views and discussion of the working group during the 1-day interactive meeting. Following the meeting, members of the writing group (JB, RF, JK, CC, ACJ, JYR) prepared a first draft of this manuscript, which was circulated to all working group members for review and input, including those who had been unable to attend the meeting (MC, NAD, MR). Following two rounds of review and comment from all 24 working group members, the final manuscript was submitted. All authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

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