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## ASSESSMENT OF BONE HEALTH

# Sarcopenia and Osteoporotic Fractures

Itamar Levinger[1,2] · Steven Phu[1,3] · Gustavo Duque[1,3]

**Abstract** Low bone mass is strongly associated with increased fracture risk. However, the importance of low muscle mass and strength—known as sarcopenia—as a risk factor for osteoporotic fractures remains overlooked and sometimes controversial. Bone and muscle are closely interconnected not only anatomically, but also physically, chemically and metabolically. Indeed, a significant proportion of individuals with sarcopenia also suffer from osteopenia/osteoporosis suggesting a link between the two tissues. This subgroup of osteosarcopenic individuals are at higher risk of falls and fractures. Therefore, we suggest that lean mass and muscle strength/function assessments should be an integral part in any fracture prevention protocol. A combination of lean mass quantification by dual-energy X-ray absorptiometry scan and assessment of muscle function by gait velocity could not only confirm the diagnosis of sarcopenia but also optimize any fracture prevention interventions. In the absence of specific therapies for sarcopenia, simple interventions such as resistance (weight-bearing) training, protein supplements and appropriate levels of vitamin D have a dual effect on bone and muscle and could have a significant effect on reducing falls and fractures in this high-risk population.

**Keywords** Osteoporosis · Sarcopenia · Osteosarcopenia · Fractures · Falls · Elderly

## Introduction

The annual loss of muscle mass with aging is between 1 and 2 % per year after the age of 50 years [1, 2]. In the case of bone, a similar decline occurs from the third decade of life, being more severe during the menopause years in women. When the age-related decline in bone mass is more than 2 % per year, the bone becomes brittle and prone to fracture, thus fulfilling the diagnostic criteria for osteoporosis [3]. In the muscle, age-related changes could be aggravated by other factors (i.e., disuse, hypogonadism, malnutrition, etc.) that affect not only muscle mass but also muscle function and strength, which fulfill the diagnostic criteria for sarcopenia [1, 2, 4].

Bone and muscle are closely interconnected not only physically but also chemically and metabolically. This connection is important because muscle mass closely correlates with bone mass and any concurrent decrease in both tissues is associated with higher risk of falls and fractures [5]. The mechanisms that explain the synchronic loss of bone and muscle mass are multiple: (1) low muscle mass is associated with abnormal glucose metabolism and changes in muscle-related proteins, known as myokines, which have a direct effect on bone metabolism [6]; (2) decreased muscle strength and physical performance is associated with low mechanical loading, thus directly affecting bone mass [3]; (3) sarcopenic individuals are at higher risk of falls, which also predispose to fractures.

✉ Gustavo Duque
gustavo.duque@unimelb.edu.au

1   Australian Institute for Musculoskeletal Science (AIMSS), Western Health and University of Melbourne, 176 Furlong Road, St. Albans, VIC, Australia

2   Clinical Exercise Science Research Program, Institute of Sport, Exercise and Active Living (ISEAL), College of Sport and Exercise Science, Victoria University, Melbourne, VIC, Australia

3   Department of Medicine, Melbourne Medical School – Western Campus, The University of Melbourne, St. Albans, VIC, Australia

From the diagnostic perspective, sarcopenia and osteoporosis could be simultaneously assessed by dual-energy X-ray absorptiometry (DXA) looking at muscle—using lean mass as a surrogate—and bone mineral density (BMD), respectively. In the case of sarcopenia, muscle (lean) mass assessment should be complemented with other clinical variables such as gait velocity and grip strength. Although there is a consensus that DXA is an accurate method to quantify muscle mass, there is still controversy regarding the clinical diagnostic criteria for sarcopenia [7–9].

In addition, since sarcopenia and osteoporosis are closely linked, the term osteosarcopenia has been proposed to describe a subset of frailer individuals suffering from both sarcopenia and osteopenia/osteoporosis and at higher risk of institutionalization, falls and fractures [10, 11]. Based on the particular clinical characteristics and poor outcomes observed in individuals with osteosarcopenia, sarcopenia should be included as a critical indicator of higher fracture risk. Therefore, limiting fracture risk assessment to BMD and bone-related risk factors without taking into consideration the presence of sarcopenia could overlook a significant proportion of individuals that, despite having normal BMD or no bone-related risk factors, are still at a high fracture risk.

From the therapeutic perspective, the presence of sarcopenia would also have a significant role in response to fracture prevention strategies. Although current drugs for osteoporosis have no effect on muscle mass, and considering that there are no current pharmacological approaches to sarcopenia, interventions that are known to improve sarcopenia, such as exercise and protein supplements, could also have an effect on bone mass and should be encouraged in osteosarcopenic patients. In this review, we will highlight the clinical relevance of sarcopenia in terms of fracture risk assessment. Initially, we will summarize new knowledge on bone and muscle communication. We will then review the clinical characteristics and recently described syndromes that involve sarcopenia as their key clinical feature. Finally, we will suggest a clinical pathway to diagnose osteosarcopenia, which we expect would facilitate clinical decisions in this particular high-risk population.

## The Muscle and Bone Interface

Until recently, bones and muscles were perceived to function independently despite the fact that both are part of the musculoskeletal system. In recent years, however, great interest was placed on the relationship and the cross talk between bone and muscle as sarcopenia and osteoporosis have become more prevalent due to the aging population.

There are many factors affecting both muscle and bone, which may indicate a close relationship between the two tissues (Fig. 1). Recent review papers describe in detail the potential factors affecting both bone and muscle [6, 12]. As such, in this review we will briefly discuss the effects of aging, mechanical loading exercise and unloading (bed rest/disuse) and the interaction between osteocalcin, a marker of bone formation and skeletal muscle.

## Aging

Both sarcopenia and a reduction in aerobic capacity are part of the normal aging process [13–15]. Between the second and the seventh decades of life, there is a 30 % reduction in muscle strength, a 25–40 % reduction in muscle mass and muscle cross-sectional area, and also 8–10 % reduction in maximal aerobic capacity each decade [16–18]. In addition, between the third and seventh decades, there is around 30 % reduction in bone mass [19]. These changes in both muscle and bone occur in healthy individuals but are accelerated in those with chronic disease or in the presence of specific risk factors. It is not yet clear why aging has such a profound effect on these two tissues, even in individuals who maintain an active lifestyle. However, it appears that increased low level of systemic and local inflammatory markers, including mitogen activated protein kinases (MAPK), nuclear factor kappa-B (NF-κB), c-Jun N-terminal kinases (JNK) and the signal transducer and activator of transcription (STAT),
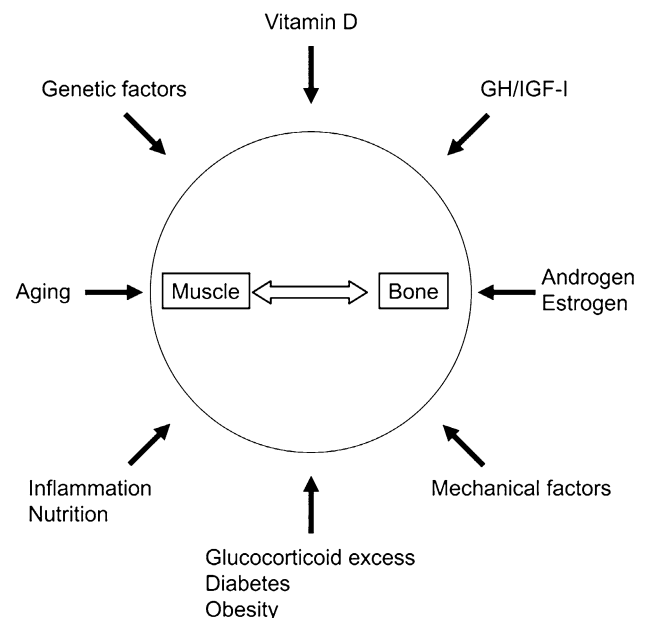


**Fig. 1** Factors affecting the interactions between muscle and bone. GH/IGF-I, growth hormone-/insulin-like growth factor-I. Adapted from Kawao et al. [6]

tumor necrosis factor (TNFα), interleukin (IL)-6, IL8, IL-1β and monocyte chemotactic protein-1 (MCP1), are involved in the development of sarcopenia, osteoporosis and other chronic diseases in older adults [20–22]. The increase in inflammatory markers may shift the delicate balance between protein synthesis and degradation in muscle and bone formation and resorption in bone in favor of degradation (muscle)/resorption (bone) leading to sarcopenia and bone loss [21].

## Mechanical Loading and Unloading

The musculoskeletal system is a mechanosensing system. It can sense a change in individual load (body mass) or other forms of loading/stress (such as exercise) or unloading (microgravity, bed rest and disuse). Bone and muscle have the ability to adapt to mechanical loading by modifying their mass and strength [23]. There is a similarity between the alteration of skeletal muscle and bone due to aging that is caused by deconditioning and disuse [14, 24, 25]. For instance, it has been reported that 4–14.4 months of microgravity environment (Mir space station) resulted in a decrease (range 0.35–1.56 % per month) in BMD as well as a reduction in leg lean mass (1 % per month) [26]. This decline was observed despite an "extensive exercise countermeasure program." Similarly, a significant reduction in muscle mass and strength and BMD was reported following bed rest [27, 28].

As was described previously by Isaacson and Brotto [12], mechanical stimulus is essential for both muscle and bone health. In contrast to the decline in muscle and bone mass in response to inactivity, mechanical loading (especially resistance and weight-bearing exercises), increases muscle mass and strength and has the potential to improve BMD [29]. It is possible that muscle contraction in response to a mechanical loading, as occurs during resistance exercise, increases strain on bone, which, in turn, stimulates bone formation. Indeed, there is a correlation between muscle and bone strength [3]. However, it is important to note that not all studies that reported an increase in muscle mass and muscle strength following resistance training also reported an increase in BMD [29]. In fact, there are conflicting data in regard to the ability of exercise training to modify bone mass [30]. For instance, McCartney et al. [31] reported that 42 weeks of progressive resistance training resulted in 5.5 % increase in the knee extensors cross-sectional areas and 65 % increase in muscle strength with no change in BMD. These data may suggest that the interaction between muscle and bone is more complicated and perhaps involves other factors than mechanical loading/stress alone. It may also suggest that muscle and bone require different exercise intensities and duration to elicit structural changes in both tissues. Indeed,

muscle hypertrophy can be visible within several weeks of resistance training whereas changes in BMD may be present in exercise intervention that is greater than 6–12 months.

## Osteocalcin and Skeletal Muscle

Both muscle and bone are now recognized as endocrine organs with both playing a role in glycemic control [32–35]. There is increasing evidence that osteocalcin (OC), a marker of bone formation [36], in its undercarboxylated form (ucOC) stimulates β-cell proliferation and insulin secretion and ucOC-deficient mice are obese and glucose intolerant [33]. In humans, ucOC and OC are also correlated with insulin sensitivity, fasting glucose, fat mass and muscle strength [37–40]. There is also increased evidence that the ucOC acts directly on skeletal muscle. Recently, we [41] and others [42] demonstrated that ucOC improves insulin-stimulated glucose uptake in C2C12 myotubes. Furthermore, ucOC treatment improves muscle (EDL) insulin-stimulated glucose uptake following an ex vivo muscle contraction [41]. The ucOC treatment promoted insulin-induced Akt phosphorylation. In humans, it has been reported that high-intensity exercise increased ucOC as well as p-AKT and p-AS160 [34]. Both p-AKT and p-AS160 are downstream proteins in the PI3-K pathway regulating GLUT-4 translocation and as such are important for muscle glucose uptake capacity [43, 44].

It is important to note that the area of bone–muscle interaction is relatively new, and many of the mechanisms involved in the "cross talk" between bone and muscle are not yet well understood. It is possible that the "cross talk" between bone and muscle is bidirectional and factors that are released by muscle, especially during muscle contraction, can act on bone and vice versa (Fig. 2) [6].

## Sarcopenia, Osteosarcopenia and Sarcopenic Obesity: Definition and Clinical Differences

### Sarcopenia

As previously described, sarcopenia is a disease in which there is a gradual, generalized loss of muscle mass associated with the aging process and aggravated by the presence of other risk factors. In the clinical setting, sarcopenia has been defined as having an appendicular skeletal mass (ASM) divided by height in meters squared which was two standard deviations below that of a young healthy adult as assessed by DXA [45]. There is a consensus that this loss of muscle mass is typically combined with decline in muscle strength and/or physical function [4]. The assessment of muscular strength via handgrip dynamometer is
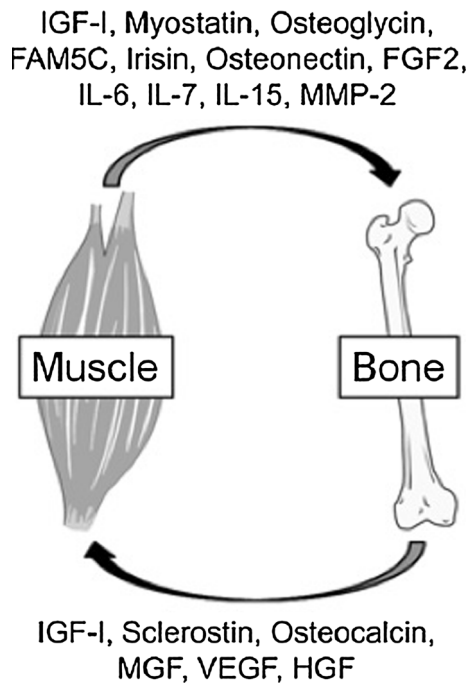
## IGF-I, Myostatin, Osteoglycin, FAM5C, Irisin, Osteonectin, FGF2, IL-6, IL-7, IL-15, MMP-2

**Muscle** **Bone**

## IGF-I, Sclerostin, Osteocalcin, MGF, VEGF, HGF

**Fig. 2** Humoral factors linking muscle to bone. FGF2, fibroblast growth factor 2; FAM5C, family with sequence similarity 5, member, C; IL, interleukin; MMP-2, matrix metalloproteinase-2; MGF, mechanogrowth factor; VEGF, vascular endothelial growth factor; HGF, hepatocyte growth factor. Adapted from Kawao et al. [6]

commonly performed and has been described as an easily conducted measure, with a correlation between upper and lower body strength, highlighting the generalized loss of muscle in sarcopenia [2]. Decline in physical performance and function is another defining component of sarcopenia and can be assessed with a simple measure of gait velocity [9].

### Osteosarcopenia

As previously described, older adults who present with both osteopenia/osteoporosis and sarcopenia are termed as being osteosarcopenic, or sarco-osteopenic/sarco-osteoporotic [46, 47].

In addition to the previously mentioned criteria for sarcopenia, individuals with osteosarcopenia will also present with low BMD (osteopenic or osteoporotic) as measured by DXA [46]. These individuals are at higher risk of falls and fractures than sarcopenic individuals [11] and have particular nutritional and physical phenotypes [11, 48].

### Sarcopenic Obesity

Sarcopenic obesity refers to the combination of excess body weight (obesity) and sarcopenia [49]. The development of obesity can be associated with a variety of factors including a lack of physical activity, poor diet and age-related hormonal and metabolic changes [50–52]. Therefore, in addition to the loss of muscle mass, those diagnosed with sarcopenic obesity will also present with excess weight with waist circumference as a measure of the obesity level [50, 51]. Recently, the term osteosarcopenic obesity was introduced to describe those overweight individuals also suffering from osteosarcopenia [49, 53]. Although the specific differences between osteosarcopenic obese and non-obese remain unknown, specific abnormalities in vitamin D levels have been reported in this particular subpopulation, which may increase their risk of falls and fractures [54].

### Clinical Outcomes Associated with Sarcopenic Syndromes

Sarcopenia is prevalent in older adults. It is estimated that more than 50 % of the people over the age of 80 years suffer from sarcopenia [55]. Sarcopenia has major clinical, functional and psychological consequences [55], and in combination with the prevalence of the condition, it places vast personal and financial cost on individuals and the community.

In addition to increased risk of falls and fractures, other clinical and functional consequences of sarcopenia include: inability to sustain muscular power and endurance, and a reduction in the capacity to perform activities of daily living [56]. Low muscle mass and strength may also lead to postural and mobility problems and increased fall risk [57]. Ultimately, it can lead to a reduced quality of life and premature mortality [55]. In addition, muscle is a major site for glucose disposal; as such, a reduction in muscle mass may have some other clinical consequences including increased risk of insulin resistance and type 2 diabetes [58]. As such, the ability to maintain and increase muscle mass and strength, particularly via weight-bearing (resistance) exercises, is crucial to minimizing the effects of sarcopenia on physical performance and fall risk [59].

### How to Predict Fractures in Sarcopenic Patients?

Although the evidence linking sarcopenia and osteoporotic fractures is controversial [60], in this review we have provided a rationale to include sarcopenia within any fracture risk assessment protocol, which is supported by the recent literature. A recent review by Oliveira and Raz [60] concluded that there is strong evidence on the association between sarcopenia, osteoporosis and hip fracture, with most authors considering that sarcopenia is a predictor of

fracture risk in the elderly and provides incremental predictive value if integrated with BMD and other risk factors. However, the question remains on how to integrate sarcopenia assessment within a fracture risk assessment protocol. Although there are very few studies looking at this question, most of the existing data suggest that DXA is an accurate method to quantify muscle (lean) mass [61].

Since many DXA machines include body composition analysis, and considering the clinical benefits of identifying sarcopenia in older persons, this additional investigation could be useful as a routine test when performing DXA analyses allowing the diagnosis of both sarcopenia and osteopenia/osteoporosis with one imaging modality.

Current consensus statements on sarcopenia state that the clinical diagnosis requires both a low muscle (lean) mass as well as decreased muscle function and/or strength [4, 9]. Once a low muscle (lean) mass is documented by DXA, it should be correlated with at least one clinical indicator of muscle function and/or strength. In clinical practice, gait velocity is a simple method to assess muscle function and identify sarcopenia. A recent study performed in a population of older fallers [48] found that the subgroup of osteosarcopenic individuals (individuals fulfilling the clinical and DXA criteria for sarcopenia and osteopenia/osteoporosis) had both slow gait velocity and lower BMD, thus suggesting that gait velocity is not only a useful diagnostic method for sarcopenia but also a strong predictor of poor outcomes (including low BMD and fractures) in this high-risk population. In terms of other function/strength parameters to diagnose sarcopenia, knee extension and grip strength positively associate with BMD [61] but require a higher level of expertise in order to be accurately measured.

In conclusion, although there is limited evidence on sarcopenia as a predictor of osteoporotic fractures, it is well known that sarcopenia and osteoporosis are closely linked and that osteosarcopenic individuals are at higher risk of falls and fractures. Therefore, sarcopenia should be included as an important risk factor for osteoporosis and fractures that is easy to diagnose and that can be considered as an additional therapeutic target when developing fracture prevention strategies.

## Conclusion

Muscle and bone are closely linked from the mechanic to the metabolic perspective. Therefore, any fracture prevention approach should also include assessment of muscle mass, strength and function. In the absence of specific medications for sarcopenia, there are other interventions that have demonstrated to be effective. These interventions include resistance training, appropriate vitamin D levels

and protein supplements [5]. In conclusion, when assessing fracture risk, the clinician should always consider the possibility that sarcopenia is also present. Simple interventions could have a direct effect on muscle mass, thus reducing the risk of falls and fractures in this particular high-risk population.

**Compliance with Ethical Standards**

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