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Osteoporosis Review of Etiology, Mechanisms, and Approach to Management in the Aging Population

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Osteoporosis

Review of Etiology, Mechanisms, and Approach to Management in the Aging Population

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KEYWORDS

• Bone loss • Aging and bone loss • Osteoporosis • Fracture risk and aging

KEY POINTS

- Review the incidence and etiology of osteoporosis.
- Understand why the aging population is at risk for osteopenia/osteoporosis.
- Recognize clinical, environmental, and lifestyle factors that may be related to bone loss.
- Delineate ways to measure bone loss over time.
- Review the available FDA-approved therapies for osteopenia/osteoporosis and how management is approached in the aging population.

Osteoporosis, the most common metabolic bone disease, is characterized by low bone mineral density (BMD) and reduced bone strength, and this results in an increased risk for fractures. It is a significant health problem particularly affecting the aging population.

This article provides an update on the epidemiology, etiology, and approach to diagnosis of osteoporosis in the aging population.

The prevalence of low bone mass and osteoporosis is high. An epidemiologic study determined that low femoral bone density is present in 14,646 US men and women from the Third National Health and Nutrition Examination Survey (NHANES III).[1] According to the World Health Organization (WHO) criteria that use T scores (standard deviations below peak bone mass), this survey revealed that 13% to 18% of women aged 50 years or more had osteoporosis and another 37% to 50% had osteopenia. Applying these numbers to the most recent US census data in 2010, this translates to over 10 million individuals with osteoporosis and over 20 million with osteopenia.[1] Worldwide, approximately 200 million women have osteoporosis.[2] Overall, the age-adjusted prevalence of osteoporosis among adults aged 50 and over has increased

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from 9.4% in 2007–2008 to 12.6% in 2017–2018. The prevalence of osteoporosis among women has increased from 14.0% in 2007–2008 to 19.6% in 2017–2018. However, osteoporosis prevalence in men did not significantly change from 2007–2008 (3.7%) to 2017–2018 (4.4%) (**Fig. 1**).

In the United States, 250,000 individuals aged 65 or greater fracture their hip each year.[3–5] Hip fractures increase exponentially with age: the incidence of hip fractures in white women (per 1000 person-years) is 2.2, age 65 to 69 years; 4.4, age 70 to 74 years; 9.5, age 75–79 years; 16.9, age 80 to 84 years; 27.9, age 85 to 90 years; and 34.2, age 90 years and older.[3,5] Hip fractures have long been considered one of the most devastating osteoporotic related fractures due to the postfracture disability and immobility. Unfortunately, hip fractures are projected to increase from an estimated 1.7 million in 1990 to 6.3 million by the year 2050.[5,6] In addition, ethnic variations in bone mass have been noted in population studies.[6] African Americans have higher and Asian Americans have lower BMD than White Americans.[6] Moreover African Americans have lower fracture rates at many skeletal sites, including hip, clinical vertebral, upper, and lower appendages. In addition, Hispanic Americans and Asian Americans also have lower hip fracture rates than White Americans.[6] In the United States for Caucasian ethnicity, it is currently estimated that the lifetime risk by age 50 of having a hip fracture is about 16% to 17.5% for women and 5% to 6% for men. For African Americans, the lifetime risk is lower but estimated to be 5.6% and 2.8% for women and men, respectively. Although the likelihood of developing osteoporosis is currently greatest in North America and Europe, as population longevity in developing countries increases so will the risk of osteoporosis.[2]

ETIOLOGY OF BONE LOSS IN AGING

Osteoporosis is a skeletal disorder characterized by compromised bone strength as well as bone quality predisposing to an increased risk of fractures. Normal bone

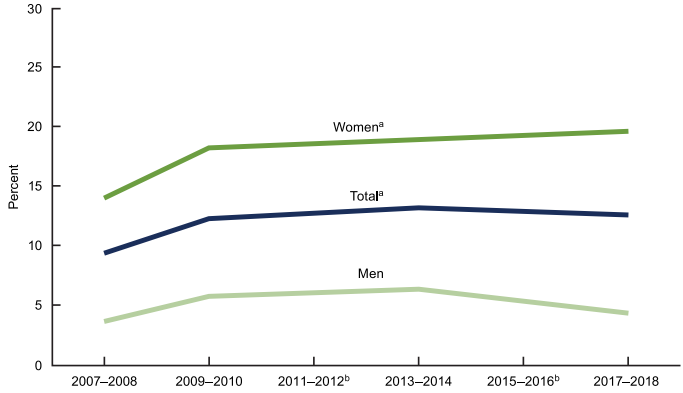

Fig. 1. Trends in age-adjusted prevalence of osteoporosis among adults aged 50 and over, by sex: United States, 2007–2008 to 2017–2018. [a]Significant increasing linear trend. [b]Data not available. Notes: Osteoporosis is defined as occurring at the femur neck or lumbar spine or both. Percentages are age adjusted by the direct method to the 2000 projected U.S. Census population using age groups 50–64 and 65 and over. Access data table for Figure. 3 at: https://www.cdc.gov/nchs/data/databriefs/db405-tables-508.pdf#3. (*From* Sarafrazi N, Wambogo EA, Shepherd JA. Osteoporosis or low bone mass in older adults: United States, 2017–2018. NCHS Data Brief, no 405. Hyattsville, MD: National Center for Health Statistics. 2021.)

remodeling involves an equilibrium between the process of bone resorption in which osteoclasts remove bone by acidification and proteolytic digestion and bone formation in which osteoblasts secrete osteoid matrix into the resorption cavity.[7] Activation of the remodeling cycle serves two functions in the adult skeleton to (1) produce a supply of calcium to the extracellular space and (2) provide elasticity and strength the skeleton. When the remodeling process is uncoupled there is either excess resorption of bone leading to bone loss versus excess bone acquisition when formation exceeds remodeling.[8] In the bone remodeling process, osteoblasts are activated through various mechanisms including growth hormone, parathyroid hormone (PTH). M-CSF and receptor activator of nuclear factor kappa-B ligand (RANKL) are the two major osteoblast mediated factors, which regulate the recruitment of osteoclasts.[7]

In older individuals, there is uncoupling of the bone remodeling cycle due to several factors, including a reduction in the number of activity of osteoblasts, so the amount of time to fill in resorption cavities is longer, and an increase in low-grade systemic inflammation, especially pro-inflammatory cytokines (TNF, IL-1, and IL-6) that seems to increase the number and activity of osteoclasts. Overtime in older individuals there is a net loss of bone. In addition to the uncoupling of bone remodeling with aging, compromise of other major organs, such as the kidney reduces the activation of 25 D to 1.25 D which reduces the amount of calcium absorbed from the gastrointestinal tract, and a negative calcium balance ensues, and osteoclasts are required to resorb calcium to fill this gap.

In addition to uncoupling of normal bone homeostasis, inherent bone quality contributes to risk for poor bone health. Small bone size, disrupted microarchitecture, cortical porosity, compromised quality of bone, and decreased viability of osteocytes are some biological factors contributing to decreased strength over time.[8–10] A major determinant of bone density in an older individual is his or her peak bone mass.[11,12] Peak bone mass is the maximum bone mass achieved in life. The time of peak bone mass is not known with certainty, but probably occurs in the third to fourth decade of life in most individuals, with differences in timing due to genetic, hormonal, and environmental variables and to skeletal site (type of bone) and method of BMD measurement.[11]

In addition to the uncoupling of bone turnover, which is so common in aging, estrogen deficiency is also a critical factor for the development of osteoporosis in both women and men. Age-related bone loss may begin immediately after the acquisition of peak bone mass for either sex, however, most bone loss occurs after the age of menopause in women and after the age of 70 years in men.[10] Nevertheless, it is unknown what contributes greater; the molecular events causing disequilibrium between bone resorption and formation in aging versus sex steroid deficiencies.[9] At menopause, there is a somewhat fast decline in ovarian function in women and a slower decline of both androgen and estrogen levels in men with advancing age, the two conditions inexorably overlap, making it impossible to separate their independent influence to the cumulative anatomic deficit.[8] In Caucasian women aged 65 and older, both low serum total estradiol and high serum concentrations of sex hormone binding globulin have been shown to increase the risk of hip and vertebral fractures without relation to BMD.[10] Interestingly, mouse models of bone loss suggest that the adverse effects of old age on the skeleton are independent of estrogens and are due to molecular mechanisms that are distinct from those responsible for the effects of sex steroid deficiency.[13–16]

Suggested causes of bone-intrinsic molecular mechanisms include mitochondria dysfunction, oxidative stress, declining autophagy, DNA damage, osteoprogenitor and osteocyte senescence, senescence-associated secretory phenotype, and lipid

peroxidation.[14] Age-related changes in bone resulting from intracellular reactive oxidative species (ROS) are not a new concept, but it has recently been proposed as a contributor to osteoporosis, especially in the older. ROS are generated during fatty acid oxidation and in response to inflammatory cytokines and it is suggested that both estrogens and androgens may protect against oxidative stress.[15,16] In addition, estrogen withdrawal and deficiency at menopause is also believed to cause increased production of inflammatory cytokines and promote T-cell activation.[17–19] The loss of estrogen results in activation of specific T-cell subsets including T helper cells that support the production of IL-17, RANKL, IL-1, TNF, and IL-6 that stimulate osteoclast maturation, activity, and lifespan that seem to prolong their lifespan and inhibit osteogenesis. In addition, estrogen deficiency and aging reduce the number and activity of Treg cells that reduce the production of inflammatory cytokines. These events that alter the immune system and inflammation with estrogen deficiency seem to increase with the addition of aging. Mouse models reveal the loss of estradiol due to ovariectomy increases osteoclast formation along with colony forming units for granulocytes and macrophages in vitro. Similarly, this deficiency increases the number of osteoclast in trabecular bone in animals. Along with elevated T cells, postmenopausal deficiency also stimulates B-lymphopoiesis. There has been a direct relationship observed with the elevated B cells and bone resorption.

In addition to the normal aging process and menopause, there are many other clinical, medical, behavioral, and nutritional risk factors involved in the etiology of bones loss in the aging population.[9] Clinical risk factors to consider include body mass. Older individuals with low body weight, low percentage of body fat, or low body mass index are at an increased risk of low bone mass and rapid bone loss.[20] In addition, a history of prior fractures is extremely relevant as several studies have documented associations between prior fracture history at any site and risk of future vertebral and hip fractures and a first-degree relative having a history of a hip fracture.[10,21–23] Moreover, women who have developed an incident vertebral fracture, 1 in 5 develop a new incident vertebral fracture in the subsequent year.[22] Impaired vision independently increases the risk of hip fracture in older white women[10] and contributes to the risk for falls which is another independent risk factor for fracture. Finally, poor hand grip strength, a component of the definition of frailty, which can be caused by cognitive decline, diabetic neuropathy or pain is a strong independent risk factor for fragility fractures in postmenopausal women.[23]

Several medical disorders as well as medications listed in **Table 1** are associated with secondary osteoporosis in the aging population. This table albeit not fully inclusive of all conditions demonstrates the number of comorbidities that are highly prevalent in the older and can interfere with bone health. These disorders include gastrointestinal disorders (eg, inflammatory bowel disease, malabsorption syndromes, and celiac), hematologic disorders (eg, leukemia and lymphoma), endocrine disorders (eg, diabetes, hyperparathyroidism), and neurological disorders (eg, Parkinson's disease, stroke), and renal insufficiency.[24,25] In addition, exposure to certain medications may contribute to and/or increase risk for bone loss. Glucocorticoids are the most implicated class of medication, affecting both bone quality and quantity of bone.[26] Several studies investigating glucocorticoid-induced bone loss suggest that the degree of increased risk of vertebral fracture in glucocorticoid treated men and women is disproportionate to observed decreases in BMD, leading investigators to surmise that in addition to reducing bone mass, glucocorticoid treatment may lead to bone quality defects mediated by increases in bone turnover and trabecular thinning.[26,27] Other medications to consider are aromatase inhibitors, proton pump inhibitors, anticoagulants (heparin), selective serotonin reuptake inhibitors, and thiazolidinediones.

Table 1
Medical conditions, disease, and medications that can contribute to bone loss and or/fractures in the elderly

Lifestyle Factors	*Neurologic Disease*
Alcohol abuse	Stroke
Low body mass index	Parkinson's disease
Frequent falling	*Miscellaneous Conditions*
Immobilization	Chronic obstructive lung disease
Smoking	Depression
Low calcium intake	Renal Disease (CKD III- CKD V/ESRD)
Vitamin D insufficiency	*Medications*
Hypogonadal States	Aluminum containing antacids
Hypogonadism	Anticoagulants (Unfractionated heparin)
Low testosterone	Anticonvulsants (eg, phenobarbital, valproate)
Premature menopause	Arornatasc inhibitors
Endocrine Disorders	Cancer chemotherapeutics
Obesity	Cyclosporine and tacrolimus
Cushing's syndrome	Glucocorticoids (>5 mg/day prednisone or equivalent for >3 months)
Diabetes mellitus (type I and II)	Methotrexate
Hyperparathyroidism	Parenteral nutrition
Gastrointestinal Disorders	Proton pump inhibitors
Celiac disease	Selective serotonin reuptake inhibitor
History of gastric bypass	Thiazolidinediones
Malabsorption syndromes	
Pancreatic disease	
Hematologic disorders	
Leukemia and lymphoma	
Monoclonal Gammopathics	
Multiple myeloma	
Rheumatologic Disease/Autoimmune Disease	
Rheumatoid arthritis	
Ankylosing Spondylitis	
Sarcoidosis	
Amyloidosis	
Musculoskeletal diseases	

Data from Refs.[1,48–50]

Behavioral factors have also been linked to the development of bone loss in the older older adults and include cigarette smoking, poor physical activity, and alcohol abuse. Cigarette smoking is believed to induce bone loss and increased hip fracture risk in the older part due to various mechanisms: (1) direct toxic effect on osteogenesis,[28,29] (2) collagen metabolism in combination with increased bone resorption and osteoclast activity and osteoclastogenesis,[30] (3) calciotropic hormone metabolism, (4) dysregulation of sex hormones,[31] and (5) decreased intestinal calcium absorption.[20,32,33] Some studies have suggested low levels of physical activity in the older,

especially weight-bearing activity are positively correlated with bone loss and risk for fracture; however, after adjusting for confounding variables (eg, neuromuscular function, self-rated health status), this correlation did not always remain significant.[10] The loss of statistical significance for the association of physical activity and bone mass in the older is probably that neuromuscular function is a mediator of physical activity and bone mass. Exercise can improve neuromuscular function and may reduce falls and fractures, more than to increase bone mass and is critical to incorporate into the treatment of osteoporosis to prevent fractures in the older.[34] Furthermore, individuals with the TT genetic variant of the vitamin D receptor appear to be at a greater risk for this deleterious effect of caffeine on bone.[34]

Nutritional deficiency in dietary calcium intake is modestly correlated with BMD; however, many epidemiological studies of calcium intake and BMD in elders do not show a large impact on bone health implying other risk factors may be of greater importance in this age group.[20] Nevertheless, age-related changes in bone strength are partly attributable to an increase in PTH secretion which in turn is related to low serum calcium and vitamin D levels.[35]

Intervention studies have revealed that calcium and vitamin D supplementation has a greater effect on serum PTH then either component alone.[35] Furthermore, several lines of evidence suggest that vitamin D has a modest role in muscular strength and that supplementation improves muscle function, body sway, and prevents falls.[36,37]

Changes in Bone Architecture with Aging

The skeleton is made up of two major bone types: cortical bone that surrounds the bone marrow cavity and makes up 80% of the bone mass of the skeleton and trabecular bone that composes about 20% of the skeleton is located within the bone marrow and has a high rate of bone turnover. The adult skeleton continuously remodels to remove old bone and replace it with newly mineralized bone. It is this remodeling that keeps the bone strong. After peak bone mass is achieved, bone remodeling is tightly coupled in that the amount of bone that is removed is replaced. However, with menopause in women and with age in both men and women, the amount of bone removed or resorbed is greater than the amount of bone that is replaced. Microscopically, this is seen as thinning of the cortical shell through endocortical remodeling and both thinning of the trabeculae, loss of the number of trabeculae, and increased space between the trabeculae in the trabecular bone compartment. Over time, there is a loss of bone mass and architecture such that the bone can become weak and with very little stress can break. These alterations in bone remodeling for women begin at menopause and continue as they age and in men, begin around the age of 70 years and continue as they age. In men additionally there can be a loss of gondal function with time that can accelerate bone loss.

The loss of bone mass and architecture with age can result in both a reduction in bone mass and bone strength. However, osteoporosis subjects also fall, due to the loss of balance and weak muscle strength, and this can result in fractures. In addition, coughing and bending over to pick up something on the floor can also result in vertebral fractures. These fractures are much more common in the older due to compromised bone and muscle strength.

Approach to the Diagnosis of Bone Loss in the Aging Population

Risk assessment/ dual-energy X-ray absorptiometry (DXA) and vertebral imaging

The approach to the diagnosis and management of the aging population must be comprehensive. A detailed history of medical conditions, medications, behavioral factors, fracture history, nutritional dietary intake in combination with a physical

examination, BMD assessment, and laboratory parameters to rule out secondary causes for bone loss should be performed in all patients. The National Osteoporosis Foundation, the US Preventative Task Force, and the American Association of Clinical Endocrinology have published guidelines that recommend that BMD is performed in all women 65 years or older, all men 70 years and older, and for younger individuals who have 1 or more risk factors including history of fracture.[25] In addition, in all postmenopausal women and men age 50 and older risk stratification based on clinical risk factors some of which are noted in **Table 1** and are needed to determine the consideration for BMD testing and/or vertebral imaging.[25] DXA is considered the gold standard of methods to establish or confirm a diagnosis of osteoporosis, predict future fracture risk, and monitor patients.[25] The test measures areal BMD expressed in grams of mineral per square centimeter scanned (gm/cm^2). Available technologies measure central sites (lumbar spine and hip) and peripheral skeletal sites (forearm, heel, and fingers), although DXA measurement at the hip is the best predictor of future hip fracture risk. In postmenopausal women and men ages 50 and older, the WHO diagnostic criterion is used to categorize the patient.[38] Some societies recognize the use of the one-third radius for diagnosis osteoporosis when other sites are unusable or uninterpretable as epidemiologic studies have shown it to be both highly correlated with axial BMD sites, and this site seems to be responsive to change in patients being treated for or to prevent osteoporosis.[39] When deemed clinically relevant, vertebral imaging for assessment of vertebral fractures is important especially in the aging population as often these fractures are asymptomatic. Vertebral atraumatic fractures are consistent with a diagnosis of osteoporosis even in the absence of BMD testing. Independent of BMD, age, clinical risk factors, and radiographic vertebral fracture are a sign of impaired bone quality.[25] Moreover, the presence of single vertebral fractures increases the risk of subsequent fractures 5-fold and the risk of hip and other fractures 2- to 3-fold.[40] To assess for these fractures, either plain radiographs of the thoracolumbar spine can be done or lateral vertebral assessment which is available on most DXA machines.[25] Trabecular bone score (TBS) is another modality to assess the consistency of mineral structural distribution in trabecular bone. TBS is an assessment of how evenly or unevenly mineral is structurally distributed in trabecular bone and thus provides more information of the bone structure. This is generated from lumbar spine BMD images using software installed on some DXA machines and is available for clinical settings. Adding TBS to FRAX a capability of late-model densitometry devices increases the ability of FRAX to predict fractures.[41] Another limitation of current DXA screening is that it does not measure strength or quality—a DXA-derived BMD does not capture a bone's overall shape and three-dimensional geometry or the consistency of cortical versus trabecular bone or variations in cortical thickness. This limitation explains some of why DXA has limited sensitivity for correctly predicting who will fracture.[25] Given these limitations, if clinically indicated a well-validated, convenient diagnostic test for osteoporosis that noninvasively assesses bone strength formally referred to as "biomechanical computed tomography" analysis can be ordered.[42,43] This novel modality allows a health care provider to obtain a qualitative CT scan that has been ordered for another indication that includes the hip and lumbar spine. The analysis allows for an assessment of both trabecular and cortical bone volume and noninvasive calculated assessment of bone strength, however, is not available in all clinical settings yet.

Biochemical markers of bone turnover

Bone turnover or remodeling occurs throughout life and biomarkers of this reflect the dynamic process of bone metabolism. It has well been reported that in

postmenopausal women, serum and urine markers of bone formation (serum bone-specific alkaline phosphatase, osteocalcin, amino terminal propeptide of type I collagen) as well as markers of bone resorption (serum cross-links C-telopeptide of type I collagen [CTX], urinary N-telopeptide of collagen cross-links [NTX]) are significantly higher than premenopausal women.[44] In addition, other studies indicate that biochemical markers of bone metabolism may help determine adequacy of patient compliance with osteoporosis therapy. Furthermore, biochemical markers of bone turnover, especially serum CTX or PINP are very useful to monitor patients who are about to embark on a drug holiday and during the drug holiday. Although there are not many studies that have carefully evaluated the change in biochemical markers of bone turnover, and bone mass in subjects on drug holidays, it is common practice to obtain these markers annually and if the change in the markers is 50% or more, it is important to obtain a DXA scan as that is a sign that the patient may be losing bone and require treatment.[45–47]

Use of WHO fracture risk assessment tool (FRAX)

FRAX was developed to calculate the 10-year probability of hip fracture and 10-year probability of major osteoporotic fracture (defined as clinical vertebral, hip forearm, or proximal humeral fracture) considering femoral neck BMD and clinical risks factors noted **Table 1**.

The FRAX is quite useful in older subjects because age is the most important risk factor for predicting fracture in this tool. FRAX is validated for women and men aged 40–90 years. The US version of FRAX is validated for one of four ethnicities (Caucasian, Black, Hispanic, and Asian). Among these populations, data indicate differences in fracture even at the same BMD. Other countries, including some with considerable ethnic diversity, have used an alternative approach, with a single version of FRAX regardless of ethnicity[51] It is also important to know that in the aging population, FRAX risk is underestimated for those with recent fractures, multiple osteoporosis-related fractures, in patients with lower BMD at the spine and those at increased risk of falling. Also, while tempting to use the FRAX to estimate fracture risk after treatment with osteoporosis medications, it is not adapted for that use and would not be accurate.

Approach to the Management of Bone Loss in the Older

Vitamin supplementation

Once the diagnosis of osteopenia/osteoporosis has been made a thorough history and clinical assessment should be taken to detect any possible secondary causes or medication-related reasons for bone loss. All individuals should be counseled on cessation of tobacco use and the avoidance of excessive alcohol. Moreover, all individuals in the aging population regardless of bone health status should be recommended adequate intake of calcium and vitamin D. The Bone Health and Osteoporosis Foundation (BHOF) formally the National Osteoporosis Foundation (NOF) supports the Institute of Medicine (IOM) daily calcium intake recommendations: women and men ages 50 to 70 consume 1000 mg/day of calcium and women ages 51 and men ages 71 and older consume 1200 mg/day calcium. Most groups suggest acquiring half the calcium amount via dietary sources and then supplementing with vitamins.[25] Vitamin D plays a major role in calcium absorption, muscle performance, and balance. The BHOF recommends an intake of 800 to 1000 international units (IU) of vitamin D per day for adults ages 50 and older. The IOM recommendations for vitamin D are 600 IU per day until age 70 and 800 IU per day for adults are 71 years and older. Many older individuals are at high risk for vitamin D deficiency related but not limited

to malabsorption, chronic renal disease, being housebound or chronically ill with limited sun exposure. It is very important if an older older patient is found to be vitamin D deficient and is supplemented that the level of vitamin D be checked after a few months to be sure the deficiency is corrected and then it should continue to be checked annually thereafter. Comorbid conditions, such as renal insufficiency and gastrointestinal issues, require adequate vitamin D for bone health. Currently, there are some differences in what is considered a normal 25 vitamin D level, with the IOM stating a level below 20 ng/mL is low, whereas the Endocrine Society states a level below 30 ng/mL is low. Additional studies will be needed to determine which recommendation is correct in older individuals.

Fall risk prevention and regular exercise

Assessment of a patients fall risk is crucial in the treatment and prevention of osteoporotic fractures. **Box 1** includes major risk factors for falling. Using these risk factors as a guide, individual risk assessments are necessary in the approach to the aging patient.[25] Strategies to mitigate these risks include but are not limited to vision testing, adjustment of narcotic and psychotropic medications, home safety assessment, and consideration for the use of assistive devices and physical and occupational therapy.[25] Multiple observational and systemic reviews have underscored the importance of regular weight-bearing and muscle-strengthening exercises in addition to balance exercises and Tai Chi in reducing the risk of falls and fractures.[49,50] The proposed mechanisms for these benefits include improved strength, posture, and balance. The BHOF strongly endorses lifelong physical activity at all ages for osteoporosis and fall prevention. As the older often have balance problems, assessment for assistive devices is critical for preventing falls and fractures.[25]

Box 1
Risk factors for falls in the elderly

Medical Risk Factors
- Arthritis
- Female gender
- Visual worsening
- Previous fall
- Unstable blood pressure
- Impaired mobility
- Medications that cause dizziness (narcotic, analgesics, anticonvulsants, psychotropics)
- Muscle wasting/physical deconditioning

Environmental Risk Factors
- Poor lighting
- Hazards in walkway
- Stairs
- Slippery/wet indoor conditions
- Lack of assistive help or devices (transferring/bathroom)

Psychological Risk Factors
- Anxiety
- Diminished cognitive acuity
- Psychomotor decline

Adapted from Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R; National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014 Oct;25(10):2359-81.

Pharmacologic therapy. The treatment of bone loss in the aging population is approached by evidence-based guidelines; however, long-term management, drug holidays, and treatment failure are areas of ongoing study. A clinical approach to the initial management of osteoporosis in postmenopausal women and men aged 50 and older has been published by the BHOF. **Box 2** is adapted from these recommendations to be specific for the aging population. When medical treatment is recommended, there are a variety of FDA-approved medications noted in **Table 2**. The choice and duration of therapy in the aging population should consider previous therapy trials, clinical risk factors, route of administration, and potential adverse effects. In the older population, not only mindfulness of polypharmacy but also consideration of medication formulations that may be easier to take are crucial for drug adherence and safety. Bisphosphonates continue to remain the mainstay for treatment given their long-term efficacy even after drug withdrawal.[51] However, bisphosphonates are not recommended older individuals with renal insufficiency (GFR $\leq$ 30 mL/min). A general recommendation is to treat for 3 years with IV bisphosphonate and 5 years with oral agents.[50] Longer treatment, up to 6 years with IV and 10 years with oral, may be recommended for individuals who are high risk: defined by those with significant risk for

Box 2
Approach to treatment of osteoporosis in postmenopausal women and men aged 50 years and older

General Principles:
- Attain a detailed patient history for clinical factors, conditions, and medications that are known risk factors for osteoporosis
- Perform a physical examination including height measurement, clinical assessment of vertebral kyphosis
- Obtain diagnostic laboratories to evaluate for bone loss and secondary causes
- Obtain vertebral imaging when deemed appropriate based on above

Consider FDA-approved medical therapies for bone loss in adults $\geq$ 50 years based on the following:
- History or current presence of fracture(s) of vertebrae, hip, wrist pelvis, or humerus
- DXA T score -2.5 or lower in the lumbar spine, femoral neck, or total hip
- DXA T score -2.5 or lower at one-third radius (Isolated measurement still being investigated use clinical judgment)
- Low bone mass T score between -1.1 and -2.4 (osteopenia) and FRAX 10-year probability of a hip fracture $\geq$ 3% or 10-year probability of any major fracture $\geq$ 20%

Consider non-medication therapeutic interventions:
- Recognize and intervene on modifiable risks factors associated with bone loss and falls
- Recommend weight-bearing, muscle-strengthening, and balance-training activities

Follow-up
- Assess bone health clinically and with imaging in all patients those on or off therapy about every 2 years
- Patients on medical therapy should have laboratory and bone density reassessment after 2 years or more frequently based on medical necessity
- If worsened height loss and or new back pain vertebral imaging should be obtained at any time course
- Assess medical compliance with medications and non-medication therapeutics on biannual or annual basis

Adapted from Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R; National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. 2014 Oct;25(10):2359-81.

Table 2
FDA-approved therapies for osteoporosis

Drug Name	Brand Name	Drug Class	Form/Dosing	FDA Approved
Alendronate	Fosamax	Bisphosphonate	Oral (daily, weekly)	Women and Men
Ibandronate	Boniva	Bisphosphonate	Oral or injection (daily, monthly)	Women
Risedronate	Actonel/Atelvia	Bisphosphonate	Oral (daily/weekly/delayed release)	Women and Men
Zoledronic acid	Reclast	Bisphosphonate	IV (yearly/once every 2 years)	Women and Men
Raloxifene	Evista	SERM	Daily	Women
Abaloparatide	Tymlos	Parathyroid hormone analog	Injection daily for 2 years	Women
Teriparatide	Forteo	Parathyroid hormone analog	Injection daily for 2 years	Women and Men
Denosumab	Prolia	RANKL inhibitor	Injection every 6 months	Women and Men
Romosozumab	Evenity	Sclerostin Inhibitor	Injection monthly for 12 months	Women

Abbreviations: PTH, parathyroid hormone; RANKL, receptor activator of nuclear factor kappa-B ligand; SERM, selective estrogen receptor modulator.
Data from Refs.[48,50–52,54]

falls, T score <−2.5, vertebral or hip fracture history and ongoing steroid use.[51] Bisphosphonate drug holiday length is not uniform and depends on the individual clinical situation. With special respect to individuals in the aging population, many may have been treated with long-term bisphosphonates in the past or cycled on and off. Recommendations to continue regular dental visits and consideration for femur imaging to investigate for the rare but feared complications of osteonecrosis of the jaw and atypical femur fractures are suggested.

When considering treatment with non-bisphosphonate medications, agents like denosumab can be continued indefinitely (safety data for 10 years):[52] the anabolic agents parathyroid hormone analogs (eg, teriparatide and abaloparatide) for up to 24 months (can be longer in higher risk patients) and romosozumab for 12 months.[53–55] However, all the non-bisphosphonate medications have more temporary bone strengthening effects, so much so that shortly after discontinuation there can be rapid bone loss so there is need for follow-up therapy with an antiresorptive agent.[48] Current recommendations suggest follow-up after anabolic therapy with an IV or oral bisphosphonate. The exact drug and time course for when these medications should be initiated are still a large are of investigation. One study revealed that after 1 year of PTH densitometric gains are maintained or increased if followed by alendronate therapy but lost if PTH is not followed by an antiresorptive agent.[56] A recent article by the European Calcified Tissue Society suggests based on an updated systemic review on this topic that individuals who have been less than 2.5 years of denosumab can transition to oral bisphosphonate drugs for 12 to 24 months or IV zoledronate for 1 to 2 years about 6 months after the last denosumab. Those individuals on denosumab therapy longer than 2.5 years should transition to zoledronate 6 months after the last denosumab with monitoring of bone turnover markers and consider to repeat zoledronate as early as in 6 or again in 12 months if bone turn over markers remain high.[57] Patients with recent or ongoing fractures and very low BMD (T score < −3.0) are at especially high risk for future fracture(s). There is accruing evidence that BMD and fracture outcomes are significantly influenced by the sequence in which antifracture agents are administered.[48] An anabolic agent administered following antiresorptive has demonstrably less impact on BMD than if an anabolic agent is administered first.[58–61] Therefore, when sequential therapy is being considered and the patient is very high risk, anabolic therapy followed by antiresorptive is preferred.[48]

One of the main challenges of treating older patients for osteoporosis is how to navigate a drug holiday. Generally, as mentioned above oral bisphosphonates are prescribed for 5 years and IV bisphosphonates for 3 years and then patients are reassessed with every 2 years DXA. If the BMD after this treatment period is greater than T score −2.5 and the patient has not fractured or lost significant height and is not a high risk for falling/fractures, the therapy with bisphosphonate can be held for a period of 2 years. During a drug holiday, it is still very important for the patient to be clinically followed about every 2 years, or sooner based on clinical risks factors. Unfortunately, in patients who are treated with oral bisphosphonates, the absorption is very low, and this may translate to less protection in the skeleton and perhaps shorter drug holidays. This information is especially important for our very older patients as the amount of bisphosphonate in the skeletal sites may be very low and the onset of bone loss after discontinuing treatment will occur soon. Finally, it is critical to measure the height of the patient when initiating the drug holiday and annually as well as obtaining a bone turnover marker (CTX or PINP). Height loss and bone turnover marker levels which increase over 50% after 1 year could indicate ongoing bone loss and then prompt DXA and/or vertebral reimaging. In individuals on non-bisphosphonate drugs such as denosumab, drug holiday is problematic due to rapid bone loss risk after

discontinuation.[52] The same is the case with parathyroid hormone analogs and romosozumab. If these non-bisphosphonate medications are used follow-up therapy with a bisphosphonate is recommended.[53]

SUMMARY

Osteoporosis is the most common metabolic bone disease. With special respect to in the older population, it is very common, not only due to changes in lifestyle and diet but as a result of the aging process there is low grade inflammation and immune system activation that directly affects bone strength and quality. A thorough screening for osteoporosis is needed to identify candidates for treatment. Treatment interventions focus on both non-pharmacologic (behavioral risk modification, diet, exercise, balance training) and pharmacologic (vitamin supplementation and medications). Careful screening and monitoring of older patients for bone health is critical to prevention of fractures and obtaining a favorable outcome.

CLINICS CARE POINTS

- Osteoporosis prevention remains an area of great public health concern as the incidence of fractures in the aging population is expected to increase yearly.
- In addition to the normal aging process and menopause, there are many other clinical, medical, behavioral, and nutritional risk factors involved in the etiology of bones loss in the aging population: low body mass, fall risk, prior fracture, frailty, and poor hand grip
- DXA is considered the gold standard of methods to establish or confirm a diagnosis of osteoporosis, predict future fracture risk, and monitor patients, however, when deemed clinically relevant measuring height and vertebral imaging for assessment of vertebral fractures is important especially in the aging population.
- Patients on medical therapy should have laboratory and bone density reassessment after 2 years or more frequently based on medical necessity.
- Assess medical compliance with medications and non-medication therapeutics on biannual or annual basis.

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The authors have nothing to disclose.

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