Osteoporosis in Older Persons – Old and New Players

Jesse Zanker, MBBS, MPHTM^{a,b} and Gustavo Duque, MD, PhD^{a,b}

^a *Australian Institute for Musculoskeletal Science (AIMSS), The University of Melbourne and Western Health, St Albans, VIC, Australia 3021*

^b *Department of Medicine-Western Health, Melbourne Medical School, The University of Melbourne, St Albans, VIC, Australia 3021*

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Corresponding author: Prof. Gustavo Duque, MD, Ph.D., FRACP, FGSA
 Australian Institute for Musculoskeletal Science
 (AIMSS)
 The University of Melbourne and Western health
 176 Furlong Road, St. Albans, VIC, Australia 3021
 Tel: +61 3 8395 8121
 Email: gustavo.duque@unimelb.edu.au
 Twitter: @DrGustavoDuque

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Impact statement: We certify that this work is confirmatory of recent novel clinical research. All cited references are evidence-based and have generated major progress to the understanding and treatment of osteoporosis in older persons.

Abstract

Osteoporosis is the most common bone disease in humans. Older persons are at higher risk of osteoporotic fractures, which also result in poor quality of life, disability, loss of independence, institutionalization, and higher mortality. Osteoporosis shares a distinct, pathophysiological relationship with sarcopenia, which is an age-related disease comprising declines in muscle mass, strength or function. The combination of these two diseases is known as osteosarcopenia. Understanding the pathophysiology of osteosarcopenia, in addition to its diagnostic and therapeutic approaches, is key in providing the best falls and fracture prevention for older adults. This review provides updated information on new discoveries on the combined pathophysiology of osteoporosis and sarcopenia, which have allowed for the development of novel therapeutic approaches. New recommendations for the use of risk calculators and densitometry are also presented in this review as well as evidence on current and upcoming pharmacological treatments to prevent falls and fractures in older persons.

Introduction

Osteoporosis is the most common bone disease in humans.¹ Prevalence of osteoporosis and incidence of osteoporotic fractures increases with age.¹ As the global population ages due to advances in socioeconomic and health-related factors, the absolute number of older adults living with osteoporosis and the incidence of osteoporotic fractures will increase.² Osteoporosis and osteoporotic fractures carry significant implications for individuals and society.³ Although the individual risk of fracture is greatest in those with osteoporosis, an absolute majority of fractures occur in those with low bone mineral density (BMD), identified as osteopenic, rather than in those with osteoporosis. This is due to both the large proportion of the population with osteopenia and the previously unknown role of other conditions that predispose older persons to falls and fractures.

Sarcopenia, a disease of low muscle mass combined low muscle strength or function, is gaining recognition as an important contributor to loss of function, independence, falls, fractures and mortality risk in older adults.⁴ Considering that muscle and bone are connected anatomically, metabolically and chemically, a new syndrome known as osteosarcopenia has been proposed to describe those patients with concomitant occurrence of osteoporosis and sarcopenia who have been identified as at higher risk of poor outcomes.^{5,6}

Minimal trauma fractures are preventable and treatable. In order to provide comprehensive care to older adults, particularly with respect to musculoskeletal health, the clinician must consider osteosarcopenia in their assessment and management. No longer should osteoporosis be considered in isolation. This review provides updated information on new discoveries on the pathophysiology of osteoporosis and osteosarcopenia, which have allowed to the development of novel therapeutic approaches. New recommendations for the use of risk calculators and dual-energy X-ray absorptiometry (DXA) are also presented in this review as well as evidence on current and emerging pharmacological treatments for osteoporosis and sarcopenia.

Definition

The World Health Organization (WHO) defined osteoporosis in 1994 based on BMD alone with a definition that only applied to post-menopausal women.⁷ Subsequent studies on different populations informed the development of the current WHO definition (Table 1).⁸ While the presence of a minimal or no trauma fracture or the criteria in Table 1 are required to establish the diagnosis of osteoporosis, these diagnostic classifications should be combined with patient risk factors to determine the most appropriate treatment.¹

In contrast, there is no universal definition of sarcopenia. The absence of a definition complicates clinical and research applications, resembling the challenges observed last century in defining osteoporosis. The most contemporaneous definitions of sarcopenia are listed in Table 2.^{9,10} There is ongoing debate as to the preferred definition of sarcopenia. Further longitudinal studies examining outcomes such as falls, fractures, immobility, loss of function and mortality are required to determine which definition best predicts these poor outcomes. Osteosarcopenia is generally accepted as the presence of both osteoporosis and sarcopenia.⁵

Pathophysiology

Bone is composed of inorganic (calcium phosphate crystals) and organic compounds (90% collagen and 10% non-collagenous proteins which constitute the bone matrix).

The bone matrix is the environment in which bone and external factors interact in a well-coordinated manner. The regulation of bone mass is a process that includes a complex set of interactions between hormones (parathyroid, gonadal, etc.), vitamin D, growth factors and specialized cells (osteoclasts, osteoblasts and osteocytes). There are two types of bone: cortical and trabecular. Trabecular bone is metabolically more active than cortical bone and more acutely responsive to alterations in sex-steroid hormone status due to its greater surface to volume ratio.

The progressive decline in bone mass with age results from changes in cell distribution. Bone mass depends on the balance between bone resorption and bone formation (bone remodeling). The formation is the product of the activity of osteoblasts, while resorption is performed by osteoclasts. These two cell types are well coordinated during the stage of obtaining peak bone mass responsible for bone modelling during growth, and bone remodeling after reaching the peak of bone mass at 25-30 years of age. From there, bone mass begins to decrease at a normal rate of 0.5% per year.

Bone remodeling is coordinated by osteocyte- and osteoblast-secreted factors, which regulate osteoclastic activity and bone resorption (Figure 1).¹¹ Two critical factors regulate the interactions between osteoblast and osteoclasts. The receptor activator of nuclear factor kappa-B ligand (RANKL), which is predominantly secreted

by the osteocytes, is a potent stimulator of osteoclast differentiation and activity.^{11,12} A second factor, osteoprotegerin (OPG), is predominantly produced by the osteoblasts and acts as a decoy receptor for RANKL, decreasing osteoclastic activity. Osteocytes also regulate bone formation through the secretion of sclerostin and Dkk1, which have an inhibitory effect on the osteoblasts (Figure 1).¹² Alterations in any of these factors could lead to either increased bone resorption or low bone formation and thus osteoporosis.

Osteoblasts are differentiated mesenchymal stem cells (MSC).¹³ MSC can differentiate not only into osteoblasts but also into adipocytes, myocytes, or chondrocytes. In the case of the young bone marrow, MSC differentiate into osteoblasts at the expense of adipocytes. This predominant differentiation of MSC into osteoblasts changes with age, shifting their differentiation into adipocytes. Accumulation of marrow fat plays a toxic role affecting osteoblasts as well as hematopoietic cells, exerted through the secretion of fatty acids and adipokines, which accumulate in the bone marrow of aging and osteoporotic bone decreasing osteoblast differentiation, function and survival while also stimulating osteoclastic activity (Figure 1).¹⁴

The pathophysiology of osteosarcopenia involves a combination of fat, muscle and bone-related mechanisms (Figure 2). Fat infiltration, and its associated lipotoxic

effect, is observed in both muscle and bone independent of body mass index (BMI).⁵ In addition, muscle and bone interact not only mechanically but also through endocrine and paracrine systems. Bone, muscle and adipose tissues are known to communicate with each other and sustain homeostasis through a hormonal and possibly nervous crosstalk. Any alterations in this crosstalk could affect these tissues simultaneously.

Alterations in any of these cellular mechanisms is determinant in the pathogenesis of osteoporosis and osteosarcopenia. As a consequence, low levels of osteoblasts are associated with decreased bone formation while a high number of osteoclasts increases bone resorption, thus inducing a permanent negative balance in bone mass, which in combination to low muscle mass and function predisposes to osteosarcopenia, falls and fractures.⁵

Epidemiology

It is estimated that by 2030, 57.4 million Americans will be living with low bone mass and 13.2 million will be osteoporotic.¹⁵ Older adults living in nursing homes have the highest rates of osteoporosis and remain undertreated despite advances in treatment options.¹⁶ Very few studies have examined the prevalence of osteosarcopenia. Recent studies of Australian persons with falls reported that 40% of this high-risk population could be classified as osteosarcopenic.¹⁷

The most common osteoporotic fractures are of the vertebral bodies (27%).¹⁸ Other common sites due to minimal trauma include fractures of the wrist (19%), hip (14%) and pelvis (7%).¹⁸ The lifetime risk of fractures at any of these sites in women is around 40%.¹⁹ Despite the burden of disease, public knowledge of the link between minimal trauma fractures and osteoporosis remains very low.²⁰

Osteoporotic fractures are associated with increased morbidity, loss of independence and a 20% increase in mortality at one year.²¹ The prevalence of these poor outcomes is higher when osteoporosis is associated with muscle weakness.²¹ Hip fractures carry the greatest risks and are associated with between 8 – 36% increased mortality at one year.²² Osteoporosis case-finding, fracture risk calculation, muscle assessment, and appropriate treatment is key to the health of older adults worldwide.

Presentation

Osteoporosis is an insidious disease and symptoms are never present until the point fracture. Conversely, sarcopenic persons can experience weakness, weight loss, decline in physical function, falls and falls-related injuries. A majority of older adults with a fracture experience acute pain and loss of function.¹⁸ Special populations, such as those with dementia or sensory impairment, may be unable to report symptoms and thus require heightened vigilance to detect pain or symptoms of

fracture. Vertebral fractures may be asymptomatic, and many remain undetected in the absence of vertebral imaging. Many older adults remain undiagnosed prior to fracture or with insufficient time to receive benefit from treatment prior to fracture.¹ Osteosarcopenia should be suspected in men older than 60 and postmenopausal women aged greater than 50 years, especially in those with the presence of risk factors, previous history of falls or fractures, or suspicion of secondary causes.^{1,5}

Secondary causes

Secondary causes of osteoporosis are those diseases or drugs that impact upon bone directly (bone cells or matrix) or indirectly (hormone production). The most common secondary causes of osteoporosis and investigations to consider are listed in Supplement 1. Whilst a majority of factors contributing to osteoporosis or low bone mass are irreversible, a diagnosis of osteoporosis or fracture should act as a trigger for investigating for secondary causes of osteoporosis and treatment of the underlying condition. Secondary causes for sarcopenia can be considered activity-related (bed rest, deconditioning), disease-related (organ failure, inflammatory states), or nutrition-related (obesity, malabsorption, inadequate protein intake).²³ A diagnosis of sarcopenic obesity should also be considered in overweight adults presenting with weakness, falls and fractures. Sarcopenic obesity, characterized by

muscle mass declines with preservation or increases in fat mass, can occur with aging and in certain inflammatory disease states.²⁴ It is the authors' opinion that secondary causes should be addressed on an individual basis, with a particular focus on those factors that if appropriately managed, may reduce falls and fracture risk.

Clinical Management

Assessment

A comprehensive approach to the diagnosis and management of osteoporosis and sarcopenia in adults is recommended.^{1,9,18} Given the recent emergence of osteosarcopenia, no international consensus guidelines on assessment and management have been established. A detailed history, physical examination and appropriate investigations should be undertaken to assist in both the calculation of fracture risk and in making patient-centered management decisions. The clinician may consider the use of SARC-F, a five-question screening tool for predicting adverse outcomes in sarcopenia, which is highly specific but poorly sensitive in determining those who should undergo further diagnostic testing for sarcopenia (Supplement 2).²⁵ The history and physical examination should also explore the possibility of risk factors followed by subsequent investigations outlined in Supplement 1.

Given the clinical end-point of osteoporosis is fracture with low or no trauma, the clinical assessment should also systematically focus on modifiable falls risk factors,

including assessment for sarcopenia, with a view to decreasing falls risk.²⁶ The physical assessments required for the diagnosis of sarcopenia are dependent upon the definition used. However, a key component of both the EWGSOP2 and FNIH definition is handgrip strength using handheld dynamometer.^{9,10}

DXA – Beyond bone density

BMD is the amount of bone per unit volume or unit area. BMD assessment is the key diagnostic tool for osteoporosis and the most widely used tool, recommended by National Osteoporosis Foundation (NOF) and WHO^{1,5}, is DXA. DXA has utility in assisting in the prediction of future fracture risk, monitoring the progression of osteoporosis in treated or untreated persons, and can assess lean mass for the diagnosis of sarcopenia. Bioimpedance analysis (BIA) can also be used to measure muscle mass, however is used more commonly in research than clinical settings. Other techniques to measure bone density include quantitative ultrasound (QUS), quantitative computerized tomography (QCT), peripheral DXA (pDXA), and radiographic absorptiometry.²⁷ These techniques have high specificity but low sensitivity in fracture prediction. The indications for BMD assessment vary internationally but in general, assessment should be considered in:

- Women ≥ 65 and older and men ≥ 70 ;
- Younger postmenopausal women and women in menopausal transition;
- Men aged 50 to 69 with risk factors for fracture;

- Adults who have a fracture age 50 years or greater; and
- Adults with a condition (e.g., rheumatoid arthritis) or taking medications (e.g., glucocorticoids) associated with low bone mass or bone loss.¹

In those with a diagnosis of osteoporosis, assessment of BMD should not delay treatment.

Vertebral Imaging

A vertebral fracture equates to a diagnosis of osteoporosis and as such, BMD assessment is not required to commence osteoporosis treatment.¹ Routine chest X-rays should always be examined for vertebral fractures. The NOF advise proactive vertebral imaging in high-risk populations by lateral thoracic and lumbar spine X-ray or DXA.¹

Bone turnover markers

Biochemical markers of bone turnover reflect the metabolic activity of bone at the cellular level.²⁸ Further, osteoporotic fractures undergo a process of bone remodeling and increased cellular activity. Bone healing can be predicted by this cellular activity, estimated by bone turnover markers (BTMs). BTMs may also predict fracture risk independently of BMD prior to fracture.²⁸ BTMs include resorption markers; serum C-telopeptide (CTX) and urinary N-telopeptide (NTX), and formation markers; serum bone-specific alkaline phosphatase (BSAP), osteocalcin (OC), and

aminoterminal propeptide of type I procollagen (P1NP). Uncertainties remain as to the predictive value of combining BTMs, BMD and risk calculation tools and international reference standards have not yet been developed.²⁸

Risk calculation tools

All individuals undergoing assessment for osteoporosis should have their fracture risk calculated using a validated tool. Forty-eight fracture risk assessment tools are available in the literature yet only seven are validated with population-based data.²⁹ Calculators integrating several risk factors that provide a ten-year fracture risk calculation include the FRAX[®],³⁰ the Garvan fracture risk calculator,³¹ and the QFracture[®].³² The Garvan and QFracture[®] calculators incorporate history of falls into the fracture risk prediction.^{31,32} The FRAX[®] is the most widely used calculator with models covering 80% of the global population³⁰. The FRAX[®] also incorporates the risk of mortality into the risk of fracture calculation.³⁰ The FRAX[®] can be applied without an assessment of BMD and can predict risk of fractures comparably to the use of BMD alone.³³ Therefore it is appropriate to use the FRAX[®] in calculating fracture risk for individuals in settings where BMD assessment techniques are not available.³³ Regionally-specific population data across 64 countries have been incorporated into the FRAX[®], available at www.shef.ac.uk/FRAX. No validated risk-calculation tools are currently available for sarcopenia or osteosarcopenia.

General management

The purpose of osteosarcopenia management is to preserve bone and muscle strength, reduce risk of falls and fractures, and maintain independence. Universal recommendations for all older adults include adequate vitamin D and calcium, participation in weight-bearing and muscle strengthening exercise, addressing modifiable risk factors (smoking and alcohol), pharmacological treatment of osteoporosis, and management of falls risk factors.^{1,5,6}

Nutrition

Adequate dietary intake of calcium, vitamin D, and protein throughout the life stages reduces risk of fracture in later life.³⁴ Deficiencies in all of these dietary elements are common in older adults.

Adequate dietary calcium is preferable to supplementation. The NOF recommends calcium intake of greater than 1000mg/day for adults and 1200mg/day for those with osteoporosis.¹ The amount of calcium in typical dietary servings can be found on the International Osteoporosis Foundation (IOF) website; <https://www.iofbonehealth.org/>. Should dietary intake not reach these targets, supplementation is required. The risk of cardiovascular events with calcium supplementation has been a source of debate,³⁵ however a recent meta-analysis did not demonstrate a significant association in the general population.³⁶

Older adults, who may have malabsorptive syndromes, malnutrition, chronic kidney disease or who are housebound, are at particular risk of vitamin D deficiency. In general, a loading dose of 50,000 international units (IU) of oral vitamin D followed by 1,000 – 2,000 IU/daily could achieve a target serum level of approximately 30ng/mL (75nmol/L) in 8-12 weeks.¹ Rapid correction of vitamin D levels (to at least 50 nmol/L) is important when osteoporosis treatment is being started, especially in parenteral treatments due to risk of hypocalcemia. Once replete, therapy can remain between 1000-2000IU per day to maintain to the target serum level. Vitamin D supplementation has been reported to reduce falls risk.³⁷ However, excess vitamin D supplementation (3000-4000IU per day or boluses exceeding 50,000IU monthly) increases the risk of falls³⁸⁻⁴⁰ but not fractures,⁴⁰ although reduces the incidence of acute respiratory infections in nursing home residents.⁴⁰

A decline in caloric intake with aging occurs in parallel with reduced energy expenditure, however reduction in protein intake can have a negative effect on bone and muscle health.¹⁸ Daily protein intake of 1-1.2g/kg/day is recommended to attenuate the effects of muscle loss with aging.⁴¹ and is most effective on muscle and bone mass when combined with exercise.⁴²

Exercise

Weight-bearing exercise and progressive resistance training reduce the risk of falls and fractures.⁴³ Tailored exercise programs incorporating weight-bearing (jogging, Thai Chi, dancing) and strengthening (yoga, Pilates and weights) exercises should be developed in accordance with an individual's preferences.

Pharmacological management

The primary focus of pharmacological therapy for osteoporosis is to reduce the risk of fractures. Current therapies for osteoporosis are either anti-resorptive or anabolic. There are no currently approved pharmacotherapies for sarcopenia with recent phase II clinical trials testing the effect of ant-myostatin antibody showing a minimal effect on muscle function.⁴⁴

Availability, indications, and regulatory approval of pharmacological agents vary globally (Table 3). NOF recommends that therapy should be initiated in an older adult meeting any of the following criteria:

- Minimal trauma vertebral or hip fracture;
- Hip or lumbar spine T-score ≤ -2.5 on DXA; or
- Low bone mass and a FRAX® 10-year fracture risk (adapted to the US) of the hip $\geq 3\%$ or of any major osteoporosis-related fracture $\geq 20\%$.¹

Treatment needs to be individualized through consideration of the risk assessment using a validated fracture risk calculator, individual patient circumstances and

preferences. In addition, regional guidelines and funding may determine or limit medication choice.

The association of bisphosphonates with atypical femoral fractures (AFFs) (subtrochanteric) in the mid-2000s saw a 50% decline in bisphosphonate prescribing between 2008 and 2012 in the US.⁵⁶ However the number needed to treat to prevent one osteoporotic hip fracture is far less than the number needed to harm to cause an AFF at 3 years.⁵⁷ Therefore the benefit-to-risk ratio is strongly in favor of treating osteoporosis with anti-resorptives.⁵⁸ The risk of AFFs is highest after 5 years of treatment with bisphosphonates or denosumab.⁵⁹ Pain in the thigh or groin typically precedes these fractures and should act as a trigger for further evaluation including bilateral X-ray of the femora as fractures are frequently bilateral. Nuclear medicine bone scans, CT and Magnetic Resonance Imaging (MRI) can also be used for diagnosis of AFFs or at-risk femora. Definitive management is surgical fixation with an intramedullary nail of the affected side, with consideration of fixation of the at-risk contralateral femur.⁶⁰ Ongoing medical management involves discontinuation of anti-resorptive treatment, continuation of nutritional interventions, and consideration of teriparatide therapy.⁶¹

The antifracture effects of bisphosphonates persist beyond cessation, whereas the benefit of non-bisphosphonate therapy, particularly denosumab, diminishes rapidly

after treatment cessation. After denosumab cessation, BMD decreases to pre-treatment levels at 12 months, which has been associated with fourfold increase in fracture risk.⁶² While no evidence-based recommendations exist, prompt transition to bisphosphonate therapy from denosumab would maintain BMD.

Extension studies with anti-resorptives have demonstrated a persistent anti-fracture efficacy for up to 10 years, with denosumab showing an additional steady increase in BMD while on treatment.⁶³ Following initial treatment of 3 to 5 years a comprehensive assessment should be undertaken to determine future fracture risk, which includes BMD assessment and where appropriate, vertebral X-rays.

Discontinuing bisphosphonate therapy after the treatment course in those at moderate risk of fracture is reasonable.¹ For those at high risk of fracture following the initial treatment period, anti-resorptive therapy should be continued or alternative therapies considered.⁶³

The anabolic therapies Teriparatide and Abaloparatide have been approved in USA but their use is limited to 24 months of treatment. These drugs should not be prescribed for patients who are at increased baseline risk for osteosarcoma including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase.⁶⁴ Alternating treatment strategies have shown promise, with the DATA-SWITCH study demonstrating significant BMD increases in patients receiving 2

years of teriparatide therapy followed by 2 years of denosumab therapy, compared with the inverse sequence which resulted in BMD reductions.⁶⁵

Monitoring

Regular review of patient risk factors and treatment programs are required to optimize the response to multifactorial interventions and re-evaluate patient needs. Monitoring should include the application of strategies described in *Assessment*, in addition to medication adherence and complications history, yearly height assessment (if >2cm height loss in 1 year, repeat vertebral imaging), and BMD assessment with DXA at least every two years unless otherwise indicated.

Models of care

As few as 10% of women with an osteoporotic fracture receive appropriate therapy.⁶⁶ Fracture liaison services (FLSs) are a proven model of care that prevent osteoporotic fractures.⁶⁷ FLSs comprise a multidisciplinary team led who together ensure people experiencing a fracture receive correct management and follow up.⁶⁷ Other models of care, such as orthogeriatric care for patients with hip fracture, have shown to reduce mortality and morbidity compared with standard care.⁶⁸ Fracture registries also provide valuable information that can be used to ensure care providers are delivering the best evidence-based care.⁶⁹

Special populations

A concern of some clinicians is whether initiating osteoporosis treatment in older adults is beneficial or carries greater rates of adverse events. Studies of the oldest old (>80 years) undergoing osteoporosis treatment showed that the recommended therapies are comparably safe.² Vitamin D and calcium alone are insufficient to treat osteoporosis. Treatment of osteoporosis with anti-resorptives in the oldest old may be more effective than in younger cohorts in terms of fracture reduction and decreased mortality and morbidity.²

Lee and Kim proposed applying a time to benefit (TTB) theory against an individual's life expectancy (LE) to individualize recommended preventative treatments.⁷⁰ The TTB of bisphosphonate therapy for individuals with osteoporosis has been estimated as 8 months for those greater than 70 years and 19 months for those less than 70 years of age.⁷¹ Therefore, if the patient's LE is less than the TTB, it may be reasonable to not recommend preventative osteoporosis treatment.

Older adults living in nursing homes are at higher risk of fracture than community dwelling older adults however there is under-diagnosis and under-treatment in these settings.⁷² Nursing homes present an opportunity to maximize osteoporosis treatment and adherence.⁷³ Fracture risk assessment should be undertaken even if BMD assessment is not possible. Falls risk factors should also be addressed coupled

with an individualized management approach involving patient, caregivers and staff.⁷³

Emerging science and future questions

Despite major investigatory and therapeutic advances in osteoporosis in recent decades, many questions remain. Improving the predictive value of risk calculation tools for osteoporosis, developing similar tools for sarcopenia, and integrating sarcopenia within current calculation tools remain future challenges. A seemingly promising treatment targeting sclerostin, Romosozumab, demonstrated significantly lower rate of fracture in osteoporotic women – mostly in vertebral fractures –⁷⁴ however, approval has been delayed due to concern over serious cardiovascular events.⁷⁵ In addition, the duration and sequence of anti-resorptive and bone forming therapy is an ongoing source of debate. Regarding the development of combined treatments for osteoporosis and sarcopenia, in a recent phase II trial, VK5211, an oral non-steroid Selective Androgen Receptor Modulator (SARM), showed a significant increase in lean muscle mass and non-significant improvement in 6 minute walk test in the treatment group at 12 weeks.⁷⁶ Additionally, the treatment group showed a significant improvement in P1NP suggesting a dual effect on bone and muscle⁷⁶; an exciting possibility for the potential treatment of osteosarcopenia.

Conclusion

Osteoporosis and sarcopenia are highly prevalent diseases in older persons that remain underdiagnosed and undertreated. Assessment for osteoporosis and sarcopenia should be included as part of the comprehensive geriatric assessment. Considering the consequences of falls and osteoporotic fractures and the high anti-fracture efficacy and safety of osteoporosis treatments, medications should be initiated when indicated and anti-falls/anti-fracture interventions should be continued especially in high-risk populations.

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Conflict of Interest

Prof. Duque has served as a member of Advisory Boards at Lilly and Amgen Australia and is a member of the board of speakers for Amgen, Lilly, Sanofi and Novartis Australia.

Dr. Zanker has no conflict of interest to declare

Author Contributions

Both authors contributed equally to this manuscript.

Sponsor's Role

N/A

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Supplemental Material

Supplement 1. Common secondary causes of osteoporosis and investigations to consider in older adults. COPD = Chronic Obstructive Pulmonary Disease, GnRH = Gonadotrophin Releasing Hormone

Adapted from Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014;25(10):2359-81

Supplement 2. SARC-F Sarcopenia Questionnaire. *Adapted from Ida S, Kaneko R, Murata K. SARC-F for Screening of Sarcopenia Among Older Adults: A Meta-analysis of Screening Test Accuracy. J Am Med Dir Assoc 2018;19(8):685-689*

Table 1. Definition of Osteoporosis and Osteopenia based on BMD

Classification	BMD at the femoral neck	T-Score
Normal	< 1 SD of the mean level for young-adult reference population	T-score at -1.0 and above
Osteopenia	Between 1.0 and 2.5 SD below the mean level for young-adult reference population	T-score between -1.0 and -2.5
Osteoporosis	2.5 SD or more below the mean level for young-adult reference population	T-score at or below -2.5

Severe or established osteoporosis	2.5 SD or more below the mean level for young-adult reference population	T-score at or below -2.5 with one or more fracture
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BMD = Bone Mineral Density, SD = Standard Deviation

Table 2. Major operational definitions of sarcopenia

Component	Cut-points
European Working Group on Sarcopenia in Older People 2 ^(EWGSOP2) 9	
Low muscle mass	ALM using whole-body DXA <i>Not adjusted for height</i> Men: < 20kg Women: <15kg

Table 3. Pharmacological agents for the treatment of osteoporosis

Class	Drug Name	Mechanism of action	Formulation (treatment dosage)	Patients studied	Efficacy	Key Side Effects/precautions
Bisphosphonate	Alendronate (<i>Foxamax</i> ®, <i>Binosto</i> ™, generic)	Inhibition of osteoclast activity	70 mg weekly orally	Men and post-menopausal women with osteoporosis	Reduced hip and vertebral fractures by approx. 50% over 3 years. ⁴⁵	Contraindicated eGFR < 35ml/min. Common – Gastrointestinal. Uncommon – Eye inflammation. Rare – ONJ (highest risk in patients with cancer), atypical femoral fracture (>5 years use).
	Ibandronate (<i>Bonvia</i> ®, generic)		150mg monthly tablet or 3mg intravenously three-monthly	Corticosteroid-induced osteoporosis	Reduced vertebral fractures by approx. 50% over 3 years. ⁴⁶	
	Risedronate (<i>Actonel</i> ®, <i>Altevia</i> ™, generic)		35mg weekly, 75mg on two consecutive days monthly, or 150mg monthly orally		Reduce vertebral fractures by 41 to 49% and nonvertebral fractures by 36% over 3 years. ⁴⁷ Approved for use in patients on glucocorticoid therapy. ⁴⁸	
	Zoledronic acid (<i>Reclast</i> ®, <i>Aclasta</i> ®)		5mg intravenous infusion yearly		Reduced vertebral fractures by 70%, hip fractures by 41%, and nonvertebral fractures by 25% over 3 years. ⁴⁹	
Synthetic parathyroid hormone	Teriparatide (<i>Forteo</i> ®)	Anabolic activity resulting in new bone	20mcg daily subcutaneous injection for maximum 24	Men and women with osteoporosis	Reduced risk of vertebral fractures by 65% and nonvertebral fractures by 53% after 18 months. ⁵⁰	<u>Caution or avoidance in those at increased risk of osteosarcoma; Paget's disease, previous radiation</u>

		formation	months	Corticosteroid-induced osteoporosis		therapy, hypercalcemia, skeletal metastases; or those with a history of prostate cancer prostate cancer, lymphoma.
Parathyroid hormone-related protein (PTHrP) analog	Abaloparatide (<i>Tymlos</i> ®) [Approved in some locations]		80mcg daily subcutaneous injection for maximum 24 months	Post-menopausal women with osteoporosis	Reduced risk of vertebral fractures by approx. 57%. ⁵¹	Common – legs cramps, nausea and dizziness. Increased risk of osteosarcoma shown in rats.
Biologic – RANK-Ligand inhibitor	Denosumab (<i>Prolia</i> ®)	Inhibits coupling of osteoclasts and reduces bone resorption	60mg six-monthly subcutaneous injection	Men with low bone mass and postmenopausal women Corticosteroid-induced osteoporosis	Reduced vertebral fractures by 68%, hip fractures by 40% and nonvertebral fractures by 20% over 3 years. ⁵²	Rapid bone loss after cessation. Uncommon – Hypocalcemia, cellulitis, skin rash. Rare – Weak immunosuppressant with increased risk bacterial infections, ONJ, atypical femoral fracture.
Hormone Replacement Therapy (HRT)	Various	Maintenance estrogen levels Prevents bone resorption	Oral or transdermal in wide variety of formulations.	Post-menopausal women or women with hysterectomy	WHI study – 5 years HRT reduced vertebral fractures by 34% and other fractures by 23%. ⁵³	Increased risk of myocardial infarction, breast cancer, pulmonary emboli, deep vein thrombosis. No increase in cardiovascular disease if starting within 10 years of menopause.

Selective Estrogen Receptor Modulators (SERMs)	Raloxifene (Evista ®)	Estrogen agonist in bone preventing resorption	60mg daily orally	Post-menopausal women	Reduced risk vertebral fractures by approx. 30% in patients with prior vertebral fracture, and by 55% in those without a prior vertebral fracture over 3 years. ⁵⁴	Uncommon – Leg cramps, deep vein thrombosis.
	Bazedoxifene (Duavee ®)		0.45mg/20mg daily orally		Reduced incidence of vertebral fracture by approx. 30% at 3 years. ⁵⁵	Uncommon – muscle spasms, gastrointestinal complaints, dizziness, neck pain. Uncommon – deep vein thrombosis.

eGFR = estimated Glomerular Filtration Rate, ONJ = Osteonecrosis of the jaw, WHI = Women's Health Initiative

Figure Legend

Figure 1. Bone turnover and Cell-cell Interactions: Osteoblasts and osteocytes regulate bone resorption through the secretion of RANKL and OPG. Osteocytes regulate bone formation through the secretion of sclerostin (SOST) and Dkk1. Progressive infiltration of bone marrow by fat is associated with the paracrine secretion of toxic fatty acids and adipokines which would affect osteoblast function and survival. In contrast, high levels of PPAR γ expression due to increasing number of bone marrow adipocytes would promote osteoclast differentiation and bone resorption.

Figure 2. Osteosarcopenia: Pathophysiology, risk factors and clinical outcomes.

GH/IGF-I, growth hormone-/insulin-like growth factor-I, FGF2, fibroblast growth factor 2; FAM5C, family with sequence similarity 5, member, C; IL, interleukin; MMP-2, matrix metalloproteinase-2; MGF, mechanogrowth factor; VEGF, vascular endothelial growth factor; HGF, hepatocyte growth factor. Adapted from Hirschfield et al.⁵

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Author/s:

Zanker, J;Duque, G

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