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Sarcopenia, osteoporosis and frailty

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ABSTRACT

Muscles and bones are intricately connected tissues displaying marked co-variation during development, growth, aging, and in many diseases. While the diagnosis and treatment of osteoporosis are well established in clinical practice, sarcopenia has only been classified internationally as a disease in 2016. Both conditions are associated with an increased risk of adverse health outcomes such as fractures, dysmobility and mortality. Rather than focusing on one dimension of bone or muscle mass or weakness, the concept of musculoskeletal frailty captures the overall loss of physiological reserves in the locomotor system with age. The term osteosarcopenia in particular refers to the double jeopardy of osteoporosis and sarcopenia. Muscle-bone interactions at the biomechanical, cellular, paracrine, endocrine, neuronal or nutritional level may contribute to the pathophysiology of osteosarcopenia. The paradigm wherein muscle force controls bone strength is increasingly facing competition from a model centering on the exchange of myokines, osteokines and adipokines. The most promising results have been obtained in preclinical models where common drug targets have been identified to treat these conditions simultaneously. In this narrative review, we critically summarize the current understanding of the definitions, epidemiology, pathophysiology, and treatment of osteosarcopenia as part of an integrative approach to musculoskeletal frailty.

1. Introduction

The musculoskeletal system is comprised of muscles, bones, cartilaginous joints and tendons. They are not only literally connected to each other, the biology and homeostasis of these tissues are heavily intertwined and interdependent. Both clinically and in experimental models, the compromise of one tissue triggers a decline in all others.

This review will focus on osteosarcopenia as part of the broader context of musculoskeletal frailty. We will update and expand our previous review on muscle-bone interactions [1], which can be considered the pathophysiological substrate for osteosarcopenia. We will first define the different concepts, before discussing the pathophysiology and treatment of osteosarcopenia.

1.1. Sarcopenia

Sarcopenia is defined as a generalized and progressive skeletal muscle disorder involving accelerated loss of muscle mass and function [2]. Rosenberg coined the term in 1988, originally referring to the progressive decline in lean muscle mass, creatinine excretion, basic metabolic rate and muscle strength, which starts after the age of 20–30 years and continues unabatedly into the oldest old [3]. Concomitant with muscle atrophy, fatty infiltration between and within the muscles (*i.e.* myosteatosis) was already noted [3].

The emphasis remained on muscle mass (which has a close association with strength and power) when Baumgartner et al. [4] operationally defined sarcopenia as an ALM/height^2 (appendicular lean mass *i.e.* of the arms and legs, measured by dual-energy X-ray absorptiometry, DXA) of more than two standard deviations below the mean of a young adult reference group. More recent sarcopenia definitions are shown in

Abbreviations: ALM, appendicular lean mass; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; EWGSOP2, European Working Group on Sarcopenia in Older People 2; GDFs, growth and differentiation factors; GWAS, genome-wide association study; IGFs, insulin-like growth factors; RANK, receptor activator nuclear factor κB; RANKL, receptor activator nuclear factor κB ligand; RCT, randomized controlled trial; SARM, selective androgen receptor modulator; SNP, single nucleotide polymorphism.

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Table 1
Diagnostic criteria for sarcopenia.

	Cut-points for women	Cut-points for men
FNIH: weakness and low lean mass		
- Weakness	Grip strength < 16 kg	Grip strength < 26 kg
- Low lean mass: ALM adjusted for BMI Alternative: Unadjusted ALM	ALM_{BMI} < 0.512 ALM < 15.02 kg	ALM_{BMI} < 0.789 ALM < 19.75 kg
IWGS: slow gait speed + low muscle mass		
- Slow gait speed	Gait speed < 1.0 m/s	
- Low muscle mass	$ALM/h^2 \leq 5.67$ kg/m^2	$ALM/h^2 \leq 7.23$ kg/m^2
EWGSOP2:		
- Probable sarcopenia (low muscle strength): any of the following	Grip strength < 16 kg >15 s for 5 chair rises	Grip strength < 27 kg
- Sarcopenia (low muscle strength + low muscle mass): previous + any of the following	ALM < 15 kg ALM/h^2 < 6.0 kg/m^2	ALM < 20 kg ALM < 7.0 kg/m^2
- Severe sarcopenia (sarcopenia + low physical performance): previous + any of the following	Gait speed ≤ 0.8 m/s SPPB ≤ 8 points TUGT ≥ 20 s 400 m walk test ≥ 6 min or non-completion	

ALM = appendicular lean mass; BMI = body mass index; EWGSOP2 = European Working Group on Sarcopenia in Older People 2; FNIH; Foundation for the National Institutes of Health; IWGS = International Working Group on Sarcopenia; SPPB = Short Physical Performance Battery; TUGT = Timed Up-and-Go Test.

Table 1 [5]. These definitions give priority to impaired physical performance and low muscle strength or power, which decline more in old age than muscle mass, and have consistently shown stronger associations with various outcomes than muscle mass *per se* [2].

Sarcopenia becomes more prevalent with age and is associated with disability, loss of functional independence [2,3,4] and osteoporosis [6]. Depending on the definition used and the population studied, the prevalence of sarcopenia may vary tremendously (*e.g.* from 0.4 % to 35 % in older men [7]) and be higher in either men or women [8]. Primary (age-related) and secondary sarcopenia are distinguished, with similar underlying causes as for secondary osteoporosis (*e.g.* cancer, chronic obstructive pulmonary disease, heart failure, critical illness, diabetes mellitus, glucocorticoids or other drugs) [2,9].

1.2. Cachexia and sarcopenic obesity

A closely related term is **cachexia** (from Greek *kakós*, bad and *héxis*, condition/state of body), which refers to a generalized loss of muscle mass, with or without fat mass [10]. Cachexia is associated with bone loss in tumor-bearing mice [11], although human studies are limited [12,13]. Cachexia causes weakness, fatigue, falls, fractures and mortality, without necessarily altering body composition. Conversely, aging adults may lose muscle and bone mass while gaining fat mass, without apparent changes in body weight.

Obesity is characterized not just by excess body weight but by excess adiposity and a relative deficit in muscle mass (*i.e.* obese people typically have normal or increased muscle mass, but not commensurate to their body weight). The term **sarcopenic obesity** refers to the combination of a body mass disorder (obesity) with low skeletal muscle mass for body weight [14]. Sarcopenia and obesity are independently associated with fall risk, and fracture risk is increased in older men with sarcopenic obesity compared to non-sarcopenic obese men [15]. Similarly, fracture risk may be increased in **osteopenic obesity** (obese people also have a relative deficit in bone mineral density [BMD] and low bone turnover, in association with insulin resistance [16]) and the trinity of **osteosarcopenic obesity** [17].

1.3. Osteosarcopenia

Osteosarcopenia [18] or **sarco-osteoporosis** [19] could be diagnosed in individuals who satisfy diagnostic criteria for both sarcopenia and either osteopenia or osteoporosis. Studies on osteosarcopenia typically use DXA, (regional) computed tomography or magnetic resonance imaging [20], although other methods like deuterated creatinine may be more accurate for whole-body muscle mass [21]. Bioelectrical impedance analysis [14,22], ultrasound-based techniques [23] or biomarkers [24,25] could be useful to screen for osteosarcopenia. The prevalence of osteosarcopenia in community-dwelling older adults varied 5–37 % across studies, with a higher prevalence at older ages and in patients with prior fractures (46 %) [26]. One large study found a similar prevalence in women and men [27].

A cross-sectional study in a falls and fracture clinic showed that osteosarcopenic individuals were older, had lower grip strength, lower T-scores, worse balance and less functional capacity compared to those with sarcopenia or osteoporosis alone [18,28]. The underlying tenet is that the combination of osteoporosis and sarcopenia should predict adverse outcomes (notably fractures, loss of functional independence, impaired mobility and mortality) beyond the predictive value of each condition separately [23,29,30]. However, some studies found no increased fall or fracture risk in osteosarcopenic individuals compared to those with either condition alone [31,32].

It is now clear from large population-based studies that (i) low muscle mass and poor physical performance are associated with bone loss and microarchitectural decay [33] without necessarily affecting DXA BMD [34], (ii) physical performance and probably also muscle strength are associated with fracture risk, independent of BMD [33,35,36], while (iii) muscle mass is not predictive *per se* [35,36]. Moreover, the MrOS study has shown that sarcopenia definitions (particularly severe sarcopenia according to EWGSOP2, albeit at low prevalence) predict major osteoporotic fractures and hip fractures independent of BMD [7], possibly *via* fall risk. Poor muscle strength and performance are also associated with post-fracture mortality but not refracture risk [37]. Based on this evidence, we propose that the direct and indirect effects of sarcopenia and osteoporosis on falls, fractures and mortality can be conceptualized as shown in Fig. 1.

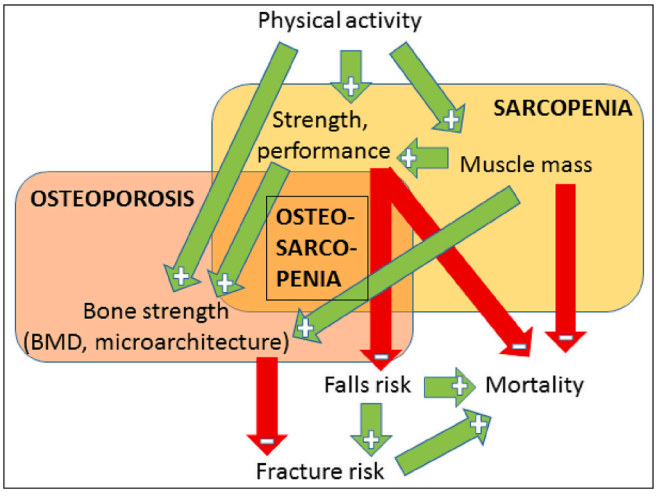

Fig. 1. Proposed diagram of the relationships between sarcopenia, osteoporosis, their determinants (such as physical activity), their components (such as muscle mass and strength or performance, for sarcopenia), and outcomes including falls, fractures and mortality. Green and red arrows indicate positive and negative associations, respectively. BMD = bone mineral density. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

1.4. Musculoskeletal frailty

In sarcopenia, low muscle mass is blamed for weakness and impaired physical function [2]. While muscle mass is indeed a prerequisite for strength, size is not all that matters, and other components of the musculoskeletal system should not be ignored. For example, rotator cuff tears are very common in older adults and lead to muscle atrophy and functional decline in the upper limbs. Falls, even if not related to musculoskeletal causes (*e.g.* from syncope or benzodiazepines), impair quality of life, increase fear of falling, reduce exercise behaviors and increase further fall risk.

In analogy to metabolic syndrome, Binkley et al. [38] proposed **dysmobility syndrome** as a constellation of six risk factors (osteoporosis, low lean mass, history of falls within the past year, slow gait speed, low grip strength and high fat mass) showing syndromic association with falls and fractures when three or more risk factors were present. Dysmobility syndrome was associated with fracture risk, independent of and with greater hazard ratios than age or FRAX score with BMD [39]. Some overlap with the Fried **frailty** phenotype (which consists of unintentional weight loss, poor handgrip strength, self-reported exhaustion, slow walking speed and low physical activity) should be noted [40]. Of note, most (if not all [41]) osteosarcopenic older adults will have frailty, and osteosarcopenia is a very strong risk factor for frailty [42].

In summary, considering the musculoskeletal system as a whole may offer diagnostic and therapeutic opportunities beyond current tissue-specific dogmas [38]. The age-related decline in physiological reserves in the musculoskeletal system could be conceptualized as musculoskeletal frailty [40], given the astonishing overlap between sarcopenia, cachexia and frailty criteria.

2. Pathophysiology of osteosarcopenia

2.1. A life course approach

Muscles and bones display a remarkable degree of covariation across the lifespan. This begins *in utero* where not only genetic and epigenetic programming but also biomechanical and paracrine interactions shape musculoskeletal development [43]. Consequently, detrimental nutritional or environmental exposures during pregnancy may influence offspring musculoskeletal health [44]. Birth weight has been independently associated with grip strength in older adults [45].

In growing children, a correlation between muscle and bone mass is evident [46]. In experimental models, muscle hypertrophy alters bone geometry in young adult mice, particularly at tendon insertion sites [47,48]. A sedentary lifestyle and lack of physical activity in turn, may determine low peak bone and muscle mass acquisition in children, particularly in vulnerable developmental windows such as puberty. Many chronic diseases in children or treatment with *e.g.* glucocorticoids can lead to concomitant osteopenia and muscle weakness [9,49]. We therefore propose a research agenda for osteosarcopenia in pediatric populations (*e.g.* in Duchenne muscular dystrophy [50], cystic fibrosis [51] or cerebral palsy [20]). Prevention and treatment of osteosarcopenia should be a lifelong consideration, especially through physical exercise recommendations.

Each of the mechanisms discussed in the following sections may determine the risk of osteosarcopenia at different stages of life.

2.2. Evidence from genetic studies

Genome-wide association study (GWAS) meta-analysis has revealed single-nucleotide polymorphisms (SNPs) at seven loci associated with lean mass [52]. These can be categorized as positively associated with both lean and fat mass (so-called sumo wrestler phenotype with adverse metabolic profile, *e.g.* SNPs near the *FTO* and *MC4R* genes), or selectively with lean mass (favorable metabolic profile). Two other SNPs showed intermediate phenotypes, and one (in/near *IRS1*) associates with a lipodystrophic phenotype [52].

In the much larger U.K Biobank, 799 loci were identified which explained ~15.5 % of the variance in ALM [53]. A GWAS specific for muscle weakness in older persons (by EWGSOP criteria) identified 15 susceptibility loci [54]. Overall, 73 loci were consistently associated with lean mass, handgrip strength and self-reported walking pace in the U.K. Biobank [55]. Individually, many of these SNPs were associated with adiposity, diabetes mellitus, tiredness, falls, BMD and physical activity, among several other phenotypes [55].

For osteosarcopenia, a Mendelian randomization study showed a causal influence of handgrip strength on fracture risk [56]. Another large GWAS meta-analysis also found an inverse association between handgrip strength and fracture risk [57]. Two recent studies found a few genetic signals associated with both BMD and (arm, leg or trunk) lean mass, particularly for signals near *MC4R* [58,59]. Interestingly, a bi-directional Mendelian randomization study found evidence of a positive effect not only of handgrip strength on BMD, but also of BMD on handgrip strength and fat-free mass [60].

We conclude that there is consistent evidence for genetic determinants of body composition. These associations extend to metabolism but are not always well aligned with the proposed phenotypes of sarcopenia, osteosarcopenia, sarcopenic obesity *etc.* Given this complex reality, a reconsideration of the current classification of body mass and body composition disorders may be warranted.

2.3. Biomechanical loading

Bones are exquisitely sensitive to mechanical signals [1]. Because of lever effects, muscle contraction forces exert much greater loads on bone than ground reaction forces (impact loading) [1]. These two types of biomechanical loading can be manipulated selectively in experimental models: bone loss is more pronounced with the combination of muscle paralysis (*e.g.* from botulinum toxin injection) and hindlimb unloading, than from either separately [61]. Conversely, skeletal muscle stimulation prevents disuse osteopenia [62]. Thus, the covariation between muscle and bone mass may be largely determined by the beneficial effects of physical exercise on both tissues, and biomechanical signals that bone derives predominantly from muscle [1]. However, the common fate of both tissues may also be determined at the cellular and molecular level by nutritional, paracrine, endocrine or neuronal regulation (Fig. 2).

2.4. Nutrition

Both muscles and bones consume large amounts of energy, which explains their common decay in catabolic states such as malnutrition, anorexia nervosa, athletes' triad or critical illness. Both sarcopenia and aging may cause dysphagia (sarcopenic dysphagia or presbyphagia), which further compromises musculoskeletal health. A small study in geriatrics found greater malnutrition in osteosarcopenia patients than in those with sarcopenia or osteoporosis alone [63]. Loss of appetite (incl. anorexia of aging) also contributes to cachexia and is a candidate target for osteosarcopenia drug development (*e.g.* using ghrelin receptor agonists, see below).

Numerous micronutrients regulate bone and muscle homeostasis. However, the evidence to support their role in osteosarcopenia is low. There are other common environmental determinants of osteoporosis and sarcopenia, including pollution, smoking, alcohol and drug abuse, education, socioeconomic status, *etc.* which lie however beyond the scope of this review.

2.5. Paracrine regulation: myokines, osteokines and adipokines

Muscle- or bone-cell derived factors that influence the neighboring tissue in a paracrine fashion are increasingly recognized. Muscle is one of the largest internal organs, with an elaborate secretome [64].

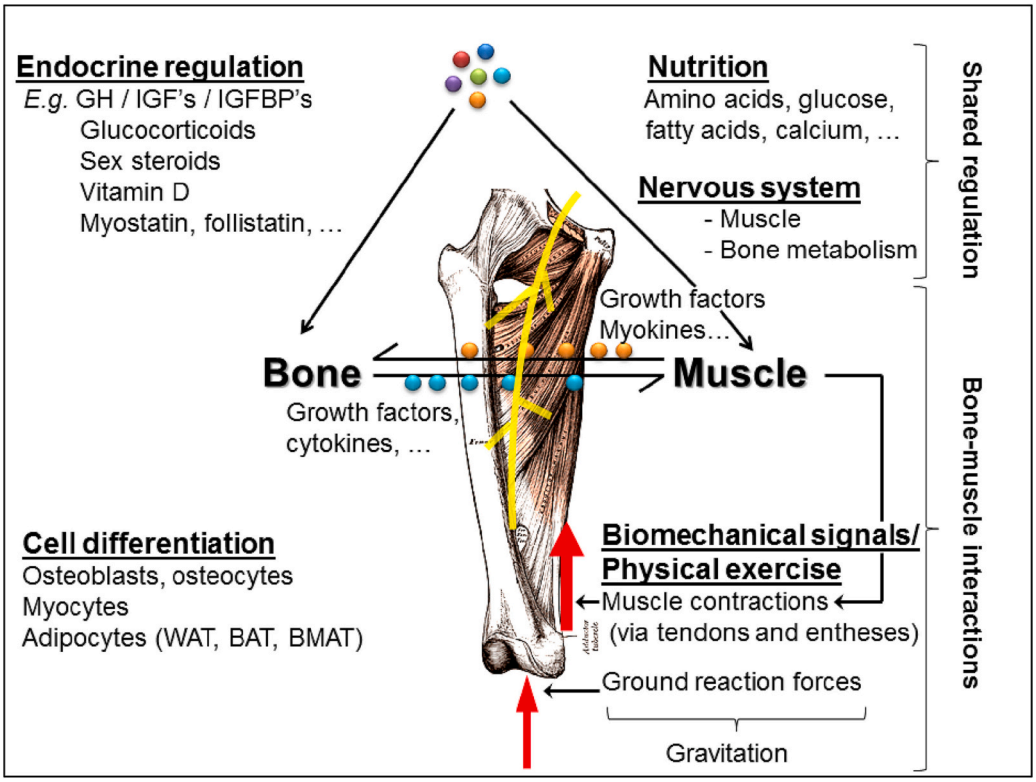

Fig. 2. Schematic diagram of pathophysiological determinants of osteosarcopenia. Muscles and bones are under shared endocrine, nutritional and neuronal control. With regards to direct muscle-bone interactions, there is reciprocal communication of growth factors, cytokines and myokines. At the cellular level, tissue homeostasis may be determined by the differentiation of pluripotent progenitor cells into either the osteoblast/osteocyte, myocyte or adipocyte lineage (white, brown or bone marrow adipose tissue; WAT, BAT or BMAT, respectively). Muscles are also essential for physical exercise and biomechanical signals on bone, mainly *via* muscle pull on tendon insertion sites but also *via* ground reaction forces. Adapted and reproduced, from Laurent et al. [1], with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Pedersen et al. [65] coined the term myokines when they showed that the cytokine interleukin 6 (which regulates bone mass) is strongly upregulated in myocytes upon contraction and released into circulation in large amounts. Other examples of myokines with known roles in bone biology are shown in Table 2. However, the importance of these muscle-derived factors for muscle-bone interactions and musculoskeletal coupling in response to exercise/disuse, is often poorly understood *in vivo*.

Irisin (which is cleaved from fibronectin type III domain-containing protein 5, *FNDC5*) is a myokine released by skeletal muscle upon contraction, which exerts favorable actions, not only on brain, muscle itself and adipose tissue [66,67], but also on bone in mouse models [66,68]. Irisin binds αV/β5 integrin [67] and may act on osteocytes to promote sclerostin expression and prevent their apoptosis [69,70]. In osteoblasts, irisin promotes differentiation [71] and may downregulate the senescence marker p21 [72]. Irisin also stimulates osteoclastogenesis directly [73]. There is also some evidence in humans for a positive association between irisin levels and BMD [72]. Furthermore, parathyroid hormone may downregulate muscle irisin expression and circulating irisin levels [74].

Apart from myokines, muscles also release peptides, lipids, amino acids, metabolites and nucleic acids that may act on distant cells [64]. For example, exercise stimulates muscle synthesis of kynurenic acid, which also regulates bone resorption in mouse models [75]. For many other muscle-derived factors however, the mechanisms and importance for bone homeostasis require further study.

Reciprocally, osteoblasts and osteocytes also release factors that influence muscle physiology. Karsenty's group has shown that in mouse models, undercarboxylated osteocalcin enhances exercise capacity, muscle metabolism and exercise-induced release of interleukin 6 from muscle [76]. Similarly, osteoglycin is a proteoglycan released from muscles and bones, which inhibits myoblast proliferation, bone formation and glucose metabolism [77]. Exercise also downregulates circulating sclerostin levels, which may influence exercise-induced adaptations in subcutaneous white adipose tissue [78]. Myotubes and muscle biopsies show expression of receptor activator nuclear factor κB (RANK), and treatment with osteoprotegerin (a decoy receptor for RANK ligand, RANKL) restores fast-twitch muscle function in *mdx* mice (a model for Duchenne muscular dystrophy) [79] and normal mice [80]. Also in mice with non-metastatic ovarian cancer, RANKL blockade reduces not only bone loss but also cachexia [11].

Adipokines such as leptin and adiponectin are adipocyte-derived cytokines that regulate bone, muscle and energy metabolism. Moreover, visceral fat recruits immune cells and leads to low-grade systemic inflammation, which compounds insulin resistance. However, to what extent low-grade inflammation in sarcopenic obesity contributes to bone loss, has been poorly studied. In mice, globular adiponectin restored ovariectomy-induced bone loss, sarcopenia and insulin resistance [81], thus offering an interesting therapeutic strategy for osteosarcopenia. On the other hand, several diabetes or cardiovascular drugs such as metformin, losartan or glucagon-like peptide receptor agonists may exert favorable effects on both sarcopenia as well as osteoporosis, although these findings require confirmation [82].

In summary, osteokines and myokines are increasingly recognized to play a role in the favorable effects of exercise on the musculoskeletal system, although more human studies and clinical applications are still needed.

2.6. Endocrine co-regulation

Deficiency in anabolic hormones might contribute to concomitant musculoskeletal deficits. We refer to previous reviews for a more in-depth discussion [1,40], but we will highlight some recent advances here. Overall, in older adults, low levels of sex steroids, 25-hydroxyvitamin D and insulin-like growth factor (IGF)-1 are associated with bone loss, but their association with incident sarcopenia remains unclear [5,83,84].

2.6.1. Vitamin D

Vitamin D deficiency impairs intestinal calcium absorption, triggers

Table 2
Examples of muscle-secreted factors with known roles in bone metabolism (none-exhaustive list, adapted and reproduced from Florin et al. [64] with permission).

Category	Examples
Cytokines and growth factors	Bone morphogenetic protein 1, 4 Brain derived neurotrophic factor Granulocyte colony-stimulating factor Insulin-like growth factor 1, 1A, 2 Insulin-like growth factor binding proteins 2, 3, 4, 5, 6, 7 Interleukin 1β, 2, 4, 6, 7, 8, 10, 13, 17A, 25, 34 Macrophage colony-stimulating factor 1 Osteoclast-stimulating factor 1 Platelet-derived growth factor A, C Secreted frizzled-related protein 2, 4 Stromal cell-derived factor 1 (C-X-C motif chemokine 12), 2 Transforming growth factor β (1,2,3) Tumor necrosis factor α Vascular endothelial growth factor A, C, D …
Extracellular matrix proteins	Basement membrane-specific heparan sulfate proteoglycan core protein (Perlecan) Biglycan Collagen I(α1, α2), II(α1), *etc.* Decorin Fibrillin 1, 2 Fibulin 1, 2, 5, 7 Matrix Gla Protein Mimecan (osteoglycin) Periostin Proteoglycan 4 Sushi, von Willebrand factor type A, EGF and pentraxin domain-containing protein 1 (SVEP1) …
Enzymes	Matrix metalloproteinase 2, 9, 14, 19 Superoxide dismutase Tissue-type plasminogen activator …
Miscellaneous	Semaphorin 3(A,B, C, D, E), 4(B, C), 5A, 6(A, B), 7A Ephrin type-A receptor 1, 2, 4, 7 Exostosin 1, 2 WNT1-inducible-signaling pathway protein 1 …

secondary hyperparathyroidism and hypophosphatemia, causing bone loss at the expense of normocalcemia.

Experimental vitamin D deficiency [85] or *Vdr* knockout triggers muscle atrophy [86]. Muscle-specific *Vdr* knockdown in rodents reduces muscle mass [87,88], running speed and strength [84], with evidence of muscle fiber remodelling [89]. Conversely, *Vdr* overexpression induces muscle hypertrophy, and *VDR* expression is upregulated in humans by resistance training [90]. Muscle atrophy during disuse was potentiated following *Vdr* knockdown in neural crest cells rather than muscle cells [86], suggesting that vitamin D influences neuronal control of musculoskeletal atrophy. In addition, *Vdr* deletion has also been associated with unfavorable metabolic effects and impaired neuromuscular control [91].

In summary, these preclinical studies suggest mechanisms by which vitamin D deficiency or excess could increase the risk of osteosarcopenia, falls and fractures.

2.6.2. Growth hormone (GH) and IGF signaling

GH exerts anabolic actions on muscles and bones during growth, partly *via* its cognate receptor and partly *via* liver-secreted IGFs [92]. During aging however, unfavorable metabolic effects may dominate, since GH-receptor knockout mice have extended lifespan and are protected from frailty and multiple age-related conditions. Muscle-specific GH-receptor deletion results in favorable metabolic changes without a clear muscle or bone phenotype, suggesting that the beneficial effects of GH on muscle are indirect [92,93]. Adipocyte-specific GH-receptor deletion produces favorable metabolic effects with improved grip strength [94].

Conditional deletion of the GH-receptor in mature osteoblasts and osteocytes compromises periosteal bone expansion and bone formation during growth [93]. Deletion of the IGF-1 receptor in osteoblasts and osteocytes, impairs cortical bone thickness and mildly reduced trabecular bone volume in female mice [93], although the importance of this pathway during aging remains unknown.

Overall, mechanistic studies suggest that GH/IGF-1 signaling is essential for musculoskeletal development during growth, whereas excess may be detrimental in old age, mainly *via* indirect unfavorable metabolic effects.

2.6.3. Androgens and estrogens

Estrogens play an important role in maintaining skeletal integrity throughout life, whereas androgens *via* the androgen receptor determine periosteal bone expansion during puberty [5]. Conditional deletion of the androgen receptor in satellite cells or fast-twitch muscle fibers produces an osteosarcopenic phenotype [95,96]. Androgens also exert antiresorptive effects in bone *via* the androgen receptor in osteoblasts as well as osteocytes, but not osteoclasts [97,98]. Indirectly, the androgen receptor in neuronal cells also prevents cortical thinning and trabecular bone loss in the vertebra in mice [99]. Interestingly, androgen deficiency increases the skeletal response to mechanical loading [100]. Moreover, both androgens and estrogens regulate physical activity behaviors *via* dopaminergic pathways [101]. Finally, both androgens [102] and estrogens regulate fat mass, insulin secretion and resistance, in part directly *via* their nuclear receptors in adipocytes [103].

Thus, testosterone could be a candidate treatment for osteosarcopenia. However, the potential side effects *e.g.* on the prostate or cardiovascular system are a concern.

2.7. Activin receptor signaling pathway

Activins and growth- and differentiation factors (GDFs), together with bone morphogenetic proteins, are part of the transforming growth factor-β superfamily. Activin A and GDF8 (myostatin) are inhibitors of muscle and bone mass, as shown by animal data in which inhibition of these ligands leads to muscle hypertrophy, decreased adiposity, increased bone formation, decreased bone resorption and altered bone geometry (particularly at entheses) [47,104]. Inhibitors of the activin receptor signaling include native antagonists (*e.g.*, follistatin that binds and neutralizes activins, myostatin and GDF11), activin type IIA or type IIB decoy receptors, anti-receptor II (anti-ActRII) antibody, and single or dual inhibitors against one or two ligands (Fig. 3). A ligand trap strategy using recombinant soluble ActRIIA or ActRIIB increases bone volume and strength in mice (as well as muscle mass and strength using a ActRIIB decoy receptor), including disuse atrophy [1,105]. Some preclinical studies suggest a beneficial effect of combining myostatin inhibition with testosterone [106], exercise or perhaps other interventions.

2.8. Mesenchymal stem cell differentiation

Mesenchymal stem cells or progenitor cells can differentiate into the adipocyte, myocyte, or osteoblast/osteocyte lineage, under the control of biomechanical, metabolic, paracrine or endocrine signals. Aged mesenchymal stem cells display reduced osteogenic differentiation and profileration capacity, and increased adipogenic differentiation capacity. Higher levels of circulating osteoprogenitor cells are associated with higher BMD and lean mass in older adults [107]. Conversely, in frail sarcopenic individuals, low circulating osteoprogenitor cells have been reported [41]. Intracellular and interstitial fatty infiltration is a hallmark of sarcopenia [108], and bone marrow adiposity is increasingly recognized as a contributory factor in osteoporosis [20,109]. Lamin A/C (a progeroid gene) stimulates osteogenic and inhibits adipogenic differentiation of mesenchymal stem cells *via* Wnt/β-catenin signaling *in vitro* [110]. *In vivo*, lamin A/C deficiency reduces bone and muscle volume

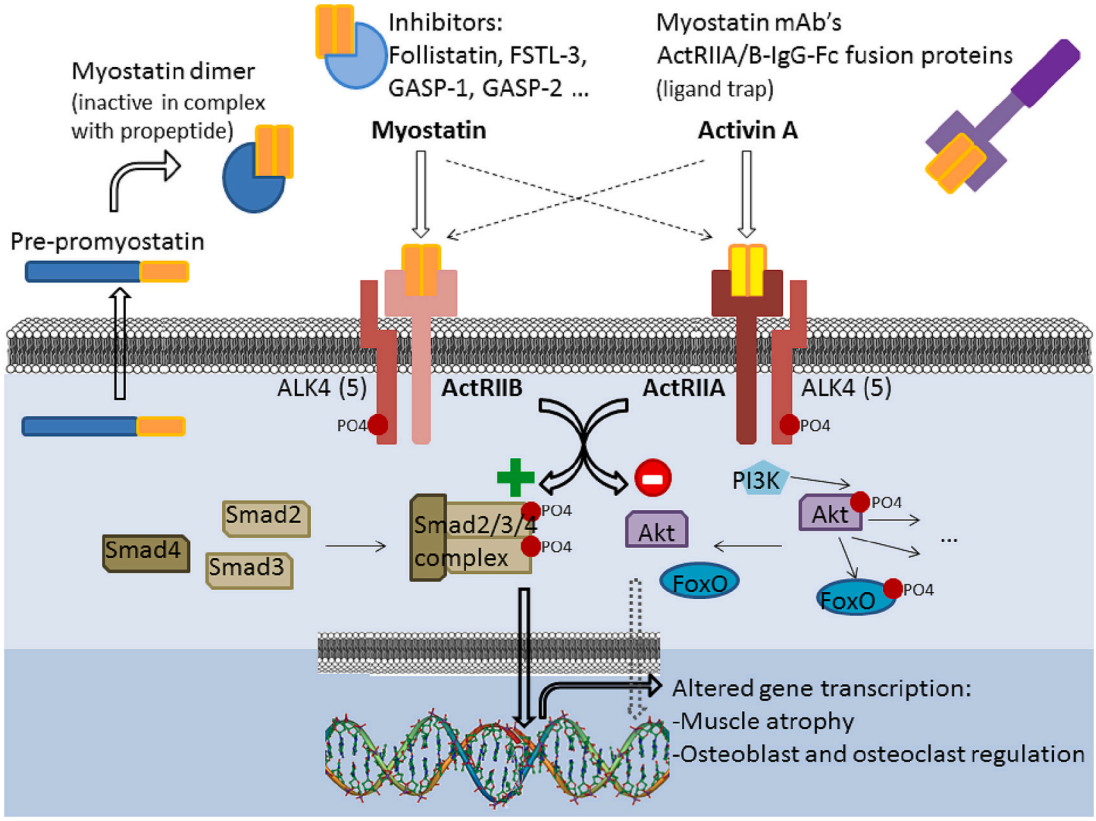

Fig. 3. Schematic overview of myostatin and activin A signaling *via* activin receptors. Upon secretion by muscle cells, pre-promyostatin is cleaved, the active C-terminal fragment dimerizes and is stored as an inactive complex with the N-terminal fragment. Follistatin, follistatin-like 3 (FSTL-3), GDF-associated serum protein 1 (GASP-1), GASP-2 and other binding proteins inhibit myostatin, activin A as well as other bone morphogenetic protein (BMP)/transforming growth factor β (TGF-β) ligands. Activin receptors type II B and A (ActRIIB, ActRIIA) preferentially bind myostatin and activin A respectively, with lower affinity for the other ligand or other TGF-β/BMP ligands. Ligand binding triggers recruitment and phosphorylation of a type I activin co-receptor, mostly the serine-threonine kinase ALK4 (activin receptor-like kinase 4, encoded by ACVR1B). This complex stimulates phosphorylation of Smad2 and 3, resulting in Smad 2/3/4 complex formation and nuclear translocation to Smad binding elements. Additionally, Akt phosphorylation and activity are inhibited which decreases the inhibition of FoxO and other transcription factors. Pharmacologically, this pathway can be inhibited by monoclonal anti-myostatin antibodies or ActRIIA/B-IgG-Fc fusion proteins (ligand trap strategy). Adapted and reproduced from Laurent et al. [1], with permission.

and strength, with concomitant fat infiltration [111]. Peroxisome proliferator-activated receptor-γ is an important transcription factor regulating the balance between adipogenesis and osteogenesis [109]. However, targeted deletion of peroxisome proliferator-activated receptor-γ in osteoprogenitor cells reduced bone marrow adipocytes, but increased cortical porosity [112]. The latter findings provide a compelling argument against the hypothesis that imbalanced progenitor cell differentiation is a culprit in osteoporosis.

Alternatively, adipocytes are known to release detrimental mediators such as RANKL or palmitate, which exert lipotoxic effects on osteoblasts [113] or stimulate osteoclasts [112], respectively. However, further studies are needed to validate these paradigms [21].

2.9. Cellular senescence

Central aging mechanisms include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction (including, but not limited to, the free radical theory and reactive oxygen species), cellular senescence and stem cell exhaustion. All of these mechanisms might contribute to osteosarcopenia, by simultaneously depleting musculoskeletal reserves with aging. Kirk et al. [114] reported that slow walking pace was associated with leukocyte telomere length in the U.K. Biobank while osteosarcopenia was not, although it was still very rare (0.5–1 %) in this cohort (mean age, 67.8 years).

Cellular senescence in particular has drawn much attention, because it may be targeted using senolytic drugs (which clear senescent cells with intermittent administration, thus potentially minimizing side effects). Mice with muscle-specific (but not osteoblast-specific) deletion of lamin A/C display not only muscle cellular senescence but also trabecular bone loss, increased bone resorption, with increased interleukin 6 release and support for osteoclastogenesis using conditioned media from myotubes [115]. Given that clearance of senescent cells prevents not only osteoporosis [116] but also muscle atrophy [117] and improves cardiovascular function, insulin sensitivity and frailty, phase 1 trials of senolytic drugs are currently ongoing.

3. Treatments for osteosarcopenia

While there has been extensive research on the pharmacological and non-pharmacological treatment of osteoporosis and sarcopenia as separate conditions, few studies have examined the concurrent effect of therapy on bone and muscle in individuals with osteosarcopenia. Notably, current guidelines on sarcopenia prevention, diagnosis and management do not mention osteosarcopenia, let alone that any guidelines exist for osteosarcopenia itself [118].

3.1. Physical exercise

Recent guidelines on the prevention and treatment of osteoporosis recommend combined physical exercise programs to prevent falls and fractures. Resistance training (*e.g.* weightlifting) and impact exercises (*e.*

g. jumping) are mostly recommended, in addition to balance training to prevent falls (*e.g.* Tai Chi) [119]. High-intensity training and supervised exercise programs appear to be more effective to reduce fracture risk [120].

There is high-quality evidence that resistance training improves muscle mass, strength and physical performance, but few studies have evaluated sarcopenia as a construct [121]. Since high-intensity resistance and impact training has been shown to improve BMD and physical function in postmenopausal women [122], it could be an effective therapeutic option for osteosarcopenia, falls and fracture prevention. Similarly, the "Osteo-cise" program has demonstrated significant benefits on BMD, muscle strength and physical performance [123].

Few studies have been performed in subjects diagnosed with osteosarcopenia [124]. The two available randomized controlled trials (RCTs) (N = 106 older adults in total) [125,126] showed that resistance training increases muscle strength and mass, with low-quality evidence for increased lumbar spine BMD [127], maintenance of total hip BMD [128], and no effect on physical performance [124]. One study (N = 63 postmenopausal women) investigated exercise in osteosarcopenic obesity [125]. The other trial (N = 43 men) compared the combination of exercise and whey protein supplementation against a control group [128]. Clearly, further studies are needed.

Overall, the optimal exercise program for osteosarcopenia would most likely involve a supervised multicomponent exercise program including weight-bearing exercises, progressive resistance and balance training [123]. There has also been considerable interest in whole-body vibration therapy [1], but the evidence supporting this strategy remains limited [129].

3.2. Nutritional interventions

Protein supplementation has been the most investigated nutritional intervention for musculoskeletal health, although individualized nutritional support should be recommended, looking broader at caloric intake, micronutrients, comorbidities *etc.*.

Protein supplementation and exercise combined are among the most likely effective interventions for muscle strength in network meta-analysis [130]. In a meta-analysis in frail older adults, protein supplementation plus exercise has been associated with a reduction in falls, improved strength, lean mass, functional performance and frailty classification [131]. Protein supplementation alone however does not appear to benefit frail older adults [132]. The evidence for an added effect of nutritional supplementation on high-intensity resistance training on muscle function (regardless of timing) appears limited [121]. Protein supplementation dose-dependently provides small additional gains in muscle mass and lower body strength (but not handgrip strength) during resistance training (but not without training), although the effect on functional performance is only marginal [133].

Currently, evidence on nutritional interventions with sarcopenia as an outcome [134], or specifically in osteosarcopenia patients, appears lacking [124]. Overall, there is no evidence for protein supplementation to prevent osteoporosis [135]. On the other hand, a cluster-randomized trial has shown that dairy product supplementation, which increases calcium and protein intake, reduces the risk of falls and fractures while slowing bone turnover and bone loss in nursing home residents [136]. As with vitamins or hormones, nutritional interventions are likely to benefit only deficient high-risk populations.

3.3. Vitamin D supplementation

There are, to our knowledge, no studies that have investigated the effect of vitamin D supplementation in persons with osteosarcopenia. However, studies in vitamin D-deficient older adults at high fracture risk (*e.g.* nursing home residents) suggest that calcium and vitamin D supplementation at moderate daily doses reduces fracture risk by about 15 % [137].

Prolonged and profound vitamin D deficiency causes rickets and osteomalacia, which are associated with muscle weakness. In RCTs however, the effects of vitamin D on muscle mass, strength, physical performance and balance are not so clear. A recent meta-analysis with 83 % vitamin D-replete individuals, found no effect on performance, muscle strength or mass, except for a small effect on the latter outcome in participants with baseline 25-hydroxyvitamin D concentrations <35 nmol/L [138]. Overall, in community-dwelling older adults, there seems to be no effect of vitamin D supplementation on indices of sarcopenia, with possible worsening of physical performance in some trials [138,139]. However, the effects may differ depending on the dose used, the degree of obesity [140,141] or the degree of balance problems at baseline [142]. Moreover, improvement in physical quality of life has been reported in subjects with 25-hydroxyvitamin D levels <25 nmol/L [140].

Further randomized trials in clearly vitamin D-deficient populations with osteosarcopenia might be considered, but raise ethical challenges.

3.4. Growth hormone (GH) and GH secretagogues

GH produces a small increase in lean body mass in men but not women, however without improving BMD [143]. Moreover, side effects include arthralgia, edema, carpal tunnel syndrome, gynecomastia, and diabetes mellitus.

Ghrelin is a polypetide expressed in the stomach and hypothalamus that stimulates GH secretion, food intake and body weight gain. A phase 2 study in healthy older adults studied the effect of capromorelin, a ghrelin receptor agonist. The study was stopped prematurely due to increased body weight and fasting glucose, although lean mass and functional performance also increased (BMD was not reported). A phase 2 RCT using the ghrelin receptor agonist anamorelin in osteosarcopenic subjects is currently ongoing (ClinicalTrials.gov: NCT04021706).

3.5. Testosterone and selective androgen receptor modulators

Declining total and bioavailable testosterone levels are associated with bone and muscle loss and increasing adiposity in older men as well as men treated with androgen deprivation therapy for prostate cancer [5]. Testosterone therapy increases fat-free mass, increases muscle strength, lowers bone turnover markers and increases BMD. There are no studies in osteosarcopenic subjects, but in one trial in older adults with testosterone <350 ng/dL and at least one Fried frailty criterion, transdermal testosterone decreased fat mass and increased ALM and BMD, but not muscle strength or performance [144]. In two recent RCTs, testosterone improved BMD [145,146], self-reported walking ability and six-minute walking distance (modestly), particularly in those with pre-existing mobility limitations [147]. An RCT in frail older adults showed improved physical performance [148]. However, there is no evidence that testosterone therapy reduces falls [147] or fracture risk, and safety concerns include cardiovascular adverse effects, stimulation of pre-existing prostate cancer, polycythemia and venous thromboembolic risk [148].

Selective androgen receptor modulators (SARMs) have been proposed to elicit favorable musculoskeletal effects while avoiding some of these adverse effects [1]. However, part of their purported specificity may simply be due to lack of conversion by aromatase or 5α-reductases, and not due to tissue-specific actions on the androgen receptor [149]. Despite improvements in lean body mass, improvements in BMD have not been demonstrated in RCTs. More studies investigating the effect of testosterone in combination with exercise programs in osteosarcopenic subjects are required. Indeed, a recent RCT in chronic obstructive pulmonary disease showed that a SARM increased leg strength and lean body mass in combination with a home exercise program [150].

3.6. Inhibitors of the activin receptor signaling pathway (IASPs)

The activin receptor signaling pathway offers an interesting therapeutic avenue for osteosarcopenia. In phase 1 RCTs, a decoy ActRIIB increased lean mass, thigh muscle volume, bone formation and lowered bone resorption [151]. Soluble ActRIIA also increased bone formation, reduced bone resorption and improved BMD [152]. Because of their stimulatory effects on erythropoiesis, ActRIIA inhibitors have been further developed and are currently marketed for anemia.

A phase 2 RCT in older fallers with low muscle power showed that myostatin inhibition using landogrozumab increased ALM, reduced fat mass and improved some functional performance measures [153]. However, bone turnover was unaffected and whole-body BMD was paradoxically reduced, which the authors interpreted as an artifact from altered fat-to-lean mass ratio on DXA measurements [153].

A recently published phase 2 RCT in older sarcopenic adults evaluated bimagrumab, which binds both ActRIIA and ActRIIB and inhibits activation both receptors. Compared to standard of care (home-based exercises, vitamin D and protein supplementation), lean mass increased, but muscle strength and physical performance did not [154]. In obese diabetic adults, bimagrumab increased lean mass while reducing fat mass, body weight and HbA1c [155]. Also in hip fracture patients, bimagrumab increased lean body mass but did not enhance recovery [156]. BMD results were not reported in any of these trials. Further clinical studies are needed to delineate the therapeutic potential of IASPs for osteosarcopenia.

3.7. Effects of osteoporosis drugs on muscle and falls

There is increasing attention to the extraskeletal effects of osteoporosis drugs, including for sarcopenia (and thus, osteosarcopenia). Denosumab (a RANKL inhibitor) has been associated with a reduced risk of falls [157]. Compared to bisphosphonates or placebo, a smaller meta-analysis found that denosumab increased handgrip strength but not gait speed [80]. Denosumab has also been associated with higher ALM [80], improve multidirectional agility [158] and improved glucose metabolism [159].

In one multicenter prospective study, only denosumab reduced the risk of falling, but denosumab, alendronate or zoledronate improved handgrip strength, gait speed and the timed up-and-go test [160]. Other studies have found mixed results [161,162]. Effects of bisphosphonates on ALM might also be related to overall prevention of weight loss (an anti-cachexia effect) [163,164,165]. In the *mdx* mouse model, pamidronate also improved muscle function [166].

Further preclinical and clinical studies in osteosarcopenia are required to confirm these findings and whether these are direct or indirect effects *via* muscle or muscle-bone crosstalk. Meanwhile, osteoporosis drugs with demonstrated efficacy should be considered to prevent fractures also in osteosarcopenic subjects. Pragmatically, screening for sarcopenia might be considered in osteoporotic patients, and *vice versa* [29].

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