Osteosarcopenia

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Abstract

Osteosarcopenia is a newly described syndrome that describes the co-existence of osteoporosis and sarcopenia, two chronic musculoskeletal conditions associated with ageing. Osteoporosis, a condition of low bone mass and micro-architectural deterioration of bone, and sarcopenia, the loss of muscle mass, strength and function, often co-exist in a frail subset of the elderly population, leading to significantly worsened outcomes than seen in either condition alone. These include a greater risk of falls, fractures, and institutionalisation, and significant socioeconomic costs. With our ageing population, osteosarcopenia is a public health concern that will become increasingly relevant in the future. Its aetiology is multi-factorial, with mechanical, biochemical, genetic and lifestyle factors all contributing to involution of the "bone-muscle unit". Our increasing understanding of the interactions between muscle and bone could facilitate the development of new therapeutic agents which target muscle and bone as one. Together with existing pharmacological, nutritional and exercise-based therapies, this should enable a more holistic approach to osteosarcopenia in the future.

MeSH Terms

Aged; Sarcopenia; Accidental Falls; Osteoporosis; Osteoporotic Fractures; Muscle Strength

Introduction

Osteoporosis and sarcopenia are two chronic musculoskeletal conditions that can have devastating impacts both on individuals and wider society. With an ageing population, both

conditions are likely to become increasingly prevalent in future, increasing the incidence of fragility fractures, and leading to greater morbidity, mortality and socioeconomic costs (Edwards et al., 2015).

Around 1 in 2 women and 1 in 5 men over 50 years old will sustain an osteoporotic fracture throughout their remaining lifetime, with more than 8.9 million osteoporotic fractures sustained annually worldwide (Hernlund et al., 2013). In 2010, the direct cost of osteoporotic fractures in EU countries was estimated at a staggering €35.4 billion, with hip fractures representing 54% of the cost. In the UK alone, around 79,000 hip fractures occurred in 2010 (Hernlund et al., 2013), with up to 1 in 3 patients dying within 1 year (Klop et al., 2014).

Osteoporosis, characterised by low bone mass and micro-architectural deterioration of bone tissue (Edwards et al., 2015), and sarcopenia, the loss of muscle mass, strength and function (Fuggle et al., 2017), are increasingly recognised as a "hazardous duet" in the pathogenesis of fragility fractures, with the sarcopenic propensity for falls acting synergistically with the osteoporotic vulnerability of bones to increase fracture risk (Crepaldi and Maggi, 2005). As such, "sarco-osteopenia", now more commonly known as "osteosarcopenia", has been proposed as a new term to represent a frail subset of the elderly population with concomitant osteoporosis and sarcopenia (Binkley and Buehring, 2009). These patients are at significantly higher risk of falls, fractures and institutionalisation (Huo et al., 2015), and have a significantly higher mortality rate than osteoporotic or sarcopenic patients alone (Yoo et al., 2018).

An increasing body of evidence demonstrates considerable overlap in the pathophysiology of osteoporosis and sarcopenia, bringing with it exciting possibilities to treat the conditions together. Bone and muscle not only interact mechanically, known as the 'mechanostat hypothesis' (Frost, 2003), but also communicate with each other biochemically via complex paracrine and endocrine mechanisms in order to maintain muscle and bone homeostasis (Girgis et al., 2014). This has facilitated development of new therapeutic agents which exploit this bone-muscle crosstalk (Girgis et al., 2014), which will be discussed later in this review.

With our ageing population and the enormous socio-economic impact of fragility fractures, it is imperative that clinicians are aware of osteosarcopenia and the ways in which we can prevent and treat it. This review summarises the latest developments in osteosarcopenia, with a focus on epidemiology, diagnosis, pathophysiology and management.

Epidemiology

Osteoporosis

Osteoporosis affects hundreds of millions of people worldwide; in the EU alone, around 27.6 million had osteoporosis in 2010, representing a prevalence of 6.6% and 22.1% respectively in men and women over 50 years of age. In the UK, around 536,000 fragility fractures occur each year, with hip (79,000), forearm (69,000) and spine (66,000) being the most frequent sites (Hernlund et al., 2013).

Hip fractures represent the most devastating consequence of osteoporosis, associated with significant morbidity and mortality. In the UK, permanent disability affects 50% of hip fracture patients (Chan et al., 2016), and UK data suggest a 1-year mortality rate after hip fracture of 34.4% and 27.7% respectively in men and women 85 years of age (Klop et al., 2014).

Osteoporotic fractures carry a significant economic burden due to the costs of treatment and long-term care. In the UK, osteoporotic fractures cost the health service £4.4 billion in 2010 (Compston et al., 2017). The economic burden of osteoporotic fractures is likely to rise significantly in the future, with costs predicted to swell by 25% in the EU between 2010 and 2025 (Hernlund et al., 2013).

Sarcopenia

Sarcopenia is also generally a condition of ageing: above 50 years of age, muscle mass is lost at a rate of 1-2% per year, with strength falling more precipitously at 1.5-3% per year (von Haehling et al., 2012). Due to a lack of consensus regarding the definition of sarcopenia, the prevalence rate varies widely; however, it is estimated at 5-13% for adults aged 60-70, and 11-50% for adults >80 years old (von Haehling et al., 2012). Sarcopenia currently affects >50 million worldwide, which is expected to rise to >200 million over the next 40 years (Cruz-Jentoft et al., 2010).

Sarcopenia contributes to frailty, disability, premature mortality, psychosocial problems and worsened quality of life (Janssen et al., 2004, Fuggle et al., 2017). It carries a significant economic burden, with direct healthcare costs attributed to sarcopenia estimated at $18.5 billion in the USA in 2000 (Janssen et al., 2004). Another major consequence of sarcopenia is that it pre-disposes many elderly patients to falls, increasing the risk of fragility fractures (Edwards et al., 2015).

Osteosarcopenia

Epidemiological measures of osteosarcopenia are fairly limited due to the recent origin of the term. However, one large study of 680 elderly adults with a history of falls found an osteosarcopenia prevalence of 37%, with these patients having a higher frequency of co-morbidities, impaired mobility and depression (Huo et al., 2015).

Osteosarcopenia is also associated with significantly increased mortality: one recent study of 324 elderly Korean patients with hip fracture found a 1-year mortality rate of 15.1% in the osteosarcopenic patients, more than that of osteoporotic (5.1%) or sarcopenic (10.3%) patients alone (Yoo et al., 2018). Another study of 316 Chinese adults 65 years old found that 10.4% of men and 15.1% of women were osteosarcopenic, with the odds of frailty being significantly higher in the osteosarcopenic patients compared to osteoporosis or sarcopenia alone (Wang et al., 2015).

Diagnosis

The diagnosis of osteosarcopenia represents co-existence of both osteoporosis and sarcopenia, as explained below.

Osteoporosis

Osteoporosis is defined as a "systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" (CDC, 1993). In 1994, the World Health Organisation (WHO) developed specific criteria to define osteoporosis in postmenopausal women, based on bone mineral density (BMD) (WHO, 1994) (See Table 1).

The reference technology to assess BMD recommended by WHO is dual-energy X-ray absorptiometry (DXA) applied to the femoral neck. The femoral neck was chosen as the reference site for diagnosis due to its higher predictive value of fracture risk (Compston et al., 2017); however, lumbar spine measurements are more effective at monitoring treatment-induced changes (Hernlund et al., 2013).

Although BMD explains part of the risk of fragility fractures, many other risk factors operate independently of BMD to increase fracture risk. These include low BMI, previous osteoporotic fracture, parental history of hip fracture, smoking, steroids, rheumatoid arthritis and alcohol (Compston et al., 2017). Thus, fracture risk algorithms were developed that incorporate these risk factors, with or without BMD, to optimise risk stratification (Binkley and Buehring, 2009).

The most famous of these is the Fracture Risk Assessment Tool (FRAX), which predicts an individual's risk of major osteoporotic and hip fracture over the next 10 years. In the UK, the National Institute for Health and Clinical Excellence (NICE) recommend screening all women and men over 65 and 75 years old respectively, assisted by either FRAX or QFracture (another fracture risk algorithm in the UK). The National Osteoporosis Guideline Group (NOGG) have created intervention thresholds for treatment based on FRAX estimates, allowing better targeting of treatment to those patients with the highest risk (Compston et al., 2017).

Sarcopenia

Sarcopenia describes the age-related loss of skeletal muscle mass, strength and function (Fuggle et al., 2017). In 2009, the European Working Group on Sarcopenia in Older People (EWGSOP) was the first to develop an operational definition of sarcopenia incorporating measures of these parameters (Cruz-Jentoft et al., 2010), with other working groups providing their own definitions since (Fielding et al., 2011, Chen et al., 2014, Studenski et al., 2014) (See Table 2).

DXA is currently the modality of choice to assess muscle mass, as it is quantitative, inexpensive, minimises radiation exposure, and is widely available with its current role in osteoporosis (Binkley and Buehring, 2009). Bioimpedance analysis (BIA) is another technique which is significantly more portable than DXA - useful in immobile, bedridden patients (Cruz-Jentoft et al., 2010). The most common means to assess muscle strength is grip strength using a hydraulic dynamometer, with the best of three attempts recorded (Fuggle et al., 2017). This technique is simple, requiring little training, and also correlates well with lower limb strength (Oliveira and Vaz, 2015). Finally, the most reliable measure of

muscle performance in clinical practice is gait speed, with EWGSOP advising a cut-off for sarcopenia of 0.8m/s (Cruz-Jentoft et al., 2010).

The heterogeneity in definitional approaches towards sarcopenia has limited comparability between studies, with differences in measured parameters, regions of interest and the absence of a standardised reference population all limiting progress (Binkley and Buehring, 2009). However, a significant breakthrough occurred in 2016, with the inclusion of a separate 'sarcopenia' diagnosis in the International Classification of Disease (ICD-10) (Anker et al., 2016).

Pathophysiology

The pathogenesis of osteosarcopenia is multifactorial, with an array of mechanical, biochemical, genetic and lifestyle factors all contributing to involution of the "bone-muscle unit" (Girgis et al., 2014).

Mechanical

The traditional view of the prominent mechanical interactions between muscle and bone is emphasised by the 'mechanostat' hypothesis. This theory states that muscle imposes mechanical forces on bone, with a certain threshold dictating whether bone is formed or resorbed (Frost, 2003). An increase in muscle mass leads to stretching of collagen fibres and periosteum, leading to stimulation of bone growth (Kaji, 2014). Both osteoporosis and sarcopenia can result from reduced physical activity observed in ageing (Daly, 2017), lending support to the role of mechanical loading in preserving the bone-muscle unit.

Biochemical

Although mechanical forces clearly have a significant role in the pathogenesis of osteosarcopenia, more recent research suggests paracrine or endocrine cross-talk is also at play.

Important hormones mediating this crosstalk include growth hormone/insulin-like growth factor-1 (GH/IGF-1), gonadal sex hormones and vitamin D, with age-related decreases contributing to the development of osteosarcopenia (Girgis et al., 2014). Muscle and bone also secrete certain factors, known as myokines and osteokines respectively, which aid the communication between muscle and bone (Girgis et al., 2014). An extensively researched myokine is myostatin, a member of the transforming growth factor beta (TGF-β) superfamily which inhibits skeletal muscle growth, but also has effects on bone and tendon (Kaji, 2014).

Bone-muscle crosstalk is mediated by several important signalling pathways. For example, the canonical Wnt-β-catenin signalling pathway controls osteoblastic activity and is also involved in muscle regeneration (Oliveira and Vaz, 2015); the GH/IGF-1 axis is a key regulator of bone and muscle growth, mediating its effects via several signalling pathways. There is hope that exploiting these pathways will facilitate the development of new therapeutic agents in the future (Girgis et al., 2014).

Genetic

Genetic polymorphisms of various genes also contribute to the pathogenesis of osteocarcopenia. As reviewed by Kaji et al., these include androgen receptor, estrogen receptor, catechol-O-methyltransferase, IGF-I, vitamin D receptor and low-density-lipoprotein receptor-related protein (Kaji, 2014). Moreover, since muscle and bone cells are both derived from mesenchymal stem cells, they are both influenced by similar genetic factors. Risk factors for both osteoporosis and sarcopenia have a heritability in the range of 60-70% (Kaji, 2014).

Lifestyle factors

Physical activity diminishes with ageing, with up to 80% of waking hours spent sedentary in the elderly (Harvey et al., 2015), leading to a loss of mechanical loading and therefore bone and muscle loss (Frost, 2003). Calorific intake diminishes by around 25% between the ages of 40 and 70 (Nieuwenhuizen et al., 2010), with reduced vitamin D levels and protein intake correlated with declining muscle strength (Marty et al., 2017). Vitamin D deficiency also leads to increased risk of falls through its multiple effects on muscle and bone (Kaji, 2014). Smoking and alcohol are significant risk factors for osteoporosis, with intake of 3 units of alcohol/day increasing fracture risk in a dose-dependent fashion (Compston et al., 2017).

Management

Treatments for osteosarcopenia include exercise, improved nutrition and pharmacotherapy.

Exercise

Exercise has many positive effects on the older population, with one meta-analysis finding exercise reduced overall fracture risk by 51% in adults over 45 years old (Kemmler et al., 2013). The optimal approach for osteosarcopenia may be targeted multi-modal programs which incorporate traditional and high-velocity progressive resistance training (PRT), weight-bearing impact exercises and challenging balance/mobility activities (Daly, 2017).

Exercise programmes are even effective for frailer adults, with a meta-analysis of elderly residents in long-term care demonstrating a 29% reduced risk of falls in those that underwent combined resistance and balance training programmes (Silva et al., 2013). Regular exercise also reduces bone loss, particularly at the femoral neck (Girgis et al., 2014).

Nutrition

Nutritional approaches to osteosarcopenia focus on vitamin D, calcium and protein intake.

Vitamin D supplementation can have many beneficial effects, including increased muscle strength, decreased mortality and falls, and functional improvement (Oliveira and Vaz, 2015). The evidence base for supplementation is stronger in older, institutionalised adults and those who are initially deficient (Girgis et al., 2014, Daly, 2017). Guidelines generally advocate 800-2000 IU/day in older adults, aiming for a target serum 25(OH)D of at least 50 nmol/L (20 ng/ml) (Girgis et al., 2014). Adequate calcium intake is also advised in patients

with osteosarcopenia, with a recommended daily intake of 700 – 1200 mg (Compston et al., 2017). Meta-analyses show combined supplementation of vitamin D and calcium is safe, and effectively reduces fracture risk in older individuals (Daly, 2017).

In the USA, 5-12% of older men and 20-24% of older women consume inadequate protein (defined as <0.66g/kg body weight per day) (Berner et al., 2013). Moreover, there is evidence to suggest a blunted anabolic response to protein in the elderly, further compounding the problem of insufficient intake (Daly, 2017). Thus, a higher protein intake of 1.0-1.2g/kg/day is recommended in the elderly, with at least 20-25g of high-quality protein with each meal and post-exercise (Rizzoli et al., 2014).

Pharmacotherapy

Most pharmacotherapies for osteosarcopenia target bone, although several new therapies are being developed which also target muscle (Girgis et al., 2014). In the UK, NOGG offer intervention thresholds for treatment based on 10 year fracture probability derived from FRAX (Compston et al., 2017).

For osteoporosis, bisphosphonates such as alendronate, risedronate and zoledronate remain the first-line treatment. They work via signalling pathways which induce apoptosis of osteoclasts, thus reducing bone resorption, and increasing BMD (Chan et al., 2016). Other major pharmacological therapies for osteoporosis include denosumab (receptor activator of nuclear factor kappa B (RANKL) inhibitor that inhibits osteoclastogenesis); selective oestrogen receptor modulators (SERMs) such as raloxifene (partial oestrogen agonist selective for bone); and anabolic agents such as teriparatide (a recombinant form of parathyroid hormone). The latter treatment is restricted to high-risk fracture patients' refractory to other treatment, due to its high expense (Chan et al., 2016).

Several new therapies are being developed which target muscle in addition to bone. Selective androgen receptor modulators (SARMs), such as andarine, have anabolic effects in muscle and bone, and due to their high tissue selectivity, limit the androgenic side-effects associated with testosterone therapy (Girgis et al., 2014). Other promising agents centre on the activin-signalling pathway, and include myostatin-neutralising antibodies/propeptide, recombinant follistatin, follistatin derivatives, and soluble activin receptors (Girgis et al., 2014).

Pathways that centrally regulate bone and muscle, such as GH/IGF-1 and androgen signalling, can also be targeted. Possible therapeutic agents include recombinant GH (which increases lean mass and lumbar BMD, but has safety issues), GH secretagogues (which increase GH/IGF-1 levels through more "physiological" means), and testosterone therapy (which has positive effects on muscle mass, strength and BMD, but is limited by androgenic side effects and concerns about cardiovascular events and prostate cancer) (Girgis et al., 2014).

In the future, improved understanding of bone-muscle crosstalk will bring further novel drugs and biomarkers for osteoporosis and sarcopenia (Kaji, 2014), bringing great therapeutic benefits to patients with osteosarcopenia.

Conclusion

Osteosarcopenia is a condition of growing importance with significant negative sequelae on both patients and society alike. For individuals, major consequences include falls and fractures, increased morbidity, mortality and disability, and reduced quality of life. For society, osteosarcopenia brings a staggering socioeconomic burden. With population ageing, the number of individuals 60 years old worldwide is set to increase from around 600 million in 2000 to 2 billion by 2050 (Cruz-Jentoft et al., 2010); as such, the incidence of osteosarcopenia will increase dramatically over the coming decades.

However, there are reasons to be hopeful. A growing consensus of the definition of sarcopenia will facilitate better recruitment to studies, and allow optimal measurement of muscle health outcomes in therapeutic trials (Edwards et al., 2015). As our understanding of the bone-muscle unit increases, there should be development of new therapies which embrace both osteoporosis and sarcopenia by targeting pathways that affect both muscle and bone. Lifestyle interventions can further help, with clear positive benefits of exercise and improved nutrition on osteosarcopenia. All of this should enable a more holistic approach to osteosarcopenia in the future, with benefits to millions of patients worldwide.

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Key points

- Osteosarcopenia is a new syndrome describing the co-existence of osteoporosis and sarcopenia.

- Osteoporosis is characterised by low bone mass and micro-architectural deterioration of bone tissue.

- Sarcopenia describes the loss of muscle mass, strength and function.

- Individuals with osteosarcopenia are at higher risk of falls, fractures, and institutionalisation, resulting in significant socioeconomic costs.

- An array of mechanical, biochemical, genetic and lifestyle factors contribute to the pathogenesis of osteosarcopenia.

- Treatment approaches include exercise, improved nutrition and pharmacotherapy.

- An increasing awareness of bone-muscle interactions should facilitate the development of novel pharmacological agents in the future.

Table 1

WHO classification of osteopenia/osteoporosis. Bone mineral density (BMD) is expressed in standard deviations (SD) relative to a sex-specific, young-adult mean (known as the T-score). (WHO, 1994).

BMD category	Definition
Normal	BMD no greater than 1 SD below the reference mean (T-score ≥ -1)
Osteopenia	BMD between 1 and 2.5 SD below the reference mean (T-score < -1 but > -2.5)
Osteoporosis	BMD 2.5 SD or more below the reference mean (T-score ≤ -2.5)
Severe osteoporosis	BMD 2.5 SD or more below the reference mean (T-score ≤ -2.5) **PLUS** one or more fragility fractures

Table 2

Cut-off thresholds for the diagnosis of sarcopenia employed by the European Working Group on Sarcopenia in Older People (EWGSOP), International Working Group on Sarcopenia (IWGS), Foundation of the National Institute of Health (FNIH) and Asian Working Group on Sarcopenia (AWGS). DXA = dual-energy X-ray absorptiometry. ALM = appendicular lean mass (kg). BMI = body mass index. (Cruz-Jentoft et al., 2010, Fielding et al., 2011, Chen et al., 2014, Studenski et al., 2014).

Working Group	Diagnostic criteria for sarcopenia		
	Muscle mass (DXA)	Muscle strength	Physical performance
European Working Group on Sarcopenia in Older People (EWGSOP)	ALM/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**: < 30kg **Women**: < 20 kg Also provide cut-offs based on patient's BMI.	Gait speed **Both sexes**: 0.8 m/s
International Working Group on Sarcopenia (IWGS)	ALM/height^2 **Men**: 7.23 kg/m^2 **Women**: 5.67 kg/m^2	N/A	Gait speed **Both sexes**: < 1m/s
Foundation of the National Institute of Health (FNIH)	ALM/BMI **Men**:< 0.789 **Women**: < 0.512	Grip strength **Men**: < 26 kg **Women**: < 16 kg	N/A
Asian Working Group on Sarcopenia (AWGS)	ALM/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