**Functional capacity, sarcopenia, and bone health**

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# Abstract

Bone and muscle are recognised as interacting tissues, the so-called ‘muscle-bone unit’, in which these two tissues communicate to coordinate their development (chemically and metabolically), and their response to loading or injury. Musculoskeletal disorders of ageing, specifically osteoporosis and sarcopenia, are highly prevalent in older individuals. They signify a significant burden for older people affecting their mobility, confidence, and quality of life, as well as being a major cost to health care systems worldwide. This review considers the coexistence of osteoporosis and sarcopenia in individuals, describing risk factors for this, the clinical consequences, approaches to management, and the link with functional capacity.

Key words: muscle; bone; ageing; functional capacity

# What is osteoporosis?

Osteoporosis is defined as a disease characterised by low bone mass and structural deterioration of bone tissue [1]. It is the most common chronic metabolic bone disease and represents a major global health problem contributing to 8.9 million fractures worldwide on an annual basis [2]. It is defined on the basis of a T score derived from bone densitometry taken at the proximal femur and spine where a T-score less than 2.5 standard deviations (SD) below the mean value of a reference young population, is indicative of osteoporosis. The diagnosis of severe osteoporosis is made when the T-Score is ≥2.5 SD below the mean level from a young reference population with the presence of one or more fractures.

Osteoporosis directly affects physical and psychological health, reduces quality of life and shortens life expectancy [2,3]. In the UK, over 300,000 patients present to hospitals annually with fractures that lead to hospital admissions and physical deconditioning [4]. Osteoporosis associated morbidity incurred an estimated £1.8 billion in UK health costs in 2000; this is predicted to increase to £2.2 billion by 2025 [5]. The prevalence of osteoporosis increases with age, predisposing both older women and men to fractures [4].

# What is sarcopenia?

Sarcopenia has been defined as the age associated loss of skeletal muscle strength, function, and mass. It is associated with a range of adverse physical and metabolic outcomes in terms of disability, morbidity, impaired quality of life and mortality [6]. Sarcopenia associated conditions incurred an estimated $18.5billion in health care costs to the USA in 2000 [7]. A diagnostic approach to sarcopenia was first described in 1988 [8]; over recent years, several international groups have developed definitions of sarcopenia adding muscle function assessment to muscle mass [9–12].

The most widely used definition for sarcopenia is the one proposed by the European Working Group on sarcopenia in Older People (EWGSOP2) [9], supported by the Asian Working Group on Sarcopenia [10] but which used different cut-offs for an Asian population. This is the only definition endorsed by a range of international scientific societies. The European Working Group on Sarcopenia in Older People (EWGSOP2) diagnostic algorithm uses normative grip strength reference values for young healthy adults where possible, with cut-off points usually set at –2 or –2.5 standard deviations compared to mean reference values [9]. Sarcopenia is probable when low muscle strength is present (grip <27 kg for men, <16 kg for women) or time taken to compete five chair rises is greater than 15 seconds. A diagnosis of sarcopenia is confirmed by the presence of low muscle quantity defined for example as ALM as a function of body height (ALM/ht2 ) <7.0 kg/m2 for men and <6.0 kg/m2 for women) measured by DXA. If these parameters are accompanied by poorer objective physical performance measures e.g. gait speed ≤0.8 m/s, then sarcopenia is considered severe [9]. The sarcopenia definition and outcomes consortium (SDOC) formed a set of position statements concluding that muscle weakness measured by grip strength and low gait speed independently predict poor health related outcomes [12].

The impact of ageing on muscle is very complex and impaired muscle function is related to both quantitative and qualitative changes; apart from ageing related changes in denervation/reinnervation process negatively affecting muscle fibre number and size causing atrophy, changes in muscle microvasculature, oxidative stress, posttranslational muscle protein modifications, and repair processes, are some of the mechanisms that might contribute to the development of sarcopenia in older adults [13].

Decline in function due to muscle loss is a hallmark in the development of sarcopenia; all definitions for sarcopenia agree on the overall concept of sarcopenia as a compound of low muscle mass and reduced muscle function, defined by muscle strength, reduced physical performance, or both [12,14,15]. A wide range of tests assessing physical performance are available; the use of grip strength to measure muscle strength and the use of 4-m gait speed or the Short Physical Performance Battery test to measure physical performance in daily practice is recommended [16].

# How does sarcopenia relate to functional capacity?

Skeletal muscle mass is essential for maintaining physical function and performing activities of daily living (ADL), and sarcopenia has been associated with ADL disability [17,18]. Muscle weakness is associated with a decline in physical function, mobility impairment and increased physical disability [19–21]. Components of sarcopenia have been shown to have a relationship with disability; poor muscle function is more closely associated than reduced muscle mass [22]. Weak muscle strength and measures of physical performance have been associated with incident or progressive disability as described in a systematic review [23], while worse performance in grip strength, chair rises and standing balance time was also associated with the development of disability [24]. Walking speed was shown to have the strongest predictive value in relation to onset of ADL disability over 9 years of follow up in older females [25]. In addition, a link between grip strength as a marker of sarcopenia and health-related quality of life (HRQoL) was established in the Hertfordshire Cohort Study cohort [26].

A few studies have reported that the likelihood of having difficulty in performing instrumental ADL, such as using transportation or shopping, is greater in elderly males and females with sarcopenia, than in those without sarcopenia [27–30]. Overall sarcopenia has been shown to be strongly associated with low levels of ADL functionality and higher-level functional capacity, and to have a substantial impact on quality of life [30]. Finally a relationship between skeletal muscle mass and higher-level functional capacity was demonstrated among elderly Japanese female community residents [31], with sex differences reported in a study where the level of functional fitness decreased with age, with more marked decreases in females [32].

Hence ADL disability increases with age and is increasingly recognised as a public health issue in an ageing world [33]; the prevalence of ADL disability is high in older adults, and especially in older hospital inpatients [34,35]. Dependence in activities of daily living is associated with an increased risk of morbidity and mortality with ADL scores recognised to be increasing with age [25,36,37]. Other studies have also found a decline in function in older adults [37–39].

If we consider the pathophysiology underlying these observations, a substantial portion of the decline of mitochondrial function with ageing is attributable to the decline of physical activity, observed even in very healthy ageing individuals [40]. A strong association between the levels of self‐reported physical activity and increased representation of all mitochondrial muscle proteins has been reported, indicating that being physically active might have a biologically detectable beneficial effect on muscle [41]. It has been suggested that an increase in physical activity can negate the effects of ageing in older adults whereas mitochondrial capacity was correlated with exercise efficiency [42].

Although observational studies assessing changes of mitochondrial function with ageing in individuals who maintain a high level of physical activity are lacking, randomized clinical trials have shown that regular physical activity and resistance exercise prevent age-related sarcopenia [43–45]. However, there is also evidence that part of the decline in muscle strength with ageing is due to a dysfunction of neurological control, both at the central and the peripheral level, and mitochondrial ageing presumably contributes to the cause of sarcopenia [46,47]. These considerations are important when we consider possible therapeutic interventions in older adults.

# What is osteosarcopenia?

The coexistence of low bone mineral density (BMD) and sarcopenia in some individuals, was first described as “sarco-osteopenia” in 2009 [48]. Several terms have been used in the past to describe the coexistence of osteoporosis and sarcopenia, such as sarco-porosis, sarco-osteoporosis and dysmotility syndrome [49]. The most common term describing the comorbid poor bone and muscle health nowadays is osteosarcopenia. Osteosarcopenia is associated with higher morbidity from falls, fracture, disability as well as mortality [50,51]. Knowledge of the overlap in the pathophysiology of osteoporosis and sarcopenia can inform the development of potential treatments for osteosarcopenia [52].

# What is the prevalence of osteosarcopenia in epidemiological studies, and what is its clinical relevance?

The prevalence of osteosarcopenia among community dwelling populations increases with age and is greater in women than men [53,54]. Estimates vary considerably, between 5 and 37% depending on the population and definition of sarcopenia used, with the highest rates observed in those individuals with prevalent fractures [53,55]. The prevalence of osteosarcopenia will inevitably increase as the population grow older [54]. A recent systematic review searched for studies that reported the association between osteosarcopenia and fracture, falls and mortality [56]. Having identified eight cohort studies including 19.836 participants, the authors reported a OR of 2.46, 95% CI 1.83-3.30 for fracture; from three cohort studies of 2601 participants osteosarcopenia was associated with an OR of 1.66 95% CI 1.23-2.26 for mortality and from three cohort studies involving 3144 participants the authors identified an OR of 1.62, 95% CI 1.28-2.04 for falls associated with the condition. The overlap between osteoporosis, sarcopenia and frailty in community dwelling adults was highlighted by our own group in a paper that reported that the likelihood of being frail was markedly higher in the presence of both sarcopenia and osteoporosis than in the presence of sarcopenia alone or OP alone [57].

# Pathophysiology with ageing

Both genetic and environmental factors are important for maintaining musculoskeletal health [58]; skeletal muscle and bone share common embryological origins from mesodermal cell populations. In the next section, we will emphasize on age related changes that affects the ‘muscle-bone unit’.

An adaptive capability of bones within an individual’s lifespan was recognised in the 1990’s. The mechanostat hypothesis, described by Frost, indicated that when muscle strength decreases with age this puts bones into partial disuse and make remodelling begin to reduce their strength and mass [59,60]. Furthermore, inflamm-aging is a condition described as chronic low level and long-term physiological stimulation of the immune system that also affects muscle and bone, and it is likely to contribute to the development of osteosarcopenia. The gut microbiome is thought to play a central role in inflamm-aging [61,62] and ageing mitochondrial dysfunction has also been linked to the condition [63,64]. Finally, sex steroids change with ageing including their concentration and activity on tissues as they become less sensitive to sex steroids over time. Broadly speaking, androgens exert anabolic effects on muscle and oestrogens have anti-resorptive effect on bone; the effects of oestrogens on muscle mass growth and maintenance appear weaker compared to their effects on the bone. Androgens appear more potent than oestrogens on muscle in both sexes. [65].

## Lifestyle factors and nutrition

Lifestyle factors affect muscle and bone ageing. Smoking decreases bone density through deleterious effects on bone quality mediated by direct and indirect effects of nicotine and other toxins [66]and has also been associated with sarcopenia [67,68]. In addition, specific nutrients affect both bone and muscle. For example, vitamin D plays a major role in muscle and bone health and undernutrition, commonly observed in older adults, and has been proposed as the cause of musculoskeletal decline rather than its consequence [69]. Low levels of Vitamin D have been found in osteosarcopenic patients [70] but effects of supplementation on muscle-bone health has not been thoroughly studied [71]. In addition, vitamin K serves as a connection agent in muscle-bone interactions through several mechanisms facilitating muscle-bone cross talk [72,73], but no effect on postural sway or physical function in older people was demonstrated in one recent study [74].

# Osteosarcopenic obesity

Osteosarcopenic obesity, was first described in 2014 [75]. The definition that was initially proposed by Ilich et al., included the presence of hip or lumbar spine T-score ≤ -1.0, ALM normalized to height ≤5.45 (women) or ≤7.26 kg/m2 (men), and total body fat >40% (women) or >30% (men) [75]. Grip strength and Short Physical Performance Battery (SBBP) was then added as the proposed definition of sarcopenia was modified [76]. Some studies have suggested that osteosarcopenic obesity is associated with poorer outcomes compared to osteoporosis and sarcopenia alone [77–81].

# Clinical approach to the osteosarcopenic patient

## Diagnosis

The presence of sarcopenia which is associated with low BMD with or without clinical fracture, has been defined by some researchers as osteosarcopenia as shown in Figure 1. Its clinical management is discussed here.

## Investigations

Further to the diagnostic classification for osteoporosis and sarcopenia described earlier, specific guidelines which provide recommendations on imaging and biochemical workup are lacking. The possibility of secondary causes of osteosarcopenia should be considered; these include screening for hyperparathyroidism, Vitamin D deficiency and other vitamin deficiencies such as Vitamin B, A and C, systemic inflammation and chronic inflammatory disorders, renal disorders, glucocorticoid use, hyperhomocysteinaemia and low protein intake. Bone turnover markers, creatinine kinase, parathyroid hormone (PTH) and Vitamin D levels should be checked where indicated as disturbances are common in osteosarcopenic patients.

# Management

## Nonpharmacological interventions and treatment

Advice to patients and referral to smoking cessation services should be encouraged. Exercise and nutritional support remain central to osteosarcopenia management. Randomised controlled trials have demonstrated the efficacy of progressive resistance exercise to stimulate osteoblastogenesis and muscle protein synthesis [82,83]. Multi-modal programs which incorporate traditional and high velocity progressive resistance training, weight bearing exercises and balance/mobility activities has been suggested as the best approach for osteosarcopenia [53].

The recommended dietary allowance of protein of 0.8 g protein/Kg/Day may be inadequate for older people to meet their metabolic and physiological needs [84]. An international study group suggested that in healthy older individuals both endurance and resistance type exercises are recommended with higher protein intake of at least 1/2g/Kg body weight/day for those who remain active [85]. Research studies have suggested that protein intake has benefited patients with osteosarcopenia [86].

Higher baseline Vitamin D concentrations and dietary protein intake have been associated with greater gain in appendicular muscle mass, skeletal muscle index and relative appendicular muscle mass in response to nutritional interventions [87]. These findings suggest that sufficient vitamin D and protein intake may be required before any pharmacological intervention in individuals with sarcopenia [88]. Administration of activated Vitamin D, alfacalcidol, has also been associated with increased muscle mass [89]. In contrast however, annual oral administration of high-dose cholecalciferol resulted in an increased risk of falls and fractures in one study and indeed [90] conflicting evidence of Vitamin D supplementation in osteosarcopenic patients was found in a recent review [71]. It has been suggested that creatine may increase muscle mass and strength as well as bone density, but further studies are required to establish any benefit of creatine in osteosarcopenic patients [85]. Finally vitamin E may reduce muscle atrophy especially when caused by long term corticosteroids use and it may be a potential treatment for steroid induced osteosarcopenia [91].

## Pharmacologic treatments

There are no approved pharmacological agents for osteosarcopenia so the focus on pharmacological treatment relies on osteoporosis treatment. Denosumab, a RANKL ligand inhibitor, has shown promising effects on muscle and bone health [92]; was associated with reduced falls [93] while handgrip strength and LBM was increased significantly when compared to treatment with IV zoledronic acid [92]. In a non-randomised study of community dwelling older adults, it has shown improvement in measurements of balance, fear of falling and physical action when compared to IV zoledronic acid [94].

As discussed previously, testosterone levels drop with age and are considered an important cause of age-related musculoskeletal disorders. It has been shown that replacement of testosterone improves muscle mass and function in older adults [95]. In studies of community dwelling frail older [96,97] and healthy individuals [98] researchers demonstrated benefits of treatment for muscle strength and gait but those effects did not last post discontinuation of testosterone. In a review of testosterone trials, increase in the distance walked, and in volumetric BMD was found in older individuals but it was also noted that treatment resulted in increased coronary plaques volume without been associated with more cardiovascular events [99]. Andarine and Ostarine have also been shown to increase lean mass and physical function in older males and post-menopausal females [100,101] but there is no clear benefit of selective androgen receptor modulators (SARMs) to bone health in humans.

Myostatin inhibitors have been suggested as a possible treatment for osteosarcopenia. In a phase II trial in older adults with a history of falls, antimyostatin antibodies increased lean body mass and improved functional measures associated with muscle strength [102] but the benefit in bone health has not been established in clinical trials. Studies in sarcopenic patients have shown that Bimagrumab, a human monoclonal antibody which binds to type II activin receptors and prevents the binding of myostatin and activin A, has demonstrated significant increases in muscle mass and strength in older adults [103].

# Summary

Osteoporosis and sarcopenia are age related conditions and is expected that the prevalence of these will grow over the coming years, negatively impacting individuals and healthcare systems. These two conditions share common pathophysiological mechanisms and for this reason an interest and attempt to treat and manage these pathologies as one is growing. The coexistence of osteoporosis and sarcopenia has been termed osteosarcopenia, with an additional subclassification of osteosarcopenic obesity. Its prevalence depends upon the population under investigation, but it is linked to several adverse outcomes including falls and fractures, and even increased mortality risk. Clinicians should now become increasingly aware of the interrelationship of muscle and bone which will facilitate the early identification, diagnosis and management of individuals suffering from osteosarcopenia. Lifestyle interventions, including promotion of physical activity and attention to nutritional status remains the cornerstone of management, with several pharmacologic therapeutic interventions under evaluation. Currently more therapeutic options are available for osteoporosis but some existing treatments such as denosumab already have evidence of benefit for both muscle and bone health.

# Practice points

* Established criteria are available for the diagnosis of both osteoporosis and sarcopenia
* Investigations should consider possible underlying conditions that might increase vulnerability to both osteoporosis and sarcopenia e.g. screening for hyperparathyroidism, Vitamin D deficiency, systemic inflammation, renal disorders, glucocorticoid excess
* Lifestyle factors including increased physical activity level and adequate protein intake remain very important in management

# Research agenda

* There is a need to better understand the interplay of muscle and bone ageing
* This should include work that considers pathophysiology, as well as shared lifestyle risk factors
* Well-designed trials of pharmacological agents that combat osteosarcopenia are urgently required

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# Conflict of interest

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HP and FL have no conflicts to declare.

CC has received lecture fees and honoraria from Amgen, Danone, Eli Lilly, GSK, Kyowa Kirin, Medtronic, Merck, Nestlé, Novartis, Pfizer, Roche, Servier, Shire, Takeda and UCB outside of the submitted work.

# Figure

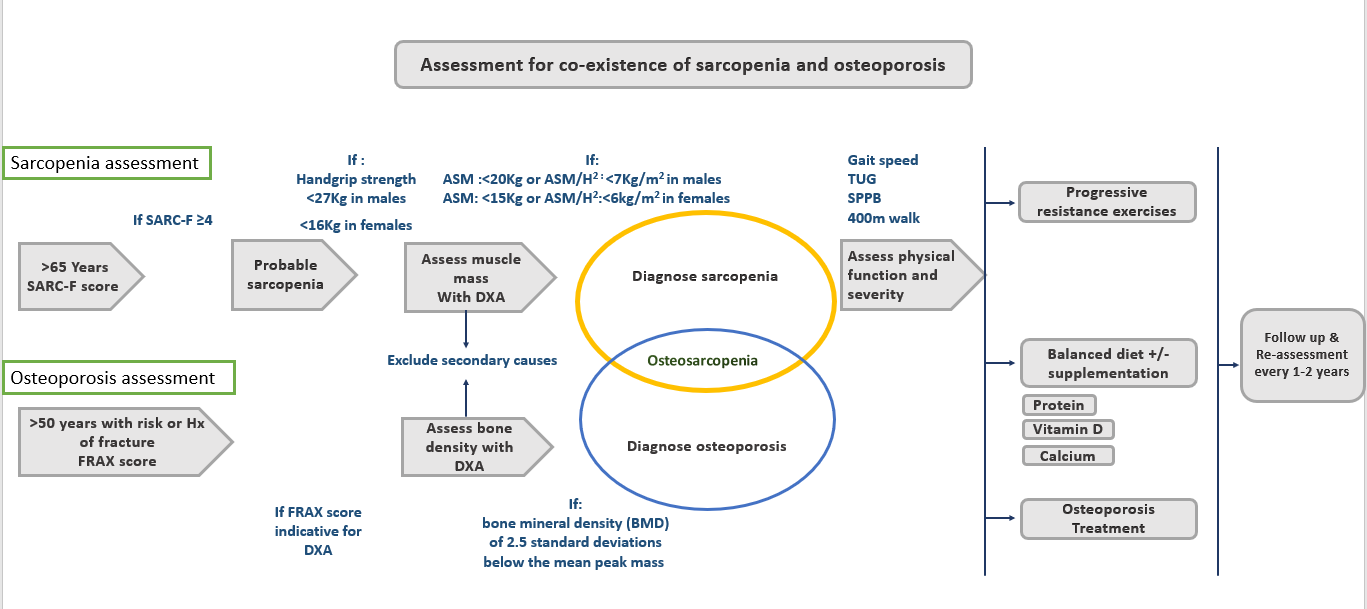


Figure :Proposed pathway to identify and diagnose patients with osteosarcopenia based on recent EWGSOP2 criteria for sarcopenia and NICE criteria for osteoporosis.

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