Current Osteoporosis Reports (2020) 18:81–84
https://doi.org/10.1007/s11914-020-00567-6

INVITED COMMENTARY

Osteosarcopenia: the Path Beyond Controversy

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Published online: 4 March 2020

Abstract

Purpose of Review Osteosarcopenia is commonly accepted as the presence of low muscle mass and function (sarcopenia) and low bone mineral density (osteopenia and osteoporosis). Osteosarcopenia remains a topic of controversy as researchers worldwide seek to elucidate whether osteosarcopenia is associated with greater risk of negative outcomes than its component parts. This review examines the latest research and controversies, and charts a path forward.

Recent Findings Osteosarcopenia may occur in 5–37% of community-dwelling adults over the age of 65. This wide range is driven by variation in population, setting, and definitions applied. These differences in study design have resulted in mixed findings in associations with adverse outcomes for older adults living with osteosarcopenia. Research into interventions to prevent or treat osteosarcopenia, such as exercise, protein supplementation, and pharmacotherapy, is in its infancy but examined herein.

Summary The absence of a consensus operational definition of sarcopenia, and inaccurate measures of muscle mass, has hampered global progress in the field. We present a case for the path forward by reflecting on our recent history.

Keywords Osteosarcopenia · Osteoporosis · Sarcopenia · Aging · Musculoskeletal

Background

Osteosarcopenia is commonly accepted as the presence of low muscle mass and function (sarcopenia) and low bone mineral density (BMD; osteopenia/osteoporosis) [1–4]. This combined condition has garnered significant attention in recent years due to growing evidence of important interactions between muscle and bone [5]. However, vibrant debate continues as to whether osteosarcopenia poses a greater risk of negative outcomes such as falls, fractures, and mortality than the sum of its component parts [3, 4]. Understanding the controversies embedded in the research first requires an examination of the way in which low BMD, sarcopenia, and "low muscle mass" are defined in competing literature.

The establishment of a universally accepted definition of osteoporosis occurred over a quarter of a century ago [6]. Osteopenia was defined as a T score of ≤ -1 standard deviation (SD) below the mean BMD of the sex-adjusted reference population. Osteoporosis was defined as a T score of ≤ -2.5 or the presence of a minimal trauma fracture [6]. Subsequent validation studies across global populations have enhanced accuracy in fracture prediction, further augmented by fracture-risk prediction tools such as the FRAX© [7]. The debate preceding the establishment of a universal definition of osteoporosis has been compared to the present climate in sarcopenia research [8].

In contrast, despite the proposal of multiple consensus-based [9–13] and data-driven definitions [14] since sarcopenia's inception in 1989 [15], a universal definition for sarcopenia remains elusive [16]. Sarcopenia is distinct from cachexia, which is defined as a loss of lean tissue mass involving $\geq 5\%$ body weight loss within 12 months, or a body mass index < 20 kg/m^2, in the presence of a chronic illness such as cancer [17]. The current definition of cachexia does not consider bone loss as part of the syndrome. Different measures of muscle strength (i.e., grip strength), physical

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performance (i.e., walk speed), and muscle mass, including operational cutpoints for "low" or "normal," have been proposed based on the temporality and choice of data informing those definitions. Furthermore, what constitutes "muscle mass" has more recently emerged as a contentious point [16, 18]. Commonly used tools such as Dual-Energy X-Ray Absorptiometry (DXA) and Bioimpedance Analysis (BIA) generate approximations of muscle mass; these techniques estimate lean mass and fat-free mass respectively, not muscle mass. In addition to DXA-estimated Appendicular Lean Mass (ALM) and BIA-estimated fat-free mass, the revised European Working Group on Sarcopenia in Older People (EWGSOP2) also include Computerized Tomography and Magnetic Resonance Imaging as options to approximate muscle mass [10], however, feasibility in clinical practice remains under investigation [19]. Evans et al. argued that incorrect terminology regarding lean- and fat-free mass in longitudinal studies has resulted in the incorrect assumption that low *muscle mass* has weak or no association with adverse outcomes in older adults [19, 20]. Consistency in terminology as posited by Cawthon [16] is key in advancing the sarcopenia field towards consensus and understanding the true impact of low muscle mass on adverse outcomes.

Until these debates are resolved, when assessing persons for osteosarcopenia, we advocate for the approach advised in recent consensus clinical practice guidelines which recommend the application of any of the accepted definitions to diagnose sarcopenia [21], in addition to applying the diagnostic criteria for osteoporosis/osteopenia [6].

There is growing appreciation of the shared putative mechanisms leading to disease of muscle and bone [5]. With normal aging, body composition and tissue distribution alterations result in progressive loss of bone and muscle mass, and an increase in intra- and intermuscular adipose tissue [22]. Knowledge of the underlying mechanical, genetic [23], biochemical, and metabolic links between pathology of muscle, bone, and fat, [5] is in its infancy, but growing. Possible mechanisms for the development of osteosarcopenia may involve an interplay of hormonal (anabolic, adrenal hormones, insulin, adipokines, and myokines), nutritional, genetic, and lifestyle factors [5]. These pathophysiological pathways are current and potential future targets for interventions that may simultaneously treat mechanisms driving disease of muscle and bone.

Assessment of older or at-risk adults for osteosarcopenia can be easily achieved in most research and clinical settings. We have previously argued that an assessment for osteosarcopenia should form part of any comprehensive geriatric assessment, which includes a multifaceted falls risk assessment [24]. Current management should involve the optimization of comorbidities and modifiable risk factors for falls and interventions targeting muscle and bone. Recommended interventions include a structured exercise program (particularly progressive resistance training), nutritional support (protein supplementation, dietary calcium), vitamin D and calcium (if inadequate dietary intake) supplementation [21], and treatment of osteoporosis where indicated (anabolic or antiresorptive therapies) [24].

Burden, Effect, and Controversy

The prevalence of osteosarcopenia is dependent upon the population being examined and the definition applied. A recent meta-analysis [25] revealed 17 studies that examined prevalence and outcomes related to osteosarcopenia in hospitalized and community-dwelling older adults. Studies used a variety of methods to define sarcopenia [9, 11, 12, 14], osteopenia or osteoporosis (the presence of fracture, or low BMD, or both). The prevalence of osteosarcopenia was estimated to be between 5 and 37% [25]. Interpretation of these findings is somewhat problematic in that included studies were heterogenous in design, participants, and most importantly, the definitions applied.

The key adverse outcomes for older adults with osteosarcopenia are falls, fractures, and mortality. The same meta-analysis demonstrated that those with sarcopenia had a greater relative risk (RR) of fracture than those without sarcopenia (RR 1.37, 95% CI 1.18–1.59; $p < .05$), and femoral neck BMD was also significantly lower in sarcopenic versus non-sarcopenic older adults [25]. However, two subsequent studies not included in this meta-analysis did not reveal an association of osteosarcopenia with falls, fractures, or mortality beyond their component parts [3, 26]. These studies examined different groups of older men in Australia, one of which did not apply current definitions of sarcopenia [26], and both called into question the value of osteosarcopenia as a distinct entity [3, 26].

In contrast, a recent study on community-dwelling older adults attending a falls and fracture clinic found strong associations with falls and fractures when applying the revised European Working Group on Sarcopenia in Older People (EWGSOP2) definition [27]. This effect was increased when DXA-ALM was removed from the definition of sarcopenia [27], which likely reflects the challenges in accurate determination of muscle mass rather than an absent effect of low muscle mass on negative outcomes.

Back to the Future

Recent research examining the role of a direct measure of muscle mass – the D_3 creatine dilution method (D_3Cr muscle mass) – is having a game-changing effect on our understanding of the impact of low muscle mass on negative outcomes [18, 28]. In longitudinal studies of older men, low D_3Cr muscle mass has shown strong relation with falls [29], fractures [30], and mortality [31] risk. These striking findings in older

men with low D_3Cr muscle mass contrasts the mixed associations of DXA ALM with the same outcomes [20], and demands that we reflect on the original concept of sarcopenia proposed by Rosenberg 30 years ago [15]; "no decline with age is more dramatic or potentially more functionally significant than the decline in lean body mass…perhaps it deserves a name from the Greek."

There is great appeal from a practical and clinical perspective at the prospect of treating disorders of muscle bone simultaneously. It is therefore unsurprising that osteosarcopenia has received attention from pharmaceutical companies globally. Current targets of interest include the myostatin, androgen, fatty acid synthesis, and receptor activator of nuclear kB (RANK) pathways.

Myostatin is an important factor in the regulation of muscle and bone. The myostatin decoy receptor, $ACVR_2B\text{-}F_c$, has been shown to increase lean body mass and bone formation [32]. However, myostatin is expressed in cardiac tissue and concerns remain as to its safety profile. Clinical studies using Selective Androgen Receptor Modulators (SARMs) have demonstrated an increase in muscle mass and strength in hypogonadal men and post-menopausal women [33]. One trial has been undertaken on women over 65 years with sarcopenia. No difference was observed between treatment groups in terms of strength and physical performance measures [34]. Denosumab, a RANK ligand inhibitor, is a commonly used anti-resorptive for treatment of osteoporosis. A recent trial delivered either denosumab or a bisphosphonate to women with osteosarcopenia [35]. Those treated with denosumab had increased ALM and handgrip strength, but no change was observed in those treated with bisphosphonates [35]. These are exciting findings that may have wide and significant implications for those living with osteosarcopenia. Further research is required to determine whether alteration of the myostatin, androgen, or RANK pathways reduce the risk of falls, fractures, and mortality in older adults with or at-risk of developing osteosarcopenia.

Resistance to change is an inherent human characteristic. In the history of both osteoporosis and sarcopenia, great resistance has preceded acceptance. Criticism of whether osteosarcopenia is an independent entity posing greater risk of falls, fractures, and mortality than its component parts are the necessary course to truth. In addition, attempts to link osteosarcopenia with obesity, which is unrelated to intra- and inter-muscular and marrow fat [36], have created additional confusion [4]. Accurate measures of muscle mass coupled with a consensus on the operational definition of sarcopenia will bring us closer to judicious acceptance or rejection of osteosarcopenia as a distinct entity. At present, the prospect of a unique pathophysiological mechanism and possible treatment for osteosarcopenia remains possible, appealing, and unanswered.

Compliance with Ethical Standards

Conflict of Interest Jesse Zanker and Gustavo Duque declare no conflict of interest. Dr. Duque is a Section Editor for Current Osteoporosis Reports. Thank you to David Burr, Andrea Bonetto, and Marco Brotto for reviewing this piece.

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

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