Osteosarcopenia: A Geriatric Syndrome

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Abstract

Population aging is causing an increase in incidence of chronic diseases like Osteoporosis and Sarcopenia. Different mechanisms cooperate to generate loss of muscle and bone: mechanical, biochemical, genetic and lifestyle factors all lead to damage the 'bone–muscle unit'.

These conditions often co-exist in a frail subset of elderly population, with a major burden characterized by risk of falls and fracture, hospitalization, disability, premature mortality and increasing healthcare costs. Here we summarize relationship between bone and muscle and the pathways leading to "osteosarcopenia".

Keywords: Osteoporosis; Sarcopenia; Osteosarcopenia; Bone; Muscle; Falls

Introduction

The rapid population aging is inevitably causing a rise in the incidence of chronic degenerative diseases. Osteoporosis and Sarcopenia often present together and are the result of the same ageing process: these diseases affect similar population, and have an analogous burden, characterized by decreased mobility, disability, frailty and increased hospitalization rate [1,2]. Since these conditions are both associated with significant morbidity and mortality, they have proved to lead to considerable health and social costs [3,4].

Osteoporotic fractures, a critical source of morbidity, correspond with an increase in mortality and generated direct costs in excess of 35 billion euros, in 2010, in the European countries [5]. The complications of sarcopenia, including nursing home admissions, depression, and mortality have been linked to a considerable rise (up to 18.5 billion USD) in the healthcare costs in USA in 2000 [6].

Considering the several common points between these two syndromes, it is reasonable that every prevention approach to Osteoporosis should go along with the assessment of muscle mass and function to early detect Sarcopenia. Recognizing the coexistence of the two conditions (Osteosarcopenia) is the major requisite to plan interventions to strengthen not only the bone, but also the muscle. Nevertheless, research into Osteoporosis and Sarcopenia are at very different stages of evolution, with research into the first being considerably ahead, and there's a growing interest into their co-presence and its clinical implications.

This review examined the recent literature regarding Osteoporosis and Sarcopenia, focusing on molecular relations and the clinical connections between them.

Main Subjects

Osteoporosis

Osteopenia/osteoporosis is a systemic bone disease characterized by reduced bone mineral density (BMD) and microarchitectural deterioration of bone, this lead to increased fracture risk [5]. The diagnosis of osteoporosis is based not only on BMD but also on the presence of fragility fracture, particularly at the spine, hip, wrist, homers, rib, and pelvis. Fractures are accompanied with the mark "fragility" when they occur from a fall from a standing height or less, without major trauma. The World Health Organization (WHO) (Table 1) criteria for diagnosis defined as osteoporotic the patients whose BMD is lower than - 2.5 standard deviations (*T*-score) compared to reference population. Severely osteoporotic are those patients with the same BMD threshold and the presence of one or more fragility fracture. The patient is defined osteopenic when BMD is between - 1 and - 2.5 SD. Several known clinical factors can contribute to increased risk of fracture. A reliable estimation of fracture risk can be achieved by the WHO Fracture Risk Algorithm (FRAX®) tool. FRAX combines clinical risk factors with BMD [5].

Bone mineral density category	Definition
Normal	Bone mineral density no greater than 1 standard deviation below the reference mean (T-score ≥ -1)
Osteopenia	Bone mineral density between 1 and 2.5 standard deviation below the reference mean (T-score <-1 but > -2.5)
Osteoporosis	Bone mineral density 2.5 standard deviation or more below the reference mean (T-score ≤ -2.5)
Severe osteoporosis	Bone mineral density 2.5 standard deviation or more below the reference mean (T-score ≤ -2.5) plus one or more fragility fracture

Table 1: *World Health Organization classification of osteopenia and osteoporosis.*
Bone mineral density is expressed in standard deviations relative to a sex-specific, young-adult mean
(known as the T-score). From World Health Organization (1994).

In Europe, around 27.6 million had osteoporosis in 2010, with a prevalence of 6.6% and 22.1% respectively in men and women over 50years of age [3]. In the same year, based on BMD, osteoporosis and low bone mass at the femoral neck or lumbar spine affected an estimated 53.6 million older US adults in 2010 [7].

Sarcopenia

The term Sarcopenia was coined in 1989 and comes from the Greek words "Sarcos", that denotes flesh, and "Penia" that indicates deficiency [8]. At first the term sarcopenia was only used to describe the loss of muscle mass with ageing. Recently it has been used with the meaning of deficiency in muscle mass along with defective muscle strength ("Dynapenia") and decline of physical performance [9]. In order to diagnose Sarcopenia, it is necessary to observe both a reduction in skeletal muscle mass and either low muscle strength or low physical performance [9]. This definition underlines the lack of linear relationship between mass and strength and the fact that muscle mass is not the exclusive element to influence muscle strength. The diagnosis of Sarcopenia relies on different techniques that are used to measure muscle mass, strength or function. Not all of these techniques find an application in the clinical practice, indeed many of them are exclusively utilized for research purpose [9,10]. The assessment of muscle mass can be achieved by dual-energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), or by anthropometry. Among the image techniques, the less expensive is represented by DXA, which is as precise as CT or MRI, but it also significantly minimizes the exposure to radiation. A real alternative to DXA is constituted by BIA, a technique used to measure muscle mass that only requires a portable equipment [11]. The anthropometry estimates body fat

measuring body circumferences and skinfold thickness. Nonetheless, anthropometry has shown vulnerability to errors (obese and elderly patients) and large variability. Several techniques have been verified for the evaluation of muscle strength, although the most used remain the handgrip strength, because of its simplicity and significant correlation with lower extremity muscle strenght. Physical performance can be assessed by different methods, but the most used in clinical practice are the valuation of gait speed and the Short Physical Performance Battery (SPPB). Which evaluates strength, endurance, balance, and gait of the patient through specific physical tests [12]. To date, there is no general consensus on diagnostic criteria for sarcopenia, with different working groups providing their own definitions (Table 2). One of the most used in clinical practice is the algorithm developed by the European Working Group on Sarcopenia in Older People (EWGSOP) (Figure 1) [9]. According to the EWGSOP definition, the estimated prevalence of sarcopenia is 1 - 33% of individuals in the community, but the prevalence rises in settings of care for older patients [13].
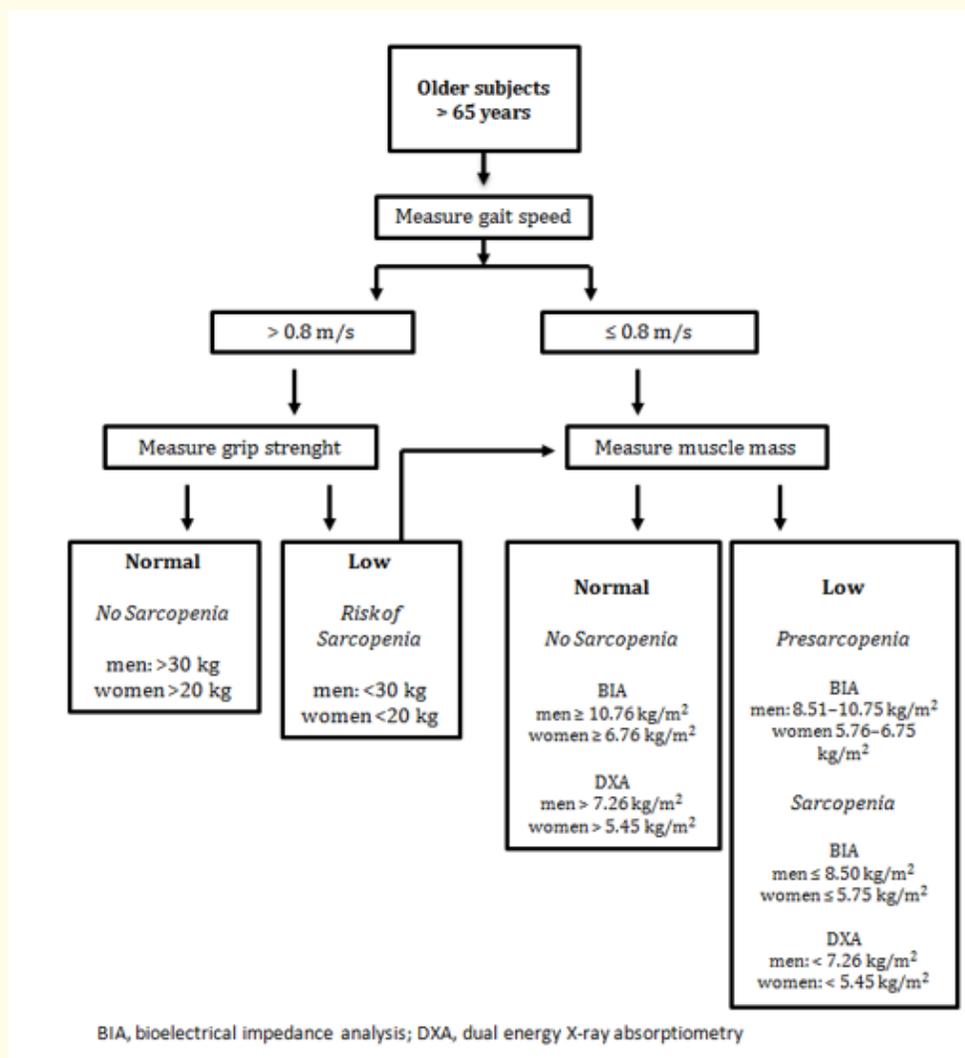

Figure 1: EWGSOP modified algorithm for screening and classification of sarcopenia.

	Diagnostic criteria for sarcopenia		
Working group	Muscle mass (dual energy X-ray absorptiometry)	Muscle strength	Physical performance
European Working Group on Sarcopenia in Older People	Appendicular lean mass/height^2 Several similar cut-offs based on different reference groups, e.g. men: ≤ 7.23 kg/m^2, women: ≤ 5.67 kg/m^2	Grip strength Men: < 30 kg, women: < 20 kg Also provide cut-offs based on patient's body mass index	Gait speed Both sexes: ≤0.8 m/s
International Working Group on Sarcopenia	Appendicular lean mass/height^2 Men: ≤ 7.23 kg/m^2, women: ≤ 5.67 kg/m2	N/A	Gait speed Both sexes: <1 m/s
Foundation of the National Institute of Health	Appendicular lean mass/body mass index Men: < 0.789, women: < 0.512	Grip strength Men: < 26 kg, women: < 16 kg	N/A
Asian Working Group on Sarcopenia	Appendicular lean mass/height^2 Men: < 7.0 kg/m^2, women: < 5.4 kg/m^2	Grip strength Men: < 26 kg, women: < 18 kg	Gait speed Both sexes: <0.8 m/s

Table 2: *Cut-off thresholds for the diagnosis of sarcopenia used by different international groups.*
From Cruz-Jentoft., et al (2010) [3], Fielding., et al. (2011) [94], Chen., et al. (2014) [96], Studenski., et al. (2014) [95].

Bone and muscle: a functional unit

Muscle and bone might be considered as a functional unit [14]. These two tissues are strictly interconnected, so that ageing and disuse cause the decay of both. Ageing causes a reduction of muscular mass; in particular it has been shown that after the age of fifty the lean mass decreases, such as the strength after the age of seventy [15], average 40% of muscle mass is lost by 80 years[16].

Muscle influences bone through several pathways, mainly through mechanical stimulus [14], architecture is influenced by muscular mass and strength: it has been demonstrated that appendicular skeletal muscle mass is associated with cortical bone thickness, trabecular volumetric bone mineral density, trabecular bone volume/tissue volume, and also with number, thickness and separation of trabeculae [17].

The interaction between muscle and bone occurs through many different types of signals. The most important are biomechanical signals which directly stimulate both tissues and influence indirectly bone through muscular contraction. The forces exerted on bone result both from muscular contractions transmitted through the tendons, both from the pull of gravity. The mechanical stimulus enhances bone turnover: bone adapts in the most effective way to face the forces it has to go through. The bone reaction depends both on the extent, both on the kind of the stimulus it receives (bone is more sensitive to dynamic rather than static loading). A neuronal regulation of adaptation to the load has been demonstrated: it's been shown that mechanical load on a rat ulna increases apposition of new bone on the ulna and also on other bones, while neuronal blocking during loading suppresses bone formation in the loaded ulna and other bones [18].

Bone's response to load is due to the ability of osteocytes to translate mechanical energy into structural and biochemical signals: this process is known as mechano-transduction [19]. The Wnt/beta-catenin pathway is a key player in mechano-transduction and in the regulation of bone metabolism. This pathway increases bone mass by enhancing the renewal of stem cells, stimulating osteoblast genesis and osteoblast proliferation, inhibiting osteoblast apoptosis, increasing mineralization [20]. Cyclic load decreases sclerostin, which inhibits Wnt pathway, with a consequent increase in mineral apposition [21].

The interaction between muscle and bone also depends on nutritional signals, glucocorticoid, sexual hormones, vitamin D, control of CNS on muscle-bone metabolism, local hormones, growth factors and cytokines which influence on both tissues, or on paracrine signals. Muscle, as well as bone, can be considered an endocrine organ. It has been demonstrated that skeletal muscles cells express the vitamin D receptor (VDR), even if its role in normal muscle has not been fully understood. VDR is a nuclear receptor which binds with high affinity vitamin D and regulates muscle protein synthesis.

Vitamin D is known to play an essential role in influencing skeletal muscle health in humans. Its deficiency causes an impairment of muscle function and integrity, called vitamin D deficiency myopathy [22]. This condition can precede bone disease and includes muscle pain, weakness of proximal muscles, impairment of gait [23,24].

In old people vitamin D deficiency has shown to be related to a decline in lower extremity muscle strength [25] to a worse physical performance, including coordination, proximal muscle strength and balance [26] and to an increased risk of falls [27].

In rats it's been shown that vitamin D depletion, due to a lack in UV exposition and low intake with diet, leads to muscular atrophy through the reduction of the activity of Notch signaling pathway and cell proliferation [28]. It's been demonstrated that in animals with depletion of vitamin D the expression of two modulators of proliferation decreased by 39% and 31% [28].

Moreover, skeletal muscle produces many molecules that influence bone, including insulin-like growth factor-1 (IGF-1), IGF-2, basic fibroblast growth factor (FGF-2), transforming growth factor-beta (TGF ß), platelet-derived growth factor (PDGF), various interleukins (IL-6, IL-8, IL-15), myostatin, osteoglycin (OGN), osteoactivin, irisin[14]. Among myokines that communicate with bone, an important role is played by irisin. Irisin is known to drive differentiation of beige adipose tissue into brown, and recently it's been shown to play a key role in the control of bone mass and in the connection between muscle and bone [29, 30]. Physical activity enhances the expression of irisin in skeletal muscle: mice exercising on wheel express more irisin than resting mice [30], Irisin induces the differentiation of bone marrow stromal cells into osteoblasts and, in tail suspended rat, recombinant irisin has an anabolic activity on bone significantly increasing cortical mass, strength, mineral density and periosteal circumference [31]. These findings suggest that irisin may become a new anabolic therapy to increase bone mass in osteopenia associated with muscular diseases.

Clinical Connections

Osteoporosis and Sarcopenia not only often coexist, but they might be part of the same disease, sharing common causes and presenting several overlaps in their epidemiology. In fact, the use of terms like osteosarcopenia, sarco-osteoporosis, or musculoskeletal frailty is significantly rising in recent literature [32]. These two diseases share several common risk factors.

Lifestyle factors

The interconnection between Osteoporosis and Sarcopenia reveals itself starting from the lifestyle habits.

The drop in physical activity with ageing has been well-established in previous studies [33]. Sedentary old patients loose mechanical loading and therefore bone and muscle mass [33].

Also, diet has a major role in the muscle-bone association. Between the ages of 40 and 70 years, the intake of calories decreases by 25% on average [34], in particular the decreased vitamin D levels and decreased protein intake were associated to deterioration of muscle performance [35]. Vitamin D deficiency increases the risk of falls, by the agency of multiple damaging pathways against muscle and bone [36].

Cigarette smoking is a significant risk factors for both Osteoporosis and Sarcopenia [38]. Also, an alcoholic intake of ≥ 3 units/day proved to increase the fracture risk in a dose-dependent manner [37]. In a recent Korean study, high-risk alcohol drinking was associated with a higher risk of sarcopenia in postmenopausal women [39].

Falls and fractures.

The bone fragility associated with Osteoporosis is a major risk factor for fractures, even with minimal or without trauma. Fragility fractures are nowadays a major public health concern as they increase mortality, persistent physical morbidity and limit every-day activities [40].

Sarcopenia alone is considered an important risk factor for falls [41,42]. The loss of the number of type II (fast) muscle fibers in sarcopenic subjects weakens particularly their strength and balance. These individuals have an increased risk of falls, a well-known contributor to fractures especially when associated with osteopenia [41]. Patients with sarcopenia are three times more likely to fall in the next two years [43]. A report of more than 300 women in Italy with hip fractures found that 58% were also sarcopenic [44]. Sarcopenia itself can be considered as a predictor of fracture risk in the older population [45]. A high prevalence of sarcopenia and reduced leg muscle mass was seen in Japanese patients immediately after a hip fracture [46].

The co-presence of Sarcopenia and Osteoporosis increases the risk with an additive effect. Patients suffering with both these conditions are reported to be at higher risk of falls and fractures [47]. The prevalence of Osteosarcopenia in old patients with history of falls reached 37% in a study of 680 patients [32]. A large 2014 study with 2000 community-dwelling men aged ≥ 65 years, discovered a 3.5-fold increased fracture risk in osteosarcopenic patients [48].

Burden caused by fractures is considerably heavy: almost 20% of patients with hip fracture require long-term nursing home care and 40% won't achieve their pre-fracture level of independence [49]. Moreover, 80 years old patients experience a 25% reduction in life expectancy [50].

Comorbidities and Mortality

A study conducted in China in 2015 showed a relevant link between the loss of bone and muscle with the risk of frailty: 26.3% of men and 38.5% of women with frailty were osteosarcopenic, with higher odds of being frail compared to osteoporosis or sarcopenia alone [51]. Furthermore, the osteosarcopenic population is at higher risk for comorbidities, depression and impaired mobility. There is significant evidence showing that the incidence of urinary tract infections and aspiration pneumonia increases in sarcopenic patients [52,53].

Sarcopenia and osteopenia/osteoporosis contribute together to generate disability [54]. The Global Burden of Disease Study in 2010 noticed that the second main contributor to global years lived with disability (YLDs) is the presence of musculoskeletal disorders, affecting nearly 2 billion people worldwide [55].

In addition, Sarcopenia showed association with frailty, functional impairment, physical disability, institutionalization and decreased quality of life [56].

In previous studies not only muscle weakness, but also loss of muscle mass where recognized as risk factors for mortality [57-60].

Sarcopenia has been associated with premature mortality among community dwelling older adults with few differences between males and females [60].

A clear excess mortality has been demonstrated in population affected by osteoporotic fractures, predominately due to comorbidities, but also attributable to fracture event alone [61].

Osteosarcopenia is associated with a remarkable increase in mortality: one recent study on elderly patients with hip fracture found a mortality rate of 15.1% at first year in the osteosarcopenic patients, with lower rates in the two diseases isolated, 5.1% in Osteoporosis and 10.3% in Sarcopenia [62].

Health system costs

It is estimated that sarcopenia currently affects approximately 50 million people worldwide and it should reach more than 200 million in the next 40 years [63].

Sarcopenia is independently related to hospitalization costs: it increases hospitalization costs by 58.5% for patients aged <65 years and 34% for patients aged ⩾ 65 years [64].

Osteosarcopenia and its complications cause significant financial burden on healthcare services. The cost of hip fracture in an 80-year-old community dweller patient has been estimated to be $81,300, with a yearly overall cost for hip fractures in the USA of approximately $20 billion [50].

In a Swiss study, fragility fractures in women determined a length of stay in hospital longer than chronic obstructive pulmonary disease, myocardial infarction, and stroke [65]. In 2010 the direct cost of all osteoporotic fractures was estimated of €38.7 billion in 27 EU countries [65].

With the fracture epidemic expected to exponentially grow by 2050, predictions on the incidence of hip fractures worldwide could exceed 21 million [66-67].

Hip fractures are associated with the highest morbidity with reported mortality rates up to 20-24% in the first year after the fracture, and greater risk of dying may persist for at least 5 years afterwards. The survivors often became disabled as 40% are unable to walk independently, and 60% still require assistance a year later. The disability impedes 33% of patients to live in their home. Over 55% of patients with hip fracture have experienced a prior vertebral fracture, these fractures are associated with an 8-fold increase in overall mortality for these reasons, the World Health Organization considers osteoporosis and osteoporotic fractures to be a health problem as acute myocardial infarction and strokes [68-70].

Treatment

The pathway that leads to the loss of muscle and bone, if well-detected in early stages, can be prevented and reverted. As shown previously, screening tests (SPPB, handgrip strength, FRAX) provide insight into the physical performance, muscle strength and risk of fracture and allow us to recognize patients at higher risk. Most therapeutic options approach these two conditions separately. Pharmacological treatments for osteoporosis, such as bisphosphonates (alendronate, risedronate and zoledronic acid), RANKL antagonist (denosumab) and teriparatide (bone anabolic) have widely shown their efficacy in improving bone density and in preventing fractures and should be administrated in osteoporotic patients or in particular conditions of risk [72-74].

Here we aim to consider the possible concomitant treatments for osteoporosis and sarcopenia. Considering all the mentioned connections between these diseases, a concerted handling would improve the results in terms of health outcome.

Changes in lifestyle and behaviors can delay the onset of sarcopenia and osteoporosis and should be recommended to everybody. They include the elimination of modifiable risk factors, such as smoke, excessive alcohol consumption and environmental factors which increased risk of falls, non-pharmacological interventions such as regular physical activity and adequate nutrition.

Physical exercise is known to reach beneficial effects in prevention in old age, treatment of pathological conditions as osteoporosis and sarcopenia, reduction of risk of falls.

As interestingly exposed by Garatachea., *et al.* regular exercise has shown to impact the major hallmarks of aging producing multisystem anti-aging effects [75].

According to Global Recommendations on Physical Activity for Health by WHO (2011), physical exercise decreases global mortality, vascular mortality, incidence of ischemic cardiac disease, diabetes, hypertension, breast and colon cancer, increases muscular mass and strength and bone density with a reduction in risk of falls and disability and improvement in cognitive skills.

The benefits of exercise in improving muscular and skeletal health and reducing bone loss, in particular in elderly patients, have been showed in several studies [76-78]. In elderly women, 30 months of exercise have shown to improve BMD at the trochanter and to reduce falls compared to the control group [76]. In old people exercise improves muscular strength and functional performance [79], and structured exercise training has a positive impact on frail older adults improving functional ability outcomes and global health [80].

There is no clear consensus on the type, intensity, or duration of exercise that is most effective.

In the elderly, WHO recommends moderate aerobic activity 30 minutes 5 days a-week, muscle strengthening activities 2 days a-week and balance exercise for subjects with poor mobility and consequent increased risk of falls. People who are unable to do these amounts of exercise are recommended to be as active as they are able.

Regular exercise and adequate nutrition, particularly dietary calcium, vitamin D, and protein, are prescribed as strategies to optimize peak bone mass, improve muscle mass and maintain bone and muscle health throughout life [81-83].

Sarcopenia and osteoporosis are often associated with malnutrition, so that a combined treatment for these pathologies might include nutritional interventions, which have shown to be effective in improving muscle health in particular if associated to exercise [82,84].

The importance of vitamin D administration and an adequate intake of calcium in osteoporosis is well known; they have shown also to increase muscle strength and balance and to reduce risk of falls in old patients [85,86] The beneficial effects of a vitamin D and leucine enriched whey protein oral nutraceutical supplement on muscle mass and lower-extremity function among sarcopenic older adults have been reported [86,87] and their importance is well known.

Concerning protein intake, it has been demonstrated that high-quality protein supplementation (2 g/kg/day in patients with normal renal function and 1.2 g/kg/day in patients with renal impairment), in addition to protein intake with diet and in particular if associated to exercise, improves muscle strength and function [88]. Old people are recommended to take 25-30 gr of proteins in each meal, containing 2.5-2.8 gr leucine [89].

It has been demonstrated that a protein intake consisting of a high amount of amino acid, leucin or high-quality proteins is effective in increasing post-prandial muscle protein anabolism [90,91]. Free leucine supplementation has shown to increase muscle protein synthesis and decrease muscle proteolysis in the postprandial [92], while even in chronic administration it failed to be effective in increasing muscle mass [93]. In conclusion, the administration of leucine or branched-chain amino acids may help improve muscle mass and function, but further studies are needed to support specific recommendation [89].

Conclusion

The present review summarizes the available literature regarding the multiple connections between Osteoporosis and Sarcopenia, considering them as a combined geriatric syndrome rather than two separate entities. We found an emerging body of evidence on Osteosarcopenia and a growing interest by reason of the deeper awareness of its significant negative sequelae. Still, more high-quality trials are required to improve knowledge regarding both basic scientific backgrounds and clinical associations. Our knowledge to date shows that Osteosarcopenia not only causes an increase in morbidity and mortality, reducing quality of life, but it is also expected to contribute to billions in annual health care costs over the next decades.

However, in last years, research in this field moved forward, promising a more precise understanding of molecular patterns involved. In clinical practice, the improvement in DXA scans use and the application of simple body and function measurement will facilitate the early detection of these conditions. Physicians may have a beneficial effect on promoting adequate protein, vitamin D and calcium intake together with appropriate physical resistance exercise. This contribution would improve functional performance and reduce falls and fracture risk as well, resulting in benefits for millions of older patients.

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