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Age-related bone loss and sarcopenia in men

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ABSTRACT

Bone and muscle are required for mobility but they also have endocrine and metabolic functions. In ageing as well as in many chronic diseases, bone loss and muscle atrophy occur simultaneously, leading to concomitant osteoporosis and sarcopenia. This occurs in both genders but compared with postmenopausal women, men appear to be better protected against age-related bone and muscle decay. Sex steroids (both androgens like testosterone and oestrogens like estradiol) are mainly responsible for musculoskeletal sexual dimorphism. They stimulate peak bone and muscle mass accretion during puberty and midlife, and prevent subsequent loss in ageing men but not post-menopausal women. Still, recent studies have highlighted the importance of intrinsic ageing mechanisms such as cellular senescence and oxidative stress in both genders. Sarcopenia may predispose to dysmobility, frailty, falls and fractures, but whether so-called osteosarcopenia qualifies as a distinct entity remains debated. Although randomized clinical trials in male osteoporosis are smaller and therefore underpowered for some outcomes like hip fractures, the available evidence suggests that the clinical diagnostic and therapeutic approach to male osteoporosis is largely similar to that in postmenopausal women. There is a clear unmet medical need for effective and safe anabolic drugs to rebuild the ageing skeleton, muscle, and preferably both tissues simultaneously. The Wnt/sclerostin and myostatin/activin receptor signalling pathways appear particularly promising in this regard. In this narrative review, we aim to provide an overview of our current understanding of the pathophysiology and treatment of male osteoporosis and sarcopenia, and interactions between these two diseases.

1. Introduction

A great deal of morbidity, mortality and health care expenditures in our ageing population is related to the musculoskeletal system. Osteoporosis, sarcopenia, impaired mobility, falls and fractures are among the commonest geriatric syndromes. The risk of these conditions increases with age and particularly affects women (Fig. 1) [1–3]. Still, studies show that osteoporotic men face greater underdiagnosis and undertreatment, with a higher subsequent risk of mortality compared to women [4]. Considering this background, the objective of this narrative review is to provide an update on male osteoporosis, sarcopenia, and interactions between these two common diseases.

2. Methods

Articles were retrieved from PubMed using combinations of keywords including osteoporosis, sarcopenia, bone, muscle, androgens, oestrogens, testosterone, male, ageing, older, elderly. Additional references were retrieved from the authors' extensive reference database. Priority was given to recent articles.

3. Definitions, diagnosis and epidemiology

3.1. Osteoporosis, falls and fractures

Osteoporosis is a skeletal disease involving low bone strength and increased risk of fractures. However, direct measurements of bone strength are not available. Dual-energy X-ray absorptiometry (DXA) is

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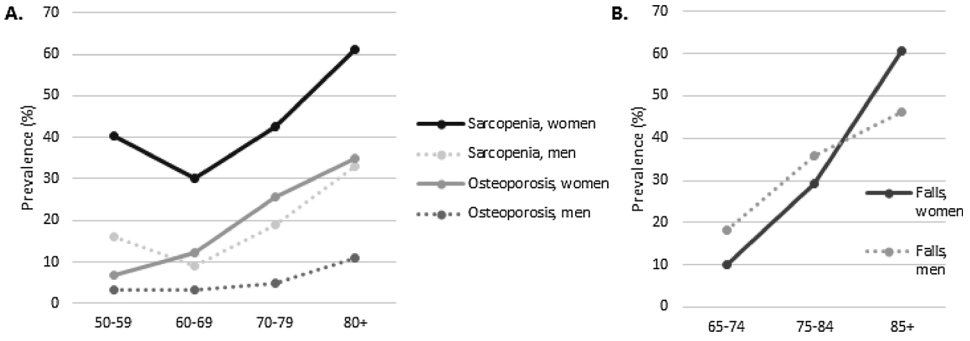

Fig. 1. A. Estimated prevalence (% of the population), according to age (decade categories) and gender, in selected studies on community-dwelling older adults in the United States, of sarcopenia (according to the FNIH appendicular lean mass without BMI correction criteria [1]), and osteoporosis (defined as a T-score ≤ -2.5 at the lumbar spine or femur [2]). **B.** Estimated annual incidence of falls, by decade and gender category [3].

used clinically to measure bone mineral density (BMD), a surrogate of bone mass, which correlates with bone strength. Fractures also require a trauma force exceeding bone's mechanical competence, often the impact from a fall. Notably, older men are less prone to falls compared to women [3,5]. The reasons for this remain unclear but may in part be related to the fact that men develop higher peak muscle mass and strength, which they also maintain slightly better during midlife [6].

Even though osteoporosis is typically regarded as a disorder affecting women, 39% of all osteoporotic fractures occur in men [4]. In women, fracture risk increases from around the age of menopause whereas in men the increase parallels that of women but only starts around age 75, at which time fracture incidence also accelerates in women (Fig. 2) [4]. There is growing awareness that ageing itself accelerates bone and muscle loss via mechanisms such as cellular senescence, oxidative stress etc. which have independent and mechanistically distinct effects in both genders [7]. However, the age-related increase in fracture incidence in both genders cannot be explained by declining bone strength alone, pointing to the importance of other influences, most importantly risk of falls [8].

3.2. Dysmobility syndrome and musculoskeletal frailty

In analogy to the metabolic syndrome concept, the "dysmobility syndrome" has been proposed as a constellation of risk factors for falls, fractures and disability [10]. This involves the presence of at least three out 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 [10].

Musculoskeletal frailty has been used to characterize frailty or increased vulnerability in multiple aspects of the musculoskeletal system; this may involve osteoporosis, sarcopenia, or their combination (so-called sarco-osteopenia), but may also entangle osteoarthritis, ruptured tendons or neurological disorders [11].

3.3. Sarcopenia and cachexia

The age-related loss of muscle mass and strength is termed sarcopenia. Cachexia is essentially the same condition i.e. characterized by loss of muscle mass with or without loss of fat mass and leading to functional impairment, although cachexia is diagnosed based on weight loss alone. The term cachexia is usually applied in the context of a severe underlying disease e.g. cancer, chronic obstructive pulmonary disease, HIV and other infectious or inflammatory diseases.

Increasing emphasis is being placed on muscle weakness (dynapenia) rather than focusing on muscle mass. However, low grip strength or gait speed may have many other causes e.g. osteoarthritis, myopathies or muscular dystrophies. Luckily, muscle strength and power are more readily measurable than bone strength. Appendicular lean mass (ALM, the non-bone non-fat mass of the limbs) measured by DXA as well as bioimpedance are commonly used surrogate markers for muscle mass. However, they likely overestimate muscle mass and are considered less accurate than e.g. magnetic resonance imaging or creatine isotope dilution, which are however less accessible [12]. Muscle "quality" (in analogy to "bone quality") are also often discussed, but these are probably vague terms, which should be discouraged.

The main proposed operational criteria for sarcopenia are the Foundation for the National Institutes of Health (FNIH) criteria, the European Working Group for Sarcopenia in Older People (EWGSOP) criteria, and the International Working Group on Sarcopenia (IWGS) criteria. Although there is no universal agreement on the most appropriate criteria, all three criteria involve gender-specific criteria for low ALM (measured either by DXA or other techniques) combined with low grip strength, gait speed, or other measures of physical performance (Table 1). The recently updated EWGSOP2 criteria put even more emphasis on muscle strength, recognizing that it is more predictive of adverse outcomes than muscle mass, and the presence of muscle weakness alone is sufficient for diagnosis and interventions in routine practice [12].

The FNIH criteria include two sets of criteria for appendicular lean

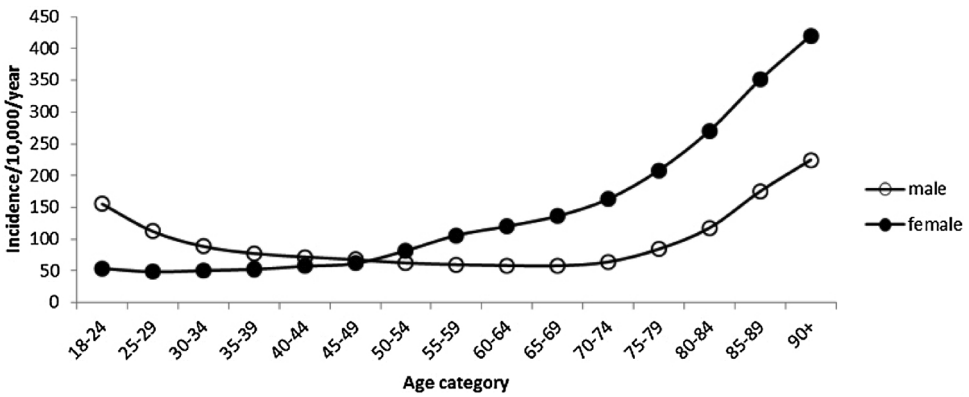

Fig. 2. Age- and sex-specific fracture incidence rate at any site among adults in the United Kingdom, 1988–2012 (reproduced with permission from Curtis et al. [9]).

Table 1
Diagnostic criteria for sarcopenia.

	Cut-points for women	Cut-points for men
FNIH [13]: weakness and low lean mass		
- Weakness	Grip strength < 16 kg	Grip strength < 26 kg
- Low lean mass: ALM adjusted for BMI	ALM_{BMI} < 0.512	ALM_{BMI} < 0.789
alternative: Unadjusted ALM	ALM < 15.02 kg	ALM < 19.75 kg
IWGS [14]: slow gait speed + low muscle mass		
- Slow gait speed	Gait speed < 1.0 m/s	
- Low muscle mass	ALM/h^2 ≤5.67 kg/m^2	ALM/h^2 ≤7.23 kg/m^2
EWGSOP2 [12]:		
- 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 ≥20s 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.

mass (ALM): with or without adjustment for body mass index (BMI). BMI correction acknowledges the entity of sarcopenic obesity i.e. the relative muscle deficit and greater risk of dysmobility in obese people [1]. On the other hand, BMI correction is not practical and may underestimate sarcopenia in cachectic subjects or the prevalence in women [1].

The EWGSOP2 and FNIH grip strength criteria (which are almost identical) correspond to 2.5 standard deviations below the gender-specific peak mean grip strength around age 30 years i.e. a gender-specific T-score [6]. As a consequence of this gender-specific approach, low grip strength affects men and women almost equally at any age [6]. This may appear counterintuitive since an average 85-year-old man may still have the same grip strength as the average 30-year-old women [6]. It also contrasts with the osteoporosis field in which female reference values are used for BMD T-scores in both genders. This is justified by the fact that men and women have equal fracture risk for the same given T-score. Since the incidence of outcomes like falls is also greater in women, we believe that the use of a female T-score approach for grip strength in both genders, or alternatively BMI-adjusted strength (or a strength/load ratio), has remained underexplored in the sarcopenia field (Fig. 3).

4. Osteoporosis + sarcopenia = osteosarcopenia?

Bone loss and muscle atrophy often coincide, not only in ageing and after menopause in women, but also in association with many chronic diseases such as COPD, HIV infection, hypercortisolism, disuse, vitamin D deficiency etc. The mechanism underlying concomitant bone and muscle decay may relate to shared regulation by e.g. nutrition, endocrine regulators or neuronal regulation of muscle and bone. Additionally, the strong correlation between muscle and bone mass may be attributed to one of several muscle-bone interactions, which include not only ground reaction forces and direct biomechanical interactions at tendon sites, but also local growth factors or myokines affecting bone, osteokines or clastokines affecting muscle, and intercellular communication at the periosteum [15].

The term osteosarcopenia (or "sarco-osteoporosis") refers to combination of these disorders in the same patient. Incident sarcopenia may confer a five-fold increased risk of developing osteoporosis, and a decline in muscle mass and strength is associated with hip and spine BMD declines [16]. A systematic review concluded that there is a high prevalence of sarcopenia in elderly fracture patients, particularly in men. However, sarcopenia was an independent predictor of fractures in only 2 out of 5 papers [17]. Other recent studies also question whether the combination of low muscle with low bone mass meaningfully implies a "double trouble". In the CHAMP study, community-dwelling older men with osteosarcopenia did not have greater falls risk than those with sarcopenia alone, nor did they have greater fracture risk than those with osteoporosis alone [18]. In MrOS, muscle strength and physical performance measures predicted fractures independent from FRAX, falls and BMD, whereas the association with muscle mass (ALM/h^2) was attenuated after BMD adjustment [19]. Similarly, dysmobility syndrome has been independently associated with fracture risk [20]. Collectively, these studies suggest that muscle mass itself is not protective against falls or fractures, and interventions to increase it may be futile if they do not improve functional performance.

5. Role of sex steroid hormones in male osteoporosis and sarcopenia

During the third decade of life, young men attain on average more than 40% greater lean body mass and more than 60% higher grip strength compared to young women [6,21]. Men also achieve 25% greater bone mass (whole-body bone mineral content, 3.36 kg vs. 2.71 in females) [21]. However, the latter is entirely expected given the fact that men are on average 8% taller (because DXA is a projection technique and in 3D, $(1.08)^3 \approx 1.25$) [4]. The main gender difference in bone is that men develop wider bones (even following adjustment for bone length) due to greater periosteal expansion. Since bone strength scales to the fourth power with diameter, this is the main driver of greater male bone strength. In fact, women have similar cortical thickness and even greater cortical volumetric BMD and lower porosity [4], but these benefits are entirely offset by the effect of bone width. During midlife cortical bone continues to expand in men but not in women [22]. Only after menopause do women have greater periosteal expansion, which partially compensates for cortical thinning driven by endosteal resorption [4,22]. In any case, peak bone mass is likely an important determinant of osteoporosis later in life, and gender differences therein.

17β-estradiol (E2, the principal oestrogen) is derived from testosterone (T, the principal androgen) by actions of the aromatase (CYP19A1) enzyme. Higher T levels are likely responsible for the superior muscle mass and physical performance in men [23]. E2 acting via oestrogen receptor α (ERα) is essential for male bone health, both during pubertal growth (as evident e.g. in rare cases of men with aromatase or ERα deficiency [4]) as well as in older men, who have higher oestrogen levels than post-menopausal women. Some studies have also suggested an effect of ERβ in female rodents [24], but evidence in male animal models or humans remains lacking.

5.1. Androgens and muscle

The anabolic effects of androgens on muscle hypertrophy are well established, particularly in combination with resistance exercise training [25]. Loss of endogenous T blunts the response to strength training [26], although exercise remains an effective countermeasure against hypogonadal muscle atrophy [27]. Both in human and rodent studies, androgens induce a greater increase in muscle mass than in muscle strength [28]. These effects of T appear similar in younger and older men [29]. However, in frail older men with mobility limitations, T treatment is not recommended due to a possible risk of cardiovascular adverse events [4].

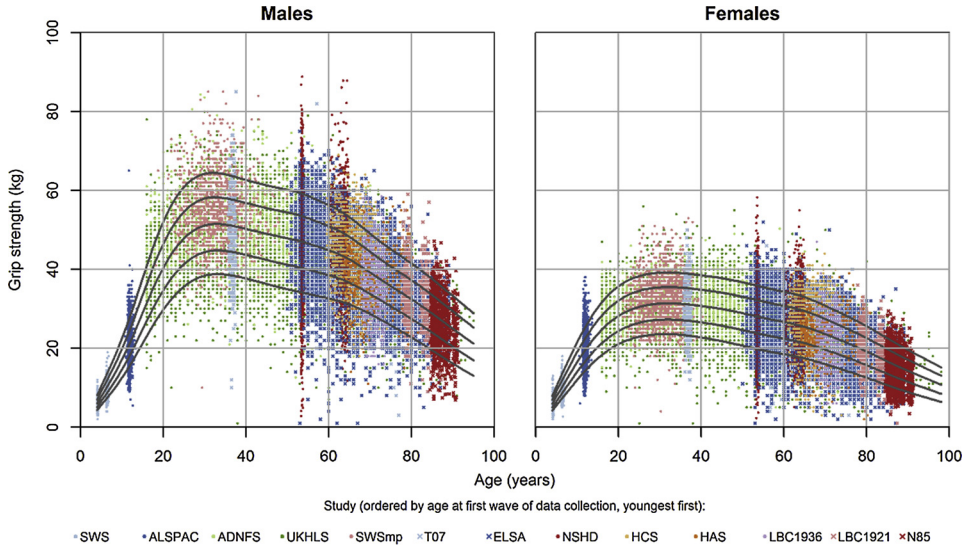

Fig. 3. Gender-specific normative curves for grip strength based on 12 British population-based studies (each indicated in different colours) (reproduced with permission from Dodds et al. [6]). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Studies in muscle-specific androgen receptor (AR) knock-out mice have further shown that the AR in the satellite cell lineage mediates part of its effects on muscle hypertrophy [28]. However, part of the androgenic effects on muscle are likely mediated via muscle-resident fibroblasts and their release of local hormones like insulin-like growth factor 1 [30]. Conditional deletion of AR in the brain also reduces fast- but not slow-twitch muscle mass, likely due to diminished spontaneous physical activity [31]. Indeed, T, both directly via the AR as well as via aromatization, stimulates the motivation to exercise in animal models, in part via dopaminergic pathways [32]. This could contribute to the beneficial musculoskeletal effects of T [27,31]. Finally, the effect of T does not require 5α-reduction into dihydrotestosterone (DHT, the principal androgen in the prostate). Thus, combination of 5-reductase inhibitors with T replacement therapy remains effective on muscle mass and improves grip strength and physical performance in older men without unwanted prostatic stimulation [33].

Notably, the early direct target genes required for AR actions on muscle remain poorly understood [25]. Several studies have also reported androgen suppression of myostatin. However, in vivo evidence shows that myostatin acts as a chalone (counter-regulatory hormone) to restrict excessive muscle hypertrophy induced by androgens [28].

Given the possible undesirable side effects of androgens such as virilization in women, on the cardiovascular system and on the prostate, attempts have been made to establish selective androgen receptor modulators (SARMs). However, no molecules have yet been described that exploit a truly molecularly distinct AR agonism in the way that selective oestrogen receptor modulators (SERMs) do. Instead, these molecules can be considered selective AR “marginators” with a wider therapeutic margin, often related to the fact that most are non-steroidal and cannot be converted to DHT or oestrogens [4].

5.2. Oestrogens and the male skeleton

Oestrogens are essential for both optimal male peak bone mass as well as maintenance. Recent Mendelian randomization studies support a causal association between E2, male bone density and fracture risk [34,35]. Rodent studies have shown that both AR and ERα actions are required for optimal cortical bone development [4]. Not only classical, nuclear ERα signalling but also non-genomic actions at the cytoplasmic membrane are required for the oestrogen effects on male cortical and trabecular bone [36]. The target cells of these effects remain unclear, since neither osteoblast- nor osteoclast-specific male ERαKO mice have a cortical or trabecular bone phenotype [37]. Osteocyte-specific ERKO mice however displayed slightly lower trabecular bone volume due to lower bone formation [38]. Some recent studies suggest that oestrogen deficiency triggers release of the osteoclastic cytokine SDF1 from bone marrow stromal cells [7]. Consistent with these results, bone turnover in men is mainly regulated by oestrogens but androgens also seem to contribute [39]. Several randomized trials in adult or older men show however that androgens alone cannot compensate for the cortical and trabecular bone loss induced by aromatase inhibition [39]. Likewise, treatment with DHT induced male bone loss due to negative hypothalamic-pituitary feedback and suppression of oestrogens [40]. Importantly however, none of these studies have been designed to investigate whether selective androgen deficiency has an effect in the face of maintained oestrogen levels.

5.3. Androgens and bone

The effects of T on preservation of bone mass in older men are best appreciated from the recent Testosterone Trials, which randomized men with total T levels < 275 ng/dl to placebo or T gel [41]. After 1 year, T increased both hip and spine trabecular and cortical volumetric BMD (vBMD). However, the effect was greater on trabecular than on cortical bone, and greater on the spine than on the hip. As a consequence, areal BMD increased at the spine but not the hip [41]. Notably, many of these men had low sex hormone-binding globulin (SHBG) levels accounting for their low total but rather normal free T levels. In contrast, low free T rather than total T may be important for male bone and muscle health, as suggested by observations in both humans as well as in SHBG-transgenic mice [42,43].

The mechanism of action of androgens on male cortical and trabecular bone have been investigated using male rodent models. The most important effect of androgens is their stimulation of periosteal bone formation and cortical bone expansion, which has important benefits for bone strength [4]. Both pre- and post-pubertal AR deletion impair cortical and trabecular peak bone mass in male mice [44]; however, the effect of inducible deletion in adult or ageing mice remains to be investigated. Notably, the target cell(s) -let alone the target genes- for the crucial effect of androgens on periosteal bone formation remain unclear [37]. The antiresorptive effects of androgens on both endosteal and trabecular bone are not mediated via osteoclasts [37,45]. The antiresorptive effects of androgens on trabecular bone are instead mediated via mature osteoblasts and osteocytes, while the effects on endosteal

resorption are not [37].

Other recent studies have shown that conditional deletion of the AR in extrahypothalamic neurons accelerated age-related cortical bone resorption, possibly by altering sympathetic regulation of bone metabolism [46]. Furthermore, muscle-specific ARKO mildly reduced trabecular bone but the antiresorptive effects of androgens on disuse osteopenia are not explained via muscle-bone interactions [47]. Finally, and in contrast to the effects on muscle, the anabolic response of mechanical stimulation on bone is inhibited by androgens [48].

6. Current and future treatment strategies

The aim of osteoporosis treatment is fracture prevention. Falls prevention is very important in this regard, but this requires multifactorial interventions, which remain only modestly effective. Randomized trials showing anti-fracture efficacy in male osteoporosis are sparse and mostly underpowered for fracture outcomes. This is because regulatory agencies such as the FDA mandate trials in men but do not require the same rigorous fracture endpoints as in large (and expensive) pivotal trials in post-menopausal women. Nevertheless, vertebral fracture prevention has been demonstrated in one larger trial in male osteoporosis [49] and in hypogonadal men receiving androgen deprivation therapy for prostate cancer [4]. Furthermore, available analyses suggest that the anti-fracture efficacy is of the same magnitude in men as it is in women [49].

Despite the availability of effective and safe antiresorptive and osteoanabolic drugs for male osteoporosis such as bisphosphonates, denosumab and teriparatide, there remains an unmet medical need for anabolic drugs, which could restore age-related declines in not only bone but also muscle mass and ideally, improve physical performance, mobility and prevent falls and fractures.

The Testosterone Trials recently showed beneficial effects of T on mainly trabecular bone in older hypogonadal men [41]. However, the improvement in physical performance was too small to be clinically meaningful, and risk of falls (27%/year!) remained unaffected [50]. Moreover, despite their role in pathophysiology, measurements of T, E2 or SHBG have limited clinical utility in bone loss or fracture risk assessment in older men [51,52]. Similarly, T levels do not appear predictive of incident sarcopenia in community-dwelling men [53]. In any case, osteoporosis or sarcopenia are not indications for T therapy in older men, given concerns about cardiovascular safety.

One of the promising future anabolic therapies for osteoporosis is romosozumab, a monoclonal antibody targeting the Wnt inhibitor sclerostin. This therapy is associated with increased bone formation and decreased bone resorption (i.e. uncoupling of formation and resorption). A phase III RCT in male osteoporosis showed rapid and marked increases in both spine and hip BMD but confirmed a numerical imbalance in cardiovascular serious adverse events [54], similar to what has previously been reported in one trial in postmenopausal women.

Several drug targets for sarcopenia have been identified, in particular myostatin [15]. However, there is increasing awareness that inhibition of the activin receptors through which myostatin acts (mostly ActRIIB but also ActRIIA) has additional benefits, likely because activin A and other ligands also limit muscle hypertrophy through these pathways [15]. Interestingly, ActRIIB inhibition has been shown not only to increase muscle but also trabecular, cortical and even periosteal bone mass in animal models [55]. More recently, a dual-specific anti-ActRIIA/IIB antibody (BYM338, bimagrumab) has been developed for maximal increases in muscle mass [56]. Trials in elderly hip fracture patients are now ongoing, in part because this population offers a regulatory pathway for an indication like sarcopenia which there are no drugs approved yet.

Contributors

Michaël R. Laurent was responsible for the concept and design of the work, interpretation of data, drafting the manuscript, critical revision of the manuscript for important intellectual content, administrative support and study supervision.

All other authors were responsible for analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.

All authors saw and approved the final version, and are accountable for the accuracy and integrity of the work.

Conflict of interest

Michaël R. Laurent has received consultancy fees from UCB (related to romosozumab), travel support and lecture fees from Amgen, and consultancy fees from Alexion, Kyowa Kirin and Sandoz, unrelated to this work.

Evelien Gielen has received consultancy fees from UCB (related to romosozumab) and non-financial support from Amgen unrelated to this work.

All other authors have no conflicts of interest to declare.

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Provenance and peer review

This article has undergone peer review.

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