**Osteosarcopenia: Where Osteoporosis and Sarcopenia Collide**

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**Abstract**

The coexistence of osteoporosis and sarcopenia has been recently considered in some groups as a syndrome termed ‘osteosarcopenia’. Osteoporosis describes low bone mass and deterioration of the micro-architecture of the bone, whereas sarcopenia is the loss of muscle mass, strength and function. With an ageing population the prevalence of both conditions is likely to increase substantially over the coming decades and is associated with significant personal and societal burden. The sequelae for an individual suffering from both conditions together include a greater risk of falls, fractures, institutionalisation and mortality. The aetiology of ‘osteosarcopenia’ is multifactorial with several factors linking muscle and bone function including genetics, age, inflammation and obesity. Several biochemical pathways have been identified which are facilitating the development of several promising therapeutic agents which target both muscle and bone. In the current review we outline the epidemiology, pathogenesis and clinical consequences of ‘osteosarcopenia’ and explore current and potential future management strategies.

**Key words**

Bone, muscle, osteoporosis, sarcopenia, osteosarcopenia, falls, fracture, strength.

**Introduction**

Osteoporosis and sarcopenia are both common age-associated diseases which often co-exist. Within an ageing population the prevalence of both these conditions is expected to rise in the future, increasing the risk of fragility fractures, which are themselves associated with significant morbidity and mortality [1]. Hence, losses in independence seen in later life are associated with both bone and muscle loss [2].

The economic burden of osteoporotic fragility fractures is high, costing approximate £4 billion per annum in the UK [3]. Osteoporosis is characterized by deterioration in bone microarchitecture resulting in reduced bone mineral density (BMD), increased bone fragility and a heightened risk of fracture even as a consequence of minor trauma [4]. [5].

Unlike osteoporosis, the economic burden of sarcopenia is poorly characterized, although one study estimated direct costs attributable to sarcopenia in the USA, in the year 2000, to be $18.5 billion [6]. A recent systematic review exploring the healthcare costs of sarcopenia showed a large heterogeneity between studies but, globally, showed trends towards greater healthcare costs for the sarcopenic population [7]. The etymology of sarcopenia is from the Greek ‘sarx’ for muscle and ‘penia’ meaning ‘loss’ [8]. It is a condition characterized by progressive, age-related loss of muscle mass and function. Unlike osteoporosis, no single broadly accepted clinical definition of sarcopenia has yet been established, although all definitions recognise that measuring muscle mass in isolation is inadequate, as a measure of muscle function is also required. Sarcopenia was previously defined, in 2010, by the European Working Group on Sarcopenia (EWGSOP) as the presence of low muscle mass, reduced muscle strength and physical performance [9]. This definition was updated in 2019 (EWGSOP2) with a greater focus on low muscle strength as the primary parameter characterising sarcopenia [10]. The new definition defines sarcopenia as reduced hand grip strength or chair stand test together with a reduced skeletal muscle mass index, with severe sarcopenia defined as additional poor physical performance, as assessed by gait speed, timed up and go, short performance battery test and 400 metre walk test. A further definition of sarcopenia proposed by the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project, similarly comprises grip strength and ALM/BMI (ratio of appendicular lean mass over body mass index [BMI]) [9]. Epidemiological studies have found an association between sarcopenia and falls history, whether defined by the EWGSOP [11,12] or by using ALM/BMI [13]. Furthermore, a study of older community-dwelling individuals from the Hertfordshire Cohort Study (HCS) has shown that sarcopenia, as defined using the FNIH definition, is associated with higher prevalent fractures [14].

When osteoporosis and sarcopenia occur in consort it has recently been suggested that they are referred to as ‘osteosarcopenia’ [7. It should be noted that the few studies that have considered this issue suggest the risks of serious morbidity are notably higher when osteoporosis and sarcopenia co-exist [15]. Furthermore, evidence showing overlap in the pathophysiology of sarcopenia and osteoporosis raises the possibility of common potential treatments for the two conditions [16]. Indeed, new medications are being developed which exploit the cross-talk between bone and muscle and will be explored in this review [17].

**Prevalence of coexistence of osteoporosis and sarcopenia**

Bone mass typically reduces by approximately 30% between the third and seventh decades [18] and it is estimated that 1 in 3 women and 1 in 5 men over the age of 50 years will suffer a fragility fracture [19]. In older people, fractures occur more frequently in females, with rates becoming approximately twice those of men over the age of 50; in older individuals, the forearm, hip and vertebrae are the sites most susceptible to fracture [20].

Muscle fibre parameters appear relatively stable until the end of the fourth decade of life, after which muscle fibre loss accelerates resulting in approximately 30% loss of muscle mass by 80 years of age [9]. Sarcopenia is a common condition of ageing with a prevalence in community-dwelling older individuals varying from between 1 and 29% in populations over the age of 50 years, based on the EWGSOP [21] and is projected to affect more than 200 million individuals worldwide in the next 40 years [9].

In contrast to osteoporosis and sarcopenia considered individually, there are few data on the epidemiology of osteosarcopenia, as the condition has only recently been proposed. A UK study has reported that in osteoporotic postmenopausal females the prevalence of sarcopenia was 50% [15], while a study by Di Monaco and colleagues of 340 Italian Caucasian women with hip fracture, who subsequently underwent DXA scanning, showed that for sarcopenic woman the adjusted OR for T-Score ≤-2.5 was 1.80 (95%CI 1.07–3.02) [22]. Evidence supports an increased prevalence of osteosarcopenia with advancing age, with a Chinese study of adults over the age of 80 years reporting rates of 10.4% in men and 15.1% in women [23]. More recently, a study of 288 older subjects in Belgian showed that sarcopenic subjects had a 4-fold higher risk of having co-existing osteoporosis compared with non-sarcopenic individuals (OR = 4.18; 95% CI 1.92–9.12) [24].

**Consequences of the coexistence of osteoporosis and sarcopenia in patients**

Coexistence of sarcopenia and osteoporosis has been associated cross-sectionally with depression, malnutrition, peptic ulcer disease, inflammatory arthritis and reduced mobility [15]. Studies from Australia and China have demonstrated that individuals with both osteoporosis and sarcopenia are at higher risk of falls and fractures than those with osteoporosis or sarcopenia alone [15,23]. The resultant fractures, and particularly hip fractures, are associated with significant morbidity; approximately half of previously ambulatory individuals are unable to mobilise independently post hip fracture [25]. Furthermore, 55% of individuals above 90 years of age are unable to live independently following fracture [25]. Frailty is defined as a multidimensional syndrome of loss of reserves (energy, physical ability, cognition, health) that gives rise to vulnerability in older people [26]. A number of older people are both frail or prefrail, and also have osteoporosis and sarcopenia; in one study the conditions were found to co-exist in 26.3% of frail men and 38.5% of frail women (compared to 1.6% of non-frail men and 1.9% of non-frail women) [23]. In a study of Korean hip fracture patients, where 1 year mortality overall was remarkably low, the presence of osteosarcopenia was associated with a 1-year mortality rate of 15.1% compared to patients with osteoporosis (5.1%) or sarcopenia alone (10.3%) [27].

**Factors associated with osteoporosis and sarcopenia**

*Genetic factors*

Genetic factors are important in the achievement of peak bone mass [28]. [29]. Recent data from UK Biobank suggest that muscle strength, and therefore likely sarcopenia, is also partially genetically regulated [30]. Vitamin D receptor polymorphisms have been shown to be associated with both sarcopenia and osteoporosis [31].

*Alcohol*

Excess alcohol intake has a detrimental effect on skeletal health. In addition to its direct toxic effect on osteoblast function, there are additional adverse effects on gonadal function, protein metabolism, calcium metabolism, physical activity and falls risk [32-34]. A meta-analysis conducted by Kanis and colleagues showed that drinking above 2 units of alcohol a day is associated with an increased risk of fracture [35]. There is limited evidence linking alcohol use to muscle mass but a study of 608 community-dwelling older men in France has demonstrated that heavy alcohol intake (>210 g/week) is associated with low muscle mass [36].

*Cigarette Smoking*

Like alcohol, cigarette smoking has a deleterious effect on both bone and muscle health. A meta-analysis by Law and colleagues demonstrated worse bone health in female smokers compared with non-smokers[37]. The mechanism through which cigarette smoking impacts upon BMD and fracture risk is multifactorial and likely to include the increased likelihood of early menopause, on average 9 months earlier, enhanced metabolism of exogenous oestrogens and reduced body weight [2]. Both smoking and alcohol intake are well established risk factors for fracture and are therefore included in the FRAXTM fracture risk assessment tool [38].

There is less evidence linking cigarette smoking to loss of muscle mass but a recent meta-analysis showed cigarette smoking was associated with an increased risk of developing sarcopenia [39]. The association between cigarette smoking and sarcopenia may be as a consequence of smoking being associated with low levels of physical activity and low BMI [40,41].

*Physical activity*

Physical activity levels have a profound impact on both bone and muscle health. Studies have demonstrated that physical activity prevents bone loss; the most effective type of exercise intervention on femoral neck BMD appears to be non-weight bearing high force exercise such as progressive resistance strength training for the lower limbs while the most effective intervention for spine BMD was combination exercise programmes[42]. Conversely, prolonged immobilisation is associated with reduction in BMD and increased fracture risk [43]. There are several trials which have shown that exercise in older people results in improved muscle mass and physical performance [44]. [45].

*Diet*

There is evidence to suggest that a good diet is essential for the development and maintenance of good bone and muscle health. For example, adequate calcium and vitamin D intake has been linked to both bone and muscle mass [46]. Weak evidence was detected to support a reduction in fracture risk when taking calcium alone [RR 0.90 (95% CI 0.80, 1.00)]. By contrast, a meta-analysis conducted by Bischoff-Ferrari and colleagues found a potentially increased risk of hip fracture in individuals taking calcium supplementation alone, although a relatively low number of participants were included [47]. The analysis performed by Tang and colleagues showed that when calcium and vitamin D supplementation were combined, the RR of any fracture was 0.87 (95% CI 0.77, 0.97), compared with 0.90 (95% CI 0.80, 1.00) for calcium alone [46]. Additionally, a meta-analysis conducted by Bolland and colleagues demonstrated that a combination of calcium with vitamin D supplementation reduced the risk of all fractures (RR 0.89 (95% CI 0.86, 0.99)) and vertebral fractures (RR 0.86 (95% CI 0.74, 1.00)), but not forearm or hip fractures [48]. Overall, these data suggest that a combination of vitamin D and calcium supplementation affords a modest reduction in fracture risk and is more effective than calcium supplementation alone. There is less evidence for the use of calcium supplementation alone in reducing muscle mass and function decline [49,50]. There is evidence to suggest that supplementation with vitamin D has a small yet significant effect on increasing muscle strength, but not muscle mass or power [51]. The effect was most pronounced in patients with baseline vitamin D deficiency. Furthermore, experimental studies have demonstrated both histological and electrophysiological changes in muscle in severe vitamin D deficiency [52-54]. There is some evidence to suggest that dietary protein intake may also be important for maintaining bone and muscle mass [55]. For example, it has been demonstrated in participants from the Shanghai Women’s health Study that that a high soy consumption is associated with a lower risk of fracture [56] and that in fasting older subjects, muscle protein synthesis is reduced [57].

*Age, sex and ethnicity*

Advancing age and female sex is associated with the development of both osteoporosis and sarcopenia. It has been estimated that in American women over the age of 85, 70% are osteoporotic at the hip, lumbar spine or forearm and a further 27% are osteopenic, whereas the majority of women under the age of 50 years have normal BMD [58]. Epidemiological studies have shown that in Caucasian women aged 50 years, the remaining lifetime risk of fragility fracture is 17.5% for hip fracture, 15.6% for vertebral fracture and 16% for distal forearm fracture. The corresponding risk for men is 6%, 5% and 2.5% [19]. It has been estimated that the prevalence of sarcopenia is 5-13% for adults aged 60-70 years and increases to 11-50% for adults aged above 80 years [59]. North American studies have shown that age‐ and sex‐adjusted hip fracture rates are generally higher in White than in Black or Asian populations [60] and higher muscle mass has been described in Black populations [61].

**Osteosarcopenic obesity**

Low BMI is a risk factor for low BMD and for fragility fracture, with individuals with a BMI <20kg/m2 at the greatest risk [2]. Conversely, studies have suggested that obesity can be a protective factor against bone loss [62-64]. Interestingly, obesity is not protective against fracture at all skeletal sites with an increased fracture risk at the proximal humerus, upper leg, and ankle [65,66]. Furthermore, low-trauma fractures are equally prevalent in obese and non-obese women [66]. The protective effect of adiposity on bone mass at some skeletal sites may be in part explained by the well documented relationship between peripheral oestrogen levels and obesity, with most circulating oestrogens produced in fat tissue via conversion of androgens post menopause [62]. Obese individuals have a greater absolute maximum muscle strength compared to non-obese persons, suggesting that increased adiposity acts as a chronic overload stimulus on muscles and so increasing muscle size and strength. However, when maximum muscular strength is normalised to body mass, obese individuals appear weaker. [67] which leads to an impairment of physical function [44,45]. With advancing age the composition of body tissue changes with an overall increase in body fat and decrease in muscle mass, which often occurs despite overall body weight remaining stable. This excess adipose tissue in combination with low muscle mass has been termed ‘sarcopenic obesity’ and has been shown to be associated with impaired function and increased disability [68,69].

**Pathophysiology**

Muscle and bone function are closely related with shared mechanical and molecular mechanisms. The mechanical interaction between muscle and bone is described by the ‘mechanostat’ theory, which states that muscle imposes mechanical forces on bone, and if these exceed a set threshold the equilibrium of bone turnover shifts away from bone resorption in favour of bone formation [70]. It is thought that this occurs as increases in muscle mass induce the stretching of periosteum and collagen fibres which results in the stimulation of bone growth [71]. As both bone and muscle mass are intrinsically linked to the reduction in physical performance observed with ageing this lends credence to the importance of mechanical loading in the maintenance of the bone-muscle unit.

The molecular mechanisms linking bone to muscle function, known as bone-muscle cross-talk, are less well defined. Hormones identified as playing a key role in the development of osteosarcopenia include growth hormone/insulin-like growth factor-1 (GH/IGF1) and gonadal sex hormones [17]. Human muscle and bone cells both express oestrogen receptors, hence hormone replacement therapy in post-menopausal women is able to both preserved bone and muscle mass [72]. Furthermore, early menopause without treatment with exogenous oestrogen is a strong risk factor for future fragility fracture [73]. The pathogenesis of male age-related osteoporosis and sarcopenia are less well characterised but it is thought that oestrogens derived from the metabolism of androgens play a role in preserving bone mass and that low testosterone results in reduced protein synthesis with the subsequent loss of muscle mass [74]. Indeed, low testosterone levels in older men are predictive of frailty and incident falls [75,76]. GH and IGF1 both exert a positive influence on osteoblasts in addition to their anabolic actions on muscle [77].

Chronic non-communicable diseases such as chronic obstructive pulmonary disease (COPD), heart failure and malignancy are associated with cachexia which describes the loss of body weight including lean muscle mass. Cachexia is associated with the increased production of pro-inflammatory cytokines (particularly IL-6, Il-1 and TNF) and the resultant inflammatory state results in loss of bone and muscle mass. ‘Inflammaging’ describes a mechanism through which bone and muscle mass are likely linked. The term inflammaging was originally coined in the year 2000 to describe chronic, low grade inflammation that increases with age and is a significant risk factor for morbidity and mortality in older people [78]. This increase in the levels of background inflammation with age is thought to occur as a result of cumulative exposure to environmental and infective antigens which result in the production of reactive oxygen species (ROS). ROS stimulate the release of additional cytokines from the innate and acquired immune system, thus tipping the immune balance in favour of a chronic inflammatory state [79]. Studies have linked chronically raised inflammatory cytokines to the development of sarcopenia, possibly through the activation of the ubiquitine-protease pathway [80,2] and increased pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6, which promote bone resorption [81,82]. Furthermore, epidemiological studies have shown positive associations between both osteoporosis and sarcopenia and C-reactive protein (CRP) which is a marker of active inflammation [83-89].

Factors known as myokines, released from muscle, and osteokines, released from bone such as osteocalcin are known to be one mechanism of communication between the two tissues. A myokine called myostatin has been extensively studied and has been shown in mice to play an important role in the impaired proliferative capacity of muscle and bone progenitor cells with ageing [90]. Furthermore, the Wnt-β-catenin signalling pathway has been shown to mediate bone-muscle crosstalk by controlling both osteoblastic activity and muscle regeneration [91]. Understanding the molecular pathways by which muscle and bone interact provides potentially exciting molecular targets for the development of therapeutics for the treatment of osteosarcopenia.

**Management of osteosarcopenia**

Both osteoporosis and sarcopenia are amenable to therapeutic interventions, although many more pharmaceutical agents are currently available for the treatment of osteoporosis. Lifestyle interventions include ensuring adequate protein intake, progressive resistance exercise and vitamin D replacement when necessary.

*Physical activity and exercise*

As previously discussed, physical activity has a profound effect on both bone and muscle strength. Prolonged immobilisation is a well-established risk factor for loss of bone density [2] and a meta-analysis has demonstrated that physical activity has a significant protective effect on BMD at the lumbar spine [42]. Furthermore, a meta-analysis of 14 prospective studies has shown a significant inverse relationship between increasing level of physical activity and risk of hip fracture in older women [92]. Similarly studies have shown that lifelong physical exercise serves to preserve muscle structure and function [93] and increases in mid-life physical activity reduces the risk of impaired mobility in later life [94,95]. There is evidence to suggest that resistance training is the most effective form of physical exercise to improve muscle strength and physical performance in older people [96].

*Nutrition*

Adequate vitamin D intake is associated with better BMD and muscle mass and function; a linear positive association was observed between BMD and serum 25(OH)D level up to a level of 75nmol/l in white US populations [97]. Indeed, to prevent age-related deterioration in musculoskeletal health the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) recommends a vitamin D intake of 800IU/daily to maintain 25(OH)D levels >50 nmol/l in post-menopausal women [2]. Adequate protein intake is essential, with 5-12% of older men and 20-24% of older women consuming inadequate levels (<0.66g/kg body weight per day) in the USA [98]. To increase the anabolic response to protein in older people, it has been suggested that a higher protein intake of 1.0-1.2g/kg body weight per day is taken post exercise [99]. A recent meta-analysis to explore whether the use of nutritional supplementations improves physical performance in older people showed nutritional supplementation can improve a number of physical performance outcomes, particularly when they include multi-nutrients and in people already affected by specific medical conditions, or by frailty/sarcopenia [100].

*Therapeutic targets*

As pharmacotherapy for osteoporosis is well established, the majority of medications currently used in the management of osteosarcopenia are focused on targeting bone separately from muscle, and include bisphosophonates, denosumab and teriparatide therapy. As osteoporosis and sarcopenia are associated, several new therapies are currently being developed to target bone and muscle in tandem. For example, selective androgen receptor modulators (SARMs), such as andarine, have an anabolic effect on muscle and bone, with few of the androgenic side effects associated with testosterone therapy [17]. Another potential therapeutic target is irisin, a hormone-like myokine produced in abundance by skeletal muscle cells in response to exercise. Following its release into the circulation, irisin acts upon white adipocytes inducing the browning response and subsequently activating non-shivering thermogenesis [101]. Promisingly, recent studies have also suggested a role for irisin on the musculoskeletal system with positive effects on cortical mineral density and geometry in mice with upregulation of the irisin precursor (FNDC5) in skeletal muscle fibres [102]. Myostatin is a myokine associated with impaired muscle and bone mass with ageing and the myostatin inhibitor ‘follistatin’ has been shown to induce significant improvement in diabetic bone regeneration in mice [103]. As detailed previously, osteosarcopenia may, at least in part, be a lipotoxic disease and *in vitro* studies have demonstrated that inhibiting fatty acid synthetase using cerulenin, which prevents adipose cells from releasing fatty acids, rescues osteoblasts from fat-induced toxicity and cell death [104]. Furthermore, treatment *in vivo* with cerulenin has been shown to protect osteoblasts from lipotoxicity while rescuing oophorectomized mice from their osteoporotic phenotype [105]. Other potential therapeutic targets which are currently being explored include anti-sclerostin antibodies, cathepsin K inhibitors and GH secretagogues.

**Conclusion**

The coexistence of osteoporosis and sarcopenia is an increasingly recognised condition which is associated with significant morbidity, mortality and societal cost. As the population ages, its prevalence is set to increase dramatically over the coming decades with an estimated 2 billion individuals over 60 years of age affected by the year 2050 [9]. Identifying those individuals at risk of developing coexisting osteoporosis and sarcopenia, may enable clinicians to intervene and ameliorate the consequences of osteosarcopenia.

**Key messages**

1. Osteosarcopenia is a newly proposed syndrome which describes the coexistence of osteoporosis and sarcopenia
2. Sequelae of osteosarcopenia include increased risk of falls and fractures, leading to significant public health burdens
3. Novel pharmacological agent that might target both bone and muscle have been proposed and are under evaluation

**References**

1. Edwards MH, Dennison EM, Aihie Sayer A, Fielding R, Cooper C (2015) Osteoporosis and sarcopenia in older age. Bone 80:126-130. doi:10.1016/j.bone.2015.04.016

2. Curtis E, Litwic A, Cooper C, Dennison E (2015) Determinants of Muscle and Bone Aging. Journal of cellular physiology 230 (11):2618-2625. doi:10.1002/jcp.25001

3. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jonsson B, Kanis JA (2013) Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Archives of osteoporosis 8:136. doi:10.1007/s11657-013-0136-1

4. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis (1993). The American journal of medicine 94 (6):646-650. doi:10.1016/0002-9343(93)90218-e

5. Liu J, Curtis EM, Cooper C, Harvey NC (2019) State of the art in osteoporosis risk assessment and treatment. Journal of endocrinological investigation. doi:10.1007/s40618-019-01041-6

6. Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R (2004) The healthcare costs of sarcopenia in the United States. Journal of the American Geriatrics Society 52 (1):80-85. doi:10.1111/j.1532-5415.2004.52014.x

7. Bruyere O, Beaudart C, Ethgen O, Reginster JY, Locquet M (2019) The health economics burden of sarcopenia: a systematic review. Maturitas 119:61-69. doi:10.1016/j.maturitas.2018.11.003

8. Hirschfeld HP, Kinsella R, Duque G (2017) Osteosarcopenia: where bone, muscle, and fat collide. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 28 (10):2781-2790. doi:10.1007/s00198-017-4151-8

9. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinkova E, Vandewoude M, Zamboni M (2010) Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age and ageing 39 (4):412-423. doi:10.1093/ageing/afq034

10. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M (2019) Sarcopenia: revised European consensus on definition and diagnosis. Age and ageing 48 (1):16-31. doi:10.1093/ageing/afy169

11. Tanimoto Y, Watanabe M, Sun W, Sugiura Y, Hayashida I, Kusabiraki T, Tamaki J (2014) Sarcopenia and falls in community-dwelling elderly subjects in Japan: Defining sarcopenia according to criteria of the European Working Group on Sarcopenia in Older People. Archives of gerontology and geriatrics 59 (2):295-299. doi:10.1016/j.archger.2014.04.016

12. Yamada M, Nishiguchi S, Fukutani N, Tanigawa T, Yukutake T, Kayama H, Aoyama T, Arai H (2013) Prevalence of sarcopenia in community-dwelling Japanese older adults. Journal of the American Medical Directors Association 14 (12):911-915. doi:10.1016/j.jamda.2013.08.015

13. Woo N, Kim SH (2014) Sarcopenia influences fall-related injuries in community-dwelling older adults. Geriatric nursing (New York, NY) 35 (4):279-282. doi:10.1016/j.gerinurse.2014.03.001

14. Clynes MA, Edwards MH, Buehring B, Dennison EM, Binkley N, Cooper C (2015) Definitions of Sarcopenia: Associations with Previous Falls and Fracture in a Population Sample. Calcified tissue international 97 (5):445-452. doi:10.1007/s00223-015-0044-z

15. Huo YR, Suriyaarachchi P, Gomez F, Curcio CL, Boersma D, Muir SW, Montero-Odasso M, Gunawardene P, Demontiero O, Duque G (2015) Phenotype of osteosarcopenia in older individuals with a history of falling. Journal of the American Medical Directors Association 16 (4):290-295. doi:10.1016/j.jamda.2014.10.018

16. Paintin J, Cooper C, Dennison E (2018) Osteosarcopenia. British journal of hospital medicine (London, England : 2005) 79 (5):253-258. doi:10.12968/hmed.2018.79.5.253

17. Girgis CM, Mokbel N, Digirolamo DJ (2014) Therapies for musculoskeletal disease: can we treat two birds with one stone? Current osteoporosis reports 12 (2):142-153. doi:10.1007/s11914-014-0204-5

18. Frost HM (1997) On our age-related bone loss: insights from a new paradigm. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 12 (10):1539-1546. doi:10.1359/jbmr.1997.12.10.1539

19. van Staa TP, Dennison EM, Leufkens HG, Cooper C (2001) Epidemiology of fractures in England and Wales. Bone 29 (6):517-522

20. Felsenberg D, Silman AJ, Lunt M, Armbrecht G, Ismail AA, Finn JD, Cockerill WC, Banzer D, Benevolenskaya LI, Bhalla A, Bruges Armas J, Cannata JB, Cooper C, Dequeker J, Eastell R, Felsch B, Gowin W, Havelka S, Hoszowski K, Jajic I, Janott J, Johnell O, Kanis JA, Kragl G, Lopes Vaz A, Lorenc R, Lyritis G, Masaryk P, Matthis C, Miazgowski T, Parisi G, Pols HA, Poor G, Raspe HH, Reid DM, Reisinger W, Schedit-Nave C, Stepan JJ, Todd CJ, Weber K, Woolf AD, Yershova OB, Reeve J, O'Neill TW (2002) Incidence of vertebral fracture in europe: results from the European Prospective Osteoporosis Study (EPOS). J Bone Miner Res 17 (4):716-724. doi:10.1359/jbmr.2002.17.4.716

21. Cruz-Jentoft AJ, Landi F, Schneider SM, Zuniga C, Arai H, Boirie Y, Chen LK, Fielding RA, Martin FC, Michel JP, Sieber C, Stout JR, Studenski SA, Vellas B, Woo J, Zamboni M, Cederholm T (2014) Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age and ageing 43 (6):748-759. doi:10.1093/ageing/afu115

22. Di Monaco M, Vallero F, Di Monaco R, Tappero R (2011) Prevalence of sarcopenia and its association with osteoporosis in 313 older women following a hip fracture. Archives of gerontology and geriatrics 52 (1):71-74. doi:10.1016/j.archger.2010.02.002

23. Wang YJ, Wang Y, Zhan JK, Tang ZY, He JY, Tan P, Deng HQ, Huang W, Liu YS (2015) Sarco-Osteoporosis: Prevalence and Association with Frailty in Chinese Community-Dwelling Older Adults. International journal of endocrinology 2015:482940. doi:10.1155/2015/482940

24. Locquet M, Beaudart C, Bruyere O, Kanis JA, Delandsheere L, Reginster JY (2018) Bone health assessment in older people with or without muscle health impairment. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 29 (5):1057-1067. doi:10.1007/s00198-018-4384-1

25. Chrischilles EA, Butler CD, Davis CS, Wallace RB (1991) A model of lifetime osteoporosis impact. Arch Intern Med 151 (10):2026-2032

26. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, Mitnitski A (2005) A global clinical measure of fitness and frailty in elderly people. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 173 (5):489-495. doi:10.1503/cmaj.050051

27. Yoo JI, Kim H, Ha YC, Kwon HB, Koo KH (2018) Osteosarcopenia in Patients with Hip Fracture Is Related with High Mortality. Journal of Korean medical science 33 (4):e27. doi:10.3346/jkms.2018.33.e27

28. Sambrook PN, Kelly PJ, Morrison NA, Eisman JA (1994) Genetics of osteoporosis. British journal of rheumatology 33 (11):1007-1011. doi:10.1093/rheumatology/33.11.1007

29. Tylavsky FA, Bortz AD, Hancock RL, Anderson JJ (1989) Familial resemblance of radial bone mass between premenopausal mothers and their college-age daughters. Calcified tissue international 45 (5):265-272. doi:10.1007/bf02556017

30. Tikkanen E, Gustafsson S, Amar D, Shcherbina A, Waggott D, Ashley EA, Ingelsson E (2018) Biological Insights Into Muscular Strength: Genetic Findings in the UK Biobank. Scientific reports 8 (1):6451. doi:10.1038/s41598-018-24735-y

31. Rolland Y, Czerwinski S, Abellan Van Kan G, Morley JE, Cesari M, Onder G, Woo J, Baumgartner R, Pillard F, Boirie Y, Chumlea WM, Vellas B (2008) Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. The journal of nutrition, health & aging 12 (7):433-450. doi:10.1007/bf02982704

32. Leslie WD, Bernstein CN, Leboff MS (2003) AGA technical review on osteoporosis in hepatic disorders. Gastroenterology 125 (3):941-966

33. Gonzalez-Reimers E, Alvisa-Negrin J, Santolaria-Fernandez F, Candelaria Martin-Gonzalez M, Hernandez-Betancor I, Fernandez-Rodriguez CM, Vina-Rodriguez J, Gonzalez-Diaz A (2011) Vitamin D and nutritional status are related to bone fractures in alcoholics. Alcohol Alcohol 46 (2):148-155. doi:10.1093/alcalc/agq098

34. Malik P, Gasser RW, Kemmler G, Moncayo R, Finkenstedt G, Kurz M, Fleischhacker WW (2009) Low bone mineral density and impaired bone metabolism in young alcoholic patients without liver cirrhosis: a cross-sectional study. Alcohol Clin Exp Res 33 (2):375-381. doi:10.1111/j.1530-0277.2008.00847.x

35. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H, Tenenhouse A (2005) Alcohol intake as a risk factor for fracture. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 16 (7):737-742. doi:10.1007/s00198-004-1734-y

36. Renoud A, Ecochard R, Marchand F, Chapurlat R, Szulc P (2014) Predictive parameters of accelerated muscle loss in men-MINOS study. The American journal of medicine 127 (6):554-561. doi:10.1016/j.amjmed.2014.02.004

37. Law MR, Hackshaw AK (1997) A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. BMJ (Clinical research ed) 315 (7112):841-846. doi:10.1136/bmj.315.7112.841

38. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E (2008) FRAX and the assessment of fracture probability in men and women from the UK. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 19 (4):385-397. doi:10.1007/s00198-007-0543-5

39. Steffl M, Bohannon RW, Petr M, Kohlikova E, Holmerova I (2015) Relation between cigarette smoking and sarcopenia: meta-analysis. Physiological research 64 (3):419-426

40. Chiolero A, Faeh D, Paccaud F, Cornuz J (2008) Consequences of smoking for body weight, body fat distribution, and insulin resistance. The American journal of clinical nutrition 87 (4):801-809. doi:10.1093/ajcn/87.4.801

41. Heydari G, Hosseini M, Yousefifard M, Asady H, Baikpour M, Barat A (2015) Smoking and Physical Activity in Healthy Adults: A Cross-Sectional Study in Tehran. Tanaffos 14 (4):238-245

42. Howe TE, Shea B, Dawson LJ, Downie F, Murray A, Ross C, Harbour RT, Caldwell LM, Creed G. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev. 2011 Jul 6;(7):CD000333.

43. Kortebein P, Ferrando A, Lombeida J, Wolfe R, Evans WJ (2007) Effect of 10 days of bed rest on skeletal muscle in healthy older adults. Jama 297 (16):1772-1774. doi:10.1001/jama.297.16.1772-b

44. Binder EF, Yarasheski KE, Steger-May K, Sinacore DR, Brown M, Schechtman KB, Holloszy JO (2005) Effects of progressive resistance training on body composition in frail older adults: results of a randomized, controlled trial. The journals of gerontology Series A, Biological sciences and medical sciences 60 (11):1425-1431. doi:10.1093/gerona/60.11.1425

45. Kemmler W, von Stengel S, Engelke K, Haberle L, Mayhew JL, Kalender WA (2010) Exercise, body composition, and functional ability: a randomized controlled trial. American journal of preventive medicine 38 (3):279-287. doi:10.1016/j.amepre.2009.10.042

46. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A (2007) Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet (London, England) 370 (9588):657-666. doi:10.1016/s0140-6736(07)61342-7

47. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burckhardt P, Li R, Spiegelman D, Specker B, Orav JE, Wong JB, Staehelin HB, O'Reilly E, Kiel DP, Willett WC (2007) Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. The American journal of clinical nutrition 86 (6):1780-1790. doi:10.1093/ajcn/86.5.1780

48. Bolland MJ, Leung W, Tai V, Bastin S, Gamble GD, Grey A, Reid IR (2015) Calcium intake and risk of fracture: systematic review. BMJ (Clinical research ed) 351:h4580. doi:10.1136/bmj.h4580

49. Thabit H, Barry M, Sreenan S, Smith D (2011) Proximal myopathy in lacto-vegetarian Asian patients responding to Vitamin D and calcium supplement therapy - two case reports and review of the literature. Journal of medical case reports 5:178. doi:10.1186/1752-1947-5-178

50. Hirata D, Nagashima T, Saito S, Okazaki H, Kano S, Minota S (2002) Elevated muscle enzymes in a patient with severe hypocalcemia mimicking polymyositis. Modern rheumatology 12 (2):186-189. doi:10.3109/s101650200032

51. Beaudart C, Buckinx F, Rabenda V, Gillain S, Cavalier E, Slomian J, Petermans J, Reginster JY, Bruyere O (2014) The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. The Journal of clinical endocrinology and metabolism 99 (11):4336-4345. doi:10.1210/jc.2014-1742

52. Boland R (1986) Role of vitamin D in skeletal muscle function. Endocrine reviews 7 (4):434-448. doi:10.1210/edrv-7-4-434

53. Sorensen OH, Lund B, Saltin B, Lund B, Andersen RB, Hjorth L, Melsen F, Mosekilde L (1979) Myopathy in bone loss of ageing: improvement by treatment with 1 alpha-hydroxycholecalciferol and calcium. Clinical science (London, England : 1979) 56 (2):157-161

54. Skaria J, Katiyar BC, Srivastava TP, Dube B (1975) Myopathy and neuropathy associated with osteomalacia. Acta neurologica Scandinavica 51 (1):37-58

55. Shams-White MM, Chung M, Du M, Fu Z, Insogna KL, Karlsen MC, LeBoff MS, Shapses SA, Sackey J, Wallace TC, Weaver CM (2017) Dietary protein and bone health: a systematic review and meta-analysis from the National Osteoporosis Foundation. The American journal of clinical nutrition 105 (6):1528-1543. doi:10.3945/ajcn.116.145110

56. Zhang X, Shu XO, Li H, Yang G, Li Q, Gao YT, Zheng W (2005) Prospective cohort study of soy food consumption and risk of bone fracture among postmenopausal women. Archives of internal medicine 165 (16):1890-1895. doi:10.1001/archinte.165.16.1890

57. Rooyackers OE, Adey DB, Ades PA, Nair KS (1996) Effect of age on in vivo rates of mitochondrial protein synthesis in human skeletal muscle. Proceedings of the National Academy of Sciences of the United States of America 93 (26):15364-15369. doi:10.1073/pnas.93.26.15364

58. McGregor RA, Cameron-Smith D, Poppitt SD (2014) It is not just muscle mass: a review of muscle quality, composition and metabolism during ageing as determinants of muscle function and mobility in later life. Longevity & healthspan 3 (1):9. doi:10.1186/2046-2395-3-9

59. von Haehling S, Morley JE, Anker SD (2012) From muscle wasting to sarcopenia and myopenia: update 2012. Journal of cachexia, sarcopenia and muscle 3 (4):213-217. doi:10.1007/s13539-012-0089-z

60. Maggi S, Kelsey JL, Litvak J, Heyse SP (1991) Incidence of hip fractures in the elderly: a cross-national analysis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 1 (4):232-241. doi:10.1007/bf03187467

61. Araujo AB, Chiu GR, Kupelian V, Hall SA, Williams RE, Clark RV, McKinlay JB (2010) Lean mass, muscle strength, and physical function in a diverse population of men: a population-based cross-sectional study. BMC public health 10:508. doi:10.1186/1471-2458-10-508

62. Reid IR (2010) Fat and bone. Archives of biochemistry and biophysics 503 (1):20-27. doi:10.1016/j.abb.2010.06.027

63. Compston J (2015) Obesity and fractures in postmenopausal women. Current opinion in rheumatology 27 (4):414-419. doi:10.1097/bor.0000000000000182

64. De Laet C, Kanis JA, Oden A, Johanson H, Johnell O, Delmas P, Eisman JA, Kroger H, Fujiwara S, Garnero P, McCloskey EV, Mellstrom D, Melton LJ, 3rd, Meunier PJ, Pols HA, Reeve J, Silman A, Tenenhouse A (2005) Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 16 (11):1330-1338. doi:10.1007/s00198-005-1863-y

65. Compston JE, Watts NB, Chapurlat R, Cooper C, Boonen S, Greenspan S, Pfeilschifter J, Silverman S, Diez-Perez A, Lindsay R, Saag KG, Netelenbos JC, Gehlbach S, Hooven FH, Flahive J, Adachi JD, Rossini M, Lacroix AZ, Roux C, Sambrook PN, Siris ES (2011) Obesity is not protective against fracture in postmenopausal women: GLOW. The American journal of medicine 124 (11):1043-1050. doi:10.1016/j.amjmed.2011.06.013

66. Prieto-Alhambra D, Premaor MO, Fina Aviles F, Hermosilla E, Martinez-Laguna D, Carbonell-Abella C, Nogues X, Compston JE, Diez-Perez A (2012) The association between fracture and obesity is site-dependent: a population-based study in postmenopausal women. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 27 (2):294-300. doi:10.1002/jbmr.1466

67. Kawao N, Kaji H (2015) Interactions between muscle tissues and bone metabolism. Journal of cellular biochemistry 116 (5):687-695. doi:10.1002/jcb.25040

68. Nielson CM, Srikanth P, Orwoll ES (2012) Obesity and fracture in men and women: an epidemiologic perspective. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 27 (1):1-10. doi:10.1002/jbmr.1486

69. Waters DL, Hale L, Grant AM, Herbison P, Goulding A (2010) Osteoporosis and gait and balance disturbances in older sarcopenic obese New Zealanders. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 21 (2):351-357. doi:10.1007/s00198-009-0947-5

70. Frost HM (2003) Bone's mechanostat: a 2003 update. The anatomical record Part A, Discoveries in molecular, cellular, and evolutionary biology 275 (2):1081-1101. doi:10.1002/ar.a.10119

71. Kaji H (2014) Interaction between Muscle and Bone. Journal of bone metabolism 21 (1):29-40. doi:10.11005/jbm.2014.21.1.29

72. Tiidus PM (2011) Benefits of estrogen replacement for skeletal muscle mass and function in post-menopausal females: evidence from human and animal studies. The Eurasian journal of medicine 43 (2):109-114. doi:10.5152/eajm.2011.24

73. Sullivan SD, Sarrel PM, Nelson LM (2016) Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. Fertility and sterility 106 (7):1588-1599. doi:10.1016/j.fertnstert.2016.09.046

74. Janssen I, Heymsfield SB, Ross R (2002) Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. Journal of the American Geriatrics Society 50 (5):889-896. doi:10.1046/j.1532-5415.2002.50216.x

75. Hyde Z, Flicker L, Almeida OP, Hankey GJ, McCaul KA, Chubb SA, Yeap BB (2010) Low free testosterone predicts frailty in older men: the health in men study. The Journal of clinical endocrinology and metabolism 95 (7):3165-3172. doi:10.1210/jc.2009-2754

76. Vandenput L, Mellstrom D, Laughlin GA, Cawthon PM, Cauley JA, Hoffman AR, Karlsson MK, Rosengren BE, Ljunggren O, Nethander M, Eriksson AL, Lorentzon M, Leung J, Kwok T, Orwoll ES, Ohlsson C (2017) Low Testosterone, but Not Estradiol, Is Associated With Incident Falls in Older Men: The International MrOS Study. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 32 (6):1174-1181. doi:10.1002/jbmr.3088

77. Cederholm T, Cruz-Jentoft AJ, Maggi S (2013) Sarcopenia and fragility fractures. European journal of physical and rehabilitation medicine 49 (1):111-117

78. Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G (2000) Inflamm-aging. An evolutionary perspective on immunosenescence. Annals of the New York Academy of Sciences 908:244-254. doi:10.1111/j.1749-6632.2000.tb06651.x

79. Cannizzo ES, Clement CC, Sahu R, Follo C, Santambrogio L (2011) Oxidative stress, inflamm-aging and immunosenescence. Journal of proteomics 74 (11):2313-2323. doi:10.1016/j.jprot.2011.06.005

80. Holm L, Olesen JL, Matsumoto K, Doi T, Mizuno M, Alsted TJ, Mackey AL, Schwarz P, Kjaer M (2008) Protein-containing nutrient supplementation following strength training enhances the effect on muscle mass, strength, and bone formation in postmenopausal women. Journal of applied physiology (Bethesda, Md : 1985) 105 (1):274-281. doi:10.1152/japplphysiol.00935.2007

81. Ding C, Parameswaran V, Udayan R, Burgess J, Jones G (2008) Circulating levels of inflammatory markers predict change in bone mineral density and resorption in older adults: a longitudinal study. The Journal of clinical endocrinology and metabolism 93 (5):1952-1958. doi:10.1210/jc.2007-2325

82. McLean RR (2009) Proinflammatory cytokines and osteoporosis. Current osteoporosis reports 7 (4):134-139

83. Nakamura K, Saito T, Kobayashi R, Oshiki R, Oyama M, Nishiwaki T, Nashimoto M, Tsuchiya Y (2011) C-reactive protein predicts incident fracture in community-dwelling elderly Japanese women: the Muramatsu study. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 22 (7):2145-2150. doi:10.1007/s00198-010-1425-9

84. Cauley JA, Barbour KE, Harrison SL, Cloonan YK, Danielson ME, Ensrud KE, Fink HA, Orwoll ES, Boudreau R (2016) Inflammatory Markers and the Risk of Hip and Vertebral Fractures in Men: the Osteoporotic Fractures in Men (MrOS). Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 31 (12):2129-2138. doi:10.1002/jbmr.2905

85. Schett G, Kiechl S, Weger S, Pederiva A, Mayr A, Petrangeli M, Oberhollenzer F, Lorenzini R, Redlich K, Axmann R, Zwerina J, Willeit J (2006) High-sensitivity C-reactive protein and risk of nontraumatic fractures in the Bruneck study. Archives of internal medicine 166 (22):2495-2501. doi:10.1001/archinte.166.22.2495

86. Pasco JA, Kotowicz MA, Henry MJ, Nicholson GC, Spilsbury HJ, Box JD, Schneider HG (2006) High-sensitivity C-reactive protein and fracture risk in elderly women. Jama 296 (11):1353-1355. doi:10.1001/jama.296.11.1353

87. Ishii S, Cauley JA, Greendale GA, Crandall CJ, Danielson ME, Ouchi Y, Karlamangla AS (2013) C-reactive protein, bone strength, and nine-year fracture risk: data from the Study of Women's Health Across the Nation (SWAN). Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 28 (7):1688-1698. doi:10.1002/jbmr.1915

88. Dahl K, Ahmed LA, Joakimsen RM, Jorgensen L, Eggen AE, Eriksen EF, Bjornerem A (2015) High-sensitivity C-reactive protein is an independent risk factor for non-vertebral fractures in women and men: The Tromso Study. Bone 72:65-70. doi:10.1016/j.bone.2014.11.012

89. Schaap LA, Pluijm SM, Deeg DJ, Visser M (2006) Inflammatory markers and loss of muscle mass (sarcopenia) and strength. The American journal of medicine 119 (6):526.e529-517. doi:10.1016/j.amjmed.2005.10.049

90. Bowser M, Herberg S, Arounleut P, Shi X, Fulzele S, Hill WD, Isales CM, Hamrick MW (2013) Effects of the activin A-myostatin-follistatin system on aging bone and muscle progenitor cells. Experimental gerontology 48 (2):290-297. doi:10.1016/j.exger.2012.11.004

91. Oliveira A, Vaz C (2015) The role of sarcopenia in the risk of osteoporotic hip fracture. Clinical rheumatology 34 (10):1673-1680. doi:10.1007/s10067-015-2943-9

92. Rong K, Liu XY, Wu XH, Li XL, Xia QQ, Chen J, Yin XF (2016) Increasing Level of Leisure Physical Activity Could Reduce the Risk of Hip Fracture in Older Women: A Dose-Response Meta-analysis of Prospective Cohort Studies. Medicine 95 (11):e2984. doi:10.1097/md.0000000000002984

93. Zampieri S, Pietrangelo L, Loefler S, Fruhmann H, Vogelauer M, Burggraf S, Pond A, Grim-Stieger M, Cvecka J, Sedliak M, Tirpakova V, Mayr W, Sarabon N, Rossini K, Barberi L, De Rossi M, Romanello V, Boncompagni S, Musaro A, Sandri M, Protasi F, Carraro U, Kern H (2015) Lifelong physical exercise delays age-associated skeletal muscle decline. The journals of gerontology Series A, Biological sciences and medical sciences 70 (2):163-173. doi:10.1093/gerona/glu006

94. Hinrichs T, von Bonsdorff MB, Tormakangas T, von Bonsdorff ME, Kulmala J, Seitsamo J, Nygard CH, Ilmarinen J, Rantanen T (2014) Inverse effects of midlife occupational and leisure time physical activity on mobility limitation in old age--a 28-year prospective follow-up study. Journal of the American Geriatrics Society 62 (5):812-820. doi:10.1111/jgs.12793

95. Beaudart C, Dawson A, Shaw SC, Harvey NC, Kanis JA, Binkley N, Reginster JY, Chapurlat R, Chan DC, Bruyere O, Rizzoli R, Cooper C, Dennison EM (2017) Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 28 (6):1817-1833. doi:10.1007/s00198-017-3980-9

96. Lai CC, Tu YK, Wang TG, Huang YT, Chien KL (2018) Effects of resistance training, endurance training and whole-body vibration on lean body mass, muscle strength and physical performance in older people: a systematic review and network meta-analysis. Age and ageing 47 (3):367-373. doi:10.1093/ageing/afy009

97. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B (2004) Positive association between 25-hydroxy vitamin D levels and bone mineral density: a population-based study of younger and older adults. The American journal of medicine 116 (9):634-639. doi:10.1016/j.amjmed.2003.12.029

98. Berner LA, Becker G, Wise M, Doi J (2013) Characterization of dietary protein among older adults in the United States: amount, animal sources, and meal patterns. Journal of the Academy of Nutrition and Dietetics 113 (6):809-815. doi:10.1016/j.jand.2013.01.014

99. Rizzoli R, Stevenson JC, Bauer JM, van Loon LJ, Walrand S, Kanis JA, Cooper C, Brandi ML, Diez-Perez A, Reginster JY (2014) The role of dietary protein and vitamin D in maintaining musculoskeletal health in postmenopausal women: a consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Maturitas 79 (1):122-132. doi:10.1016/j.maturitas.2014.07.005

100. Veronese N, Stubbs B, Punzi L, Soysal P, Incalzi RA, Saller A, Maggi S (2019) Effect of nutritional supplementations on physical performance and muscle strength parameters in older people: A systematic review and meta-analysis. Ageing research reviews 51:48-54. doi:10.1016/j.arr.2019.02.005

101. Colaianni G, Cinti S, Colucci S, Grano M (2017) Irisin and musculoskeletal health. Annals of the New York Academy of Sciences 1402 (1):5-9. doi:10.1111/nyas.13345

102. Colaianni G, Cuscito C, Mongelli T, Pignataro P, Buccoliero C, Liu P, Lu P, Sartini L, Di Comite M, Mori G, Di Benedetto A, Brunetti G, Yuen T, Sun L, Reseland JE, Colucci S, New MI, Zaidi M, Cinti S, Grano M (2015) The myokine irisin increases cortical bone mass. Proceedings of the National Academy of Sciences of the United States of America 112 (39):12157-12162. doi:10.1073/pnas.1516622112

103. Wallner C, Jaurich H, Wagner JM, Becerikli M, Harati K, Dadras M, Lehnhardt M, Behr B (2017) Inhibition of GDF8 (Myostatin) accelerates bone regeneration in diabetes mellitus type 2. Scientific reports 7 (1):9878. doi:10.1038/s41598-017-10404-z

104. Pizer ES, Chrest FJ, DiGiuseppe JA, Han WF (1998) Pharmacological inhibitors of mammalian fatty acid synthase suppress DNA replication and induce apoptosis in tumor cell lines. Cancer research 58 (20):4611-4615

105. Bermeo S, Al Saedi A, Vidal C, Khalil M, Pang M, Troen BR, Myers D, Duque G (2019) Treatment with an inhibitor of fatty acid synthase attenuates bone loss in ovariectomized mice. Bone 122:114-122. doi:10.1016/j.bone.2019.02.017