Osteosarcopenia: A Geriatric Giant of the XXI Century

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In the second half of the XX century, Bernard Isaacs coined the term «geriatric giants»: immobility, instability, incontinence, and impaired intellect/memory (1). He considered them as «giants» because of «their high statistical frequency in older persons and the huge personal burden of sufferers, escalating the need for socio-medical interventions.» Since then, lots of research has been dedicated to understanding and treat those giants, especially dementia (impaired intellect/memory), where the development of a biomarker or an effective treatment has remained elusive. Nevertheless, geriatricians have adopted these giants as the main targets in their clinical practice. However, other diseases that are equally highly prevalent in older persons affecting their functional independence, and reducing their quality of life (QoL) and survival have not received the same recognition and priority in geriatrics practice. This is the case of osteoporosis and sarcopenia, which are not being widely integrated in medical training programs and clinical practice despite being characterized in the second half of the XX century. Even with a large amount of evidence, clear diagnostic criteria, and high effectiveness of current treatments, osteoporosis remains underdiagnosed and undertreated (2). On the other hand, sarcopenia was introduced in 1988 (3), and a new ICD-10-CM (M62.84) code in September 2016 represented a significant step forward in recognizing sarcopenia as a disease (4). However, and despite its clinical significance, as with osteoporosis, integrating sarcopenia in clinical practice remains challenging (5).

In 2009, in their pivotal editorial, Binkley and Buehring proposed the term «sarco-osteopenia» to describe a subset of frailer older individuals with both osteopenia/osteoporosis and sarcopenia, and that could be at a higher risk of falls, fractures, frailty and mortality (6). Since then, the term has evolved into «osteosarcopenia» and is generating growing interest from multiple angles and by several research groups worldwide (7). Together, skeletal muscle and bones constitute 55% of a healthy person's body mass, provide postural stability and facilitate movement. Interestingly, new knowledge has demonstrated that the muscle/bone interaction is significantly more complex than portrayed by traditional siloed approaches that have focused on and studied these organs separately while limiting their interaction to primarily mechanical. We now understand that, in addition to their anatomical connections, muscles and bones communicate via hormonal and biochemical messengers (8).

Importantly, these biochemical interactions and endocrine roles affect other organs and systems; thus, alterations in bone and muscle mass and function have clinical consequences that go far beyond the musculoskeletal system (9).

Some questioners of the term osteosarcopenia have referred to the multiple cross-talks between organs and systems that could be equally affected by disease. Indeed, although «cardiosarcopenia» could be observed in heart failure, or «thyrosteoporosis» could occur in hyper or hypothyroidism, there are multiple reasons to propose osteosarcopenia as a separate entity, consequence of shared pathophysiology, with common clinical outcomes and potential combined therapeutic targets. Importantly, no two tissues in the body show a similar decline in their structure and function under aging and pathological conditions as bone and muscle do. For instance, immobility (one of the geriatric giants) is rapidly associated with a decline in both tissues, thus predisposing to adverse outcomes (i.e. falls, disability), which prevents an effective response to rehabilitation (10).

Regarding its pathophysiology, osteosarcopenia is the consequence of multi-directional abnormalities in the bone muscle cross-talk and local changes that have been fully summarized elsewhere (11), and that could be closely associated with the geroscience model (12), in which several age-related diseases share similar pathophysiological mechanisms. Interestingly, fat has become a third player in the pathophysiology of osteosarcopenia (13), not necessarily because of the presence of obesity, but because of the increasing levels of fat infiltration that are observed inside the bone marrow in osteoporotic bone and the dramatic levels of intramuscular fat infiltration observed in sarcopenic muscle (13). These high levels of fat infiltration, which are independent of the subject body mass index, are known to be lipotoxic, affecting the function and structure of the local tissues (14). Whether high levels of fat infiltration could be used as a diagnostic or therapeutic tool for osteosarcopenia remains unknown but offers a novel and exciting approach that deserves further exploration.

A major source of confusion in the field comes from a specific clinical phenotype and adverse outcomes associated with osteosarcopenia (15). Being a geriatric syndrome (giant) and not a specific disease, osteosarcopenia is considered as the combined presence of osteopenia/osteoporosis and sarcopenia in the same patient, which is expected to predispose them to adverse outcomes such as falls, fractures, frailty, disability,

Figure 1. Osteosarcopenia renders older people significantly more vulnerable to adverse outcomes. A single fall or fracture markedly increases the risk of future events. Fear of falling and injury then erodes physical confidence, swiftly followed by compromised mobility, independence, and overall wellbeing

reduced QoL, and increased mortality. However, exploring this association has been challenging due to the original design of multiple clinical studies in the field, which did not include clear criteria for osteosarcopenia or used a potpourri of sarcopenia definitions (16, 17). Nevertheless, recent studies have attempted to investigate the existence of a specific osteosarcopenia phenotype and its association with adverse outcomes in older persons. Regarding prevalence, it ranges between 5–37% in community-dwelling older adults, with the highest rates observed in those with fractures (7). Risk factors associated with osteosarcopenia include older age, sex [men: 14.3% (60–64yrs) to 59.4% (≥ 75 yrs); women: 20.3% (60–64yrs) to 48.3% (≥ 75 yrs)], physical inactivity, and low BMI (7, 18). Among 148 geriatric inpatients, osteosarcopenic individuals demonstrate poorer nutritional status versus osteoporosis or sarcopenia alone (19). Interestingly, osteosarcopenia was also highly prevalent in older subjects with high serum levels of parathyroid hormone in the absence of vitamin D deficiency or renal failure (20).

By simply defining osteosarcopenia as the combination of sarcopenia (independently of the definition used) and osteopenia/osteoporosis (defined using densitometry criteria), several teams have demonstrated that osteosarcopenic patients are at a higher risk of adverse outcomes (21–24). In 253 older subjects (77% women; aged 77.9 ± 0.42 years) assessed at our Falls and Fractures Clinic (Western Health, Melbourne), we found that osteosarcopenia was associated with worse function and balance. Additionally, the presence of severe sarcopenia in osteosarcopenic patients conferred an increased rate of falls [odds ratios (ORs) from 2.83 to 3.63; $P < .05$ for all] and fractures (ORs from 3.86 to 4.38; $P < .05$ for all) when employing the European Working Group on Sarcopenia in

Older People (EWGSOP2) and Foundation for the National Institutes of Health (FNIH) definitions, respectively (22). Furthermore, in a Chilean cohort of 1119 participants (68.5% female; mean age 72 years), Salech et al. (23) reported that osteosarcopenia was a predictor of falls, fractures, and mortality in this population. High levels of mortality in osteosarcopenic subjects were also observed in the Geelong Osteoporosis Study (24). Overall, the evidence on the association between osteosarcopenia and a higher risk of adverse outcomes when compared to osteoporosis or sarcopenia alone is growing. This could induce osteosarcopenic subjects to enter into a dynamic vicious cycle that could result in frailty, disability, institutionalization, and premature death (Figure 1).

However, some authors expect this augmented risk of adverse outcomes to be the result of one plus one equal two. In the case of osteosarcopenia, this is not as simple because here we are describing a syndrome composed of two diseases sharing a common pathophysiology and risk factors and simultaneously occurring in the same subject, thus the presence of osteosarcopenia and the physiological disturbances generated by this syndrome could lead to new equations that could also have cardiometabolic implications. This intriguing hypothesis could only be tested by designing studies that specifically look at osteosarcopenia using a highly needed standardized definition for sarcopenia without excluding osteopenic subjects; a population that represents 50% of minimal trauma fractures, which could be precipitated by the simultaneous presence of sarcopenia (22).

Regarding biomarkers and treatments for osteosarcopenia, the current evidence is limited mainly to non-pharmacological interventions (25, 26). Nevertheless, the growing understanding

of the pathophysiology and clinical phenotype of this syndrome has generated a variety of approaches that have involved geroscience-related strategies (12). New knowledge on the role of stem cells in the pathophysiology of this syndrome has allowed us and others to propose quantification and/or characterization of these cells (which are common precursors of muscle and bone) as a new diagnostic and therapeutic approach to osteosarcopenia (27, 28). Also, the associations between hormones such as sex steroids or vitamin D and osteosarcopenia have opened new potential diagnostic and therapeutic approaches to this condition (20, 29-31). Specifically for treatment, having a drug with a dual therapeutic effect on bone and muscle would constitute a significant advancement in geriatrics and musculoskeletal fields (32). In contrast to osteoporosis, where pharmacological treatments are very effective, pharmacological approaches for sarcopenia have been mostly disappointing (33, 34), possibly because these drugs are being directed to the wrong biological target. Interestingly, there is growing evidence that Denosumab, an antibody against receptor activator of nuclear factor kappa-B ligand (RANKL) widely used for osteoporosis, could be that very much searched compound with dual effect on muscle and bone. However, more evidence is still needed (35). Overall, a combined therapeutic approach that would simultaneously improve muscle condition and bone mass while reducing the risk for falls and fractures and their associated adverse outcomes is still lacking.

In summary, osteosarcopenia should be considered a geriatric giant of the XXI century due to its high prevalence in older persons and the vast personal burden of sufferers. To understand and effectively diagnose and treat osteosarcopenia, we still require a clear definition of sarcopenia, innovative biomarkers and diagnostic methods, and interventions with dual effect on bone and muscle. As a combination of two somewhat neglected and recently understood conditions, awareness of osteosarcopenia as a geriatric syndrome (36) should be increased, and its prevention, identification and treatment should become a priority in our geriatrics practice. In a set of fragmented fields in which osteoporosis and sarcopenia and falls and fracture risk are identified and managed at different settings and by various specialties and teams, osteosarcopenia could be the unifier concept that will finally improve care to these devastating conditions.

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