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Sarcopenia, Osteoporosis and Frailty: A Triad Comes of Age

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Abstract

The epidemiology and the clinical characteristics of three entities that lead to dysmobility, falls and fractures (osteoporosis, sarcopenia, and frailty) are reviewed. Osteoporosis is a worldwide health problem causing bone fragility and fractures. Sarcopenia is an age-associated decline of skeletal muscle mass and function. Frailty results from the accumulation of age-related deficits in different physiological systems and is a clinical state that leads to greater risks of adverse health outcomes, such as falls, fractures, hospitalizations, loss of independence, and death. The three entities have a common denominator (aging), but they can be secondary to other diseases. There are patients presenting with all three pathologies, which should be properly identified by the treating physicians.

Keywords: Osteoporosis; Sarcopenia; Frailty; Aging; Dysmobility

Introduction

Chronic pathologies affecting the health of elderly people are a source of concern for physicians and sanitary authorities. In this review we shall consider three entities that have aging as a common denominator: osteoporosis, sarcopenia, and frailty. The nature of this association remains controversial, but the available evidence suggests that it leads to poor clinical outcomes, increases the risk of deleterious health effects in older adults and raises health resources utilization [1].

Pathophysiologically, leptin appears as a candidate link between bone and muscle. This cytokine-like hormone is a classic adipokine, increases with weight gain, and decreases with weight loss. It is also produced by skeletal muscle, and leptin receptors are abundant in both muscle and bone-derived mesenchymal stem cells [2]. Other cytokines and growth factors such as IGF-1 have anabolic effects on muscle and bone [3]. Myostatin, a negative regulator of muscle growth, has a direct effect on bone, and periods of muscle atrophy due to disuse also result in bone loss [3].

The European male ageing study showed significant longitudinal age adjusted relationships between higher levels of IGF-1, IGFBP-3, and vitamin D, and lower risks of worsening frailty in men. In unadjusted analysis, higher levels of DHEA-S were associated with lower risk of worsening frailty [3]. Presently the role of klotho, a powerful longevity protein produced by muscle, is being evaluated to better understand the mechanisms leading to sarcopenia in old age [4].

The loss of Lean Body Mass (LBM) is the primary reason for the age-associated decrease in basal metabolic rate and energy requirement. Weight loss due to caloric restriction leads to a loss of body fat, lean mass, and bone density [2]. Chronic inflammation, neurological problems (in the central nervous system, or loss of innervation in the periphery), sensory loss (sight, hearing) and many other conditions are frequently implicated in the tendency to fall and the high risk of fractures.

Sarcopenia and osteoporosis

The term sarcopenia (from the Greek sarx = flesh, and penia = poverty, lack) was first used by Rosenberg more than 20 years ago to describe an age-related loss of muscle mass and function, and raise the question if it is a disease or a process of normal aging [5]. One year after, Baumgartner proposed an operational definition of sarcopenia based on Appendicular Skeletal Muscle mass (ASM) corrected for height [ASM/height^2(kg/m^2)] and defined the cutoff values for sarcopenia as being 2 standard deviations below the level of healthy young person's [6].

Several expert groups worldwide have proposed complementary definitions of sarcopenia,

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but in 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) proposed a sarcopenia definition that has been widely used worldwide, which allowed a better identification and care of these patients [7,8].

This definition was revised in 2018 [9]; in this new version, an operative definition for sarcopenia was updated: "Sarcopenia is probable when low muscle strength is detected. A sarcopenia diagnosis is confirmed by the presence of low muscle quantity or quality. When low muscle strength, low muscle quantity/quality and low physical performance are all detected, sarcopenia is considered severe". After a careful review of the techniques and validated tests and tools for measuring the sarcopenia parameters, the EWGSOP recommends cut-off points usually set at -2 or -2.5 standard deviations based on European populations and normative references from healthy young adults. For muscle quantity measured by Dual-energy X-ray Absorptiometry (DXA), the recommended cut-off points are ASM/height^2<7.0 kg/m^2 for men and <5.5 kg/m^2 for women [9].

It is widely recognized that sarcopenia is a public health burden and associated with several harmful outcomes. The age associated decline of skeletal muscle mass and function is known to lead to frailty, cachexia, osteoporosis, metabolic syndrome and death [10]. Therefore, it is necessary to implement preventive and therapeutic measures to face the growing number of older people affected by sarcopenia and its complications, especially because the prevalence of sarcopenic patients will dramatically increase in the next 30 years [11,12].

Sarcopenia is frequent among the population aged 60 or older; the prevalence found in the NHANES III survey was 7% to 10%, but in the New Mexico study the prevalence rose to 50% in persons older than 80 years of age [2]. However, we must consider that the prevalence varies widely depending on the diagnostic method used (8.4% to 27.6% in 250 patients with a mean age of 74.1 ± 6.4 years). It has been reported that bioelectrical impedance analysis overestimated muscle mass compared to DXA; while in the assessment of muscle strength pneumatic dynamometer diagnosed sarcopenia two times more frequently than a hydraulic dynamometer [13].

In aging as well as in many chronic diseases, bone loss and muscle atrophy occur simultaneously, leading to concomitant osteoporosis and sarcopenia [14]. This relationship has been extensively analyzed in the literature and it is important to highlight this aspect because sarcopenia predisposes to dysmobility, frailty, falls and fractures, potentially increasing morbidity, mortality and risk of complications in the osteoporotic patient [14,15].

One of the initial questions is how often the association between osteoporosis and sarcopenia occurs, and the nature of this association. In community dwelling elderly Japanese women, osteoporosis was found to be associated with loss of skeletal muscle mass, but not with muscle weakness [16]. In the SARCOS study, 332 subjects over 65 years of age were evaluated. Osteoporosis was diagnosed in 68% of sarcopenic women, however only 20.7% of women with osteoporosis had sarcopenia; in older men, 44.7% of individuals with sarcopenia presented osteoporosis, and 42.9% of men with osteoporosis showed sarcopenia. In an adjusted logistic regression analysis for sarcopenia, osteoporosis presented a statistically significant association with sarcopenia in men but not in women [17].

The relationship between bone mineral density and muscle has been assessed from different points of view. Swedish 70 year olds with confirmed sarcopenia demonstrate poorer BMD and bone architecture than those with probable and no sarcopenia, and have increased likelihood of incident falls [18]. In the SarcoPhAge study of elderly people, lower muscle mass and function was associated with lower BMD values, but also with a microarchitecture deterioration evaluated with Trabecular Bone Scores (TBS), and individuals with incident sarcopenia had an approximately fivefold higher risk of concomitantly developing osteoporosis [19,20].

Moreover, among elderly women, the degree of sarcopenia correlates with the degree of osteoporosis as determined by DXA; whole-body and femoral neck BMD values were significantly lower among all sarcopenia stages when compared to non-sarcopenia [21]. Data from the National Health and Nutrition Examination Survey (NHANES) 1999 to 2002 indicated an association of dysmobility with increased mortality risk in adults aged 50 years and older [22]. In the same survey, data from the 2013 to 2014 period were analyzed: irrespective of sex or ethnicity, increased muscle strength may help protect against the odds of developing osteoporosis [23].

The deleterious effect of sarcopenia on muscle function seems to generate a series of additional risks in the osteoporotic patient, as reduced levels of muscle function reflected in functional tests, increased risk of falls and indeed fractures. In the WHI trial, women with low BMD, with or without sarcopenia, had greater risk of fracture (including hip fracture) than women with normal BMD; women with sarcopenia alone had similar risk to women with normal BMD [24]. In 7,531 elderly men of the Mr. OS Study, better values of muscle mass, strength and function were associated with lesser risk of major osteoporotic fractures [25].

Sixty-eight prefrail adults between 65 and 94 years were assigned to four groups according to mean DXA results: sarcopenic (low aLM), osteopenic (low T-score), osteosarcopenic (the combination of low T-score and low aLM) and controls. Multiple linear regression analysis adjusted for age, gender, physical activity, and 25-(OH)D serum level, was used to identify the influence of being osteosarcopenic, sarcopenic, or osteopenic on physical performance (hand grip, chair rise test, Sit-To-Stand (STS) power, and gait speed), and serum markers for increased bone. Only osteosarcopenic participants showed significantly reduced hand grip strength, increased chair rising time, and STS power time as well as significantly increased bone turnover markers. The authors conclude that up-to-date osteoporosis and post-fracture management of older persons should aim at both, bone and muscle [26].

Postmenopausal women with recent wrist fracture studied with peripheral quantitative tomography had lower estimated bone strength at the distal radius and tibia, and lower muscle density; their grip strength and the ability to stand up from a chair showed diminished muscle function [27]. In women aged 60 to 75 years, a positive association exists between lumbar muscle mass (evaluated with magnetic resonance imaging) and Bone Mineral Density (BMD) [28]. Lumbar compression fractures in postmenopausal women with underlying osteoporosis are associated with less paraspinal and psoas muscle volumes [29].

Women presenting with the combination of obesity, sarcopenia and osteoporosis have poorer functionality scores compared to obese women, and are at increased risk for bone fractures and immobility from the combined decline in bone and muscle mass, and increased fat mass. This combination, called osteosarcopenic obesity, was found

to be associated with the frailty syndrome in Mexican women aged 50 years or older [30].

In Korean men and women, low appendicular lean mass and grip strength were indicators of higher risk of fragility fractures [31]. Using the data from the Korean National Health and Nutrition Examination Survey (KNHANES IV) 2009, it was determined that aLM was associated with proximal femur (but not with lumbar) BMD in both sexes; another valuable conclusion of that study was that with aging muscle mass is lost faster in men than in women [32].

The balance test, gait speed test, and self-reported history of fall all hold independent fracture predictability, the consideration of these clinical risk factors for fracture would improve the fracture risk assessment and subsequently also fracture prevention [33]. However, physical exercise has a positive impact on muscle mass and muscle function in healthy subjects aged 60 years and older.

Frailty

The term "frailty" is becoming more and more popular in geriatric medicine and is defined as "a multidimensional geriatric syndrome characterized by a cumulative decline in multiple body systems or function with pathogenesis involving physical as well as social dimensions" [9]. Frailty results from the accumulation of age related deficits in different physiological systems and is a clinical state that leads to greater risks of adverse health outcomes, such as falls, fractures, hospitalizations, loss of independence, and death [32].

In older people, frailty is a strong predictor of major negative health-related outcomes (disability, care home admission, hospitalization, institutionalization and mortality), affecting the quality of life of the individual, and economically overloading health care systems [34,35].

"Frailty has physical and cognitive components and clinical criteria of the frail phenotype are: Unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity. Three phenotypes have been identified: Robust: 0 criteria; prefrail: between 1 and 2 criteria; frail: 3 or more criteria [36]".

Fragility and sarcopenia share some physical components as low grip strength and slow gait speed, and weight loss is an etiological factor for sarcopenia; but there are important differences. Frailty is considered a geriatric syndrome while sarcopenia is considered a disease and a decline in several physiological systems with physical, psychological cognitive and social consequences [9]. Treatment options for physical frailty and for sarcopenia likewise overlap: Provision of optimal protein intake, supplementation of vitamin D, and physical exercise [31].

Although sarcopenia and frailty are considered distinct entities, the association of both with osteoporosis is clearly established. Likewise, the association of sarcopenia, osteoporosis and frailty with aging is supported by clinical and epidemiological evidence. In community dwelling, 75 year old women followed 10 years a frailty index was created at each of three visits. Frailty score increased by 6% to 7% annually. A higher frailty score was equivalent to being 5 to 10 years chronologically older. Frailty was associated with low BMD and higher risk of dying [37]. In the ROAD study surveys, osteoporosis was significantly associated with sarcopenia and frailty occurrence within 4 years [38,39].

Incident clinical fracture was associated with an elevated risk of death independently of pre-fracture levels of frailty in community dwelling elderly men [40]. Higher abdominal obesity and sarcopenia were associated with frailty among men with and without HIV. Assessment of these body composition parameters may help detect frailty in the clinical setting [41].

In the CaMos study baseline obesity was associated with faster frailty progression: Incident hip fractures augmented frailty index in both sexes, although vertebral fractures worsened frailty only in women; older women and men with new vertebral fractures, hip fractures or obesity represent high risk groups that should be considered for frailty interventions [42].

Which intervention would be appropriate?

Role of nutrition and vitamin D: A Mediterranean diet was associated with a lower incidence of frailty over an 8-year follow-up period (40) [43]. In a cross-sectional study of a sample of postmenopausal women of non-Mediterranean origin, a Mediterranean diet improved BMD at the spine, and increased appendicular lean mass [44]. The origin of dietary protein (animal or vegetal) does not make a difference, but Isanejad et al. [46] found no protective effect of plant protein against frailty [45-47].

In the osteoporosis risk factor and fracture prevention study, associations were detected between protein intake and physical function in non-sarcopenic women but not in sarcopenic women [47].

Protein supplementation has a significant positive influence on lumbar BMD but shows no association with relative risk of hip fractures [48]. Whey supplements above the RDA (0.8 g/kg) may preserve fat free mass without adversely affecting skeletal health or renal function in healthy older adults [49].

In the Framingham study a higher protein intake was associated with reduced risk of hip fracture [50]. Both combined administration of proteins through diet and supplements, and single administration through protein supplements may reduce the risk of fracture in postmenopausal osteoporotic women [51].

Protein intake >1.0 g/kg day promotes gains in skeletal muscle mass and muscular strength after resistance training in untrained older women [52]. The osteoporosis risk factor and prevention-fracture prevention study also found that daily protein intake >1.1 g/kg day prevents the onset of frailty in older women [53]. The origin of the protein consumed (plant, animal) does not imply any advantage for bone, according to the National Osteoporosis Foundation [54].

The importance of hormonal replacement therapy together with proper dietary protein intake and exercise in order to prevent loss of muscle mass in postmenopausal women has been reviewed [55].

Both ESCEO and IOF state that in older people with osteoporosis, higher protein intake (≥0.8 g/kg body weight/day, i.e., above the current RDA) is associated with higher BMD, a slower rate of bone loss, and reduced risk of hip fracture, provided that dietary calcium intakes are adequate. Intervention with dietary protein supplements attenuate age-related BMD decrease and reduce bone turnover marker levels, together with an increase in IGF-I and a decrease in PTH [56]. These recommendations are strengthened by the findings of a recent systematic review and meta-analysis [57].

Consistent relationships exist between vitamin D status and muscle function, especially in the elderly frail patient. There is evidence that Vitamin D Deficiency (VDD) is associated with a

decline in muscle function. VDD is consistently associated with frailty. Vitamin D supplementation can be used in patients at risk for falls. Another systematic review of the effect of vitamin D supplementation on muscle found a small but significant effect of vitamin D on muscle strength, but not on muscle mass or power. Supplementation was more effective in subjects with low levels of 25-OHD initially [58]. They are most likely to have VDD and muscle loss/dysfunction, thus justifying supplementation independent of a putative effect on the prevention of falls [55,38]. VDD is associated to obesity, the metabolic syndrome, and diabetes. Muscle cells express the vitamin D receptor. In aging, there is intramuscular adipose accumulation. The possibility of a causative link between VDD and decreased muscle function, due to excess muscular fat, has to be considered [59].

Some studies of association suggest a preventive effect of vitamin D on falls. Results of intervention studies giving vitamin D to community dwelling elderly subjects have been contradictory. Tang comments that this discrepancy could be attributed to the heterogeneity of the included clinical studies because some have not incorporated all the important parameters in their design to analyze this association, such as the type of population studied (sufficient or deficient vitamin D patients), the form and dose of administration of the supplements and the way to collect information on falls [60]. If documented, VDD should be treated, keeping in mind that for older people the daily maintenance dose should not exceed 1,000 IU [61].

A meta-analysis found a significant inverse relationship between serum levels of 25-OHD and the risk of frailty [62]. In a Belgian study, incident immobility and mortality could be accurately predicted on the basis of sarcopenia and frailty characteristics; serum 25-OHD and BMD scores were the most important predictors [63].

Frailty and osteoporosis share common risk factors such as age, sarcopenia, lack of physical activity, low body weight, and smoking. In a prospective study of a community sample of older women, it was found that those who were frail at baseline had a statistically significantly lower hip and spine BMD at follow-up than women who were non-frail at baseline [64].

Role of calcium: For the prevention and treatment of osteoporosis in adults, the recommended daily calcium intake (preferably from dietary origin, especially from dairy products) is 1 g to 1.5 g [65].

Role of exercise: The benefits of exercise (both aerobic and resistance) to combat age related sarcopenia have been recently reviewed [66]. Exercise can prevent BMD deterioration when initiated in early menopause; its benefit does not wear off with time, if continued [67]. It has been suggested that a threshold of exercise intensity and frequency exists to provoke a benefit to bone [68].

Traditional and high-velocity physical resistance training, weight-bearing impact exercises and challenging balance/mobility activities appear to be most effective for optimizing musculoskeletal health and function [69]. Exercise is associated with a reduction in falls, injurious falls, and probably fractures in older adults, including people with cardio metabolic and neurological diseases [70].

Although the favorable effects of High-intensity resistance and Impact Training (HiRIT) on bone strength have been demonstrated, it is generally considered unsuitable for older adults. A recent study reports that 8 months of HiRIT was efficacious and induced no adverse effects in older postmenopausal women with, or at risk of, osteoporosis. It improves kyphosis in osteoporotic women [71,72].

Simple interventions, such as 6 months practice of aerobic dancing, could result in a lower incidence of bone fracture through increasing BMD and decreasing fall risk for postmenopausal women [73], but there are not enough studies in older men [74].

It is unclear which exercise program is optimal [75]. A Delphi consensus acknowledges the benefit of moderate exercise programs for patients with osteoporosis, but warns about the risks for those who have sustained vertebral fractures. Daily balance and endurance training for spinal extensor muscles are recommended for all subjects [76]. A recent review confirms the positive impact of physical exercise on muscle mass and function in healthy subjects aged 60 years and older [77].

Finally, some clinical trials suggest that protein supplementation as hydrolyzed collagen in combination with resistance training may increase muscle mass and muscle strength in elderly subjects, albeit in the short term, and this aspect deserves more research [78,79].

Clinical evaluation of patients

The ESCEO working group on frailty and sarcopenia recommends the following tests in primary care settings [80]:

a) For assessment of muscle mass: Anthropometric measurements, handgrip strength, repeated chair stands test

b) For assessment of muscle strength: Handgrip strength

c) For assessment of physical performance: Gait speed

In order to assess the impact of frailty and sarcopenia on the quality of life of patients, several questionnaires have been implemented. Perhaps the most complete is SarQoL, which has been translated to several languages [81]. The Society of Sarcopenia, Cachexia and Wasting Disorders suggests the use of the SARC-F questionnaire [82]. Bone densitometry continues to be the gold standard for diagnosing osteoporosis.

Conclusion

In this review the meaning of the frequent associations found in the literature between osteoporosis, sarcopenia and frailty has been explained. The three entities are different aspects of the same process: aging. Each can be associated to several causing conditions and diseases. The role of proper nutrition, exercise and vitamin D sufficiency in old age has been addressed. A good understanding of aging will help the clinician to better evaluate and treat elderly patients [83-85].

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