REVIEW ARTICLE

Osteoporosis in Older Persons: Old and New Players

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Osteoporosis is the most common bone disease in humans. Older persons are at higher risk of osteoporotic fractures that also result in poor quality of life, disability, loss of independence, institutionalization, and higher mortality. Osteoporosis shares a distinct pathophysiologic relationship with sarcopenia, 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 older adults with the best falls and fractures prevention strategies. This review provides updated information on new discoveries on the combined pathophysiology of osteoporosis and sarcopenia that have led to 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 pharmacologic treatments to prevent falls and fractures in older persons. **J Am Geriatr Soc 67:831–840, 2019.**

INTRODUCTION

Osteoporosis is the most common bone disease in humans.[1] Prevalence of osteoporosis and the 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 both to 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 with low muscle strength or function, is gaining recognition as an important contributor to loss of function, loss of 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 was proposed to describe those patients with a 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. To provide comprehensive care to older adults, particularly with respect to musculoskeletal health, clinicians 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 that have led 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 pharmacologic 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 postmenopausal women.[7] Subsequent studies on different populations informed the development of the current WHO definition (Table 1).[8] Although 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]

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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 SDs below the mean level for young adult reference population	T-score between −1.0 and −2.5
Osteoporosis	2.5 SDs or more below the mean level for young adult reference population	T-score at or below −2.5
Severe or established osteoporosis	2.5 SDs or more below the mean level for young adult reference population	T-score at or below −2.5 with one or more fracture

Abbreviations: 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 *Not adjusted for height* Men: <20 kg Women: <15 kg *Adjusted for height²* Men: <7.0 kg/m² Women: <6.0 kg/m²
Low muscle strength	Hand grip strength using dynamometer Men: <27 kg Women: <16 kg Chair stand (5 rises) Men and women: >15 s
Low physical performance	Men and women: Gait speed: ≤0.8 m/s SPPB: ≤8-point score TUG: ≥20 s 400 m walk test: noncompletion or ≥6 min to complete
Foundation for the National Institutes of Health (FNIH)[9]	
Low muscle mass	ALM adjusted for BMI (kg/m²) using whole-body DXA Men: <0.789 Women: <0.512
Low muscle strength	Hand grip strength using dynamometer Men: <26 kg Women: <16 kg

Abbreviations: ALM, appendicular lean mass; BIA, bioimpedance analysis; BMI, body mass index; DXA, dual X-ray absorptiometry; SD, standard deviation; SPPB, short physical performance battery; TUG, timed up and go.

In contrast, there is no universal definition of sarcopenia. The absence of a definition complicates clinical and research applications, resembling the challenges observed during the 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% noncollagenous proteins that 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). The two types of bone are 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, whereas resorption is performed by osteoclasts. These two cell types are well coordinated during the stage of obtaining peak bone mass responsible for bone modeling during growth and bone remodeling after reaching the peak of bone mass at 25 to 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 that 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 κ-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 that 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 (MSCs).[13] MSCs can differentiate not only into osteoblasts but also into adipocytes, myocytes, or chondrocytes. In the case of young bone marrow, MSCs differentiate into osteoblasts at the expense of adipocytes. This predominant differentiation of MSCs 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 that accumulate in the bone marrow

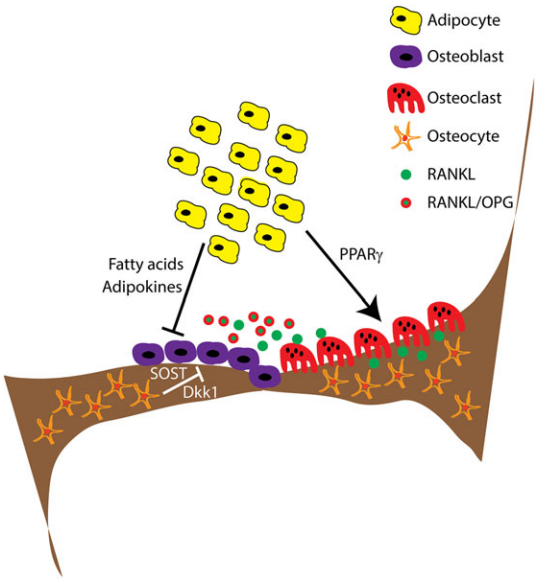

Figure 1. Bone turnover and cell-cell interactions. Osteoblasts and osteocytes regulate bone resorption through the secretion of RANKL and osteoprotegerin (OPG). Osteocytes regulate bone formation through the secretion of sclerostin (SOST) and Dkk1. Progressive infiltration of bone marrow by fat is associated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

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.[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 cross talk. Any alterations in this cross talk 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 that in combination with 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 approximately 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 1 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% and 36% increased mortality at 1 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 of fracture. Conversely, sarcopenic persons can experience weakness, weight loss, decline in physical function, falls, and falls-related injuries. Most 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 before fracture or with insufficient time to receive benefit from treatment before fracture.[1] Osteosarcopenia should be suspected in men older than 60 years and postmenopausal women older 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 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. Although most factors contributing to osteoporosis or low bone mass are irreversible, a diagnosis of osteoporosis or fracture should act as a trigger to investigate for secondary causes of osteoporosis and treatment of the underlying condition. Secondary causes of 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 our opinion that secondary causes should be addressed on an individual basis, with

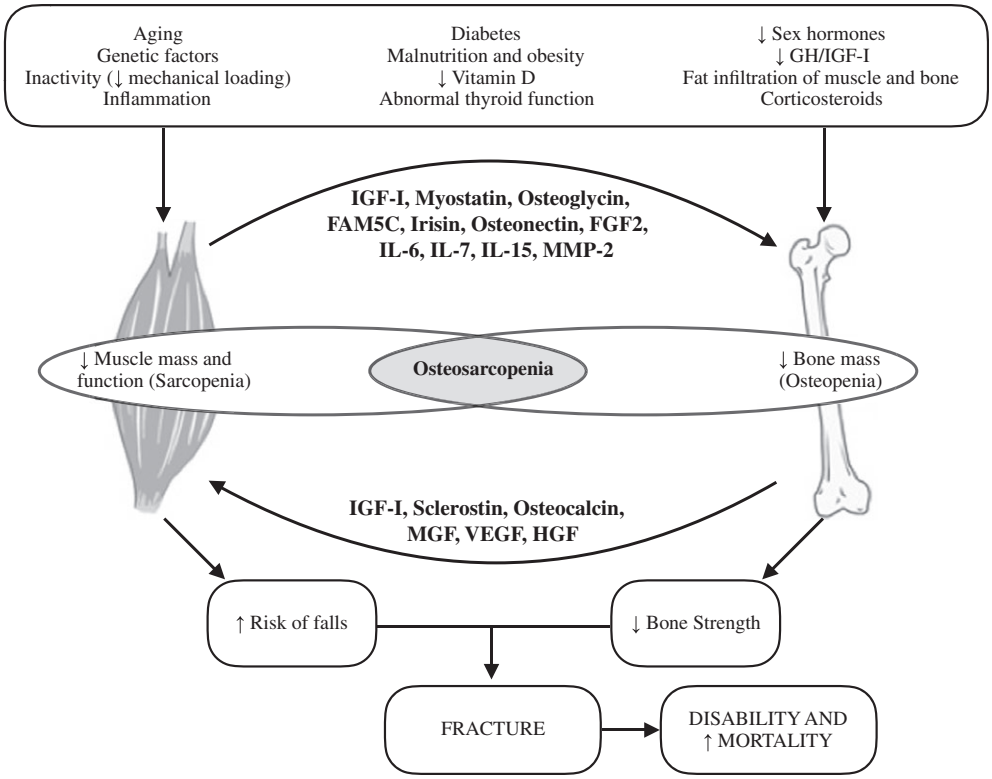

Figure 2. Osteosarcopenia: Pathophysiology, risk factors and clinical outcomes FAM5C, family with sequence similarity 5, member, C; FGF2, fibroblast growth factor 2; GH/IGF-I, growth hormone/insulinlike growth factor-I; HGF, hepatocyte growth factor; IL, interleukin; MGF, mechano-growth factor; MMP-2, matrix metalloproteinase-2; VEGF, vascular endothelial growth factor. Adapted from Hirschfield et al.[5]

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.[1,10,18] 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 that 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 that the clinical end point of osteoporosis is fracture with low or no trauma, the clinical assessment should also focus systematically 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 depend on the definition used. However, a key component of both the European Working Group on Sarcopenia in Older People 2 and Foundation for the National Institutes of Health definition is handgrip strength using a 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 the 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 can also be used to measure muscle mass; however, it is used more commonly in research than clinical settings. Other techniques to measure bone density include quantitative ultrasound, quantitative computed tomography, peripheral DXA, 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 these groups:

- Women 65 years and older and men 70 years and older;
- Younger postmenopausal women and women in menopausal transition;

- Men age 50 to 69 years with risk factors for fracture;
- Adults who have a fracture age 50 years or greater; and
- Adults with a condition (eg, rheumatoid arthritis) or taking medications (eg, 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 begin osteoporosis treatment.[1] Routine chest radiographs should always be examined for vertebral fractures. The NOF advises proactive vertebral imaging in high-risk populations by lateral thoracic and lumbar spine radiograph 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 before fracture.[28] BTMs include resorption markers; serum C-telopeptide, urinary N-telopeptide, and formation markers; and serum bone-specific alkaline phosphatase, osteocalcin, and aminoterminal propeptide of type I procollagen (P1NP). Uncertainties remain about 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 10-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 population.[30] The FRAX also incorporates the risk of mortality into the risk of fracture calculation.[30] It can be applied without an assessment of BMD and can predict risk of fractures comparably with 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 weightbearing and muscle-strengthening exercise, addressing modifiable risk factors (smoking and alcohol), pharmacologic 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 greater than 1000 mg/day for adults and 1200 mg/day for those with osteoporosis.[1] The amount of calcium in typical dietary servings can be found on the International Osteoporosis Foundation 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 (IUs) of oral vitamin D followed by 1000 to 2000 IU/day could achieve a target serum level of approximately 30 ng/mL (75 mmol/L) in 8 to 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 and 2000 IU/day to maintain to the target serum level. Vitamin D supplementation was reported to reduce falls risk.[37] However, excess vitamin D supplementation (3000-4,000 IU/day or boluses exceeding 50 000 IU monthly) increases the risk of falls[38–40] but not fractures,[40] although it 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 to 1.2 g/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

Weightbearing exercise and progressive resistance training reduce the risk of falls and fractures.[43] Tailored exercise programs incorporating weightbearing (jogging, tai chi, dancing) and strengthening exercises (yoga, Pilates, and weights) should be developed in accordance with an individual's preferences.

PHARMACOLOGIC MANAGEMENT

The primary focus of pharmacologic therapy for osteoporosis is to reduce the risk of fractures. Current therapies for osteoporosis are either antiresorptive or anabolic. There are no currently approved pharmacotherapies for sarcopenia with recent phase 2 clinical trials testing the effect of anti-myostatin antibody showing a minimal effect on muscle function.[44]

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

- Minimal trauma vertebral or hip fracture;
- Hip or lumbar spine T-score −2.5 or less on DXA; or
- Low bone mass and a FRAX 10-year fracture risk (adapted to the United States) of the hip 3% or greater or of any major osteoporosis-related fracture 20% or greater.[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 United States.[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 antiresorptives.[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 radiograph of the femora because fractures are frequently bilateral. Nuclear medicine bone scans, computed tomography, and magnetic resonance imaging can also be used for the 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 antiresorptive 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 pretreatment levels at 12 months, associated with a 4-fold increase in fracture risk.[62] Although no evidence-based recommendations exist, prompt transition to bisphosphonate therapy from denosumab would maintain BMD.

Extension studies with antiresorptives demonstrated a persistent antifracture 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 that includes BMD assessment and, where appropriate, vertebral radiographs. 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, antiresorptive therapy should be continued or alternative therapies considered.[63]

The anabolic therapies teriparatide and abaloparatide have been approved in the United States, 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 has 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 that 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 reevaluate patient needs. Monitoring should include the application of strategies described in the Assessment section here, in addition to medication adherence and complications history, yearly height assessment (if >2 cm height loss in 1 year, repeat vertebral imaging), and BMD assessment with DXA at least every 2 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 members 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, were 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 antiresorptives 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 preventive treatments.[70] The TTB of bisphosphonate therapy for individuals with osteoporosis was estimated as 8 months for those greater than 70 years and 19 months for those younger than 70 years of age.[71] Therefore, if the patient's LE is less than the TTB, it may be reasonable not to recommend preventive osteoporosis treatment.

Table 3. Pharmacologic Agents for the Treatment of Osteoporosis

Class	Drug name	Mechanism of action	Formulation, treatment dosage	Patients studied	Efficacy	Key side effects/Precautions
Bisphosphonate	Alendronate (Fosamax, Binosto, generic)	Inhibition of osteoclast activity	70 mg weekly orally	Men and postmenopausal women with osteoporosis Corticosteroid-induced osteoporosis	Reduced hip and vertebral fractures by approx. 50% over 3 y[45]	Contraindicated eGFR <35 mL/min Common: Gastrointestinal Uncommon: Eye inflammation Rare: ONJ (highest risk in patients with cancer), atypical femoral fracture (>5 y use)
	Ibandronate (Boniva, generic)		150 mg monthly tablet or 3 mg intravenously every 3 mo		Reduced vertebral fractures by approx. 50% over 3 y[46]	
	Risedronate (Actonel, Atelvia, generic)		35 mg weekly, 75 mg on 2 consecutive days monthly, or 150 mg monthly orally		Reduce vertebral fractures by 41%-49% and nonvertebral fractures by 36% over 3 y.[47] Approved for use in patients on glucocorticoid therapy.[48]	
	Zoledronic acid (Reclast, Aclasta)		5 mg intravenous infusion yearly		Reduced vertebral fractures by 70%, hip fractures by 41%, and nonvertebral fractures by 25% over 3 y[49]	
Synthetic parathyroid hormone	Teriparatide (Forteo)	Anabolic activity resulting in new bone formation	20 μg daily subcutaneous injection for maximum 24 mo	Men and women with osteoporosis Corticosteroid-induced osteoporosis	Reduced risk of vertebral fractures by 65% and nonvertebral fractures by 53% after 18 mo[50]	Caution or avoidance in those at increased risk of osteosarcoma; Paget's disease, previous radiation therapy, hypercalcemia, skeletal metastases, or those with a history of prostate cancer prostate cancer, lymphoma. Common: legs cramps, nausea, and dizziness. Increased risk of osteosarcoma shown in rats
Parathyroid hormone-related protein (PTHrP) analog	Abaloparatide (Tymlos) [approved in some locations]		80 μg daily subcutaneous injection for maximum 24 mo	Postmenopausal women with osteoporosis	Reduced risk of vertebral fractures by approx. 57%[51]	

(Continues)

Table 3 (Contd.)

Class	Drug name	Mechanism of action	Formulation, treatment dosage	Patients studied	Efficacy	Key side effects/Precautions
Biologic: RANK-ligand inhibitor	Denosumab (Prolia)	Inhibits coupling of osteoclasts and reduces bone resorption	60 mg every 6 mo 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 y[52]	Rapid bone loss after cessation Uncommon: Hypocalcemia, cellulitis, skin rash Rare: Weak immunosuppressant with increased risk of 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	Postmenopausal women or women with hysterectomy	WHI study 5 y 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 y of menopause
Selective estrogen receptor modulators (SERMs)	Raloxifene (Evista)	Estrogen agonist in bone preventing resorption	60 mg daily orally	Postmenopausal 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 y[54]	Uncommon: Leg cramps, deep vein thrombosis
	Bazedoxifene (Duavee)		0.45 mg/20 mg daily orally		Reduced incidence of vertebral fracture by approx. 30% at 3 y[55]	Uncommon: muscle spasms, gastrointestinal complaints, dizziness, neck pain Uncommon: deep vein thrombosis

Abbreviations: eGFR, estimated glomerular filtration rate; ONJ, osteonecrosis of the jaw; WHI, women's Health Initiative.

Older adults living in nursing homes are at a higher risk of fracture than community-dwelling older adults; however, there is underdiagnosis and undertreatment 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 a significantly lower rate of fracture in osteoporotic women, mostly in vertebral fractures.[74] However, approval was delayed due to concern over serious cardiovascular events.[75] In addition, the duration and sequence of antiresorptive and bone-forming therapy is an ongoing source of debate. Regarding the development of combined treatments for osteoporosis and sarcopenia, in a recent phase 2 trial, VK5211, an oral nonsteroid selective androgen receptor modulator, showed a significant increase in lean muscle mass and a nonsignificant improvement in the 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 muscle, 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 antifracture efficacy and safety of osteoporosis treatments, medications should be initiated when indicated and anti-falls/antifracture interventions should be continued, especially in high-risk populations.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1. Common secondary causes of osteoporosis and investigations to consider in older adults. COPD = chronic obstructive pulmonary disease; GnRH = gonadotrophin-releasing hormone. Adapted from Cosman et al.

Table S2. SARC-F Sarcopenia Questionnaire. Adapted from Ida et al.