Therapeutic approaches to osteosarcopenia: insights for the clinician

Mizhgan Fatima, Sharon L. Brennan-Olsen and Gustavo Duque (iD)

Abstract: Osteopenia/osteoporosis and sarcopenia are both age-related conditions. Given the well-defined bone and muscle interaction, when osteopenia and sarcopenia occur simultaneously, this geriatric syndrome is defined as 'osteosarcopenia'. Evidence exists about therapeutic interventions common to both bone and muscle, which could thereby be effective in treating osteosarcopenia. In addition, there are roles for common nonpharmacological strategies such as nutritional intervention and physical exercise prescription in the management of this condition. In this review we summarize the evidence on current and upcoming therapeutic approaches to osteosarcopenia.

Keywords: aging, bone, elderly, falls, fractures, frailty, muscle, Osteosarcopenia, osteoporosis, sarcopenia

Introduction

Bone and muscle function are an integral part of locomotion, both of which are affected by advancing age. Osteopenia/osteoporosis and sarcopenia are age-related musculoskeletal diseases that lead to loss of independence, poor quality of life, and an increased likelihood of transition to residential aged care.[1] The bone and muscle interaction is now being increasingly recognized,[2–4] including direct mechanistic interaction through endocrine pathways and activating receptor signaling.[2–4] The concept of a 'bone–muscle unit' encompasses the notion that there exists communication between both tissues; thus, disease affecting one part of the musculoskeletal unit is likely to affect the other, and *vice versa*. In this context, the term osteosarcopenia has been coined to describe the concomitant occurrence of osteopenia/osteoporosis and sarcopenia,[5] and thus indicative of a new geriatric syndrome. Based on the concept of a bone-muscle unit, this article summarizes evidence regarding therapeutic approaches to manage osteosarcopenia.

Osteosarcopenia as a new geriatric syndrome

In 2009, Binkley and Buehring coined the term sarco-osteopenia, which referred to adults with an increased risk of falls and fractures secondary to underlying weak muscle (sarcopenia) and weak bones (osteopenia/osteoporosis).[6] That concept has since evolved, and now is known as 'osteosarcopenia', which is a geriatric syndrome characterized by the concomitant presence of osteopenia or osteoporosis and sarcopenia.[5]

Although biological bases of this syndrome are proposed owing to the robust evidence on bone and muscle interaction[2–4] and the common developmental origin from mesenchymal precursors,[7] it is the clinical phenotype of this syndrome that makes it peculiar owing to its increased vulnerability to adverse events.[8] Older adults with osteosarcopenia have poorer physical function and are at increased risk of fracture, functional decline, and mortality when compared with those with sarcopenia or osteoporosis alone.[9,10] Yoo *et al.* reported, in a cohort of older people with hip fracture, that the prevalence of osteosarcopenia was 28.7%, and mortality rate was 1.8 times higher than those without it or its components.[8]

Osteosarcopenia must be discerned from the concept of frailty, a term that has been used to describe age-related decline in physiological reserves with increased vulnerability to minor stressors.[11] Frailty encompasses many organ

Correspondence to:
Gustavo Duque
Australian Institute for Musculoskeletal Science (AIMSS), The University of Melbourne and Western Health, 176 Furlong Road, St. Albans, VIC 3021, Australia

Department of Medicine-Western Health, Melbourne Medical School, The University of Melbourne, St Albans, VIC 3021, Australia
gustavo.duque@unimelb.edu.au

Mizhgan Fatima
Sharon L. Brennan-Olsen
Australian Institute for Musculoskeletal Science (AIMSS), The University of Melbourne and Western Health, St Albans, VIC, Australia

Department of Medicine-Western Health, Melbourne Medical School, The University of Melbourne, St Albans, VIC, Australia

systems whereas osteosarcopenia is confined to musculoskeletal tissue.[5,11] It is possible that osteosarcopenia exacerbates frailty, however temporal association between two needs to be investigated in a longitudinal study.

Osteopenia and osteoporosis are defined as per World Health Organization (WHO) criteria with bone mineral density (BMD) T-scores less than −1 and −2.5 SD below young adult mean, respectively.[12] Sarcopenia represents a progressive and generalized pathological decline in skeletal muscle mass and strength which is more than what could be expected as a part of aging.[13] It is defined as per European Working Group of Sarcopenia in Older People (EWGSOP) as loss of muscle strength associated with loss of muscle quality[13] (Table 1). Various tools have been used to measure the muscle parameters, outlined in Table 2.

Table 1. Operational definition of sarcopenia (adapted from the European Working Group on Sarcopenia in Older People, EWGSOP2).[13]

Probable sarcopenia is identified by Criterion 1.
Diagnosis is confirmed by additional documentation of Criterion 2.
If Criteria 1, 2, and 3 are all met, sarcopenia is considered severe.
1. Low muscle strength assessed by **Grip strength** (cut point <27 kg for men and <16 kg for women) or **Chair stand test** (cut point >15 s for 5 rises).
2. Low muscle quantity or quality assessed by measuring **appendicular skeletal muscle mass** (ASM) by dual-energy X-ray absorptiometry (DXA) with cut point <20 kg for men and <15 kg for women
3. Low physical performance measured by **gait speed** with cut-point ≤0.8 m/s, **short physical performance battery** (SPPB) with cut point ≤8 point score, **timed up and go test** (TUG) with cut point ≥20 s and **400-meter walk (400 m walk)** with cut point ≥6 min for completion or noncompletion

Table 2. Clinical tools for measurement of muscle strength, muscle mass and physical performance in sarcopenia (adapted from European Working Group on Sarcopenia in Older People, EWGSOP2).[13]

Variable	Clinical tools
Case finding	SARC-F (5 item questionnaire)
	Ishii screening tool
Skeletal muscle Strength	Grip strength
	Chair stand test
Skeletal muscle mass or Skeletal muscle quality	ASM by DXA
	Whole-body ASM predicted by BIA
	Lumbar muscle cross-sectional area by CT or MRI
Physical performance	Gait speed
	SPPB
	TUG
	400 m walk or long-distance corridor walk

ASM, appendicular skeletal muscle mass; BIA, bioelectrical impedance analysis; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging; SPPB, Short Physical Performance Battery; TUG, timed up and go.
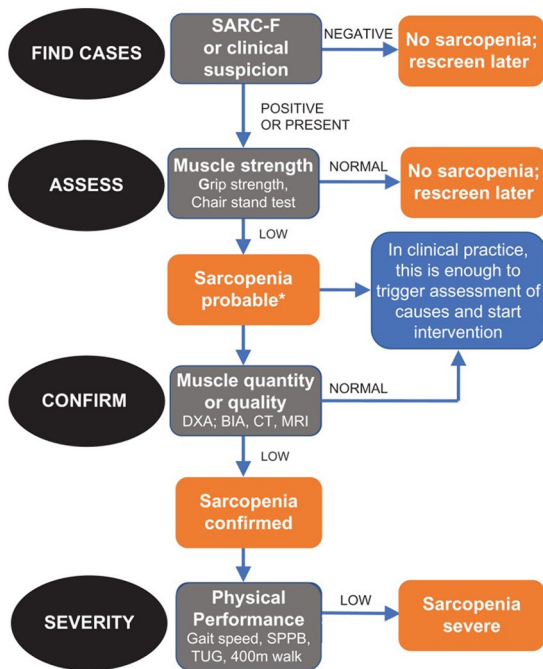
Figure 1. Sarcopenia: EWGSOP2 algorithm for case-finding, making a diagnosis and quantifying severity in practice (adapted from Cruz-Jentoff *et al.*[13]).

Overall, when diagnosing osteosarcopenia, the clinician should take into consideration the EWGSOP2 proposed algorithm for early identification and diagnosis of sarcopenia (Table 1 and Figure 1) and osteopenia or osteoporosis should be investigated by BMD score on dual-energy X-ray absorptiometry (DXA) scan.[12]

Risk factors for osteosarcopenia

Primary osteosarcopenia is a result of age-related declines in bone and muscle function; however, there are many risk factors that affect bone and muscle, thereby aggravating osteosarcopenia.[13,14] While treating osteosarcopenia, these risk factors should be considered by the managing clinicians (Table 3).

Potential therapeutic targets in osteosarcopenia

Given the interconnectedness between bone and muscle, treatment targets common to both have been proposed; however, to date, there is a lack of data from randomized controlled trials (RCTs) that have investigated a common pharmacological target for osteosarcopenia. In addition to mechanical interactions between bone and muscle, there are common chemokines that act on

these tissues, in addition to the interactions of osteokines and myokines[2] (Figure 2).

Commonalities in pathophysiology suggest that potential therapeutic strategies may include focusing on (i) targets that affect bone and muscle, such as insulin-like growth factor-1 (IGF-1), androgens, selective androgen receptor modulators (SARMs), or vitamin D, amongst others,[16] or (ii) targets involved in the cross-talk between muscle and bone, for instance activin signaling inhibitors, myostatin neutralizing antibodies, recombinant follistatin derivatives, and soluble activin receptors or myokines.[2,16,17] Another novel therapeutic target is the prevention of fat infiltration, which is a common feature observed in primary and secondary osteoporosis, and sarcopenia. A decrease in marrow and intrafiber fat in bone and muscle, respectively, would be expected to have a beneficial effect on their mass and function. Although this has been demonstrated in separate studies in muscle and bone,[18] a combined experiment targeting fat in these both tissues is still lacking.

Nonpharmacological management of osteosarcopenia

Role of lifestyle modification in treating osteosarcopenia

Whilst various genetic factors determine peak bone mass and muscle strength,[19,20] environmental factors that exacerbate the loss of bone and muscle are suggested to be imperative in the pathogenesis of osteoporosis and sarcopenia, and thus osteosarcopenia.[1]

Among these factors, the roles of smoking and alcohol consumption are well studied. However, despite the well-described association of smoking and alcohol consumption with poor bone and muscle health, the therapeutic benefits of smoking cessation and decreasing alcohol consumption are less clear.

Current smoking status is associated with increased risk of fracture at any site[21] and hip fracture in females[22] and one meta-analysis reported the therapeutic benefit of smoking cessation for more than 10 years in decreasing the risk of hip fractures.[22]

Similarly, although the negative effects of alcohol consumption on bone and muscle are documented,[23] the therapeutic benefit of minimizing alcohol consumption is not described so far.

Table 3. Risk factors for osteosarcopenia.[1,15]

Osteoporosis	Sarcopenia	Osteoporosis and sarcopenia
Asian or Caucasian race	Low albumin	Age
History of fragility fracture	Use of angiotensin-converting enzyme inhibitors	Female
History of maternal hip fracture	Stroke	Genetic factors
	Dyslipidemia	Low body weight
		Obesity
		Sedentary lifestyle/poor mobility
		Smoking
		High alcohol consumption
		Glucocorticoids
		Low dietary calcium and protein
		Low vitamin D
		Hypogonadism (male)
		Menopause (female)
		Hyperparathyroidism
		Low growth hormone
		Rheumatoid arthritis
		Chronic kidney disease
		Living in residential aged care facility

However, it is expected that decreasing alcohol consumption may have beneficial effect in improving bone and muscle function, thus decreasing risk of fall and fracture.

Nutritional strategies to treat osteosarcopenia

Role of dietary calcium and calcium supplements. Calcium is well-documented as an important mineral of bone, and its importance in muscle function is suggested by its role in calcium-induced muscle contraction and calcium-induced calcium release from sarcoplasmic reticulum.[24] Therefore, it could have a role in treatment of osteosarcopenia. Calcium intake from the diet and supplements has shown to produce marginal increases in BMD, although no convincing influence on the risk of hip fracture has been observed.[25] The therapeutic benefit of calcium supplements in sarcopenia is yet to be studied.

Current guidelines recommend an adequate intake of calcium (1000–1300 mg/day) in diet for optimal bone health.[26] If dietary intake of calcium is below the recommended level, supplementation of 500–600 mg/day is recommended in older adults.[26] However, there is controversy regarding supplementing the diet with higher doses of calcium (>2000 mg/day) as it is associated with increase cardiovascular side-effects in older adults aged ⩾50 years.[27]

Role of dietary protein and protein supplements. Importance of dietary protein is evident from being not only a source of the bone and muscle matrix but also through its direct effect on regulatory proteins and growth factors involved in
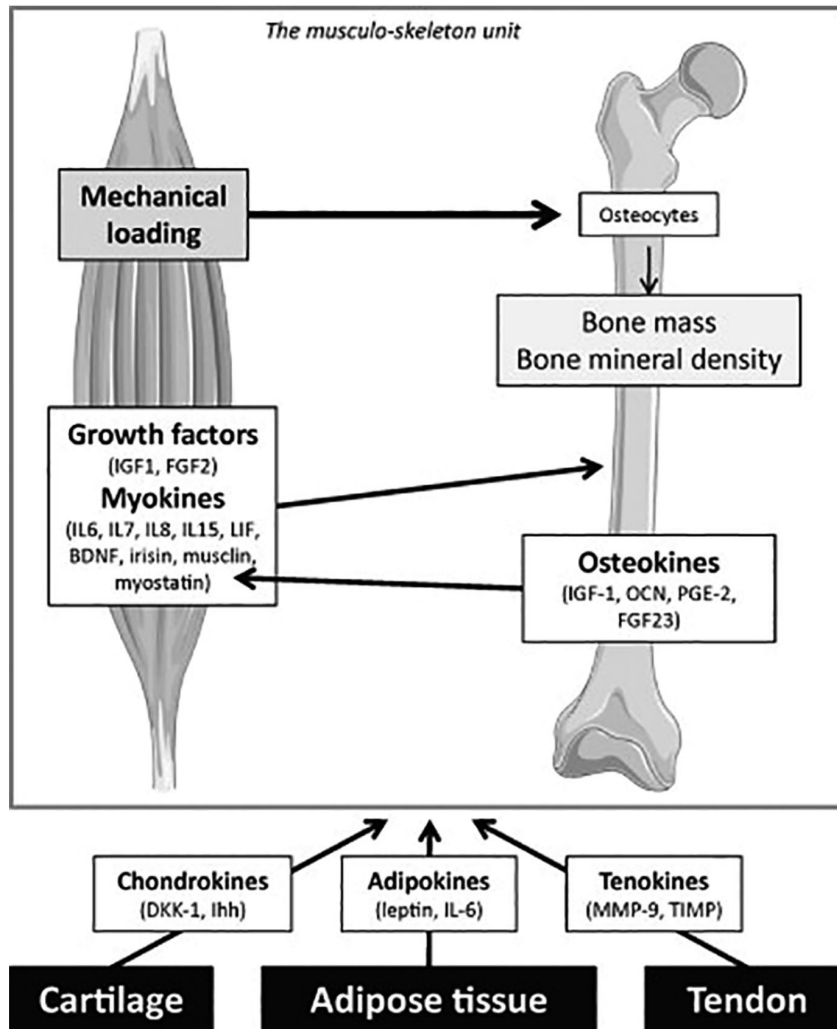
Figure 2. Interaction between muscle and bone. Bone and muscle are clearly interconnected *via* a two-way cross talk (adapted from Tagliaferri *et al.*[2]).
BDNF, brain-derived neurotrophic factor; DKK1, Dickkopf WNT signaling pathway inhibitor 1; FGF2, fibroblast growth factor 2; FGF23, fibroblast growth factor 23; IGF1, insulin-like growth factor 1; ihh, Indian hedgehog; IL-, interleukin; LIF, leukemia inhibitory factor; MMP-9, matrix metallopeptidase 9; OCN, osteocalcin; PGE2, prostaglandin E2; TIMP, tissue inhibitors of metalloproteinases.

bone and muscle function through assisting in calcium absorption, suppression of parathyroid hormone, and release of IGF-1.[28,29]

Clinical evidence of the role of dietary protein in bone health stems from the Framingham Osteoporosis Study, which showed that low protein intake was associated with bone loss at proximal femur and spine over 4 years.[30] Regarding association of protein with sarcopenia, low dietary protein ($\leqslant 0.45$ g/kg/day) in older persons aged $\geqslant 65$ years was associated with muscle atrophy[31], and a moderate or high consumption of protein ($\geqslant 1.1$ g/kg/day) in adults aged 70–79 years was associated with less muscle loss.[32] In addition, high

intake of protein (>1.0 g/kg/day) has been associated with better lower limb physical performance when compared with protein intake lower than 0.8 g/kg/d in community-dwelling older people.[33]

Given this association between protein and bone and muscle strength, the role of protein supplements was proposed. In clinical trials, protein supplements have been demonstrated to improve osteopenia by increasing BMD and decreasing the risk of fracture.[34,35] Similarly, protein supplements (6–30 g/day) over 3–24 months helped to correct sarcopenia by improving muscle strength over 12–24 weeks in healthy older people when combined with resistance exercise[36] (Table 4).

Table 4. Summary of findings from meta-analyses that investigated the role of dietary protein and protein supplements on osteopenia/osteoporosis and sarcopenia related outcomes.

Reference	Description of studies	Results
Osteopenia/osteoporosis		
Koutsofta et al.[34]	Systematic review (best evidence synthesis) of 5 RCTs (n = 677 postmenopausal women; mean age 61.4 years) *Treatment with protein supplements	Protein supplements alone or in combination with dietary protein improved BMD and reduced risk of fracture.
Shams-White et al.[37]	Systematic review and meta-analysis of 36 studies 16 RCTs (n = 1553 healthy adults; age ≥18 years) 20 prospective cohort studies (n = 452,443 healthy adults; age ≥18 years) *Association with high protein intake	(1) Higher protein (>0.8 g/kg/day) intake in diet or supplements have a protective effect on lumbar spine BMD (pooled net percentage change in BMD: 0.52%; 95% CI 0.06–0.97%) (2) There is limited evidence to support role of protein with calcium and vitamin D at lumbar spine BMD, hip BMD, or forearm fracture.
Wallace et al.[35]	Systematic review and meta-analysis of 29 studies 16 RCTs (n = 1375 healthy adults; age 18–80 years) 13 Prospective cohort studies (n = 271,963 adults; age 26–96 years) *Association with high protein intake	High protein intake above 0.8 g/kg/day resulted in 16% decrease in hip fractures (SMD = 0.84; 95% CI 0.73–0.95), compared with low protein intake.
Sarcopenia		
Coelho-Junior et al.[33]	Meta-analysis of 7 studies; 4 prospective and 3 cross-sectional studies (n = 8754, mean age 74.5 years) *Association with high protein intake	Very high (≥1.2 g/kg/day) and high (≥1.0 g/kg/day) intake of protein is associated with better lower limb physical function (ES = 0.18; 95% CI 0.01–0.35) and walking speed (ES = 0.06; 95% CI 0.02–0.11) respectively when compared to low protein (≤0.8 g/kg/day) intake.
Komar et al.[38]	Meta-analysis of 16 RCT (n = 999; mean age 69.72 years) *Treatment with protein supplements	Leucine-containing protein supplements improved lean mass (mean differences 0.99 kg, 95% CI 0.43–1.55, p = 0.0005) but not strength in older people prone to sarcopenia.
Liao et al.[36]	Meta-analysis of 17 RCTs (n = 892; mean age 73.4 years) *Treatment with protein supplements	Protein supplements in combination with resistance exercises improved lean mass and strength (SMD = 0.58; 95% CI 0.32–0.84) in older people when compared with resistance exercise alone.
Tieland et al.[39]	Meta-analysis of 8 RCTs (n = 557, mean age 74.6 years) *Treatment with protein supplements	Protein or amino acid supplements did not have significant positive effect on muscle mass (mean difference: 0.014 kg: 95% CI 0.152–0.18) and strength (mean difference: 2.26 kg: 95% CI 0.56–5.08) in healthy older people.

BMD, bone mineral density; CI, confidence interval; ES, effect size; RCT, randomized controlled trial; SMD, standardized mean difference.
*Whether study described association with osteoporosis or sarcopenia or treatment of osteopenia or sarcopenia.

The recommended dietary intake of protein is 0.8 grams per kg of body weight per day (g/kg/day) for healthy populations, irrespective of age or sex.[40] However, the sensitivity of musculoskeletal tissue to dietary protein intake is influenced by advancing age, therefore adults aged 65 years and above require higher than recommended protein (up to 1.2 g/kg/day).[28] Meta-analysis incorporating trials investigating the different amounts of proteins concluded that high intake of dietary protein (higher than recommended >0.8 g/kg/day) in older adults with osteoporosis was associated with preservation of BMD at lumbar spine[37] and reduced risk of hip fracture.[35] Older adults in residential aged care facilities are likely to have lower dietary protein intake,[41] therefore dietary protein intake of at least 1–1.2 g/kg/day with 25–30 g of protein with each meal is recommended.[42]

The distribution of dietary protein across meals is another area that is contested in the literature, whereby some studies suggest beneficial outcomes from pulse feeding concentrated in the lunch or evening meal,[43] whilst others show benefits of distributing the dietary protein throughout the daily intake.[44]

Exercise

Bone is a dynamic tissue and responds to multiple physical and dynamic stimuli encompassing movements, traction, and vibration.[45] These forces come into play constantly during locomotion and have an important role in bone and muscle remodeling, thereby they are important to consider in the management of osteopenia and sarcopenia in older adults.[45] The most appropriate type, intensity, duration, and frequency of exercise to positively influence osteosarcopenia is not known, however role of different types of exercises has been previously described individually for osteopenia and sarcopenia (Table 5).

As different types of exercise have distinct effects on bone and muscle, not all exercises are beneficial.

Table 5. Summary of findings from systematic reviews and meta-analyses regarding the effect of different types of exercises on osteopenia/osteoporosis and sarcopenia.

Reference	Brief description of studies	Results
Osteopenia/osteoporosis		
Marin-Cascales et al.[46]	10 RCTs ($n = 462$ postmenopausal females aged ≥55 years) *Effect of WBV	WBV for 3–12 months did not improve total or femoral neck BMD, however improved BMD at lumbar spine (MD = 0.02; 95% CI 0.00–0.03; $p = 0.03$) in postmenopausal women aged ≥65 years.
Xu et al.[47]	Overview of 12 systematic reviews (best evidence synthesis). ($n = 12,219$ premenopausal and postmenopausal females) *Effect of combined impact and resistance exercises	Combined impact and resistance exercises are best choice to preserve and improve BMD in premenopausal and postmenopausal women
Zhao et al.[48]	11 RCTs ($n = 1061$ postmenopausal females) *Effect of multiple physical activities	Combined exercise interventions involving multiple physical activities for 8–30 months were effective in preserving BMD at lumbar spine (SMD = 0.170; 95% CI 0.027–0.313; $p = 0.019$), femoral neck (SMD = 0.177; 95% CI 0.030–0.324; $p = 0.018$), total hip (SMD = 0.198; 95% CI 0.037–0.359; $p = 0.016$), and total body (SMD = 0.257; 95% CI 0.053–0.461; $p = 0.014$). Effect of individual type of physical activity on outcome could not be ascertained.
Sarcopenia		
Jepsen et al.[49]	4 RCTs ($n = 746$ adults aged ≥50 years) *Effect of WBV	WBV for 6 months reduced rate of fall with a rate ratio of 0.67 (95% CI 0.50–0.89, $p = 0.0006$).
Sardeli et al.[50]	6 RCTs ($n =$ not reported; adults aged ≥50 years) *Effect of resistant exercises	In obese older people undergoing calorie restriction, resistant exercises 3 times a week over 12–24 weeks can prevent muscle loss related to calorie restriction.
Vlietstra et al.[51]	6 RCTs ($n = 480$ adults aged ≥60 years) *Effect of multiple physical activities	Exercise intervention for 3–6 months improved knee-extension strength (MD = 0.14; 95% CI 0.03–0.26; $p \leq 0.01$), timed up and go (MD = 0–1.67; 95% CI −2.43–0.91; $p < 0.0001$), appendicular muscle mass (MD = 0.45; 95% CI 0.03–0.87; $p = 0.04$), and leg muscle mass (MD = 0.35; 95% CI 0.02–0.68; $p = 0.04$). However, heterogeneity of exercise program was noted and effect of individual type of exercises could not be ascertained.

BMD, bone mineral density; CI, confidence interval; MD, mean difference; RCT, randomized controlled trial; SMD, standardized mean difference; TUG, timed up and go; WBV, whole-body vibration.
*Type of physical activity in the treatment of osteopenia or sarcopenia.
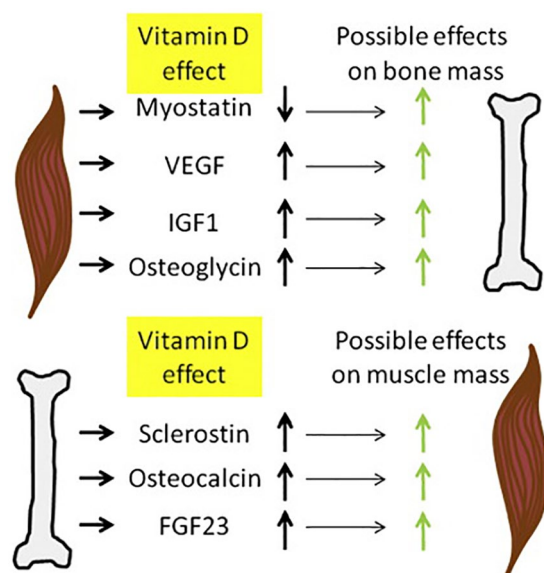
Figure 3. Vitamin D mediates several mechanisms of the bone–muscle cross-talk (adapted from Gunton et al.[59]).
IGF1, insulin-like growth factor 1; FGF23, fibroblast growth factor 23; VEGF, vascular endothelial growth factor.

For osteopenia, aerobic and low-impact exercises such as cycling or walking have failed to show beneficial effects on BMD at any site,[52] however resistance exercises or high-impact exercises such as running have a positive effect on bone by improving BMD.[47] Similarly resistant exercises play a positive role in sarcopenia by a direct effect on muscles.[53] A recent meta-analysis investigated the role of exercise on sarcopenia related outcomes, and reported improvement in some operational measures of muscle mass, strength and physical function.[51] In addition, resistant exercises 3 times a week over 12–24 weeks have shown to prevent loss of muscle mass in obese older people on calorie restricted diet.[50] In older people, resistant exercises have been described to improve self-reported physical function and activities of daily living (ADLs).[54]

Whole-body vibration (WBV) is a process in which a vibrating force is transmitted to muscle and bone, an intervention that has been proposed to have a positive role in both osteopenia and sarcopenia. Although the effects of WBV on BMD are not consistent,[55–57] these discrepancies may be explained due to the optimum frequency or duration of WBV therapy currently being unclear.[46]

Vitamin D

Vitamin D is well recognized as an integral part of bone and muscle physiology through its role in calcium and phosphate absorption to calcium-mediated muscle functions such as contractility, mitochondrial function, and insulin sensitivity.[58] Vitamin D acts as a mediator in the cross-talk between muscle and bone by affecting myokines (myostatin, VEGF, IGF-1, osteoglycin) and osteokines (sclerostin, osteocalcin, FGF-23), which have a positive effect on bone and muscle, respectively (Figure 3).[59] Under effect of sunlight (UV light), vitamin D is synthesized in the skin from 7-dehydrocholestrol:[60] it is converted into 25-hydroxy vitamin D in the liver and then into 1,25 hydroxy vitamin D ($1,25(OH)_2D$) in the kidneys.[60] $1,25(OH)_2D$ is a biologically active form of vitamin D and exerts its effect on bone and muscle through the vitamin D receptor (VDR), which binds to the vitamin D response element (VDRE) in DNA as well as directly without genomic transcription.[60]

Association of vitamin D with osteosarcopenia or role of vitamin D supplements in treating osteosarcopenia has not yet been evaluated in a single study; however, its therapeutic benefit can be inferred from studies on osteopenia and sarcopenia (Table 6).

Many studies have already described association of low vitamin D status with osteoporosis and increase risk of fracture.[67] For sarcopenia, although there are few studies, evidence exists regarding association of low vitamin D levels with negative muscle-related outcomes.[68] A recent epidemiological study in Australian population reported that low vitamin D levels (<40 nmol/l) were associated with increased incidence of sarcopenia over 5 years.[69]

The role of vitamin D supplements in treating osteopenia, preventing fall and fracture has been a subject of controversy recently. Many randomized trials have been conducted and although earlier data suggested a reduced risk of nonvertebral fracture with vitamin D supplements,[70] recent meta-analyses have failed to show its persistent benefits in reducing risk of fall or fracture at any site in community-dwelling older adults.[62,63] Analysis by Bolland et al. reported that vitamin D supplements did not prevent falls or fractures, or improve BMD in adults aged ≥20 years.[61] This lack of apparent benefit of vitamin D supplementation could be due to the inclusion of a substantial number of younger adults and healthy older adults with minimal or no risk factors for bone disease.[62] Moreover, the aggregate results could

Table 6. Summary of the effect of vitamin D supplements on osteopenia/osteoporosis and sarcopenia related outcomes.

Study	Description	Results
Osteopenia/osteoporosis		
Bolland *et al.*[61]	Pooled analysis of 81 RCTs (n = 53,537 adults aged ≥18 years) *Therapeutic effect of vitamin D supplements.	Vitamin D supplements (regardless of dose) did not prevent fall (37 trials; *n* = 34,144, RR 0.97, 95% CI 0.93–1.02), total fracture (36 trials; *n* = 44,790, RR 1.00, 95% CI 0.93–1.07) or hip fracture (20 trials; *n* = 36,655, RR 1.11, 95% CI 0.97–1.26).
Kahwati *et al.*[62]	Meta-analysis of 11 RCTs (*n* = 51,419 community-dwelling older adults aged ≥50 years) *Therapeutic effect of vitamin D supplements.	Vitamin D supplements did not decrease risk of fracture in community-dwelling older adults (3 RCTs; *n* = 5496; pooled ARD = −0.01; 95% CI −0.80 to −0.78) without known Vitamin D deficiency, osteoporosis, or prior fracture.
Zhao *et al.*[63]	Meta-analysis of 33 RCTs (*n* = 51,145 community dwelling older adults aged ≥50 years) *Therapeutic effect of calcium supplements and vitamin D supplements.	There was no association of risk of hip fracture with calcium supplements (RR 1.53; 95% CI 0.97–2.42) or vitamin D supplements (RR 1.21; 95% CI 0.99–1.47) compared with placebo in community-dwelling older adults.
Sarcopenia		
Beaudart *et al.*[64]	Meta-analysis of 30 RCTs (*n* = 5615 adults, mean age 61.1 years) *Therapeutic effect of vitamin D supplements.	Vitamin D supplements have positive effect on muscle strength (SMD 0.25; 95% CI 0.01–0.98) in older adults aged ≥65 years but optimal treatment modalities including dose, mode of administration, and duration are unclear.
De Spiegeleer *et al.*[65]	Review of 7 systematic reviews (best evidence synthesis) (*n* = not reported; age ≥65 years) *Therapeutic effect of vitamin D supplements.	Vitamin D supplements in older women (with low vitamin D levels <25 nmol/l) improved muscle mass (pooled SMD = 0.058; 95% CI 0.118–0.233), strength (pooled SMD = 0.25; 95% CI 0.01–0.48) and physical function (pooled SMD TUG −0.19; 95% CI −0.35 to −0.02).
Rosendahl-Riise *et al.*[66]	Meta-analysis of 10 RCTs (*n* = 2866 community-dwelling older adults aged ≥65 years) *Therapeutic effect of vitamin D supplements.	Vitamin D supplements did not improve handgrip strength (7 studies; MD 0.2 kg; 95% CI −0.3 to 0.7) but improved physical performance on TUG (5 studies; MD TUG−0.3; 95% CI −0.1 to −0.05).

ARD, absolute risk difference; BMD, bone mineral density; CI, confidence interval; MD, mean difference; RCT, randomized controlled trial; SMD, standardized mean difference; TUG, timed up and go.
*Association with osteoporosis or sarcopenia or treatment of osteopenia or sarcopenia.

be affected due to the dose of vitamin D used. While frequently used vitamin D supplements (400–2000 IU) have shown beneficial effects, studies with a bolus dose of vitamin D have consistently revealed increased risk of falls.[71] Despite these controversies, it is acknowledged that vitamin D supplements have a role particularly in those with vitamin D deficiency or osteoporosis.[67] Regarding role of vitamin D supplements in treating sarcopenia, there are only few studies with some showing a positive while others produced nonsignificant results. In older women aged ≥65 years who had low vitamin D levels (<25 nmol/l), vitamin D supplements (1000 units) improved muscle mass and strength.[65] In community-dwelling older adults, vitamin D supplement improved physical performance as indicated by timed up and go (TUG) test, however improvement in muscle strength as measured by handgrip strength was not significant.[66]

Despite the long-standing availability of vitamin D supplements, there remains insufficient evidence with regards to the most appropriate dose, mode of administration, and duration of treatment on the functional outcome in older adults.[64]

Current recommendations are for oral vitamin D supplements (800–1000 units/day) and calcium supplements (500 mg/day).[72] Ideal vitamin D levels should be 50–60 nmol/l with a conservative upper limit of 100 nmol/l, only if dietary intake is inadequate.[72] Importantly, there is no evidence that loading doses have a positive effect on falls or fracture outcomes.[72]

Pharmacological management of osteosarcopenia

Treatment of osteosarcopenia with pharmacological agents is a new area of investigation. There is paucity of evidence in this regard. Nevertheless, the therapeutic effects of some compounds on osteoporosis and sarcopenia hint at a possible dual effect on muscle and bone mass and therefore could be useful in treatment of osteosarcopenia (Table 7).

Denosumab

Denosumab in humanized monoclonal antibody to RANKL (receptor activator of nuclear factor-κB ligand). The binding of RANKL to RANK receptor on osteoclast is responsible for its activation, differentiation and osteoclastic action. By blocking RANKL, denosumab blocks the activation of osteoclasts and leads to a subsequent increase in BMD.[74] Denosumab is proposed to have an action on muscle as well through blockage of RANK/RANKL. In nonclinical studies, RANK/RANKL blockade has shown to improve muscle function.[82]

Evidence of the efficacy of denosumab emerged from the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 months) trial. Results of the FREEDOM trial indicated that denosumab treatment reduced the risk of vertebral, nonvertebral, and hip fracture over 36 months.[74] It was also observed that group treated with denosumab experienced fewer falls (4.5%) compared with the untreated group (5.7%) ($p = 0.02$).[74] This led to further investigation of the effect of denosumab on muscle strength. A recent study by Bonnet *et al.*[75] tested the effect of denosumab on animals and humans (postmenopausal women); the authors reported that RANKL deteriorates, while its inhibitor improves muscle strength and insulin sensitivity in osteoporotic mice and humans, and concluded that, in addition to its role as a treatment for osteoporosis, denosumab could represent a novel therapeutic approach for sarcopenia and, thus, for osteosarcopenia. Further mechanistic studies are needed to investigate the direct effect of denosumab on muscle mass and function.

Table 7. Summary of the evidence regarding the effect of pharmacological agents on osteoporosis and sarcopenia related outcomes.

Pharmacological agent	Osteoporosis	Sarcopenia
Denosumab	Meta-analysis of 4 RCTs, investigating the effect of denosumab on BMD reported significant improvement in BMD at lumbar spine, hip, and radius.[73]	Reduction in falls in the Denosumab treatment group of the FREEDOM Study. No evidence of effect on muscle function.[74] Improves muscle strength and insulin sensitivity in osteoporotic humans.[75]
Testosterone	Intramuscular testosterone increased lumbar spine bone density in men.[76]	Testosterone in older men with decreased testosterone levels and muscle weakness can improve muscle mass, strength and physical performance.[65]
Growth hormone	Meta-analysis of 7 RCTs and one extension trial concluded that growth hormone may not improve bone density but decrease fracture risk in women with age related bone loss.[77]	Low growth hormone levels with age contribute to decrease in lean body mass and increase adipose tissue.[78]
Antimyostatin antibodies	Antimyostatin antibody in combination with resistance exercise improved bone health in rats.[79]	(1) Antimyostatin antibodies increased muscle mass and strength in mice.[80] (2) Antimyostatin antibodies increased lean mass and may improve functional measures of muscle power.[81]

BMD, bone mineral density; RCT, randomized controlled trial.

Testosterone and SARMs

Testosterone levels decrease with age and are considered an important cause of age-related decline in bone mass[76] and muscle function.[83] Testosterone exerts its effect on bone through estradiol and increased bone mineralization and strength,[76,84] and increases muscle mass and strength by increasing protein synthesis.[85] Although the dual effect of testosterone on osteosarcopenia has not been tested in a single study, we suggest biological plausibility for positive effects, given results from separate trials of bone- and muscle-related outcomes. For instance, testosterone replacement in hypogonadal men improved bone mass and strength.[86] Testosterone improved muscle mass and function in older adults (aged 60–65 years), as well as young adults (aged 19–35 years):[87] results are not suggested as being sex-specific.[88] Moreover, positive effects of testosterone on muscle strength have been reported in community-dwelling frail older adults (aged ≥65 years),[89] as well as healthy community dwelling older adults (aged ≥60 years).[90] In addition, testosterone replacement improved muscle strength and gait speed in older adults (aged ≥65 years)[91] and has shown to be safe in chronic heart failure.[92]

Owing to the fear of side-effects with testosterone treatment, interest in research into SARMs has advanced. Several of these have been trialed in sarcopenia and include LDG-4033, BMS-564929 in phase I trial, and enobasarm in phase II trials but at present, SARMs do not appear to have an advantage over testosterone.[93]

Given its role in both osteoporosis and sarcopenia, it would be interesting to see testosterone effect on both in a single study. Two major trials, 'The Testosterone Trial in Older Men' (ClinicalTrials.gov identifier:) and T4DM (www.t4dm.org.au), are underway and should clarify the role of testosterone in the management of osteosarcopenia.

Growth hormone and IGF-1

Normal ageing is associated with decrease in growth hormone (GH) and IGF-1 levels.[78] GH efficacy in osteoporosis management has been studied in many RCTs.[77] A recent meta-analysis of seven RCTs and one extension trial suggested that it may have a role in fracture prevention in postmenopausal osteoporosis, however it has failed to show a positive effect on BMD.[77]

It was first described in 1990 that low GH levels contributes to a decrease in lean body mass and increase in adipose tissue.[78] However, since then, it has failed to show a consistent benefit in improving muscle mass or function.[93] Furthermore, there are various side-effects to consider, including carpal tunnel syndrome, gynecomastia, joint and muscle pain, edema, and hyperglycaemia.[94] Similarly, there is limited data regarding the role of IGF-1 in sarcopenia.[93] IGF-1 is also associated with multiple side-effects: myositis, edema, orthostatic hypotension, and gynecomastia.[95]

Anti-myostatin antibodies

Myostatin is produced in skeletal muscle and inhibit muscle growth. Lack of myostatin leads to muscle hypertrophy. In mice, antimyostatin antibodies increased muscle mass and strength.[80] In phase II trials in older adults (aged ≥75 years) with a history of fall, antimyostatin antibodies increased the lean body mass and mildly improved functional measures associated with muscle strength.[81] Regarding role of myostatin antibodies in improving bone health, data from animal studies indicate that in combination with resistant exercise, myostatin antibodies improved bone mass,[79] however, this effect has not been confirmed in clinical trials.

Future directions

In conclusion, the notion of bone muscle interaction through direct and indirect interaction imply the possible presence of the geriatric syndrome 'osteosarcopenia'. Those with osteosarcopenia have worse prognosis than adults with either osteopenia or sarcopenia alone. Therapeutic strategies that have a dual effect on bone and muscle are critical in the management of osteosarcopenia. Adequate protein and calcium intake, maintaining sufficient vitamin D levels, and undertaking regular muscle and bone strengthening exercises are important nonpharmacological therapies for consideration by the treating clinician. Future research should be directed toward pharmacological agents with therapeutic actions on both bone and muscle and investigating the efficacy of agents that are currently used for osteoporosis and sarcopenia alone, in terms of a dual effect on bone and muscle.

Funding

Conflict of interest statement

ORCID iD

Gustavo Duque https://orcid.org/0000-0001-8126-0637

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