Chapter 112: Osteoporosis

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UPDATE SUMMARY

Update Summary

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The following sections, tables, and figures were updated:

- Added discussion of the FRAX tool and FRAXPlus
- Updated Figure 112-3 to include additional clinical risk factors
- Added 2023 osteoporosis guideline recommendations for treatments of first choice
- Added section on the care of transgender people with osteoporosis

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 3, Osteoporosis.

KEY CONCEPTS

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1. Osteoporosis is a public health epidemic that affects all ages, genders, races, and ethnicities. Lifestyle behaviors, diseases, and medications should be reviewed to identify the risk factors for developing osteoporosis and osteoporotic fractures. Healthcare professionals should identify and resolve reversible risks. Secondary causes of bone loss should be explored, especially for patients with early-onset or severe osteoporosis.

2. Bone physiology and pathophysiology are complex involving coupled bone resorption and formation in bone remodeling processes. These processes result from many different cell lines, transmitters, pathways, and biofeedback systems. As these processes become more delineated, additional targets are identified for medications.

3. All patients taking medications known to increase bone loss, falls, and fractures should practice a bone-healthy lifestyle, be evaluated for a switch to a safer alternative medication, and/or be considered for osteoporosis therapy. The most common causes of medication-induced osteoporosis are long-term oral glucocorticoids and certain chemotherapeutic agents.

4. Ten-year probabilities for a major osteoporotic and hip fracture can be estimated for women (postmenopausal to 90 years old) and men (50-90 years old) with the fracture risk assessment tool (FRAX) tool. This tool is a questionnaire that can be used in any setting, including pharmacies, health fairs, and clinics. Central bone mass densitometry can determine bone mass, predict fracture risk, and influence patient and provider treatment decisions. A newer version, FRAXPlus, includes more risk factors and will soon be available.

5. Throughout life, everyone should practice a bone-healthy lifestyle, which emphasizes regular exercise, nutritious diet, tobacco avoidance, minimal alcohol use, and fall prevention to prevent and treat osteoporosis.

6. Treatment should be considered for postmenopausal women and men older than 50 years who have a low-trauma hip or vertebral fracture, T-score of −2.5 or less at the femoral neck, total hip, or spine, or low bone mass (T-score between −1.0 and −2.5) and a FRAX 10-year probability of major osteoporotic fracture of 20% or more or hip fracture of 3% or more. Patients with secondary causes might receive therapy at younger ages or higher T-scores.

7. The recommended dietary calcium intake for American adults is 1,000 to 1,200 mg of elemental calcium daily with diet as the preferred source. Supplements are added when diet is insufficient.

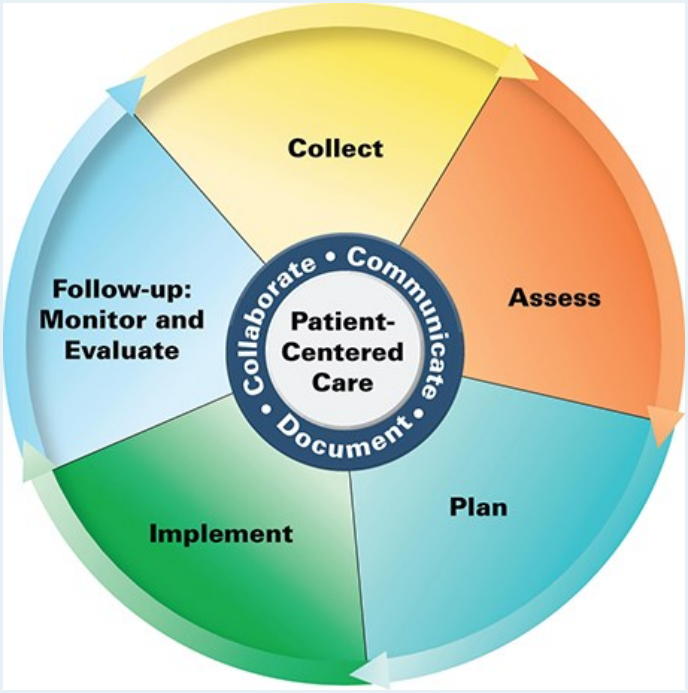
8. The recommended daily dietary vitamin D intake for American adults is 600 units and for older adults 800 units. Some organizations and guidelines recommend higher doses of at least 800 to 1,000 units daily. Vitamin D intake is achieved through sun exposure, fortified foods, and supplements. Vitamin D insufficiency and deficiency, defined as 25-hydroxyvitamin D (25[OH] vitamin D) concentrations of less than 30 ng/mL (mcg/L; 75 nmol/L) and less than 20 ng/mL (mcg/L; 50 nmol/L) respectively, are common in Americans. Higher vitamin D daily intakes and/or replenishment doses are then required.

9. Alendronate, risedronate, zoledronic acid, and denosumab decrease vertebral, hip, and nonvertebral fractures and in most guidelines are first-line osteoporosis treatments for those with high fracture risk. Bisphosphonates are low in cost, leading a 2023 guideline to recommend bisphosphonates first with denosumab as second line therapy. Bisphosphonate therapy continues for about 5 years in mild osteoporosis and 5 to 10 years in moderate-to-severe osteoporosis. Other antiresorptive (ibandronate, raloxifene), anabolic (abaloparatide, teriparatide), and combination anabolic and antiresorptive (romosozumab) medications are alternatives. These medications decrease osteoporotic fracture risk but not hip fractures. In patients with very high fracture risk, sequential therapy with abaloparatide, romosozumab, or teriparatide followed by an antiresorptive agent is recommended.

10. Adherence to osteoporosis medications is suboptimal. Poor adherence is associated with less fracture prevention. Healthcare professionals should assess medication administration technique and adherence at each visit, provide education, and resolve medication-related problems.

PATIENT CARE PROCESS

Patient Care Process for Osteoporosis



Collect

- Patient characteristics (eg, age, sex, race, ethnicity, postmenopausal status)
- Medical history (personal and family; eg, maximum height, falls, fractures, dental issues, gastroesophageal reflux/heartburn, and for women age at menarche and menopause)
- Social history (eg, tobacco and alcohol use, physical activity, and dietary habits, including calcium-containing food and beverage intake)
- Current medications including calcium and vitamin D, dietary supplements, multivitamins, and herbal product use
- Past medications (eg, hormone therapy and medications causing osteoporosis; see Table 112-3)
- Objective data
  - Height, weight
  - Laboratory results (see Table 112-4) and secondary causes
  - Central dual-energy x-ray absorptiometry (DXA) at the spine and hip
  - Fracture evidence (eg, vertebral fracture assessment [VFA], radiographs)

Assess

- Adequacy of dietary calcium and calcium/vitamin D supplement intakes
- Bone mineral density (BMD): Categorize lowest T-score as normal, low bone mass, or osteoporosis

- FRAX 10-year risk of major osteoporotic fractures and hip fracture
- Laboratory data and presence of secondary causes (see Tables 112-2 and 112-3)
- Patient preferences including injectable medications and concern about adverse effects
- Potential barriers to adherence (eg, administration route, frequency, cost, health literacy)

Plan

- Medication regimen including specific agent, dose, route, frequency, and duration (see Fig. 112-3, Tables 112-7 and 112-8), and calcium and vitamin D supplements as necessary
- Monitoring parameters including efficacy (eg, BMD, fracture, 25(OH)-vitamin D concentration) and safety (eg, common and serious adverse effects, serum creatinine, calcium). Include frequency and timing of follow-up

Implement*

- Provide patient education regarding treatment plan (eg, purpose of treatment, dietary calcium sources, medication-specific administration/injection technique in patient's primary language, adverse effects) (see Tables 112-7 and 112-8)
- Consider risk communication tool to explain medication benefit and rare adverse effects
- Schedule laboratory tests as needed and DXA (generally 2-5 years after initiation)
- Schedule referrals when appropriate (eg, physical therapist for fall prevention, dietitian)
- For zoledronic acid, coordinate with infusion center for administration
- For nongeneric therapies, coordinate prior authorization process as necessary

Follow-up: Monitor and Evaluate*

- Patient adherence to treatment plan and administration instructions
- Presence of adverse effects (see Table 112-8)
- BMD, fractures, falls, and laboratory parameters
- Changes in habits (eg, dietary calcium, exercise, alcohol, and tobacco use)
- Re-evaluate duration of therapy after 1 year (romosozumab), 2 years (abaloparatide, teriparatide), 3 years (intravenous bisphosphonate), 5 years (oral bisphosphonate), or as suggested by response to therapy and adverse effects

****Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Create a team of three classmates. Each team member selects one of the below patients to workup. This activity is useful to enhance your understanding of the COLLECT, ASSESS, and PLAN steps in the patient care process, the osteoporosis treatment algorithm, and individualization of patient care.

In your patient workup:

- Identify osteoporosis risks and secondary causes.
- Calculate a FRAX score (https://www.sheffield.ac.uk/FRAX/).
- Estimate calcium intake (https://www.osteoporosis.foundation/educational-hub/topic/calcium-calculator).
- Determine the calcium and vitamin D Institute of Medicine recommended daily intakes and deficits.
- Develop a prevention or treatment plan.
- Present your patient's risk factors, assessments, and treatment plan to each other.
- Compare and contrast these three women's cases and treatment plans.

Patient 1: A 57-year-old White, nonsmoking woman living in the United States. Patient's weight is 77 kg and height is 5 ft 6 in (168 cm). She has had no previous fractures and has no family history of fracture. Her T-scores are femoral neck −2.2 and spine −2.0. She has hypertension, hyperlipidemia, and GERD. The patient's current medications are omeprazole (Prilosec), atorvastatin (Lipitor), and amlodipine (Norvasc). The patient reports no vitamins or supplements. The patient drinks 1 glass of milk daily and eats 1 serving of yogurt daily. She does not drink alcohol.

Patient 2: A 67-year-old Hispanic woman living in the United States. Patient's weight is 77 kg and height is 5 ft 6 in (168 cm). She has had no previous fractures, but her mother had a hip fracture. Her T-scores are femoral neck −2.4 and spine −2.0. She has hypertension, diabetes type 2, and hyperlipidemia. The patient's current medications are canagliflozin (Invokana), atorvastatin (Lipitor), and enalapril (Vasotec). The patient reports taking Centrum(R) Silver(R) Women's 50+ every day. Social history: the patient drinks 1 glass of milk daily and eats 1 serving of yogurt daily. She smokes tobacco products but does not drink alcohol.

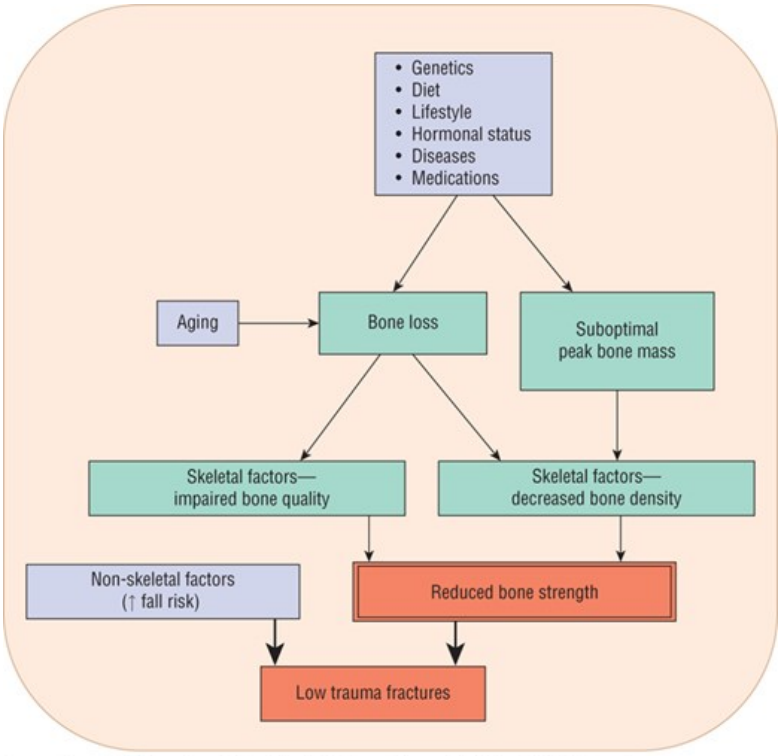
Patient 3: A 77-year-old Asian woman living in the United States. Patient's weight is 77 kg and height is 5 ft 6 in (168 cm). She has had no previous fractures and no family history of fracture. Her T-scores are femoral neck −2.6 and spine −2.9. She has diabetes type 2, rheumatoid arthritis, hypertension, and lactose intolerance. The patient's current medications are metformin (Glucophage), lisinopril (Prinivil), adalimumab (Humira), and celecoxib (Celebrex) as needed. Prior to adalimumab, she had used prednisone 5 to 10 mg daily for over 5 years. The patient uses no vitamins or supplements. The patient drinks 1 glass of fortified soy milk daily and eats 1 serving of tofu daily. She does not drink alcohol or smoke.

INTRODUCTION

1 Osteoporosis is a bone disorder characterized by low bone density, impaired bone architecture, and compromised bone strength that predisposes a person to increased fracture risk. Osteoporosis is a major public health threat, with about 50% of people 50 years of age and older expected to develop this disease.[1] In the United States, 10.2 million Americans are estimated to have osteoporosis.[2] An additional 43.4 million Americans are estimated to have low bone density and are at risk for osteoporosis. Attention to bone health is required throughout life. Osteoporosis and osteoporotic fractures are multifactorial conditions, beginning at birth with genetics and continuing throughout life due to health behaviors that influence bone growth and maintenance, skeletal factors that lead to compromised bone strength, and nonskeletal factors that lead to falls (Fig. 112-1). Healthcare professionals should educate people about bone-healthy lifestyles and empower them to practice these health behaviors. Osteoporosis is underdiagnosed and undertreated. Bone health screenings, osteoporosis prevention programs, accurate diagnoses, and optimal medication management are needed to prevent and treat osteoporosis and prevent fractures.

FIGURE 112-1

Etiology of osteoporosis and osteoporotic fractures.



Editors' note: In this and other chapters in Pharmacotherapy, references to biologic sex (as assigned at birth) are used based on prior literature being discussed or anatomical or physiologic differences. We recognize that not all individuals later identify with their sex at birth, and to the degree possible when discussing therapeutics, we avoid use of references to gender. In this chapter on Osteoporosis, "men" and "women" are used in discussing prior studies, published guidelines, and other recommendations for diagnosis and treatment based on biological sex and do not necessarily reflect an individual's gender identity.

EPIDEMIOLOGY

1 Low bone density, osteoporosis, and osteoporotic fractures are common in all people, with race and ethnic differences in osteoporosis detection, treatment and outcomes likely due to health disparities.[3,4] The prevalence of osteoporosis in women is 16.5%.[4] Low bone density was estimated to occur in 45% of non-Hispanic White, 43% of Mexican American, and 30% of non-Hispanic Black women aged 50 years and older.[3,5] Osteoporosis affects 13.4% of Mexican American, 10.2% of non-Hispanic White, and 4.9% of non-Hispanic Black women aged 50 years and older. Disease prevalence greatly increases with age; from 7% in women aged 50 to 59 years to 35% in women aged 80 years and older.[4] White American (17%) and Hispanic American (14%) women have the highest fragility fracture rate followed by Black American (6%) women.

Although more prevalent in women, men can also have low bone density and osteoporosis. Based on FRAX estimates, approximately 16% of men aged 50 years and older have low bone density rising to 46% in men aged 80 years and older.[6] Osteoporosis rises from 3% in men aged 50 to 59 years to 11% in men aged 80 years and older.[5] Osteoporosis prevalence also varies by race and ethnicity in men: 6% in Mexican American, 4% in non-Hispanic White American, and 1% in non-Hispanic Black American men.[3,5]

Fragility wrist and vertebral fractures are common throughout adulthood, with hip fractures more common in older adults. Although osteoporosis is common in adults with fractures, 12% of fracture patients have normal BMD and 52% have low bone density, supporting fractures can occur in all.[7]

Gender differences in osteoporotic fractures exist with 70% occurring in women and 30% in men.[2] As a woman ages, her risk of any fracture increases from 10% at age 50 years to 22% at 80 years old; with hip fractures increasing from 0.3% to 9% over the same time frame.[8] For men over the same time frame, fracture risk increases from 7% to 8% and hip fracture increases from 0.2% to 3%. Fracture outcomes are worse for people of color.[3]

Osteoporosis creates an economic health burden. In 2011, 1.7 million hospitalizations occurred for fragility fractures with 3 million osteoporotic fractures expected in 2025.[9] By 2025, osteoporosis treatment costs are estimated to be about $25 billion.[2] Because of associated morbidity, hip fracture is the costliest complication of osteoporosis, accounting for almost 72% of fracture costs. Osteoporosis costs exceed costs for breast cancer, heart attack, or stroke.

ETIOLOGY

Figure 112-1 depicts a model describing osteoporosis and fracture etiology. The major risk factors (see Table 112-1) influencing bone loss are hormonal status, genetics, exercise, aging, nutrition, lifestyle, concomitant diseases, and medications. Nonhormonal risk factors are similar between women and men

TABLE 112-1

Risk Factors for Osteoporosis and Osteoporotic Fractures

Low bone mineral density (BMD)[a]
Female sex[a]
Advanced age[a]
Race/ethnicity[a]
History of a previous fragility (lowtrauma) fracture including radiographic vertebral fracture as an adult[a] (especially clinical vertebral fracture or hip fracture)
Osteoporotic fracture in a first-degree relative (especially parental hip fracture[a])
Low body weight or body mass index[a]
Premature menopause[b]
Secondary osteoporosis[a,b]
Rheumatoid arthritis[a]
Past or present systemic oral glucocorticoid therapy (prednisolone 5 mg daily or more for >3 months)[a,c]
Current smoking[a,c]
Alcohol intake of 2 or more drinks/day[a,c]
Low calcium intake
Low physical activity or immobilization
Vitamin D insufficiency and deficiency
Recent falls
Cognitive impairment
Impaired vision

[a]Factors included in World Health Organization fracture risk assessment tool (FRAX).

[b]Secondary causes included in the FRAX tool are type 1 diabetes, osteogenesis imperfecta as an adult, long-standing untreated hyperthyroidism, hypogonadism, premature menopause, chronic malnutrition, malabsorption, and chronic liver disease.

[c]Risk is higher with greater exposure.

Data from References 2,4, and 10-13.

Low Bone Density

BMD is a major predictor of fracture risk. Every standard deviation decrease in BMD in women represents a 10% decrease in bone mass and a 1.6- to 2.6-fold increase in fracture risk.[2] In contrast, increasing peak bone mass in younger years by 10% was estimated to create 13 more years without a fracture in older women.[16] Low BMD can occur as a result of failure to reach a normal peak bone mass, bone loss, or both. Genetics accounts for 50% to 85% of peak bone mass variability.[4,14] Bone loss occurs when bone resorption exceeds bone formation, which also can result from high bone turnover when the number or depth of bone resorption sites greatly exceeds the rate and ability of osteoblasts to form new bone. Women and men begin to lose a small amount of bone mass starting in the third to fourth decade of life, about 0.5% to 1% per year.[12,14] During perimenopause and menopause, bone loss occurs predominantly due to increases in bone resorption. By age 80 years, 30% of a woman's bone mass is lost.[4] Older adults steadily lose bone mass because of an accelerated rate of bone remodeling combined with reduced bone formation.

Impaired Bone Quality

Bone strength is highly affected by the quality of the bone's composition and its structure and is a better predictor of fracture than BMD.[9] Changes in bone mass do not fully reflect changes in bone thinning and decreased connectivity, both related to strength. BMD explains only 70% of femur and 44% of spine bone strength. Even women with normal bone mass (3.4%) and low bone mass (5.3%) fracture, rates slightly lower than women with osteoporotic bone mass (6.8%). Accelerated bone turnover can increase the amount of immature bone that is not adequately mineralized. Sex differences exist with thinning of trabeculae, with aging in men causing less bone quality damage and impaired bone strength than in women.[12] With aging, fracture risk increases for a given T-score, partly related to bone quality changes; for example, at a T-score of −2.5, a 50-year-old postmenopausal woman has about a 4% probability of a hip fracture, whereas a 70-year-old woman has about a 9% probability.[23]

Falls

Each year, 15% to 45% of community-dwelling older adults and up to 60% of nursing home residents fall with more women falling than men.[4,24] Hip fractures only occurred in 1% to 2% of falls; however, 90% of hip fractures resulted from a fall.[8,25] Falls lead to accidental death in about 70% of older adults.[24] Inpatient and outpatient fall care is expensive.[24] The risk factors for falls overlap with the risk factors for osteoporosis and osteoporotic fractures.[2,24] Environmental factors also contribute to falls (eg, electric cords, throw rugs, and poor lighting).

PATHOPHYSIOLOGY

Normal Bone Physiology

2 The skeleton has two types of bone. Cortical bone makes up most of the skeleton (80%) and is found mostly in the long bones (eg, forearm and hip).[14] Trabecular bone is found mostly in the vertebrae and ends of long bones. This bone type is metabolically more active compared with cortical bone due to a much higher bone turnover rate because of its large surface area and honeycomb-like shape.

Bone is made of collagen and mineral components.[9,14] The collagen component gives bone its flexibility and energy-absorbing capability. The mineral component (mostly calcium and phosphorus), which accounts for 50% to 70% of bone mass, gives bone its stiffness and strength. The correct balance of these substances is needed for bone to adequately accommodate stress and strain and resist fractures. Imbalances can impair bone quality and lead to reduced bone strength.

Bone strength reflects the integration of bone mass, bone strength and quality (composition and microarchitecture).[9,16] Bone mass increases rapidly throughout childhood and adolescence. Peak bone mass is attained by age 18 to 25 years. Peak bone mass is highly dependent on genetic factors, which accounts for 60% to 80% of the variability. The remaining 20% to 40% is influenced by modifiable factors such as nutritional intake (eg, calcium, vitamin D, and protein), exercise, adverse lifestyle practices (eg, smoking), hormonal status, and certain diseases and medications (see Tables 112-2 and 112-3). Optimizing peak bone mass is important for preventing osteoporosis. The higher the peak bone mass, the more bone a person can lose before being at an increased fracture risk. As the microarchitecture of bone deteriorates, the bone strength greatly decreases.

TABLE 112-2

Select Medical Conditions Associated with Osteoporosis in Children and Adults

Endocrine/Hormonal
Primary or secondary ovarian failure
Testosterone deficiency
Hyperthyroidism
Cushing's syndrome (hypercortisolism)
Growth hormone deficiency (in children)
Hyperparathyroidism
Diabetes, type 1 and type 2
Gastrointestinal
Nutritional disorders (eg, anorexia nervosa)
Malabsorptive states (eg, Crohn's disease, celiac disease, cystic fibrosis, gastrectomy, and bariatric surgery)
Chronic liver disease (eg, primary biliary cirrhosis)
Disorders of Calcium Balance
Hypercalciuria
Calcium and or vitamin D deficiency
Inflammatory Disorders
Rheumatoid arthritis
Chronic Illness
Chronic kidney disease
Malignancies (eg, multiple myeloma, lymphoma, and leukemia)

Human immunodeficiency virus infection/acquired immunodeficiency syndrome
Organ transplant
Disuse/Immobility
Immobilization
Muscular dystrophy
Multiple sclerosis
Stroke/cerebrovascular accident
Genetic
Osteogenesis imperfecta
Cystic fibrosis
Hemochromatosis
Hypophosphatasia

Data from References 2,4, and 10-16.

TABLE 112-3

Select Medications Associated with Increased Bone Loss and/or Fracture Risk

Medications	Comments
Antiseizure therapy (phenytoin, carbamazepine, phenobarbital, and valproic acid)	↓ BMD and ↑ fracture risk; increased vitamin D metabolism leading to low 25(OH) vitamin D concentrations
Aromatase inhibitors (eg, letrozole and anastrozole)	↓ BMD and ↑ fracture risk; reduced estrogen concentrations
Calcineurin inhibitors (eg, cyclosporine and tacrolimus)	↓ BMD and ↑ fracture risk; increase osteoclast activity
Glucocorticoids (long-term oral therapy)	↓ BMD and ↑ fracture risk; increased bone resorption and decreased bone formation, and decreased calcium absorption and reabsorption; dose and duration dependent; see "Special Populations" section
Gonadotropin-releasing hormone agonists (eg, leuprolide and goserelin) or analogs (ganirelix)	↓ BMD and ↑ fracture risk; decreased sex hormone production
Heparin (unfractionated, UFH) or low molecular weight heparin (LMWH)	↓ BMD and ↑ fracture risk (UFH >>> LMWH) with long-term use (eg, >6 months); decreased osteoblast replication and increased osteoclast function
Loop diuretics (eg, furosemide)	↑ fracture risk; increased calcium renal elimination
Medroxyprogesterone acetate depot administration	↓ BMD, fracture risk unknown; possible BMD recovery with discontinuation; decreased estrogen concentrations
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) (tenofovir disoproxil fumarate > other NRTIs)	↓ BMD, fracture risk unknown; greater risk when combined with pharmacological boosters
Proton pump inhibitor therapy (long-term therapy)	↓ BMD and ↑ fracture risk; possible calcium malabsorption secondary to acid suppression for calcium carbonate salts
Selective serotonin reuptake inhibitors	↓ BMD and ↑ fracture risk; decreased osteoblast activity
Sodium glucose cotransporter 2 (SGLT2) inhibitors (canagliflozin; class effect uncertain)	↓ BMD and ↑ fracture risk; alteration in calcium and phosphate homeostasis; increased bone resorption
Thiazolidinediones (pioglitazone and rosiglitazone)	↓ BMD and ↑ fracture risk; decreased osteoblast function
Thyroid—excessive supplementation	↓ BMD and ↑ fracture risk associated with suppressed serum TSH; possible increase in bone resorption
Vitamin A—excessive chronic intake (>10,000 units of retinol form)	↓ BMD and ↑ fracture risk; decreased osteoblast activity and increased osteoclast activity

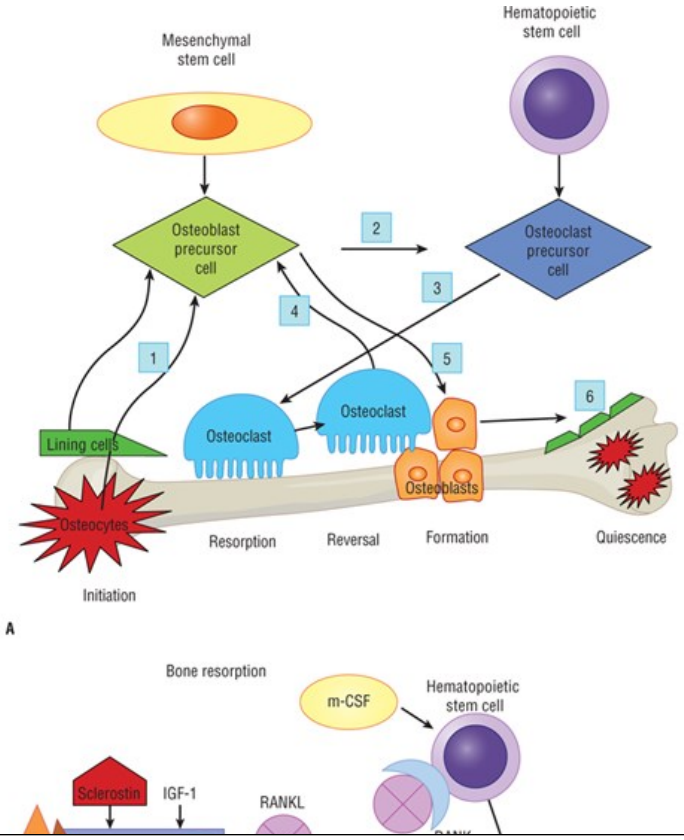
BMD, bone mineral density; TSH, thyroid-stimulating hormone.

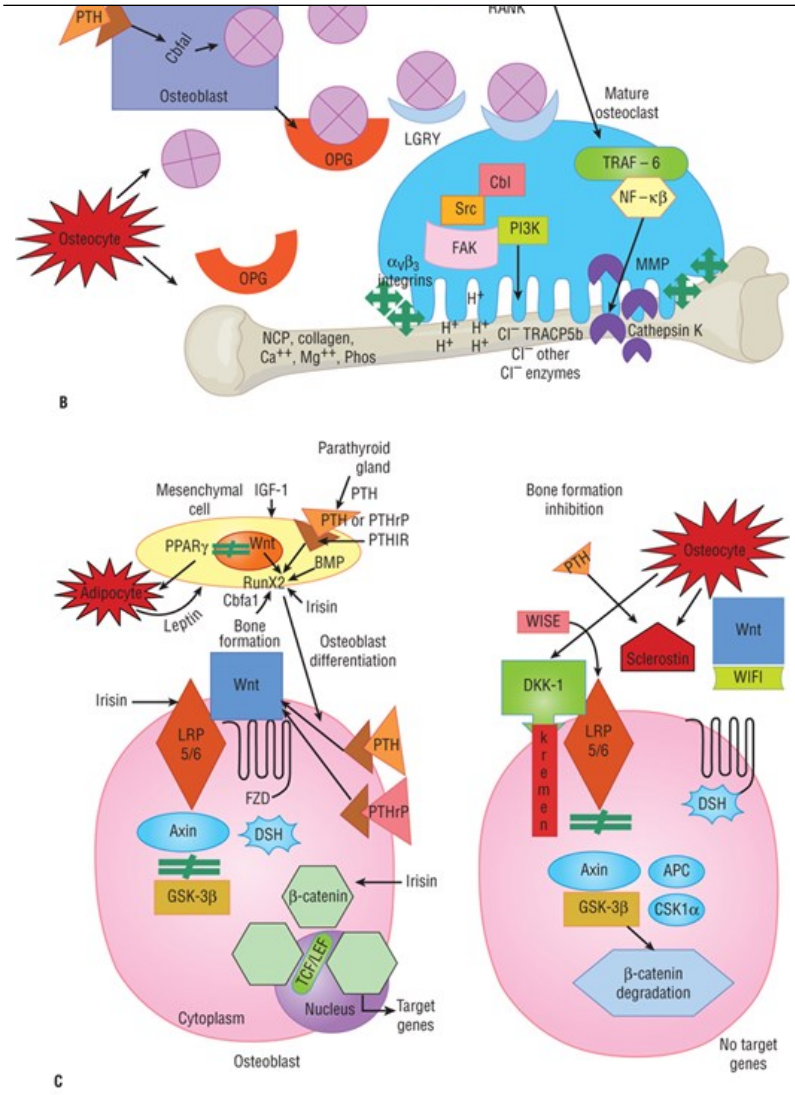
Data from References 2,14, and 17-22.

Bone remodeling is a dynamic process that occurs continuously throughout life (see Fig. 112-2A-C).[14,17] One to two million tiny sections of bone are in the process of remodeling at any given time. Within these sections, the bone remodeling activities of bone resorption and bone formation are coupled and balanced. Bone remodeling is triggered to repair microdamage to the skeleton and serves to support calcium homeostasis by maintaining a normal serum calcium, releasing calcium from the bone into the blood stream as needed. Within an active bone remodeling unit, osteoclasts (bone resorbing cells) work to resorb bone during the resorptive phase, then this process reverses and osteoblasts (bone-forming cells) work to form bone during the formation phase. Osteoblasts then become incorporated into the bone matrix as osteocytes or cover the surface as lining cells, both with bone-communication activities. The unit then becomes inactive and enters a quiescent phase. If remodeling becomes unbalanced and bone resorption surpasses bone formation or if the phases become uncoupled and bone resorption occurs without adequate formation, a decrease in BMD results. Osteocytes and lining cells play key roles in the process and can trigger a new remodeling cycle.

FIGURE 112-2

Bone remodeling cycle. *(A)* Overview of remodeling process, Step 1 = initiation, Steps 2 and 3 = resorption, Step 4 = reversal, Step 5 = formation, and Step 6 = quiescence. *(B)* Molecular level detail of major pathways during bone resorption steps 2 and 3, which also showcase osteoporosis medication targets. *(C)* Molecular level detail of major pathways during bone formation steps 4 and 5, which also showcase osteoporosis medication targets.[14,17] (APC, adenomatous polyposis coli; BMP, bone morphogenetic protein; Ca^{++}, elemental calcium; cbfa1, core-binding factor alpha 1; Cbl, E3 ubiquitin ligase; Cl^{-}, chloride ion; Csk1α, casein kinase 1α Dkk-1, Dickkoff1; DSH, disheveled cytoplasmic protein; FAK, focal adhesion kinase; GSK-3β, glycogen synthase kinase-3β; H^{+}, hydrogen ion; IGF-1, insulin-like growth factor 1; LGR4, leucine-rich repeat-containing G protein; LRP5/6, lipoprotein-receptor–related protein 5 or 6; m-CSF, macrophage-colony-stimulating factors; Mg^{++}, magnesium; MMP, matrix metalloproteinases; NF-kβ, nuclear factor kappa beta; NCP, noncollagenous proteins; OPG, osteoprotegerin; Phos, phosphorous; Pl3K, phosphatidylinositol 3-kinase; PPARγ, peroxisome proliferator-activated receptor; PTH, parathyroid hormone; PTH1R, PTH and PTHrP receptor; PTHrP, parathyroid hormone-related protein; RANK, receptor activator of nuclear factor-kβ; RANKL, receptor activator of nuclear factor-kβ ligand; RunX2, runt-related transcription factor; Scr, nonreceptor tyrosine kinase; sFRP, secreted frizzled-related proteins; TCF/LEF, T cell specific transcription factor 4/lymphoid enhancer factor 1; TRACP 5b, tartrate-resistant acid phosphate isoenzyme 5; TRAF-6, tumor necrosis factor receptor associated factor 6; WIFI, Wnt inhibitory factor 1; WISE, Wnt modulator insurface ectoderm; Wnt, wingless tail ligands.)





Three schemas show the overview and molecular level details of the bone remodeling cycle. Schema (A) on the top gives the overview of remodeling process with the six steps involved in bone remodeling: Step 1 = initiation, Step 2 and 3 = resorption, Step 4 =reversal, Step 5 = formation, and Step 6 = quiescence. The schema (B) in the middle gives the molecular level detail of major pathways during bone resorption (mainly steps 2 and 3). The schema (C) at the bottom gives the molecular level detail of major pathways during bone formation (mainly steps 4 and 5). Hence, steps 2 to 5 are also points of osteoporosis medication targets. A mature osteoclast is formed from hematopoietic stem cell under the action of receptor activator of nuclear factor kappa β ligand (RANKL), interleukins 1 and 6 (IL-1, IL-6), macrophage colony stimulating factor (m-CSF), parathyroid hormone (PTH), parathyroid-releasing protein (PTHrP), 1,25(OH) vitamin D, tissue growth factor-β (TGF-β), prostaglandin E2 (PGE_2), insulin-like growth factor (IGF), sclerostin, integrins, platelet-derived growth factor, bone morphometric proteins (BMP), fibroblast growth factor (FGF), and tumor necrosis factor-α (TNF-α).

The signaling of the bone remodeling cycle through the steps from resorption through quiescence is highly complex.[14,17] Many cytokines, growth factors, and hormones influence each step. The complete physiology of bone remodeling is not fully known but appears to begin with signals from lining cells or osteocytes that are triggered by stress, microfractures, biofeedback systems responsive to cytokines and growth factors and potentially certain diseases and medications (see Fig. 112-2B, step 1). A major stimulus for hematopoietic stem cell differentiation to become mature osteoclasts is the receptor activator of nuclear factor kappa β ligand (RANKL), which is a cytokine emitted from osteoblasts or osteocytes in step 2. IL-1, IL-6, m-CSF, PTH through RUNX2/cbfa1, PTHrP, 1,25(OH) vitamin D, TGF-β, PGE_2 IGF, sclerostin, and TNF-α stimulate RANKL release, whereas estrogen and calcitonin inhibit RANKL release. RUNX2/cbfa1 also inhibit osteoprotegerin. The RANKL then binds to the receptor activator of nuclear factor kappa β

(RANK) on the surface of osteoclast precursors initiating differentiation. The RANKL also stimulates mature osteoclast activation and bone adherence via $\alpha_v\beta_3$ integrins to resorb bone (step 3). This step is influenced by TGF-β, IGF 1 and 2, platelet-derived growth factor, BMP, and FGF. After bone attachment, the osteoclasts secrete hydrogen and chloride ions and proteinases, such as cathepsin K, collagenase, gelatinase, tartrate-resistant acid phosphate isoenzyme 5 (TRACP5b), and matrix metalloproteases (MMP) to dissolve the mineralized bone. Hydrogen ion production is under nonreceptor tyrosine kinase (Src) control, which needs to be bound to other compounds such as E3 ubiquitin ligase (Cbl), focal adhesion kinase (FAK), and phosphatidylinositol 3-kinase (Pl3K).

After bone is resorbed and a cavity is created, osteoclasts produce cytokines and growth factors to elicit osteoblast differentiation from mesenchymal stem cells, maturation, and activity (step 4).[14,17] Osteoblast differentiation can be inhibited by PPARγ, which directs mesenchymal cell maturation to adipocytes instead of osteoblasts. However, leptin produced by adipocytes can stimulate bone formation. Mature osteoblasts and osteocytes produce osteoprotegerin (OPG) that binds to RANKL, thereby stopping bone resorption. Leucine-rich repeat-containing G protein (LGR4) also binds RANKL and stops resorption.

The process of bone formation is complicated (see Fig. 112-2C).[14,17] First, wingless tail ligands (Wnt) bind to low-density lipoprotein receptor–related protein 5 or 6 (LRP5/6) and a frizzled coreceptor. Wnt binding is influenced by PTH and PTHrP, which fit into the same receptor PTH1R, IGF-1, and irisin, which is increased during exercise. Next, LRP5/6 binds to disheveled cytoplasmic protein (DSH), which then binds to axin. Axin now cannot bind to glycogen synthase kinase-3β (GSK-3β), thereby preventing degradation of β-catenin by casein kinase 1α (Csk1α) (step 5). Irisin also increases β-catenin. Accumulated β-catenin then enters the nucleus and binds to T-cell-specific transcription factor 4/lymphoid enhancer factor 1 (TCF/LEF). This complex signals target genes to create proteins to fill the resorption cavity with osteoid. Growth hormone and IGF-1 also increase bone collagen production. Next mineralization of bone with calcium, magnesium, and phosphorus follows to give the new matrix strength.

Once the cavity is mineralized, bone formation can be stopped through multiple signaling processes.[14,17] Secreted frizzled-related proteins (sFRP) or Wnt inhibitory factor 1 (WIF1) can bind to Wnt, preventing it from binding to LRP 5/6. Both sclerostin and Dickkopf-1 (Dkk-1 or Kremen) are secreted from osteocytes and bind to LRP5/6, which also prevents Wnt from binding with LRP 5/6. Axin can then bind to adenomatous polyposis coli (APC), Csk1α, and GSK-3β, which then can cause β-catenin degradation, osteoblast apoptosis, and the end of osteoblastic activity (step 6). The mature osteoblasts can become lining cells or osteocytes.

Quiescence is the phase when bone is at rest until another remodeling cycle is initiated.[14,17] Later, osteocytes can trigger initiation of a new remodeling cycle through secretion of sclerostin or RANKL to stimulate osteoclasts and bone resorption.

Hormones can influence the remodeling steps. Estrogen has many positive effects on the bone remodeling process in people of both genders. Most of estrogen's actions help to maintain a normal bone resorption rate.[26] Estrogen suppresses the proliferation and differentiation of osteoclasts and increases osteoclast apoptosis. Estrogen decreases the production of several cytokines that are potent stimulators of osteoclasts, including IL-6, IL-7, IL-17, TNF-α, and m-CSF, and increases IL-4, IL-10, TGF-β, and TGF-α, which increases osteoclast apoptosis. Estrogen also decreases RANKL and increases OPG to reduce osteoclastogenesis.

Most of testosterone's bone effects relate to its metabolism to estradiol and the above estrogen bone effects; however, testosterone does have some direct and indirect effects on osteoblasts.[13,27] Testosterone increases osteoblast proliferation and differentiation directly via the androgen receptor, and indirectly by increasing TGF-β, IGF-2, and decreasing IL-6 stimulation of osteoclasts. Testosterone also increases muscle strength, which can decrease falls leading to fractures. Leydig cells secrete insulin-like factor 3 (INSL3) that stimulates relaxin family peptide receptor 2 (RXFP2) thereby increasing osteoblast and osteocyte functions.[13] A 25-hydroxylase is also secreted that increases vitamin D metabolism to 25(OH) vitamin D.

Bone physiology has many genomic and genetic influences. Isolating one or a few genes for correction will unlikely resolve the problems in an aging population for whom osteoporosis is a common problem.[16] Genetic mutations do result in bone disorders such as osteoporosis, osteogenesis imperfecta, and juvenile idiopathic osteoporosis. Heredity is important since family history, especially of a hip fracture in a parent, is a strong risk factor for osteoporosis development and fracture.

At least 56 loci have been identified that influence BMD and 14 loci for fracture risk, ranging from impacts on bone resorption (RANKL, OPG) to formation (Wnt, LRP5, and sclerostin).[28,29] Calcium, vitamin D, and estrogen receptors are also under genetic influence. Studies are conflicting as to whether an association exists between response to currently available antifracture medications and genetic profiles. Genetic modulation is in its

infancy for osteoporosis prevention and treatment, but epigenomics and gene editing might lead to the creation of new medications and/or the ability to tailor medication choices to an individual's genetic profile.[29]

Calcium Homeostasis, Vitamin D, and Parathyroid Hormone

2 Calcium homeostasis is maintained by vitamin D and PTH, which influence calcium gastrointestinal (GI) absorption and renal reabsorption. Calcium absorption under normal conditions is approximately 30% and is improved with vitamin D sufficiency.[30,31] Calcium absorption is lower in the winter due to decreased exposure to required ultraviolet light that converts cholesterol in the skin to vitamin D. Absorption is reported to be higher in obesity, which is associated with greater vitamin D storage. Calcium absorption is predominantly an active rate-limited process in the duodenum and jejunum, which is controlled by many hormones, such as 1,25-dihydroxyvitamin D (1,25[OH] vitamin D), estrogen, and transient receptor potential cation channel subfamily V member 6 (TRPV6). A calcium transporter (calmodulin or calbindin) is required to bring calcium from the gut into the tissue wall and then across the enterocyte. Calcium is extruded into the circulation via calcium (Ca^{++}) adenosine triphosphatase (ATPase) and the sodium-calcium exchanger. Throughout the intestine, paracellular passive calcium diffusion occurs. This diffusion accounts for less than 15% of absorbed calcium, is not rate limited, and possibility is sensitive to 1,25(OH) vitamin D. Solvent drag plays a minor role in calcium absorption.

When the calcium-sensing receptor on parathyroid cells detects low serum calcium, PTH production increases. PTH then directly (minimal effect) and indirectly (predominant effect via increasing calcitriol production) causes calcium reabsorption by the kidney.[30,32] Calcium reabsorption increases as 25(OH) vitamin D concentrations increase, plateauing around 10 to 15 ng/mL (mcg/L; 25-37 nmol/L). Loop diuretics decrease, and thiazide diuretics increase calcium resorption in the kidney.

Sometimes, the increased fractional calcium absorption is insufficient to maintain normal serum calcium, requiring bone resorption for correction.[30,31] Consistent and high concentrations of PTH and calcitriol increase RANKL and decrease OPG, resulting in increased osteoclast activity, which releases calcium from bone to restore calcium homeostasis. Of note, low PTH concentrations for a short time (eg, teriparatide) increase bone formation.

Active 1,25(OH) vitamin D concentrations depend on skin conversion, dietary and supplemental intake, and PTH control.[30,32] The sun's ultraviolet B rays convert 7-dehydrocholesterol in the skin to cholecalciferol (vitamin D_3), which is the most abundant vitamin D source. A few foods contain ergocalciferol (vitamin D_2). Supplements and multivitamins contain cholecalciferol or ergocalciferol. Subsequent conversion of cholecalciferol and ergocalciferol to 25-hydroxyvitamin D (25[OH] vitamin D; calcidiol) occurs in the liver, and then, PTH stimulates conversion of 25(OH) vitamin D via 25(OH) vitamin D-1α-hydroxylase (CYP27B1) to its final active form, 1,25-dihydroxyvitamin D (calcitriol; 1,25[OH] vitamin D), in the kidney. Calcitriol binds to the intestinal vitamin D receptor (VDR) and then increases the action of calcium-binding proteins calmodulin and calbindin. As a result, the intestinal absorption of calcium and phosphorus is increased. The feedback system is completed with CYP27B1 activity inhibited by adequate calcium and phosphorus, and FGF23 inhibiting PTH synthesis.

Postmenopausal Osteoporosis

2 Estrogen deficiency causes significant bone density loss and compromises bone architecture.[4,26,66] Estrogen deficiency increases proliferation, differentiation, and activation of new osteoclasts and prolongs survival of mature osteoclasts. Interleukins 7 and 17, TNF-α, and interferon γ increase and TGF-β decreases resulting in more RANKL and less OPG. Loss of estrogen also increases calcium excretion and decreases calcium gut absorption through decreases in TRPV6 activity and 1,25(OH) vitamin D binding proteins. Estrogen deficiency can also be seen in other settings such as anorexia nervosa and lactation, and from medications, such as prolonged depot medroxyprogesterone acetate implants, aromatase inhibitors, and gonadotropin releasing hormone agonists.

Accelerated bone loss of both mass and strength begins during perimenopause (1-5 years premenopause) and continues up to 10 years after menopause due to increased bone resorption that exceeds bone formation.[2] During this time, increased bone loss can be as high as 2% per year, with total BMD loss due to menopause about 10% to 12%.[4] About 30% of peak bone mass is lost by the age of 80 years. Bone strength decreases by about 2.5% per year.[9] The number of remodeling sites increases, and resorption pits are deeper and inadequately filled by normal osteoblastic function. During menopause, trabecular bone is most susceptible, leading predominantly to vertebral and wrist fractures. Initially, women with early menopause (ie, before the age of 40 years) due to natural or induced causes have lower BMD than matched premenopausal women. After the age of 70

years, risk for fractures and low bone density becomes the same between the groups.

Male Osteoporosis

2 Men lose about 0.8% of bone mass per year after the age of 60 years and 20% experience hypogonadism in their older adult years.[12] Men are at a lower risk for developing osteoporosis and osteoporotic fractures because of larger bone size, greater peak bone mass and connectivity, increase in bone width with aging, fewer falls, and shorter life expectancy. With aging, sex hormone binding globulin increases, which results in less free testosterone and thereby less testosterone available for conversion to estrogen. Estrogen inhibits bone resorption in men; however, androgen deficiency increases RANKL release and bone resorption. Mortality rate after a fracture is greater for men (19.5%) than women (12.5%).

Male osteoporosis results from aging or secondary causes (see Tables 112-2 and 112-3).[12,13,27] The most common risk factors for men are smoking, alcohol abuse, low body weight, weight loss, age, long-term glucocorticoid use, androgen deprivation therapy, and low testosterone concentrations. Medical conditions and medications that cause hypogonadism can increase bone loss. Although many causes and serious fracture outcomes, osteoporosis is underdiagnosed in men.

Age-Related Osteoporosis

2 Age-related bone mass and strength loss begin after peak bone mass is reached.[16] About 0.5%-1% of BMD is loss each year after the age of 30 years in men and until menopause for women.[4] Bone loss accelerates to 2% for 1 to 3 years before and 5 to 10 years post menopause before returning to normal aging bone loss.[4] After the age of 60 years, bone loss for both sexes is 1% to 1.5% per year.[8] Age-related osteoporosis occurs in older adults because of accelerated bone turnover rate and reduced osteoblast bone formation.[23,90] These bone changes occur from hormone deficiencies; calcium and vitamin D deficiencies due to changes in intake, absorption, and metabolism; decreased production or function of cytokines or other bone biochemicals; decreased molecular signaling; increase in redox status and free radical formation; increase in adipocytes; decreased body water; telomere shortening; and less exercise. Fracture risk for a given BMD value increases with aging.[8] For example, at a T-score of −2.5, a 50-year-old postmenopausal woman has about a 4% probability of a hip fracture, whereas a 70-year-old woman has about a 9% probability.[23] Hip fracture risk rises dramatically in older adults because of the cumulative loss of cortical and trabecular bone and an increased risk for falls.

Sarcopenia increases with aging with risk factors similar to osteoporosis.[14] The decrease in muscle strength and function results in weakness and balance instability leading to a greater likelihood of falls and fractures. Falls accounted for 87% of fractures in older adults.

Illness-Induced Secondary Causes of Osteoporosis

1 2 A secondary medical cause of osteoporosis is common (see Table 112-2). Symptoms, laboratory test results, certain diseases and medications, and/or a decreased Z-score from a DXA can suggest a secondary cause, warranting a more comprehensive workup.

Medication-Induced Secondary Causes of Osteoporosis

1 3 Medication-related reductions in BMD and associated fractures are a common secondary cause of osteoporosis. Table 112-3 lists select medications associated with bone loss and/or fracture risk as well as the proposed mechanisms of bone loss.[18-22] Alternative medications should be used when possible, with consideration given to patients' individual risk and baseline BMD status. When these medications cannot be avoided, periodic re-assessment of benefits and risks should be performed, as reversal of bone loss might be possible upon discontinuation of some of these medications. Two of the most common causes of medication-induced osteoporosis, glucocorticoids, and certain cancer chemotherapies are discussed later in this chapter.

CLINICAL PRESENTATION

Table 112-4 outlines the clinical presentation of osteoporosis. Osteoporosis is a silent disease, frequently not detected until a fracture is experienced or noticed on x-ray. Many vertebral fractures are asymptomatic, with patients sometimes attributing mild back pain to other factors, such as advanced age or work. Some new vertebral fractures present with moderate-to-severe back pain that can radiate down the leg. The pain usually subsides after 2

to 4 weeks; however, residual chronic back pain can persist. Multiple vertebral fractures decrease height and sometimes curve the spine (kyphosis or lordosis). Patients with a nonvertebral fracture frequently present with severe pain, swelling, and reduced function and mobility at the fracture site.

TABLE 112-4

Clinical Presentation of Osteoporosis

General • Many patients are unaware they have osteoporosis until testing or fracture. • Fractures can occur after bending, lifting, or falling, or independent of any activity.
Symptoms • Frequently asymptomatic • Pain • Immobility • Depression, fear, and low self-esteem from physical limitations and deformities
Signs • Shortened stature (>1.5 in. [4 cm] loss from maximum height; >0.8 in. [2 cm] loss in 1 year), kyphosis, or lordosis • Fragility (low-trauma) vertebral, hip, wrist, or forearm fracture
Laboratory tests • Routine tests: comprehensive metabolic profile (creatinine, calcium, phosphorous, electrolytes, alkaline phosphatase, and albumin), 25(OH) vitamin D, thyroid-stimulating hormone, complete blood count, total testosterone (for men), and 24-hour urine calcium and creatinine concentrations • Bone turnover markers (eg, serum NTX, serum CTX, and serum PINP) are sometimes used, especially to determine if high bone turnover exists • Additional testing if the patient's history, physical examination, or initial laboratory and or diagnostic tests suggest a specific secondary cause (eg, intact parathyroid hormone, free testosterone, serum parathyroid, and celiac panel)
Other diagnostic tests • Spine and hip bone density measurement using central dual-energy x-ray absorptiometry (DXA) • Vertebral fracture assessment (VFA) with DXA technology • Radiograph ordered for other reasons that shows low bone density • Radiograph to confirm fracture • Balance and mobility tests

CTX, C-terminal crosslinking telopeptide of type 1 collagen; NTX, N-terminal crosslinking telopeptide of type 1 collagen; PINP, procollagen type 1 N-terminal propeptide.

Data from References 2,4,6,10,21,33, and 34.

Consequences of Osteoporosis

Osteoporosis can lead to fragility/low-trauma fractures defined as fracture that occurs as a result of a fall from standing height or less or with minimal to no trauma.[2] Fractures of the vertebrae, hip, forearm, and humerus are considered major osteoporotic fractures, whereas other fractures are generally not considered osteoporosis-related. Osteoporotic fractures can lead to increased morbidity and mortality and decreased quality of life. Pain and physical deformity are common, and these changes can lead to other health consequences.[4] For example, severe kyphosis can lead to respiratory problems as a result of compression of the thoracic region and GI complications such as poor nutrition from intra-abdominal compression.

Depression is common because of fear of falling/fracture, pain, loss of self-esteem from physical deformity, and loss of independence and mobility after fracture.

Hip fractures are associated with the greatest increase in morbidity and mortality. After a hip fracture, 40% of patients have mobility limitations, 50% no longer can live independently or require long-term care (25%), and about 12% to 20% die within the year from complications of the hip fracture or other comorbid disease processes.[2,8] Men have a higher 1-year mortality rate after hip fracture than women.[12] People of color have greater morbidity and mortality after a fracture than non-Hispanic White people.[3]

Wrist fractures occur more commonly in younger postmenopausal women and are frequently a result of a fall on an outstretched hand. Although they cause less disability than other fracture sites, negative outcomes include prolonged pain and weakness, and difficulty with activities such as meal preparation, using a keyboard, and lifting at work.

Once a low-trauma fracture has occurred, the risk for subsequent fractures goes up exponentially.[8] Vertebral fractures, even if asymptomatic, are a major predictor of a future fracture with up to a five- to seven-fold increase in future vertebral fractures and an increased risk at other sites.[4] Patients with a hip fracture have a 2% to 10% chance of a second hip fracture.[4]

Patient Assessment

Laboratory tests and other assessments are described in Table 112-4. Height should be measured annually using a wall-mounted stadiometer. Low bone density (sometimes called osteopenia) reported on routine radiographs is a sign of significant bone loss and requires further evaluation for osteoporosis. Additional tests will be required that are specific to potential secondary causes (Tables 112-2 and 112-3). In addition to physical examination and laboratory tests, patients can be assessed with risk factor assessment tools, osteoporosis quality of life questionnaires, peripheral and central DXA, ultrasonography, and bone turnover markers (BTM).

Risk Factor Assessment

The aim of an initial osteoporosis risk assessment screening is to identify those patients who are at risk for osteoporosis and osteoporotic fractures (see Table 112-1) and/or would benefit from further evaluation or pharmacologic intervention. The most used assessment is the fracture risk assessment (FRAX) tool[2]; the Garvan tool[35] is another option.

4 The FRAX tool was created to be used for screening and diagnosis.[2] It can be used without DXA results; however, estimates improve when T-scores are available (https://frax.shef.ac.uk/FRAX/tool.aspx?country=9). This tool is free and uses 11 risk factors: age, race/ethnicity, sex, previous fracture, parent history of hip fracture, body mass index, glucocorticoid use (current use or past use for three or more months of the equivalent of at least 5 mg of prednisolone daily), current smoking, alcohol use of three or more drinks per day, rheumatoid arthritis, and select secondary causes of osteoporosis (see Table 112-1); with optional entry for femoral neck BMD (g/cm^2 or T-score). Trabecular bone score may be included in the most recent version of the tool. Some important risk factors for fracture, such as falls, multiple fractures, recent fracture, or other common secondary causes like type 2 diabetes, are not accommodated in the FRAX model. If a patient has type 2 diabetes, 'yes' can be checked for rheumatoid arthritis to model this additional risk.

The FRAX tool calculates an individual's percent probability of any major osteoporotic fracture and hip fracture in the next 10 years. For postmenopausal women younger than 65 years, a 10-year major osteoporotic fracture risk of greater than 8.4% would result in a referral for a central DXA.[2,36] Each country establishes cut-off points for fracture risk treatment decisions. For the United States, they are 20% or higher for major osteoporotic fracture and 3% or higher for hip fracture. Most guidelines use these universal cutoffs, but others are beginning to recommend age-adjusted FRAX cutoffs to prevent undertreatment of younger people and overtreatment of older people or create a middle zone in which BMD would be needed to determine treatment.[34] For example, for a 55-year-old person, a 10% 10-year risk of major osteoporotic fracture would be used, and for an 80-year-old person, 30% would be used.

To accommodate additional fracture risk factors, FRAXPlus, a fee-for-use prediction tool, is in beta testing (https://www.fraxplus.org/frax-plus). The new and/or adjusted risk factors are recency of osteoporotic fracture, higher than average exposure to oral glucocorticoids (greater than 7.5 mg daily), a new trabecular bone score calculation, number of falls in the previous year (options for 0, 1, 2, and 3 falls), duration of type 2 diabetes mellitus,

lumbar spine BMD, and hip axis length (longer than average).

The Garvan calculator uses four risk factors (age, sex, low-trauma fracture, and falls) with the option to also use BMD.[2,6,35] It calculates 5- and 10-year risk estimates of any osteoporotic/fragility fracture and hip fracture. This tool corrects some disadvantages of the FRAX tool since it includes falls and number of previous fractures, but it does not use as many other risk factors.

Screening Using Peripheral Bone Mineral Density Devices

Peripheral bone density devices that use DXA (pDXA) or quantitative ultrasonography (QUS) are helpful as screening tools to determine which patients require further evaluation with central DXA or for decision making if central DXA testing is not available.[2,36,37] Peripheral DXA of the forearm, heel, or finger uses a low amount of radiation and requires personnel with special training. Quantitative ultrasonography at the heel and other peripheral sites uses sound waves without radiation, and specially trained personnel are not needed. The heel is the only skeletal site at which QUS has been validated.[37] The QUS has better fracture predictive value than pDXA and has demonstrated the ability to predict fractures in postmenopausal women and in men 65 years of age or older. The specific peripheral T-score threshold for referral is not universally defined and varies by device. These tests should not be used for diagnosis or for monitoring response to therapy.[37]

Peripheral devices are considerably less expensive than central DXA, easy to use, portable, fast (less than 5 minutes), and can predict general fracture risk. They are popular for screening patients at health fairs and community pharmacies. Patients already identified as being at high risk for osteoporosis based on risk factors, fragility fracture, or secondary causes for osteoporosis should be referred for central DXA testing.

Central Dual-Energy X-Ray Absorptiometry

4 BMD measurements at the hip or spine can be used to assess fracture risk, establish the diagnosis and severity of osteoporosis, and confirm osteoporosis following a low-trauma fracture.[2,34] Multiple techniques are available for measurement of BMD and include DXA, quantitative computed tomography (QCT), digital x-ray radiogrammetry, and radiographic absorptiometry. Central DXA is the most widely used technique and preferred for making therapeutic decisions.[37] It has high precision, short scan times, low-radiation dose (comparable to the average daily dose from natural background), and stable calibration. Measurements of lumbar spine, femoral neck, and total hip BMD are recommended with the lowest BMD value used for diagnosis. The forearm (distal third of the radius) can be used as an alternative if the preferred areas cannot be scanned.[2,4,34,37] Trabecular bone score (TBS) is a newer technology available on some densitometers that can provide measurements of bone quality and microarchitecture. Low TBS is independently associated with increased fractures and can be used in combination with BMD and FRAX scores to better identify those at increased fracture risk.

Several consensus guidelines and position statements are consistent in recommending central BMD testing for all women aged 65 years or older, men aged 70 years or older, postmenopausal women younger than 65 years and men 50 to 69 years old with risk factors for fracture, and patients with an identified secondary cause for bone loss.[2,4,12,37] The US Preventive Services Task Force (USPSTF) provides similar recommendations for screening in women 65 years or older and in women under the age of 65 years with additional risk factors as determined by a clinical risk assessment tool, such as FRAX.[36] This group, however, has concluded that current data are insufficient to make recommendations for screening in men. Patients with a fragility fracture do not need a DXA for an osteoporosis diagnosis, but the results are helpful for determining the severity of osteoporosis and as a baseline for monitoring response to therapy.[2] The DXA results can also help patients make decisions about the need for lifestyle changes and prescription osteoporosis medications. In the absence of a suspected or known secondary cause for osteoporosis or a history of a low-trauma fracture, central BMD testing is not recommended for children,[15] women,[38] or men younger than 50 years.[13]

A central DXA BMD report provides the actual bone density value (in g/cm^2), T-score, and Z-score.[37] The T-score is used for diagnosis and is a comparison of the patient's BMD to the mean BMD of a healthy, young (20-29 year olds), and sex-matched White reference population. It is not adjusted for age, race, or ethnicity. The T-score is the number of standard deviations from the mean of the reference population.[37] The Z-score is similar but compares the patient's BMD to the mean BMD for a healthy sex- and age-matched population. The patient's race and ethnicity should be used for the Z-score if available. The Z-score is sometimes helpful in determining whether a secondary cause for osteoporosis is present and is used for diagnosis (value ≤ −2.0) in children, premenopausal women, and men younger than 50 years. The actual bone density value is most useful for serial monitoring of therapy response. Follow-up BMD is recommended every 1 to 3 years by some guidelines,[2,4] although other guidelines recommend every 5 years in

postmenopausal women.[1,34] The DXA results after medication initiation need to be above the machine's least significant change to be clinically relevant. For patients with normal bone density or those in the upper range of low bone mass, time between follow-up scans can be lengthened. Most insurance carriers, including Medicare, cover BMD testing every 2 years.

Using the spine DXA image, a VFA can be performed to assess for vertebral fractures that might otherwise go undetected.[2,4,37] Each vertebra is visually evaluated for fracture and fractures are assessed for severity. This result becomes important for treatment decisions in patients with low bone mass. Because many vertebral fractures are asymptomatic, VFA is recommended for those at high risk of an undiagnosed vertebral fracture. This includes patients with a T-score less than −1.0 when one or more of the following criteria are also present: women aged at least 70 years or men aged at least 80 years; a historical height loss of more than 1.5 in. (4 cm); a self-reported but undocumented prior vertebral fracture; or patients on glucocorticoid therapy (≥5 mg prednisone or equivalent daily for 3 months or more).

Laboratory Tests

Routine laboratory testing (see Table 112-4) is used for initial bone health assessment.[2,4,10,12,15] To evaluate secondary causes, additional testing is conducted, which will be specific to the suspected secondary cause.

Bone Turnover Markers

BTM are commonly used in clinical trials and sometimes in clinical practice.[2,4] They can be used to assess bone pathophysiology, predict fracture risk, monitor response to osteoporosis medications, evaluate medication adherence, and determine the need for restarting bisphosphonates after a drug holiday. Although many BTMs exist, serum carboxyterminal propeptide of type-I collagen (PINP) and bone-specific alkaline phosphatase (BSAP) are the preferred bone formation markers, and serum C-terminal telopeptide type-1 collagen (CTX) is the preferred bone resorption marker. Response to osteoporosis therapy can be measured with BTMs as early as 2 to 3 months; however, monitoring is usually done 3 to 6 months after osteoporosis medication initiation. Goal values would be at or below median premenopausal concentrations for antiresorptive medications and significant increase for formation medications.[2] Circadian variability, seasonal variations, food intake, recent exercise, some diseases and conditions, and assay variability can affect results and decrease utility in clinical practice. Fasting morning samples should be obtained with repeat tests done at the same facility with the same assay to decrease interassay variability. Of note, fractures increase BTMs for a short time frame. These tests can be expensive with coverage varying by health insurance plan. As an alternative, bone-specific alkaline phosphatase can be used, which is usually covered.

Diagnosis of Osteoporosis

6 The diagnosis of osteoporosis is based on a low-trauma fracture or femoral neck, total hip and/or spine DXA using World Health Organization (WHO) T-score thresholds.[2] Low bone mass (preferred term) or osteopenia is a T-score between –1 and –2.5, and osteoporosis is a T-score at or below –2.5. Although these definitions are based on data from postmenopausal white women, they are also applied to perimenopausal women, men aged 50 years and older, and adults from different races and ethnicities. The diagnosis of osteoporosis in children,[15] premenopausal women,[11] and men under 50 years of age[13] should be based on a Z-score at or less than –2.0 in combination with other risk factors or fracture. Without a history of clinically significant fracture, children, premenopausal women, and men are given a diagnosis of bone mass below the expected range for age.

PREVENTION AND TREATMENT

Desired Outcomes

The primary goal of osteoporosis care should be prevention. Optimizing skeletal development and peak bone mass accrual in childhood, adolescence, and early adulthood will ultimately reduce the future incidence of osteoporosis. Once low bone mass or osteoporosis develops, the objective is to improve or stabilize bone mass and strength, and prevent fractures. In patients who have already suffered osteoporotic fractures, reducing pain and deformity, improving functional capacity, improving quality of life, and reducing future falls and fractures are the main goals.

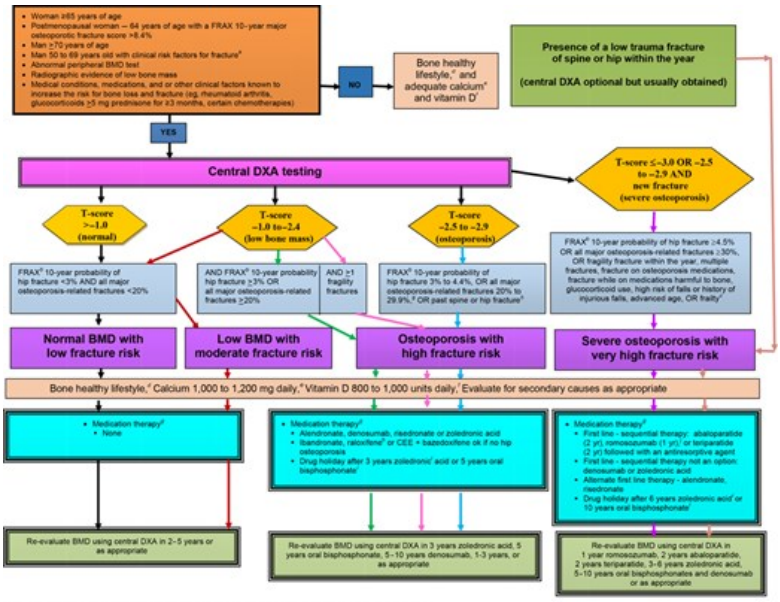
General Approach to Prevention and Treatment

5 6 A bone-healthy lifestyle should begin at birth and continue throughout life. The foundation of osteoporosis prevention and treatment is a

bone-healthy lifestyle. Supplements and medications are used when lifestyle habits are insufficient or suboptimal, osteoporosis has developed, and/or a low-trauma fracture occurs. Guidelines and position statements recommend considering prescription therapy in any postmenopausal woman or man aged 50 years and older presenting with one of the following scenarios: a hip or vertebral fracture; T-score of −2.5 or lower at the femoral neck, total hip, or spine; or low bone mass (T-score between −1.0 and −2.5 at the femoral neck, total hip, or spine) with a FRAX 10-year probability of hip fracture of 3% or more or any major osteoporosis-related fracture of 20% or more. Figure 112-3 provides an osteoporosis management algorithm for postmenopausal women and men aged 50 years and older that incorporates both nonpharmacologic and pharmacologic approaches.

FIG. 112-3

Algorithm for osteoporosis management in postmenopausal women and men 50 years of age and older. [a]Major clinical risk factors for fracture: advanced age, current smoker, low body weight or body mass index, personal history of fracture as an adult (after age 50 years), history of osteoporosis/low trauma fracture in a first-degree relative, excessive alcohol intake. [b]Some providers use age adjusted FRAX thresholds versus set thresholds for all age groups. [c]Fragility fracture is high risk for ES guidelines, and very high risk for AACE/ACE guideline. [d]Bone-healthy lifestyle includes well-balanced diet with adequate calcium, vitamin D, and protein intakes; smoking cessation; limited alcohol intake; weight-bearing/resistance exercises; and fall prevention. [e]Dietary calcium preferred. If diet is inadequate, supplement as necessary. [f]Higher vitamin D doses might be needed to achieve 25(OH) vitamin D concentrations > 30 ng/mL. [g]Some increased BMD effects will be seen for women using menopausal hormonal therapy and for men using testosterone for hypogonadism. For women and men on hormonal therapy and at high risk or very high risk for osteoporotic fractures, an osteoporosis medication will also be prescribed, creating a case for combination therapy. [h]Bisphophonates are low in cost and thus favored over denosumab [i]Raloxifene option for postmenopausal women < 60 years old with low hip fracture, stroke, and venous thromboembolic risk and high breast cancer risk. [j]Restart therapy when BMD goes below T-score ≤ -2.5 or a fracture; alternative is to use raloxifene or denosumab, or in some cases a bone formation medication during the drug holiday. [k]Do not use romosozumab in patients with at high risk for or past myocardial infarction and/or stroke. (BMD, bone mineral density; CEE, conjugated equine estrogens, DXA, dual-energy x-ray absorptiometry, FRAX = World Health Organization fracture risk assessment tool) *Data from references 1,3,7,42,43*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Nonpharmacologic Therapy

Nonpharmacologic therapy, referred to as a bone-healthy lifestyle, includes proper nutrition, moderation of alcohol intake, smoking cessation, exercise, and fall prevention. A bone-healthy lifestyle that is employed early in life will help to optimize peak bone mass, and if continued throughout life, it will minimize bone loss over time. A bone-healthy lifestyle not only maintains or increases BMD but it also helps decrease falls and fragility

fractures.

Diet

5 Overall, a diet well balanced in nutrients and minerals with limited salt, alcohol, and caffeine use are important for bone health. Adequate amounts of calcium and vitamin D have documented impacts on bone health. Protein is required for bone, thus the recommended dietary allowances (RDAs) of 0.8 g/kg body weight per day is recommended for adults increasing to 1 to 1.2 g/kg body weight in older adults and to 1.5 g/kg body weight for some chronic illnesses.[8] Magnesium, boron, and vitamin K have a physiologic role in bone development and maintenance but either no or insufficient data exist to establish them independently as supplemental agents for prevention and treatment of osteoporosis. Some of these agents are included in calcium combination products and are found in multivitamins. Strontium ranelate has documented positive bone effects and is marketed in Europe for prevention of osteoporosis.

Eating disorders are associated with increased bone loss and fractures.[11,15] Being thin or having anorexia nervosa are well known to decrease bone mass. In the past, obesity was thought protective due to increased estrogen production and stimulation of bone remodeling due to weight bearing; however, emerging literature suggests adipocytes have negative impacts on bone health.

Calcium

5 7 Adequate calcium intake is necessary for calcium homeostasis throughout life, bone development during growth, and bone maintenance thereafter. The Institute of Medicine (IOM) recommended calcium intakes are based on age and gender (Table 112-5).[2,34,39] These values represent the average daily amount needed to meet requirements for 97% to 98% of healthy people. Higher intakes might be needed when concomitant diseases and medications known to negatively affect calcium and vitamin D homeostasis exist. Ingesting calcium-containing and/or calcium-fortified foods and beverages is the preferred method to achieve daily calcium requirements. Dairy products generally have the highest amount of calcium per serving and are available in low-fat options. Some food sources result in good calcium absorption but have low elemental calcium content (eg, broccoli). Carbohydrates increase calcium absorption, whereas phylates (eg, beans, seeds, wheat bran) and oxalates (eg, spinach and rhubarb) decrease absorption.[6,35]

TABLE 112-5

Calcium and Vitamin D Recommended Dietary Allowances (RDAs) and Tolerable Upper Intake Levels (ULs)

Group and Ages	Elemental Calcium RDA (mg)	Calcium Tolerable Upper Intake Level (mg)	Vitamin D RDA (units)[a]	Vitamin D Tolerable Upper Intake Level (units)
Infants				
Birth to 6 months	200[b]	1,000	400[b]	1,000
7-12 months	260[b]	1,500	400[b]	1,500
Children				
1-3 years	700	2,500	600	2,500
4-8 years	1,000	2,500	600	3,000
9-18 years	1,300	3,000	600	4,000
Adults				
19-50 years	1,000	2,500	600[b,c]	4,000
51-70 years (men)	1,000	2,000	600[b,c]	4,000
51-70 years (women)	1,200	2,000	600[b,c]	4,000
>70 years	1,200	2,000	800[b,c]	4,000

[a]Some guidelines recommend intake to achieve a 25(OH) vitamin D concentration of >30 ng/mL (mcg/L; 75 nmol/L),[1,3,8] which is higher than the Institute of Medicine goal of >20 ng/mL (mcg/L; 50 nmol/L).[40]

[b]Adequate intake (evidence insufficient to determine an RDA).

[c]Guidelines recommend 800-1,000 units[1] or 1,000-2,000 units[3,8] for adults with osteoporosis.

Data from References 2,34, and 39.

People should be encouraged to evaluate their food and beverage intake to determine if they are receiving adequate amounts of calcium. To calculate the amount of calcium in a serving of food, consumers can add a zero to the percent of the daily value listed on food labels. For example, a serving of milk (8 oz. [~240 mL]) has 30% of the daily value of calcium. This translates to 300-mg calcium per serving. Websites can be used to identify foods and beverages high in calcium.[31]

Although many foods and beverages are high in calcium, the average daily dietary calcium intake is insufficient in many children and adults.[31] In addition, lactose intolerance limits dietary calcium intake. The incidence in Asian Americans (15%-100%), Native Americans (79%), African Americans

(75%), and Hispanic Americans (51%) are higher than in White Americans (21%).[41] Patients with lactose-intolerance have several options to increase dietary calcium intake, including products containing lactase (Lactaid®), lactose-reduced milk, lactose-free milk, calcium-fortified milk alternatives (eg, soy and almond milk), certain aged cheeses, or yogurt with active cultures along with other nondairy calcium-fortified products (eg, orange juice, breakfast cereals, and energy bars). Vegan diets sometimes have insufficient calcium intake, but products such as tofu, calcium-fortified milk alternatives, and juices can be used. When diet cannot be enhanced to achieve adequate intakes, calcium supplements will be required.

Vitamin D

5 8 Table 112-5 also lists the IOM recommended adequate intakes for Vitamin D.[2,34,39] The three main sources of vitamin D are sunlight (conversion of 7-dehydrocholesterol to vitamin D3), diet, and supplements. Vitamin D3 comes from oily fish, eggs, and fortified dairy products. Vitamin D2 comes from fungi and eggs (chickens given vitamin D2 in their diet). Websites can be used to identify the few foods high in vitamin D.[42] To calculate the amount of vitamin D in a serving of food, consumers can multiply the percent daily value of vitamin D listed on the food label by 4 (eg, 20% vitamin D = 80 units).

The overall prevalence of hypovitaminosis D (<20 ng/mL [mcg/L; 50 nmol/L]) in American adults has been estimated at 29%; with higher prevalence ratios observed in those who are older than 60 years, from a minority, have lower education levels, obese, physically inactive, and/or current smokers.[43] Low vitamin D concentrations can result from insufficient intake, dietary fat malabsorption, decreased sun exposure, decreased skin production, and/or decreased liver and renal metabolism. Endogenous synthesis of vitamin D can be decreased by factors that affect exposure to or decrease skin penetration of ultraviolet B light rays. Sunscreen use, full body coverage with clothing (eg, women wearing veils and full-length dresses), and darkly pigmented skin can all decrease vitamin D production. Seasonal variations in vitamin D concentrations are also seen with nadirs in late winter and peaks in late summer. Because few foods are naturally high or fortified with vitamin D, most people, especially older adults, require supplementation to achieve IOM recommended adequate intakes.

Isoflavones

5 Phytoestrogens (isoflavones, lignans, and coumestans) are plant-derived compounds that possess weak estrogenic agonist and antagonist effects throughout the body. Isoflavones are found in soy products, lignans in seeds, berries, and grains, and coumestans in peas, beans, broccoli, and alfalfa sprouts. Genistein and daidzein are biologically active isoflavones found in soybeans. Isoflavones, genistein, and daidzein are also available as single-agent or combination supplements. Isoflavones produce estrogenic activity and increase IGF-1. The evidence supporting a positive bone benefit from phytoestrogen intake is conflicting with most studies showing little or no effect. The effect is greater on trabecular bone. Doses and products studied are quite varied with potentially more BMD activity with higher doses. Spine but not hip BMD is increased in some studies when compared to placebo. Isoflavones from soy foods appear safe; however, more information is needed, especially in women with breast cancer and for isoflavone supplements versus food sources.[44]

Alcohol

3 Chronic and excessive but not moderate alcohol consumption is associated with an increased risk for osteoporosis and fractures.[2,45] Alcohol increases bone resorption by increasing RANKL and decreases bone formation by inhibiting Wnt signaling pathway and increasing oxidative stress that results in osteoblast apoptosis. Patients with alcohol-use disorder might also have poor nutrition, decreased calcium absorption, altered vitamin D metabolism, estrogen inhibition, decreased testosterone production, chronic liver disease, and balance impairments resulting in more falls and fractures. Typical recommendations for alcohol consumption should be suggested, which are not to exceed 2 drinks per day for women and 3 drinks per day for men.

Caffeine and Tea

5 Although results are conflicting, excessive caffeine consumption is associated with increased calcium excretion, increased rates of bone loss, and a modestly increased risk for fracture.[45] Greater negative effects are seen in women. Ideally, caffeine consumption should be limited to two servings or less per day. For those with greater intakes, the increased calcium excretion might be compensated by additional calcium intake. Chronic tea drinking might have a positive benefit on bone mass, but no fracture outcomes exist.

Smoking

Cigarette smoking is an independent risk factor for osteoporosis and is associated with increased relative risk for fracture at all sites.[46] The effect is dose- and duration-dependent, but even passive smoking shows adverse effects on BMD. The negative bone effects are associated with reduced intestinal calcium absorption, lower 25(OH) vitamin D concentrations possibly due to increased hepatic metabolism, an increase in bone resorption from a decrease in production and increase in metabolism of estradiol leading to an increase in RANKL and decrease in OPG, decrease in osteoblasts and bone formation secondary to increase in cortisol and dehydroepiandrosterone sulfate, and impairment of osteoid production and mineralization.[16,46] The detrimental effects of smoking on physical function and balance can contribute to an increased risk of falls. Per guidelines, counseling patients of all ages on smoking cessation can help to optimize peak bone mass, minimize bone loss, and ultimately reduce fracture risk[2]; however, few studies have explored these outcomes.[46]

Exercise

Physical activity or exercise is an important nonpharmacologic approach to preventing osteoporotic fractures. Exercise increases bone mechanical strain, especially in weaker bone, thus stimulating osteocytes leading to bone resorption and then new stronger bone formation.[9] Weight-bearing exercise inhibits myostatin, which increases muscle and bone mass and decreases fat mass, and sclerostin and Dickoff-1, which prevents them from stopping bone formation.[17] Irisin is increased by exercise leading to increased bone formation by stimulating runX2, LRP 5/6, and β–catenin. Exercise can decrease the risk of falls and fractures by stabilizing bone density and improving muscle strength, coordination, balance, and mobility.[2,14,16,47] Physical activity is especially important early in life since peak bone mass is gained at that time and lack of exercise during growth can lead to suboptimal loading/straining, decreased stimulation of bone deposition, and reduced peak bone mass.[9] Although bone mass might not increase, bone strength will increase in older adults. All people of any age who are medically fit should be encouraged to perform a moderate-intensity weight-bearing activity (eg, running), plyometric (eg, jumping, hopping, bounding), and resistance activity (eg, weight machines, free weights, or elastic bands). Walking, swimming, cycling, and yoga have less impact on osteogenics but are still important. People at risk of osteoporosis should participate in exercise, including weight-bearing activities, at least three to four times weekly for 30 to 40 minutes per session. Adult recommendations for exercise from the American Heart Association can be suggested, which are 150 minutes of moderate-intensity aerobic exercise weekly or 75 minutes of vigorous-intensity exercise per week, and moderate- to high-intensity muscle strengthening at least twice a week.[48]

Fall Prevention

Risk of falling increases with advanced age predominantly as a result of balance, gait, and mobility problems, poor vision, reduced muscle strength, impaired cognition, multiple medical conditions (eg, arrhythmias, postural hypotension, Alzheimer's disease, and Parkinson disease), and polypharmacy (especially psychoactive, cardiovascular, diabetes, seizure, and pain medications).[2,24] The ability to adapt to falls also decreases with aging. Older adults are more likely to sustain a hip or pelvic fracture because they tend to fall backward or sideways instead of forward.

Because of the link between falls and fractures, all older adults should be asked at least annually if they have fallen. The US Centers for Disease Control and Prevention have created an assessment tool.[49] If an older adult scores 4 or more, a comprehensive falls assessment should be conducted. Many other assessment tools exist to evaluate falls.

Generally, intervention programs that are multifactorial have greater effects on decreasing falls, fractures, other injuries, and nursing home and hospital admissions than single interventions.[24,40,47,50] Medication profiles should be reviewed for any unnecessary medications that can affect cognition and balance, and potentially increase fall risk. Consideration should be given to deprescribing or substitution with safer medications. Although Vitamin D supplementation has been advocated to reduce falls and fractures in some guidelines, the most recent USPSTF recommendation states the evidence is inadequate to prescribe this therapy for fall and fracture prevention. Maintenance of a regular individualized exercise program, such as tai chi, resistance training, and strengthening, should be recommended to improve body strength, balance, and agility. Other recommendations include resolving heart rate/rhythm irregularities, low blood pressure, and vision and foot problems, and using proper footwear. A home environment safety assessment is helpful to identify environmental solutions to decrease falls.[24,40,51] External hip protectors are specialized undergarments designed to pad the area surrounding the hip, decreasing the force of impact from a sideways fall.[8] Conflicting results and poor adherence limit their use. Many patient education materials exist with the US Centers for Disease Control and Prevention older adult falls prevention

program being an excellent resource for patients and providers.[40]

Vertebroplasty and Kyphoplasty

During vertebroplasty and kyphoplasty cement is injected into fractured vertebra(e) for patients with debilitating pain from vertebral compression fractures. Although used to stabilize damaged vertebrae, reduce pain, and decrease opioid intake, this therapy is decreasing based on results showing effects that are similar to sham interventions, being short-term, and having no major pain benefit, and or are associated with vertebral fracturing around the cement, cement leakage into the spinal column, and nerve damage (rare).[52] The AACE/ACE guideline lists vertebral augmentation as an uncertain therapy due to limited data, potential for adverse treatment outcomes, and lack of long-term effects.[2]

Pharmacologic Therapy

9 Because nonpharmacologic interventions alone are frequently insufficient to prevent or treat osteoporosis, medication therapy is often necessary. Osteoporosis medication effects on fracture risk and BMD (Table 112-6), dosing (Table 112-7), and adverse effects and monitoring (Table 112-8) are described. Medication use should be combined with a bone-healthy lifestyle. People of color were less likely to receive osteoporosis prescription medications[3]; thus, health disparities need to be resolved to provide osteoporosis prevention to all women and men.

TABLE 112-6

Fracture and Bone Mineral Density Effects of Osteoporosis Medications from Pivotal Fracture Trials[a] in Postmenopausal Women

Medication	Vertebral Fracture	Nonvertebral Fracture	Hip Fracture	% Change in Spine BMD[b]	% Change in Hip BMD[b,c]
Abaloparatide	86%↓	43%↓	↔	10.4%↑	4.3%↑
Bazedoxifene	35%-42%↓	↔[d]	↔	2.1-3.0%↑	0.5%↑
Bazedoxifene with conjugated equine estrogens	ND	ND	ND	0.24%-1.6%↑	0.2%-1.5%↑
Bisphosphonates	41%-70%↓	20%-38%↓[e]	28%-50%↓[f]	3.1%-6.0%↑	1.8%-4.0%↑
Calcitonin	33%↓	↔	↔	3%↑	↔
Denosumab	68%↓	20%↓	40%↓	9.2%↑	6.0%↑
Estrogen with or without a progestogen	33%-40%↓	13%-27%↓	30%-50%↓	3.5%-7%↑[f]	1.7%-5%↑[g]
Raloxifene	30%-68%↓[h]	↔	↔	2.6%↑	2.1%↑
Romosozumab	73%↓	ND/19%↓[i]	ND/38%↓[i]	11.3%-13.7%↑[g]	4.1%-6.9%↑
Teriparatide	65%↓	53%↓	↔	8.6%-9.7%↑	3.5%↑

[a]Fracture reductions are relative risk reductions, no head to head fracture studies except for raloxifene and bazedoxifene. Data should only be used for relative between class comparisons. Clinical trials have different patient samples and study designs. Most pivotal fracture trials were of 3-year duration except for abaloparatide (2 years), romosozumab (1 year) and teriparatide (18 months) studies.

[b]Relative to placebo; may vary based on duration of therapy and timing relative to menopause.

[c]Total hip (alendronate, ibandronate, zoledronic acid, bazedoxifene, denosumab, estrogen, abaloparatide, teriparatide, romosozumab) or femoral neck (calcitonin, estrogen, risedronate, and raloxifene).

[d]50% decreases in nonvertebral fractures in subgroup of high-risk postmenopausal women (very low BMD and/or previous fractures).

[e]Risedronate and zoledronic acid only; nonvertebral fracture reductions with ibandronate were not significant.

[f]Alendronate, risedronate, and zoledronic acid only; hip fracture data not reported with ibandronate.

[g]Data obtained from nonpivotal fracture trials.

[h]Includes data from a pivotal bazedoxifene trial with raloxifene as one of the comparators.

[i]Second year results after 1 year of romosozumab followed by alendronate or denosumab for 1 year.

[j]Includes data from teriparatide versus romosozumab study.

%, percent; BMD, bone mineral density; ↓, decrease; ↑, increase; ↔, no significant change; ND, no data.

Data from References 1,2,4,39, and 53-56.

TABLE 112-7

Dosing of Medications for Osteoporosis

Medication	Brand Name	Dose	Comments
Antiresorptive Medications—Nutritional Supplements			
Calcium	Various	Adequate daily intake*: IOM:* 200-1,200 mg/day, varies per age; see Table 112-5); supplement dose is the difference between required adequate intake and dietary intake. Immediate-release doses should be <500-600 mg.	Recommend food sources first to achieve goal intake. Available in different salts including carbonate and citrate, absorption of other salts not fully quantified. Different formulations including chewable, liquid, gummy, softgel, drink, and wafer; different combination products. Review package to determine number of units per serving size and desired amount of elemental calcium. Give calcium carbonate with meals to improve absorption.
Vitamin D D3 (cholecalciferol) D2 (ergocalciferol)	**Over the counter** • Tablets, 400, 1,000, and 2,000 units • Capsules, 400, 1,000,	Adequate daily intake: IOM: 400-800 units/day to achieve adequate intake (see Table 112-5); guidelines: 800-2,000 units orally daily; if low 25(OH) vitamin D concentrations, malabsorption, or altered metabolism higher doses (>2,000 units daily) might be required. Vitamin D deficiency: 5,000 units or higher daily preferred over 50,000 units orally once to twice weekly for 8-12 weeks; repeat as needed. Higher doses until therapeutic	Vegetarians and vegans need to read label to determine if the vitamin D source is plant-based. Slight advantage of D3 over D2 for increasing serum 25(OH) vitamin D concentrations. For drops, make sure measurement is correct for desired dose. Ability of sprays, lotions, and creams to resolve deficiencies or maintain adequate intakes is

	2,000, 5,000, and 10,000 units • Gummies, 300, 500, and 1,000 units • Drops, 300, 400, 1,000, and 2,000 units/mL or drop • Solution, 400 and 5,000 units/mL • Spray, 1,000 and 5,000 units/spray • Creams and lotions, 500 and 1,000 units per ¼ teaspoonful **Prescription** • Capsule, 50,000 units • Solution, 8,000 units/mL	concentrations reached.	unknown.
Antiresorptive Prescription Medications			
Bisphosphonates			
Alendronate	Fosamax Fosamax Plus D Binosto (effervescent tablet)	Treatment: 10 mg orally daily or 70 mg orally weekly Prevention: 5 mg orally daily or 35 mg orally weekly	Generic available, effervescent tablet is brand only. 70-mg dose is available as a tablet, effervescent tablet, solution, or combination tablet with 2,800 or 5,600 units of vitamin D3. Administered in the morning on an empty stomach with 6-8 ounces (180-240 mL) of plain water. Do not eat and remain upright for at least 30 minutes following administration. Do not coadminister with any other medications or supplements, including calcium and vitamin D. Caution if CrCl <35 mL/min (0.58 mL/s).
Ibandronate	Boniva	Treatment: 150 mg orally monthly, 3-mg intravenous	Generics available.

		quarterly Prevention: 150 mg orally monthly	Administration instructions same as alendronate, except must delay eating and remain upright for at least 60 minutes. Caution if CrCl <30 mL/min (0.50 mL/s).
Risedronate	Actonel Atelvia (delayed-release)	Treatment and prevention: 5 mg orally daily, 35 mg orally weekly, 150 mg orally monthly	Generics available. 35-mg dose is also available as a delayed-release product. Administration instructions same as for alendronate, except delayed-release product is taken immediately following breakfast with at least 120 mL (ounces) of plain water. Caution if CrCl <30 mL/min (0.50 mL/s).
Zoledronic acid	Reclast	Treatment: 5-mg intravenous infusion yearly Prevention: 5-mg intravenous infusion every 2 years	Generic available. Can premedicate with acetaminophen to decrease infusion reactions. Contraindicated if CrCl <35 mL/min (0.58 mL/s). Also marketed under the brand name Zometa (4 mg) with different dosing for oncology-related indications.
RANK Ligand Inhibitor			
Denosumab	Prolia	Treatment: 60-mg subcutaneously every 6 months	Administered by a healthcare practitioner. Correct hypocalcemia before administration. Also marketed under the brand name Xgeva (70 mg/mL) with different dosing for treatment of hypercalcemia of malignancy, multiple myeloma, bone metastases from solid tumors, and giant cell tumor of bone.
Estrogen Agonist/Antagonist and Tissue Selective Estrogen Complex			
Raloxifene	Evista	60 mg daily	Generic available.
Bazedoxifene with conjugated equine estrogens (CEE)	Duavee	20 mg plus 0.45 mg CEE daily	For postmenopausal women with a uterus; no progestogen needed. Bazedoxifene monotherapy available in some countries.
Calcitonin			
Calcitonin (salmon)	Fortical	200 units (1 spray) intranasally daily, alternating nares every other day.	Nasal formulation only available as a generic. Refrigerate nasal spray until opened for daily use, then room temperature. Prime with first use. Also available as a subcutaneous injection.

Formation Medications			
Recombinant Human Parathyroid Hormone (PTH 1-34 units)			
Teriparatide	Forteo Bonsity	20-mcg subcutaneously daily	First dose sitting or lying. Refrigerate before and after each use. Use new needle with each dose. Inject in thigh or abdomen. Discard after 28 days or if cloudy. Forteo and Bonsity not interchangeable.
Human Parathyroid Hormone–Related Peptide (PTHrP [1-34]) Analog			
Abaloparatide	Tymlos	80-mcg subcutaneously daily for up to 2 years	First dose sitting or lying. Refrigerate before use then keep at room temperature. Use new needle with each dose. Inject in abdomen. Discard after 30 days.
Formation and Antiresorptive Medication			
Sclerostin Inhibitor			
Romosozumab	Evenity	210-mg subcutaneously monthly for 1 year; administered as two single use 105-mg/1.17-mL prefilled syringes	Correct hypocalcemia before administration. Refrigerate. Leave at room temperature for at least 30 minutes before use. Provider administration, exploring patient self-administration. Inject in abdomen, thigh, or upper arm; preferably each injection at a different site.

IOM, Institute of Medicine; NSAID, nonsteroidal anti-inflammatory drug.

TABLE 112-8

Medication Adverse Reactions and Monitoring

Medication	Adverse Reactions	Monitoring Parameters	Comments
Antiresorptive Medications—Nutritional Supplements			
Calcium	Constipation, gas, upset stomach, kidney stones	Dietary calcium intake, constipation	Education about a bowel healthy lifestyle (eg, adequate water, fiber, and exercise).
Vitamin D	Hypercalcemia, hypercalciuria, weakness, headache, somnolence, nausea Rare: cardiac rhythm disturbance	Serum 25(OH) vitamin D concentration, symptoms	Adverse effects usually not experienced until 25(OH) vitamin D concentration more than 100-150 ng/mL (mcg/L; 250-

			375 nmol/L), which are generally not achieved with recommended therapeutic doses.
Antiresorptive Prescription Medications			
Bisphosphonates			
Bisphosphonates	Dyspepsia (oral), transient or chronic musculoskeletal pain, nausea, transient flu-like illness (injectable) Rare: GI perforation, ulceration, and/or bleeding (oral); osteonecrosis of the jaw; atypical femoral shaft fracture, severe musculoskeletal pain	Bone density, fractures, GI symptoms, muscle aches Serum calcium for zoledronic acid	Adherence is suboptimal, thus it should be assessed frequently. Assess correct use of product with refills. Risk outweighs benefit in pregnancy, use prior to or during pregnancy might cause fetal medication exposure.
RANK Ligand Inhibitor			
Denosumab	Back pain, arthralgia, eczema, dermatitis, and infection Rare: osteonecrosis of the jaw, atypical femoral shaft fracture	Bone density, fractures, serum calcium	REMS: Medication guide and monitoring plan due to risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral shaft fractures, serious infections, and dermatologic adverse reactions. Contraindicated in pregnancy.
Estrogen Agonist/Antagonist and Tissue Selective Estrogen Complex			
Raloxifene	Hot flushes, leg pain, spasms, or cramps, peripheral edema, venous thromboembolism (warm swollen leg, chest pain, shortness of breath, coughing up blood, and change in vision)	Bone density, fractures, hot flushes, leg cramps, and blood clots	Contraindicated in pregnancy. Warning for fatal stroke; rare events predominantly seen in women at high-risk for stroke.
Bazedoxifene with conjugated equine estrogens	Similar to raloxifene and estrogens	Bone density, fractures, leg cramps, blood clots	Contraindicated in pregnancy.
Calcitonin			
Calcitonin (salmon)	Rhinitis, epistaxis	Bone density, fractures, nasal irritation	Limited information regarding use in pregnancy.
Formation Prescription Medications			
Recombinant Human Parathyroid Hormone (PTH 1-34 units) Analog			
Teriparatide	Orthostasis with first few injections, pain at injection site, nausea, headache, dizziness, leg cramps, increase in uric acid, transient hypercalcemia, hypercalciuria	Bone density, fractures, trough serum calcium concentration 1 month after therapy initiation, urinary calcium if prior hypercalciuria or active urolithiasis	If serum calcium is high (>10.6 mg/dL [2.65 mmol/L]), calcium intake should be decreased. Warning about osteosarcoma in rats and therefore contraindicated in patients at high risk for this adverse event.

			In pregnancy, adverse events noted in animal studies. Not for use in pregnancy.
Human Parathyroid Hormone–Related Peptide [PTHrP (1-34)] Analog			
Abaloparatide	Orthostasis with first few injections, pain at injection site, headache, dizziness, leg cramps, increase in uric acid, hypercalcemia, hypercalciuria	Bone density, fractures, serum calcium concentration, urinary calcium if prior hypercalciuria or active urolithiasis	Warning about osteosarcoma in rats and therefore contraindicated in patients at high risk for this adverse event. Not for use in pregnancy.
Formation and Antiresorptive Prescription Medication			
Sclerostin Inhibitor			
Romosozumab	Arthralgias, headache, muscle spasms, hypocalcemia, mild injection site pain, myocardial infarction, stroke, cardiovascular death. Antibody production with some neutralizing, an effect on efficacy or toxicity not reported. Rare: osteonecrosis of the jaw, atypical femoral fractures	Bone density, fractures, joint pain, injection site, serum calcium prior to and during therapy	Box warning about myocardial infarction, stroke, and cardiovascular death. Not for use in pregnancy.

REMS, risk evaluation and mitigation strategies.

Data from Reference 1; product prescribing labeling.

The North American Menopause Society guidelines for postmenopausal women, Endocrine Society guideline for postmenopausal women, the American Association of Clinical Endocrinologists and American College of Endocrinology guideline for postmenopausal women, the American College of Physicians guideline for women and men, and the Bone Health and Osteoporosis Foundation guideline for women and men provide guidance on osteoporosis prevention and treatment strategies.[1,2,4,39]

Medication Treatments of First Choice

Alendronate, risedronate, zoledronic acid, and denosumab reduce both hip and vertebral fracture risks.[2] Abaloparatide, calcitonin, ibandronate, raloxifene, romosozumab, and teriparatide reduce vertebral but not hip fracture risks. Estrogen and testosterone therapies are not used for osteoporosis treatment, but when prescribed for other conditions will have a positive bone effect.[27] In theory, sequential therapy starting with bone formation medications and followed by antiresorption medications is recommended, especially in patients with osteoporosis and very high risk for fracture. Formation medication cost and injectable dosage forms limit sequential therapy as initial therapy. Therefore, a 2023 guideline recommends starting with bisphosphonates first due to cost and reserving denosumab as second line when bisphosphonates cannot be used.[1] Sequential therapy could be used for patients at very high fracture risk. The algorithm (see Fig. 112-3) helps determine for whom medication therapy should be used. In general, prescription therapy combined with adequate intakes of calcium and vitamin D should be considered for any postmenopausal woman or man aged 50 years and older presenting with a fragility fracture, osteoporosis, or low bone mass combined with a FRAX 10-year probability of hip fracture of 3% or more or any major osteoporosis-related fracture of 20% or more. Type of fracture risk (spine, hip, or both) will also determine medication of choice. Calcitonin is a last-line therapy. The use of osteoporosis prescription medications in children,[10,15,57,58] premenopausal women,[11] and men younger than 50 years[12,13] occurs in special cases and is generally related to secondary medical and medication causes or genetic disorders. Newer guidelines reinforce that osteoporosis prevention therapy should be individualized based on fracture risk factors for postmenopausal women[4] and female older adults[1] with low bone mass (osteopenia).

Antiresorptive Therapies

Antiresorptive therapies include calcium, vitamin D, bisphosphonates, denosumab, estrogen agonists/antagonists (EAA), tissue selective estrogen complexes (TSEC), calcitonin, estrogen, and testosterone.

Calcium Supplementation

7 Calcium imbalance can result from inadequate dietary intake, decreased fractional calcium absorption, enhanced calcium excretion, and diseases and medications altering these processes. Adequate calcium intake (see Table 112-5) is considered a foundation for osteoporosis prevention and treatment in the guidelines and should be combined with vitamin D, especially when osteoporosis medications are taken.[2,34,39] If dietary intake cannot be increased to achieve adequate intake, calcium supplements can be used.

Efficacy

Calcium generally maintains BMD, although small BMD increases (0.6%-1.8%) have been documented.[2,59] These BMD effects are less than those observed with other osteoporosis medications. A USPSTF report states insufficient data exist to support using calcium and vitamin D supplementation to reduce fracture incidence.

Adverse Events

Calcium's most common adverse reaction, constipation, can first be treated with increased water intake, dietary fiber, and exercise. If still unresolved, smaller and more frequent calcium administration or a lower total daily dose can be tried. Calcium carbonate can create gas and cause upset stomach. Calcium citrate, a formulation with fewer GI side effects, is often recommended if calcium carbonate is not tolerated.

Calcium supplementation when combined with vitamin D can increase the risk of kidney stone formation. However, in some cases, calcium binds to oxalate in the gut, which decreases urinary oxalate excretion thereby decreasing kidney stones. Increased fluid intake and decreased salt intake might be warranted to prevent kidney stones. Calcium supplements resulting in total calcium intakes above the upper limit of intake can slightly increase coronary artery calcification and cardiovascular disease events.[1,31,60]

Interactions

Since calcium carbonate requires acid for disintegration, medications such as proton pump inhibitors and histamine type-2 receptor antagonists can decrease absorption from the carbonate product.[31] Fiber laxatives can also decrease the absorption of calcium if given concomitantly. Calcium can decrease the oral absorption of some medications including iron, tetracyclines, quinolones, bisphosphonates, and thyroid supplements.

Dosing and Administration

Many patients, especially those aged 60 years or older, do not ingest sufficient dietary calcium and therefore require supplements. To ensure adequate calcium absorption, 25(OH) vitamin D concentrations should be at least 10 to 15 ng/mL (mcg/L; 25-37 nmol/L). Because fractional calcium absorption is dose-limited, maximum single doses of 500 to 600 mg or less of elemental calcium are recommended.[2] Despite this, slow-release and/or absorbable calcium formulations (eg, Citracal Slow Release 1,200) are available in doses of 1,200 mg and advertised to be taken once daily. These high-dose products are sometimes two 600-mg tablets that can be taken at different times. Supplemental doses this high are usually not needed unless a severe dietary deficiency of calcium exists. Calcium carbonate is the salt of choice as it contains the highest amount of elemental calcium (40%) and is typically the least expensive. Calcium carbonate should be taken with meals, which increases gastric acidity resulting in product disintegration and dissolution. Calcium citrate (21% elemental calcium) has acid-independent absorption and does not need to be administered with meals. Although tricalcium phosphate contains 38% elemental calcium, calcium-phosphate complexes could limit overall calcium absorption. This product might be helpful in patients with hypophosphatemia that cannot be resolved with increased dietary intake.

Disintegration and dissolution rates vary significantly between products and lots. Products labeled United States Pharmacopeia "USP Verified" should be recommended. This indicates that the products have undergone the voluntary USP verification program, which ensures that the product contains the ingredients shown on the label at the stated strength/potency, and has been produced using safe, clean, and controlled manufacturing processes as specified by the USP and the US Food and Drug Administration (FDA). Products from unrefined oyster shell or coral calcium should not be

recommended because of concerns for high concentrations of lead and other heavy metals. Some calcium products come in alternative dosage forms (eg, chewable tablets, dissolvable tablets, and liquid), which can be beneficial for select patients with issues such as swallowing large tablets. For all products, encourage patients to read the labeling carefully as the serving size is often more than just one tablet. In addition, product labeling sometimes recommends taking doses providing 1,000 to 1,200 mg/day, which often provides more calcium than needed to meet IOM requirements and could exceed tolerable upper limits when dietary calcium intake is adequate.

Some commercial calcium supplements contain other nutrients associated with bone physiology such as magnesium, vitamin K, "natural estrogens," or isoflavones. Minimal BMD and no fracture data exist for these combination products. These products are also typically more expensive. Additionally, combining too many vitamins and supplements might exceed upper-tolerable nutrient limits and increase toxicities.

Vitamin D Supplementation

The IOM recommends adequate intakes of vitamin D from diet and/or supplementation for all ages (see Table 112-5). Current osteoporosis guidelines recommend slightly higher vitamin D maintenance doses (800-2,000 units daily).[2,34,38]

The desired therapeutic range for vitamin D is controversial. The IOM defines 20 ng/mL (50 nmol/L; 1 ng/mL = 2.5 nmol/L) as the cut point for normal 25(OH) vitamin D, below which a patient would be considered deficient. Current guidelines recommend treating patients with osteoporosis to a concentration of at least 20 ng/mL (mcg/L; 50 nmol/L) or 30 to 50 ng/mL (mcg/L; 75-125 nmol/L) 25(OH) vitamin D. Concentrations higher than 50 to 60 ng/mL (mcg/L; 125-150 nmol/L) can be associated with adverse effects.[2,38]

The major effects of vitamin D are achieved with 25(OH) vitamin D concentrations between 6 and 20 ng/mL (mcg/L; 15-50 nmol/L), including increasing calcium absorption (16 ng/mL [mcg/L; 40 nmol/L]) and decreasing BMD loss (up to 20 ng/mL [mcg/L; 50 nmol/L]).[61] Daily vitamin D doses of 500 to 700 units generally are sufficient to achieve vitamin D concentrations more than 20 ng/mL (mcg/L; 50 nmol/L), leading some experts to suggest the higher daily doses recommended in guidelines are not warranted. Other experts state not everyone achieves a 25(OH) vitamin D concentration greater than 30 ng/mL (mcg/L; 75 nmol/L), and therefore recommend 800 to 2,000 units daily, especially in adults at high risk or with osteoporosis. Furthermore, since most products are inexpensive and safe, the higher recommended doses are appropriate.[2,34,39] These higher recommendations are within the upper limit for vitamin D in adults, which is 4,000 units daily.

Serum 25(OH) vitamin D is the best indicator of total body vitamin D status.[42] Interassay variability exists; thus, the same laboratory should be used for repeat testing. Measurement of 25(OH) vitamin D concentration can be considered in anyone with high risk for low vitamin D, low bone density, history of a low-trauma fracture, frequent falls, unexplained muscle weakness, and/or bone pain.

Efficacy

Supplemental vitamin D given at doses of 700 to 800 units per day significantly reduces the incidence of both hip and nonvertebral fractures.[2] Small increases in BMD, improvement in muscle strength, and improvement in balance have also been observed. Several studies have analyzed the effect of supplemental vitamin D on falls; however, the USPSTF recommends against the use of supplemental vitamin D specifically for fall prevention.[24]

Interactions

Some medications can induce vitamin D metabolism including rifampin, phenytoin, barbiturates, valproic acid, and carbamazepine. Vitamin D absorption can be decreased by cholestyramine, colestipol, orlistat, and mineral oil. Vitamin D can enhance the absorption of aluminum; therefore aluminum-containing products should be avoided to prevent aluminum toxicity.

Dosing and Administration

Dosing of supplemental vitamin D should be based on IOM adequate intakes (see Table 112-5) or to achieve a 25(OH) vitamin D concentration of ≥30 ng/mL (mcg/L; 75 nmol/L), especially in those with osteoporosis.[2] Almost 30% of older adults have hypovitaminosis D (≤20 ng/mL [mcg/L; 50 nmol/L]), with higher prevalence in Black (72%) and Hispanic (43%) patients.[43,62] Replenishment doses will first be required in these patients before recommended maintenance doses.

Vitamin D can be taken as a single-agent or combination product. Supplements and multivitamins contain vitamin D3 or D2. Synthesized vitamin D3 can be made from irradiated sheep's wool and vitamin D2 from irradiated mushrooms. Guidelines suggest either product for prevention and treatment of vitamin D deficiency. Current guidelines recommend dosing with 5,000 units once daily for 8-12 weeks to achieve a target 25(OH) vitamin D concentration of ≥30 ng/mL (mcg/L; 75 nmol/L), followed by a maintenance dose of 1,000 to 2,000 units daily.[2,63] The preferred dosage form is vitamin D_3 (cholecalciferol).[2] Higher-dose prescription vitamin D regimens have less support[8] but are sometimes used,[63] especially when adherence and cost are concerns. An example regimen is 50,000 units given once weekly for 8 to 12 weeks, or until the 25(OH) vitamin D concentration reaches 30 ng/mL (mcg/L; 75 nmol/L), followed by 1,000 to 2,000 units daily to maintain this concentration. More than one multivitamin or large doses of cod liver oil daily are no longer advocated because of the risk of hypervitaminosis A, which can increase bone loss. Because the half-life of vitamin D is about 1 month, approximately 3 months of therapy are required before a new steady state is achieved and a repeat 25(OH)-vitamin D concentration should be obtained to assess efficacy of therapy.

Individuals with deficient concentrations of vitamin D are at risk for osteomalacia, a condition that can be mistaken for osteoporosis, which is characterized by decreased mineralization or "softening" of bone matrix. In patients who are pregnant, obese, or with disorders (eg, celiac disease, cystic fibrosis, Crohn's disease, chronic kidney disease) or medications (eg, anticonvulsants, glucocorticoids, antifungals, and antiretroviral medications used in treatment of acquired immunodeficiency syndrome) affecting vitamin D absorption and/or metabolism, higher doses and more frequent monitoring might be required.

Bisphosphonates

9 Alendronate, risedronate, and intravenous zoledronic acid are approved by the FDA for postmenopausal, male, and glucocorticoid-induced osteoporosis. Intravenous and oral ibandronate and some specialized oral formulations of other bisphosphonates are indicated only for postmenopausal osteoporosis but generally used in all people.

Pharmacology

Bisphosphonates mimic pyrophosphate, an endogenous bone resorption inhibitor.[2,64] Bisphosphonate antiresorptive activity results from binding to hydroxyapatite in bone with preference for areas with active bone remodeling. This leads to decreased osteoclast maturation, number, recruitment, bone adhesion, and life span.

Pharmacokinetics

Oral bisphosphonate bioavailability is less than 1% and is greatly decreased with concomitant food and beverages.[64,65] Within 24 hours of administration, bisphosphonates undergo rapid skeletal uptake and any medication not incorporated into bone is renally excreted. Elimination decreases linearly with declining renal function. Incorporation into bone gives bisphosphonates long biologic half-lives of up to 10 years. Bisphosphonates differ in the strength of binding to bone (zoledronic acid greater than alendronate which is greater than ibandronate which is greater than risedronate) with zoledronic acid having the greatest bone absorption and longest bone retention.

Efficacy

Bisphosphonates consistently provide fracture risk reduction and BMD increases (see Table 112-6) with noted difference in sites of fracture reduction between agents.[53] Fracture clinical trial data are from daily oral bisphosphonate or annual intravenous therapy, not weekly, monthly, or quarterly regimens.[65] Few bisphosphonate comparative fracture prevention studies exist, but one claims-based study found delayed-release risedronate to significantly decrease pelvis fractures in women, and in older female adults greater than 70 years old any fracture and pelvis fractures compared to immediate-release risedronate and alendronate.[91] Hip-fracture reduction has not been demonstrated with daily oral ibandronate; however, the study might have been underpowered.[2] Because of the lack of hip-fracture reduction data, ibandronate is not a first-line therapy (see Fig. 112-3). Annual intravenous zoledronic acid has documented secondary fracture prevention and a decrease in mortality when given after a first hip fracture.[53] Administration of intravenous zoledronic acid at an extended 18-month interval in women 65 years of age or older with osteopenia also decreased both vertebral and nonvertebral fractures over 6 years.

Bone turnover reaches an equilibrium with a lower rate of bone turnover evident within 3 to 6 months of bisphosphonate starting therapy, which results in BMD increases and a reduced fracture risk seen within the first 6 to 12 months.[53,65] For all bisphosphonates, increases in BMD are typically greater at the spine than at the hip.[53] Small increases in BMD continue for 4 to 5 years before plateauing. After discontinuation, the increased BMD is sustained for a prolonged period of time that varies based on different binding affinities of the individual bisphosphonates.[2] Because of the sustained effects, drug holidays can be considered for bisphosphonates.

The BMD increases with alendronate, risedronate, zoledronic acid, and oral ibandronate in men are similar to those in postmenopausal women.[6] Because of a lack of fracture data from pivotal trials in men, bisphosphonates are only FDA indicated to increase BMD, not to reduce fracture risk in men. No evidence suggests that efficacy profiles are expected to be different in men, thus, the 2023 osteoporosis guideline recommended bisphosphonates as first line therapy in men.[1]

Adverse Effects

Oral bisphosphonates are well tolerated if patients are selected for therapy appropriately and the patient takes them correctly (see Table 112-8). Patients with creatinine clearances (CrCl) less than 30 to 35 mL/min (0.50-0.58 mL/s), who have serious GI conditions (abnormalities of the esophagus that delay emptying, such as stricture or achalasia), or who are pregnant should not take bisphosphonates. Some evidence suggest bisphosphonates can be used in select patients with age-related decline in renal function without added adverse effects.

GI complaints, including heartburn and dyspepsia, are one of the most common reasons cited by patients for discontinuing therapy.[2,65] While these mild GI effects are common, bisphosphonates are also associated with rare severe GI events, such as esophageal erosion, ulcer, or GI bleeding. If GI adverse events occur, switching to a different bisphosphonate or less frequent administration schedule might resolve the problem. Patients should be encouraged to discuss GI complaints with a healthcare provider. Intravenous zoledronic acid or ibandronate can be used for patients with GI contraindications or intolerances to oral bisphosphonates. Other common bisphosphonate adverse effects include injection reactions and musculoskeletal pain. If severe musculoskeletal pain occurs, the medication can be discontinued temporarily or permanently. Acute phase reactions (eg, fever, flu-like symptoms, myalgias, and arthralgias) are typically associated with intravenous administration, but rarely reported with oral bisphosphonates. This reaction usually diminishes with subsequent administration.

Rare adverse effects include osteonecrosis of the jaw (ONJ) and subtrochanteric femoral (atypical) fractures.[2] ONJ occurs more commonly in patients with cancer, receiving higher-dose intravenous bisphosphonate therapy. In osteoporosis, the incidence of ONJ is 0.001% to 0.01%. Maxillary or mandibular bone surgery and poor oral hygiene are dental-specific risk factors for development of ONJ. When possible, major dental work should be completed before bisphosphonate initiation. For patients already on therapy, some practitioners withhold bisphosphonate therapy during and after major dental procedures, but no data exist to support any benefit of such practice. Atypical femoral shaft fractures are rare but can occur without trauma. Some evidence suggests the risk could increase with longer duration of bisphosphonate use (greater than 5 years). Since some patients with atypical fracture experience prodromal thigh or hip pain, any such pain should be evaluated.

Interactions

Because of poor bioavailability, oral bisphosphonates should not be administered at the same time as other medications. The administration instructions described below should be followed.

Dosing and Administration

Because bioavailability is poor for bisphosphonates and to minimize GI side effects, each oral tablet should be taken with at least 6 ounces (~180 mL) of plain water (not coffee, juice, mineral water, or milk) at least 30 minutes (60 minutes for ibandronate) before consuming any food, supplements (including calcium and vitamin D), or medications (see Table 112-7). The patient should also remain upright (ie, either sitting or standing) for at least 30 minutes after alendronate and risedronate and 1 hour after ibandronate administration. For patients with swallowing difficulties (eg, stroke and tube feeding), an effervescent tablet form of alendronate, which is dissolved in 4 ounces (~120 mL) of room temperature water, could be used. This formulation has the same food restrictions as traditional oral tablets. In contrast, delayed-release risedronate is available, and it is administered immediately following breakfast with at least 4 ounces (~120 mL) of plain water. A patient who misses a weekly dose can take it the next day. If more than 1 day has lapsed, that dose is skipped. If a patient misses a monthly dose, it can be taken up to 7 days before the next administration.

Before intravenous bisphosphonates are used, the patient's serum calcium concentration must be normal. Serum creatinine should be monitored before each dose of zoledronic acid. The intravenous products need to be administered by a healthcare provider. The quarterly ibandronate injection is given intravenously over 15 to 30 seconds or can be diluted and given with a syringe pump. Zoledronic acid should be infused once yearly over at least 15 minutes with a pump. Acetaminophen can be given to decrease acute phase reactions.

Although these medications are effective, adherence is poor and results in decreased effectiveness.[2,66] Adherence is improved with once-weekly bisphosphonate administration over daily therapy; however, it is unclear if once-monthly therapy improves adherence more. While dosing frequency is a common barrier to adherence, adverse effects and concerns about adverse effects remain important predictors of adherence and persistence. Using decision aids in discussions about medication therapy choices and periodic follow-up with a healthcare professional could improve adherence and persistence to therapy. These decision aids visually display the pros of bisphosphonate therapy (ie, fracture avoidance) to the cons (ie, adverse effects) based on an individualized fracture risk.[67] To help overcome barriers associated with oral dosing frequency, intravenous ibandronate and zoledronic acid could be used as alternatives.

Duration

The ideal duration of bisphosphonate therapy is not known.[1,2] Bisphosphonates are deposited into the bone and continue to suppress bone turnover after discontinuation. Some adverse effects, such as atypical fracture, are associated with duration of therapy. To balance risk and benefit, some clinicians recommend a "bisphosphonate/drug holiday," defined as disruption of therapy during which medication effects exist with a plan for medication reinstitution. Two randomized, double-blind studies with a bisphosphonate/drug holiday after therapy with alendronate for 5 years or zoledronic acid for 3 years showed a continued fracture benefit after discontinuation of therapy. Because a beneficial response was predicted by hip T-score, experts recommend that a bisphosphonate holiday could be considered in postmenopausal women after 5 years of oral bisphosphonates or 3 years of intravenous bisphosphonates if no significant fracture history, hip BMD T-score is above –2.5, and fracture risk is not high. In women initially with very high fracture-risk who remain high-risk, continuing oral bisphosphonates for 10 years or intravenous bisphosphonates for 6 years should be considered. These recommendations are based on limited data and questions remain regarding what therapy to reinitiate and the applicability of this approach for men and patients with glucocorticoid-induced osteoporosis. Patients should be monitored during the drug holiday and restarting therapy considered if fractures occur or if there are significant BMD losses.

Denosumab

9 Denosumab is approved by FDA for the treatment of osteoporosis in postmenopausal women and men at high risk for fracture. It is also approved for glucocorticoid-induced osteoporosis and to increase bone mass in men receiving androgen deprivation therapy for nonmetastatic prostate cancer and in women receiving adjuvant aromatase inhibitor therapy for breast cancer who are at high risk for fracture.

Pharmacology

Denosumab is a fully human monoclonal antibody that binds to RANKL, blocking its ability to bind to its RANK receptor on the surface of osteoclast precursor cells and mature osteoclasts.[68] Denosumab inhibits osteoclastogenesis and increases osteoclast apoptosis.

Pharmacokinetics

Following subcutaneous injection, rapid suppression of bone turnover occurs within 12 hours.[68,69] Denosumab achieves peak concentration in approximately 10 days. The half-life is approximately 25 days, and the concentration slowly declines over a period of 4 to 5 months. The medication does not accumulate with repeated dosing at 6-month intervals. No dosage adjustment is necessary in renal impairment; however, hypocalcemia is more common in severe renal impairment. No studies have been conducted in hepatic impairment.

Efficacy

Over 3 years, denosumab significantly decreased vertebral fractures, nonvertebral fractures, and hip fractures in postmenopausal women with low bone density (see Table 112-6).[53] Continued increases in BMD are demonstrated with long-term treatment over 10 years. For postmenopausal women previously treated with oral bisphosphonates, switching to denosumab for 1 year provided greater increases in BMD at the spine and hip over

switching to zoledronic acid; however, fracture outcomes are unknown.[2] Denosumab is not incorporated into bone and drug holidays are not recommended. Upon medication discontinuation, a rapid increase in bone turnover above baseline is noted with a corresponding loss of protection against vertebral fractures and case reports of multiple vertebral fracture. Therefore, for those with high fracture risk, denosumab therapy should be continued or alternative antiresorptive therapy (ie, bisphosphonate) should be initiated if denosumab is discontinued.

Adverse Events

In trials up to 10 years in duration, denosumab was generally well tolerated (see Table 112-8).[2] Dermatologic reactions not specific to the injection site and serious infections were noted in initial clinical trials, although an increased incidence has not been noted in long-term, follow-up trials nor with denosumab used in higher doses (Xgeva) for oncologic indications.[2]

As with bisphosphonates, rare, serious adverse effects from bone turnover suppression have been reported with denosumab including ONJ and atypical femoral fracture.[68] Major dental work should be completed before use when possible. Hypocalcemia can occur and any existing hypocalcemia should be corrected prior to use. Severe hypocalcemia is more common in patients with underlying kidney dysfunction. The manufacturer recommends monitoring of serum calcium, magnesium, and phosphorus within 14 days of administration in those with a CrCl less than 30 mL/min (0.50 mL/s).

Interactions

No interactions have been identified with denosumab.

Dosing and Administration

Denosumab is administered subcutaneously in the upper arm, upper thigh, or abdomen by a healthcare professional including pharmacists in some states. The product is available as a refrigerated prefilled syringe that can be stored at room temperature up to 14 days before administration (see Table 112-7).

Duration

After 5 to 10 years of therapy, patients should be reevaluated for medication continuation, discontinuation, or switching to a different medication.

Mixed Estrogen Agonists/Antagonists and Tissue Selective Estrogen Complexes

9 Raloxifene is a second-generation mixed estrogen agonist/antagonist (EAA; previously known as a selective estrogen receptor modulator, or SERM) approved by the FDA for prevention and treatment of postmenopausal osteoporosis and for reducing the risk of invasive breast cancer in postmenopausal women with and without osteoporosis. Raloxifene might be considered as a treatment option for women with no to minimal postmenopausal symptoms at low risk for hip fracture and with an increased breast cancer risk. Bazedoxifene is a third-generation EAA combined with conjugated equine estrogens (CEE) making it a TSEC that is approved by FDA for prevention of postmenopausal osteoporosis and vasomotor menopausal symptoms.[55,56] Bazedoxifene with CEE can be considered for younger postmenopausal women with a uterus, menopausal symptoms, and at risk for osteoporosis.[2,4,55,56]

Pharmacology

EAAs bind with α- and β-estrogen receptors and coactivators or corepressors to cause varying agonist or antagonist effects at different tissue sites.[55,56] Raloxifene is an agonist at bone receptors and antagonist at breast receptors and has minimal effect on the uterus. Bazedoxifene is an agonist at bone, and antagonist at the uterus and breast; however, reduction in breast cancer risk has not yet been demonstrated in large-scale clinical trials.

Pharmacokinetics

Food has a nonsignificant effect on absorption, which is about 2% for raloxifene and 6% for bazedoxifene due to extensive presystemic

glucuronidation.[56,70,71] Raloxifene is 95% protein bound. The half-life of both raloxifene and bazedoxifene is 28 hours. EAAs are predominantly metabolized via glucuronidation and eliminated in the feces.

Efficacy

Raloxifene and bazedoxifene decrease vertebral but not hip fractures. In a post hoc analysis of the Multiple Outcomes with Raloxifene Evaluation trial, raloxifene decreased nonvertebral fractures in postmenopausal women with the most severe vertebral fractures at baseline. Bazedoxifene also decreased nonvertebral fractures in a subgroup of women with a higher fracture risk at baseline.[55,56] The fracture prevention effects of bazedoxifene combined with CEE are not known. EAAs increase spine and hip BMD, but to a lesser extent than bisphosphonates (see Table 112-6). Raloxifene's vertebral fracture prevention is greater in women without previous fracture.[4] Upon discontinuation, the medication effect of EAAs is lost, with bone loss returning to age- or disease-related bone loss rates. EAAs have a positive impact on the lipid profile but have not demonstrated a benefit on cardiovascular disease.[4,55]

Adverse Events

Hot flushes are common with raloxifene but decreased with bazedoxifene with CEE (see Table 112-8).[55,56,70,71] Raloxifene rarely causes endometrial thickening and bleeding; bazedoxifene decreases these adverse events making progestogen therapy unnecessary when it is combined with CEE. Leg cramps and muscle spasms are also common with both medications. Thromboembolic events are uncommon (less than 1.5%), but can be fatal. In large trials, no change in overall death, cardiovascular death, or overall stroke incidence was seen with raloxifene; however, a slight increase in fatal stroke (0.7/1,000 women – year difference) was documented, which resulted in a boxed warning for raloxifene.[55] Fatal stroke with raloxifene occurred most frequently in women with an increased risk of stroke at baseline. Bazedoxifene with CEE also has all the adverse effects listed for estrogens as a class including increased thromboembolic events.

Interactions

Because of raloxifene's highly protein bound nature (95%), when given concomitantly with other highly protein bound medications, like warfarin, a potential for binding interactions exists and, therefore, monitoring of both medications is suggested. Cholestyramine can decrease raloxifene absorption. Rifampin, phenytoin, carbamazepine, and phenobarbital can decrease bazedoxifene concentrations by inducing intestinal and liver uridine diphosphate glucuronosyltransferase (UGT) metabolism. Estrogen metabolism is altered with CYP3A4 and CYP1A2 inducers and inhibitors.

Dosing and Administration

EAAs/TSECs are administered orally once daily (see Table 112-7).[70,71] They are contraindicated for women with an active or past history of venous thromboembolic disease, pregnancy, or childbearing potential. Therapy should be stopped if a patient anticipates extended immobility. Women at high risk for a stroke or coronary events and those with known coronary artery disease, peripheral vascular disease, atrial fibrillation, or a prior history of cerebrovascular events might not be good candidates for EAAs/TSECs. These medications should be used with caution in patients with severe liver impairment or moderate-to-severe renal impairment due to a lack of data. Bazedoxifene with CEE has all the contraindications and precautions for estrogens as a class.

Calcitonin

9 Calcitonin is FDA-indicated for osteoporosis treatment for women who are at least 5 years past menopause.[72] Intranasal calcitonin therapy (200 units daily) decreases vertebral fractures alone with no fracture reduction demonstrated with higher and lower doses (see Table 112-6).[2] Once calcitonin is discontinued, the benefits are lost over the next 1 to 2 years. A meta-analysis revealed a higher incidence of cancer in patients taking calcitonin. While the FDA found that evidence was insufficient for a causal relationship, calcitonin is considered a last-line therapy since there are more effective treatment options. Intranasal calcitonin might provide some short-term pain relief to some patients with acute vertebral fractures.

Dosing and Administration

Some patients do not like to administer medications intranasally (see Table 112-7). In clinical trials of calcitonin, a high dropout rate exists. If the nasal

product is used for vertebral fracture pain, calcitonin should be prescribed for short-term (4 weeks) treatment and should not be used in place of other more effective and less-expensive analgesics nor should it preclude the use of more appropriate osteoporosis therapy.

Hormone Therapies

Estrogen

In women, estrogens with or without a progestogen significantly decrease fracture risk and bone loss (see Table 112-6).[2,4,34,36] Estrogen therapy is approved by FDA for prevention of postmenopausal osteoporosis but not for treatment. For women going through early menopause, estrogen therapy can be considered when protection against bone loss is needed in addition to reduction of vasomotor symptoms.[4,73] Other anti-osteoporosis therapies are reserved for treatment closer to the average age of natural menopause. Estrogens should not be prescribed solely for the prevention or treatment of osteoporosis if other anti-osteoporosis therapies can be used.[1,2,38] Oral and transdermal estrogens at equivalent doses and continuous or cyclic hormone therapy regimens have similar BMD effects. Effect on BMD is dose-dependent, with some benefit seen with lower estrogen doses. Fracture risk reduction has not been demonstrated with the lower doses. When estrogen therapy is discontinued, bone loss accelerates and fracture protection is lost. A complete discussion of adverse events, drug interactions, dosing, and administration for estrogen can be found in Chapter 102, "Hormone Therapy in Women."

Testosterone

No fracture data are available, but some data demonstrate BMD improvements with testosterone use.[74] Testosterone is used to treat hypogonadism in men, but an osteoporosis medication should be added when risk for osteoporotic fracture is high.[12,74] A complete discussion of adverse events, drug interactions, dosing, and administration for testosterone products for men can be found in Chapter 103, "Erectile Dysfunction."

Formation Medications

Parathyroid Hormone Analogs

9 Abaloparatide is an analog of PTHrP and teriparatide is an analog of PTH.[2,54] These agents are FDA-indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture defined as multiple risk factors for fracture, a history of osteoporotic fracture, or failed or intolerant to other therapies. They are also approved to increase bone mass in men who are at high risk for fracture, failed, or intolerant to other osteoporosis medications. Teriparatide is approved forglucocorticoid-induced osteoporosis in all adults. Patients who have a very high fracture risk, history of osteoporotic fracture, low bone density (eg, T-score less than –3.5), or have failed or are intolerant of previous bisphosphonate therapy could be candidates for PTH analog therapy.

Pharmacology

Teriparatide is a recombinant human product representing the first 34 amino acids in human PTH.[54] Unlike continuous PTH effects from primary hyperparathyroidism that can decrease BMD, when administered intermittently (ie, subcutaneously once daily) teriparatide increases bone formation with a minor increase in bone resorption for a net anabolic effect. Abaloparatide is a synthetic analog of PTHrP sharing the first 22 amino acids but with differing amino acids at positions 23 to 34. While both agents bind to the PTH type I receptor, abaloparatide binds with higher affinity to the RG confirmation, which results in an increased anabolic effect. Further, abaloparatide demonstrates less of an effect on activating bone resorption and remodeling than teriparatide. With both medications bone mass is improved.

Pharmacokinetics

Bioavailability for teriparatide and abaloparatide are 95% and 36%, respectively. The peptides are cleared through hepatic and extrahepatic pathways, with a half-life of 1 hour and 1.7 hours, respectively. Increases in the area under the curve are noted with decreasing renal function but there are no dosage adjustments noted in renal insufficiency. No studies have been performed in hepatic impairment. Alternative delivery formulations are being investigated.[54]

Efficacy

Two years of teriparatide or abaloparatide reduce vertebral and nonvertebral fracture risk in postmenopausal women (see Table 112-6).[53] Compared with alendronate, teriparatide has demonstrated reductions in vertebral fracture rates in patients taking glucocorticoids; however, no reductions in nonverterbral fractures were evident.[54] Lumbar spine BMD increases are greater than with antiresorptive agents. Observational data for teriparatide suggest a similar fracture benefit in men. In men, abaloparatide significantly increased BMD but no fracture data are available.[92] Discontinuation of parathyroid hormone analog therapy results in a decrease in BMD, which can be alleviated with subsequent antiresorptive therapy.[2]

Adverse Events

Transient hypercalcemia can occur and is less common with abaloparatide than with teriparatide (3.4% vs 6.4%, respectively) (see Table 112-8).[54] Because of an increased incidence of osteosarcoma in rats, both medications contain a box warning against use in patients at increased baseline risk for osteosarcoma (eg, Paget's bone disease, unexplained elevations of alkaline phosphatase, pediatric patients, young adults with open epiphyses, or patients with prior radiation therapy involving the skeleton). This adverse effect has not been seen in humans.

Interactions

An increased calcium concentration could be a concern in patients on digoxin therapy.

Dosing and Administration

Teriparatide and abaloparatide are commercially available as a prefilled pen delivery device (see Table 112-7). A daily subcutaneous injection is delivered to the abdominal area with site rotation. Teriparatide can also be given in the thigh. The administration of the first dose should take place with the patient either sitting or lying down in case orthostatic hypotension occurs. Both medications should be stored in the refrigerator before first use. After first use, abaloparatide can be kept at room temperature for up to 30 days. In contrast, teriparatide must be returned for storage in the refrigerator after each use and special precautions must be taken for travel. The teriparatide pen should be discarded after 28 days. Due to the theoretical risk for osteosarcoma, these medications are generally limited to 2 years of use cumulatively in a patient's lifetime with additional use of teriparatide considered on a risk-benefit basis. In select patients, a second trial with teriparatide can be tried. Suboptimal adherence is documented to decrease efficacy.

Besides the conditions listed above, parathyroid hormone analogs should not be used in patients with hypercalcemia, metabolic bone diseases other than osteoporosis, metastatic or skeletal cancers, previous radiation therapy, or premenopausal women of childbearing potential.

Formation and Antiresorptive Medication

Romosozumab

9 Romosozumab is approved by FDA for postmenopausal women at high risk for fracture defined as multiple risk factors for fracture, a history of osteoporotic fracture, or failed or intolerant to other therapies. This medication might be the anabolic osteoporosis medication of choice for patients with previous radiation therapy,[2] and those at risk for osteosarcoma and hypercalcemia.[75]

Pharmacology

Romosozumab is a humanized monoclonal antibody that binds to sclerostin to prevent inhibition of bone formation and decrease bone resorption, an activity that separates this medication from other anabolic medications.[54,75] By binding sclerostin, Wnt signaling can continue to increase gene transcription, which results in increased osteoblast synthesis, differentiation, and bone matrix building. This medication inhibits bone resorption by decreasing RANKL and m-CSF, and increasing OPG.

Pharmacokinetics

About 50% to 70% of a dose is absorbed. Peak serum concentrations after subcutaneous administration are reached within 3 to 4.5 days, with no accumulation with subsequent doses. Romosozumab has a half-life of 6 to 7 days.

Efficacy

After 1 year of romosozumab, vertebral fractures are statistically decreased by 73%, with a nonsignificant decrease in nonvertebral fractures by 25% in postmenopausal women (see Table 112-6).[2,39,54,75] Fracture prevention was higher if the study participants in Latin America were removed from the multi-country study analysis because this cohort had lower fracture rates even in the placebo arm. Fracture risk was also decreased by 48% for vertebral fractures, 19% for nonvertebral fractures, and 38% for hip fractures after 1 year of romosozumab followed by 1 year of alendronate. Lumbar spine and hip BMD statistically increased after 1 year of romosozumab treatment. To prevent BMD loss after discontinuation, therapy with denosumab or alendronate for 1 year after romosozumab resulted in BMD continuing to increase at hip and bone sites. Vertebral, femoral neck, and hip BMD and hip bone strength increased after romosozumab therapy in postmenopausal women who had received at least 3 years of prior bisphosphonate therapy.[73] These BMD increases were not as large as reported in bisphosphonate naïve women but were greater than teriparatide therapy BMD effects after bisphosphonate therapy. Comparing published results in postmenopausal women, romosozumab might be better to prevent hip fractures compared to abaloparatide and teriparatide while these last agents might be better for vertebral fracture prevention.[75] Romosozumab increased BMD in men by 12.1% at the lumbar spine, 2.5% total hip, and 2.2% femoral neck, all significantly different than placebo after 1 year of therapy.[54] Fracture data were not captured in men.

Adverse Effects

Headache and arthralgia were the most common adverse effects, followed by hypercalcemia (<1%) (see Table 112-8).[2,39,54] Mild injection site irritation occurred in 6% to 8% of patients. Romosozumab antibodies developed in 10% to 20% patients, sometimes being transient. The antibodies generally are not neutralizing antibodies nor did they alter efficacy. Serious cardiovascular events have been reported in a few trials, but the incidence is low (<2.5%) and not much higher nor significantly different from the alendronate treatment arm (1.9%) in postmenopausal women at 1 year. The serious cardiovascular events increased to 6.5% and 6.1%, respectively, after both arms were switched to alendronate for year 2. In men, the cardiovascular event rates were 4.9% in men receiving romosozumab versus 2.5% receiving placebo. Myocardial infarction, stroke, and cardiovascular death are listed as a boxed warning. Romosozumab should not be used within 1 year of a myocardial infarction or stroke and benefit risk evaluation should be conducted in patients at risk for these conditions or with these conditions in their past medical history. Rare cases of ONJ and atypical femoral fractures have been reported. Because Wnt signaling is also related to malignancies, the medication-induced increased activity could be a concern. However, this adverse effect was not seen in the premarketing clinical trials.

Interactions

None

Dosing and Administration

The medication comes as two prefilled syringes requiring refrigeration until administered by a healthcare provider. Each syringe is injected into two different sites during the same visit (see Table 112-7). Patient self-administration is being explored.

Sequential and Combination Therapy

9 In sequential therapy, an anabolic agent is given first to increase bone remodeling units and bone mass, followed by an antiresorptive agent to continue with bone formation. Although this sequential therapy is recommended in the guidelines, in practice this regimen is generally reserved for patients with severe osteoporosis because of the cost of anabolic agents. Starting with an antiresorptive first and then switching to teriparatide results in lower BMD compared to starting with the bone formation medication first. Thus starting teriparatide after antiresorption therapy is not preferred.[2] However, this therapy will be used, especially for patients who have fractured or continue to lose bone mass while on antiresorptive therapy. Romosozumab can be used after previous treatment with parathyroid hormone analogs.[2] Small increases in BMD can be seen when switching from an oral bisphosphonate to denosumab. Switching to denosumab thus can be used during a bisphosphonate drug holiday or for bisphosphonate treatment failures (ie, BMD decreases or fracture).

Because of no documented fracture benefit, increased cost, concern for dual suppression of bone turnover, and potential for more adverse effects,

combination therapy is rarely used.[2,53,54] Combination therapy of two antiresorptive agents or two anabolic agents did not increase bone mass compared to monotherapy even though they have different pharmacologic properties. Combination of teriparatide with oral bisphosphonates generally resulted in less BMD gains than monotherapy, and thus is not used. Combination teriparatide and denosumab resulted in greater hip BMD effects, but long-term results were generally similar to sequential therapy. Estrogen therapy combined with a bisphosphonate did not increase bone mass more than monotherapy. Antiresorptive therapy can be initiated after estrogen discontinuation to help negate the accelerated bone loss that occurs once estrogen is stopped. For postmenopausal women with menopause symptoms and an osteoporosis diagnosis, an osteoporosis medication should be prescribed along with menopausal hormone therapy. When raloxifene is used for breast cancer prevention, sometimes another antiresorptive agent will be prescribed, especially if hip fracture risk is high.

SPECIAL POPULATIONS

Osteoporosis is a particular threat in some subgroups because of age, genetic abnormalities, diseases, and medications.

Children and Adolescents

6 Osteoporosis in children and adolescents is uncommon but can lead to significant pain, deformity, and chronic disability. Pediatric osteoporosis is due to genetic disorders such as osteogenesis imperfecta and idiopathic juvenile osteoporosis, or secondary causes including chronic inflammatory diseases, growth hormone deficiency, celiac disease, diabetes, anorexia nervosa, and glucocorticoid use (see Tables 112-2 and 112-3 for other causes). Female athlete triad and anorexia nervosa, which are common in this age group, can lead to osteoporosis and fractures.

The diagnosis and treatment of osteoporosis in children and adolescents are challenging. Low bone mass is defined as a Z-score of −2.0 or less (adjusted for gender, age, and race/ethnicity) or T-score <−2.5 when adult height has been achieved using central DXA of the spine or total body minus head.[10,15] Ability to lie still during the DXA and radiation doses of some tests create concerns for this age group. Routine DXA monitoring is not required[10]; however, some criteria for this test have been suggested.[15] An osteoporosis diagnosis requires a DXA Z-score of −2.0 or less and 2 long-bone fractures by age of 10 or 3 long-bone fractures by the age of 19.[10] DXA monitoring is done every 1 to 2 years for bone health and annually for children on bisphosphonate therapy.[10] Spine x-rays can also be monitored every 6 months to 2 years. Genetic testing might be required to identify an underlying cause.[15]

The first step in management is correcting any underlying primary or secondary causes and instituting a bone-healthy lifestyle especially adequate calcium, vitamin D, and exercise.[10,15,58] This step includes weight gain for anorexia nervosa and decreased exercise intensity for those with the female athlete triad.

Pharmacologic treatment has been used for children and adolescents with low bone mass and fragility fractures. Unlike adults, many children can reshape vertebral fractures and reclaim more BMD with treatment.[58] Growth hormone can be helpful in children with a documented deficiency but has no effect if no underlying deficit.[57] The optimal osteoporosis medication, dose, and duration of therapy are unknown and can vary by age and cause of osteoporosis. More safety data are needed.[15,58]

Bisphosphonates can be used off-label in children/adolescents but should be discontinued when the Z-score goes above −2.0.[10] Children and adolescents on glucocorticoids frequently need bisphosphonate therapy for longer periods.[10,15,58] For children less than 40 kg, the alendronate dose is 5 mg/day or 35 mg/week and risedronate is 15 mg/week.[10] Zoledronic acid is dosed 0.0125 to 0.05 mg/kg (maximum dose 4 mg) every 6 to 12 months. A major concern with bisphosphonates is their effect on longitudinal bone growth and modeling. Fracture healing, skeletal growth/maturation, and the appearance of growth plates do not appear to be impaired by bisphosphonates. Because bisphosphonates are released from bone for many years and cross the placenta, teratogenic effects are also a concern. Bisphosphonates should not be used if pregnancy is planned within the year. Pediatric experience with denosumab is limited but positive.[57]

Teriparatide has a box warning to avoid use in children due to a concern for osteosarcoma. Newer agents have not been evaluated in pediatric patients.

Premenopausal Women

6 Clinically significant bone loss and fractures in healthy premenopausal women are rare.[73] Risk factors are similar between premenopausal and postmenopausal osteoporosis. While bone loss occurs during pregnancy and lactation, it is usually gained back 6 to 12 months after pregnancy or breastfeeding is complete. Secondary causes are involved in 50% to 90% of premenopausal women with osteoporosis (see Tables 112-2 and 112-3) for the bone loss.[11] Common secondary causes in this group are amenorrhea, anorexia nervosa, glucocorticoid use, and celiac disease. Premenopausal women with prior fracture have a higher risk of postmenopausal osteoporotic fractures.[11,73,76]

Routine bone density screening should not be performed in healthy premenopausal women. Premenopausal women with known osteoporosis risk factors and low-trauma fractures can undergo central DXA examinations.[73] In this case, the Z-score is used, with Z-scores of −2.0 or less defined as bone mass below the expected range for age.[11,37,73,76] The categorization of osteopenia or osteoporosis based on T-score alone should be avoided in premenopausal women unless there is a history of low-trauma fracture or a secondary cause of osteoporosis.

Pharmacologic therapy for osteoporosis should be used with caution in premenopausal women as antifracture efficacy and safety have not been adequately demonstrated.[11,73] All premenopausal women should practice a bone-healthy lifestyle, including adequate calcium and vitamin D intake. Secondary causes of bone loss should be resolved. For example, gaining weight and resumed menses are more effective in correcting bone loss secondary to anorexia nervosa than oral contraceptives.[73,76] If the contributing factor cannot be eliminated, for example, chemotherapy or glucocorticoids, pharmacological therapy can be considered. Women with an unidentified cause for osteoporosis and no history of fracture should be treated with a bone-healthy lifestyle and watchful waiting.

Osteoporosis medication safety during pregnancy and breastfeeding have not been adequately studied. While some data suggest that use prior to conception and during the first trimester of pregnancy is safe, bisphosphonates are generally not used in women of childbearing age due to concern for fetal harm resulting from the long half-lives of these agents.[73,76] Bisphosphonate use should be avoided within 12 months of conception and use of contraceptive agents should be encouraged to reduce the likelihood of becoming pregnant during therapy. Human data on the safety of denosumab and bone-forming agents such as teriparatide in pregnancy are lacking; however, some animal data suggest congenital defects following exposure. Therefore, these agents should be avoided during pregnancy.[11]

Older Adults

Although osteoporosis, osteoporotic fractures, and postfracture morbidity and mortality increase with age, osteoporosis is underdiagnosed and undertreated in older adults. One-third of older adults older than 65 years old and about 50% of older adults older than 80 years old fall annually; with 20% to 30% of these falls resulting in moderate to severe injury.[2] More than 50% of women older than 75 years old have osteoporosis. Fewer than 25% of older adults had a DXA completed or received osteoporosis medications after a fracture. After a hip fracture, more than 50% of older adult women will require assistance including long-term nursing home residence (25%).[2,4] Only 33% of nursing home residents with an osteoporosis diagnosis or past fracture received an osteoporosis medication, even though 89% of them were considered at high risk for a fracture.[77] Hypogonadism is present in about 29% of older men.[12] Sarcopenia resulting in decreased muscle mass and function is prevalent in older adults[8] and is associated with increased falls and fractures.[78]

Guidelines recommend central DXA for adults aged 65 years and older; however, all older adults are not evaluated for osteoporosis. Reference standards for osteoporosis assessment tools are generally not available for the oldest older adults (eg, maximum age for FRAX is 90 years). In clinical practice, estimates for a 90-year-old person are applied to those adults older than 90 years. FRAX slightly overestimates, whereas ultrasound underestimates osteoporosis in nursing home residents. In an older adult with falls, the Garvan calculator might be preferred since it includes falls, whereas FRAX does not.[2]

Older adults should practice a bone-healthy lifestyle, ingest adequate calcium and vitamin D, and implement measures to prevent falls (see above sections).[2,8,12,14,79] While some guidelines recommend adequate amounts of calcium and vitamin D, the USPSTF feels evidence is insufficient to support fall and fracture prevention with supplementation. Lactose intolerance and hypercholesterolemia increase with aging and can lead to lower calcium intake from dairy products, which can increase the need for calcium supplements. Limited sun exposure due to frailty and institutional residence can increase the need for vitamin D supplementation for bone and muscle health. Protein intakes of 1 g/kg/day (up to 1.5 g/kg/day for some chronic illnesses) are suggested, and these also help with decreasing sarcopenia. Exercise might be difficult in older adults due to osteoarthritis or

limited by underlying cardiac and respiratory diseases. However, walking and lifting light weights can still stimulate bone remodeling. Encouraging older adults to do a home safety evaluation for falls can assist with fracture prevention. Multidisciplinary fall prevention programs with multiple interventions generally have greater impact on fall prevention than single discipline or single intervention.[47] Exercise is a major component of these interventions. Many fall prevention materials are available without cost on the Internet.

Some data exist to support osteoporosis medication benefits in older adults; however, data are limited for the oldest older adults.[8,14,75] In a Medicare study, antiosteoporotic medications after a fracture lowered subsequent fracture risk by 21%. When deciding whether to use prescription medications in older adults, the following factors need to be taken into consideration: remaining life span, ability to take and afford medications, cognitive function, swallowing ability, GI disorders, polypharmacy, desire to avoid additional medications, and regimen complexity. Challenges with oral bisphosphonate administration requirements exist for older adults who are bed bound, have difficulties swallowing, have fluid restrictions for cardiovascular or kidney diseases, forget to drink adequate amounts of fluid, or cannot stay upright for the given time. Diuretics, nephrotoxic medications, and dehydration can increase acute and chronic renal failure when zoledronic acid is administered too quickly.[2] As of 2023, older female adults can be considered for therapy with an osteoporosis prevention medication when a DXA identifies low bone mass.[1]

The cost of osteoporosis medications can quickly cause an older adult with Medicare Part D to enter the coverage gap/"donut hole," which is the period when out-of-pocket medication expenses can be higher, or the catastrophic coverage phase when beneficiaries pay 5% of medication costs. Osteoporosis medication costs most likely will have less impact as out-of-pocket Medicare Part D brand name medication costs will be capped at about $3,300 in 2024 and $2,000 in 2025 (later small adjustments for cost indexing) and coinsurance during catastrophic coverage removed.[93] Having to pay for osteoporosis medications might create adherence problems. Sometimes not initiating or stopping osteoporosis medications might be warranted for older adults with conditions such as severe Alzheimer disease or during palliative or hospice care. Comprehensive medication reviews and deprescribing can decrease all-cause mortality and potentially inappropriate medication use but does not increase nor decrease falls.[50]

Chronic Kidney Disease

Low BMD and fractures occur in patients with chronic kidney disease (CKD, glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 [0.58 mL/s/m^2]), using chronic dialysis, and/or after kidney transplant.[80] Some medications for CKD and transplant can further compromise bone health. Fractures occur earlier and have greater 1-year mortality rates (64%). Osteoporosis and decreased renal function due to aging are different from other chronic kidney disease-mineral and bone disorders (CKD-MBD) such as renal osteodystrophy (see Chapter 69 "Calcium and Phosphorus Homeostasis" and Chapter 62 "Chronic Kidney Disease"), which can be related to high bone turnover, adynamic bone, or a combination of both. A DXA with VFA when appropriate can be used to assess bone loss and FRAX can be used to determine fracture risk; however, neither assessment distinguishes between renal and nonrenal causes of bone loss.[81] The DXA result can underestimate fracture risk since changes in bone quality from CKD are not captured. Similarly, FRAX can underestimate risk since renal failure is not included as a risk factor. When the diagnosis of the underlying bone disease pathophysiology could influence treatment, a bone biopsy can be conducted but is no longer a Kidney Disease Improving Global Outcomes (KDIGO) requirement.[80] Laboratory tests such as serum calcium, 25(OH) vitamin D, intact PTH, and serum phosphorus can help with identifying underlying CKD-MBD. Non-kidney-retained BTM such as bone-specific alkaline phosphatase (BSAP), PINP and tartrate-resistant acid phosphatase 5b (TRAP 5b) can be used to monitor therapy and guide reinstitution of therapy after a bisphosphonate drug holiday.[81] Other markers are being investigated.[80]

The first treatment step is to manage underlying disease conditions, including calcium and vitamin D abnormalities, hyperphosphatemia, and hyperparathyroidism (discussed in Renal Disorders chapters of this textbook).[80] Limited data exist on anti-osteoporosis medications for patients with CKD, dialysis, and/or post kidney transplant.[2,80,81] Calcium intake is preferred by diet with supplements used only to achieve RDAs when diet is insufficient. A 25(OH) vitamin D level is obtained to assess bone health with vitamin D treatment prescribed as needed to maintain therapeutic concentrations, which are the same as non-CKD patient recommendations. Sometimes 1,25-$(OH)_2$-vitamin D might also be used for underlying CKD-induced deficiencies, creating a need for adding prescription calcitriol therapy to over-the-counter vitamin D therapy.

Osteoporosis medication studies in patients with CKD are lacking and often with insufficient sample sizes or were post hoc analyses.[2,80,81] Denosumab is not renally eliminated and thus can be used. When denosumab is used in CKD-MBD or dialysis, serum calcium levels need to be monitored since these patients can develop hypocalcemia, especially if also receiving calcium-sensing receptor agonists. According to product labeling, oral bisphosphonates are not recommended and zoledronic acid is contraindicated if CrCl is less than 30 or 35 mL/min (0.50 or 0.58 mL/s). However,

guidelines suggest bisphosphonates can be used, particularly when decreased renal function is the result of aging alone. Insufficient data exist to support lower doses for shorter durations, which have been suggested to account for decreased renal bisphosphonate elimination. Dialysis does eliminate bisphosphonates, but if the dose is given after dialysis, a lower dose or longer interval is suggested.[80] Bisphosphonates should not be given at the same time as phosphate binders or other medications. Patients with CKD should be reassessed in 3 years or after a fracture for bisphosphonate continuation decisions. Raloxifene is not suggested for patients with severe renal impairment. Teriparatide and abaloparatide can help patients with adynamic bone and those with low PTH and BMD but not for patients with high bone turnover. Minimal research with romosozumab has evaluated its efficacy and safety in CKD. The cardiovascular adverse effects of romosozumab could limit its use in patients with decreased renal function and cardiovascular disease.. Fracture risk increases with osteoporosis medication discontinuation, so a post-discontinuation plan is needed. Kidney and/or bone specialists usually provide care to patients with significant kidney disease and osteoporosis.

Transgender People

Data are emerging for transgender people to expand upon previous studies listing sex as a binary term and analyze the effects of gender-affirming surgeries and medications on bone, especially during adolescence.[1,94] Emerging data have documented osteoporosis in transgender people. Additional fracture risk factors for this group include age of gonadectomy and various hormone or hormone-altering therapy. Gonadotropin-releasing hormone analogue therapy for adolescents could decrease peak bone mass; however using gender-affirming hormone therapy later could increase BMD. Various combinations of surgery or no surgery with hormone replacement or altering therapy suggest individualization of assessment and treatment to prevent osteoporosis and osteoporotic fractures. Controversy exists regarding the most appropriate reference for assessment of BMD with varied approaches including using the Z-scores of both the gender identity and sex assigned at birth as a reference population due to lack of current data. Monitoring with DXA scans can start before puberty blockers and then repeated every one to two years until gender-affirming hormone therapy is initiated. Once gender-affirming replacement therapy has begun, DXAs should be obtained every one to two years until peak bone mass is achieved around age 25 – 30 years old. DXA monitoring is restarted after the age of 60 years. Poor adherence to gender-affirming hormone therapy after surgery can warrant additional DXA monitoring every one to two years until BMD has stabilized and thereafter at longer intervals.

Drug-Induced Osteoporosis

Glucocorticoid-Induced Osteoporosis

3 Glucocorticoid use is the most common cause of medication-induced osteoporosis. Up to 40% of patients taking chronic oral glucocorticoids will experience a clinical fracture or show evidence of vertebral fracture on x-ray.[82,83] In patients who take 2.5 to 7.5 mg/day of prednisone or the equivalent, the relative risk of vertebral fracture doubles and the relative risk of hip fracture increases by 50%.[84] All glucocorticoid doses and formulations have been associated with increased bone loss and fractures; however, risk is much greater with prednisone doses of 5 mg or more daily or equivalent and with oral therapy versus inhaler and intranasal therapy.[84,85] Although a well-documented risk, many patients receiving glucocorticoids are not evaluated or treated for glucocorticoid-induced osteoporosis (GIO); therefore, greater vigilance by all healthcare professionals is needed.[82,84]

Bone losses with glucocorticoids are rapid with up to 12% loss over the first year. The greatest decrease occurs in the first 3 to 6 months of therapy. Afterward, bone loss is about 2% to 3% per year.[84] The risk of fracture increases within 3 months of initiating glucocorticoid therapy and peaks at 1 year. Trabecular bone is affected more than cortical bone; therefore, vertebral fractures are more common. The pathophysiology of glucocorticoid-induced bone loss is multifactorial.[83] Glucocorticoids decrease bone formation through decreased proliferation and differentiation and enhanced apoptosis of osteoblasts. They can interfere with the bone's natural repair mechanism through increased apoptosis of osteocytes. Glucocorticoids increase RANKL and decrease OPG, leading to an increase in the number of osteoclasts and increased bone resorption. They can reduce estrogen and testosterone concentrations. A negative calcium balance is created from decreased calcium absorption and increased urinary calcium excretion via alterations in calcium transporters. The underlying disease requiring glucocorticoids (see Table 112-2) also can negatively affect bone metabolism.

FRAX and central DXA are recommended by current guidelines for evaluation, though neither adequately accounts for the rapid increase in fracture risk following glucocorticoid initiation.[82,83] Since FRAX does not account for specific dose, duration or accumulation of glucocorticoids, scores must be adjusted based on prednisone dose or equivalent.[82] For those taking more than 7.5 mg or equivalent per day, FRAX risk of major osteoporotic fracture should be increased by 15% (ie, multiplied by 1.15) and FRAX risk of hip fracture by 20% (ie, multiplied by 1.2). Based on glucocorticoid-adjusted FRAX

estimates of the 10-year risk of major osteoporotic fracture and hip fracture, the patients are risk stratified into low, moderate, and high risk for fracture. Criteria for classification into a risk category is detailed in Table 112-9. An initial BMD assessment is recommended prior to or within 6 months of glucocorticoid initiation for adults 40 years of age or older and for adults under the age of 40 with a history of fragility fracture or other risk factors. Repeat BMD testing is recommended every 2 to 3 years during osteoporosis therapy for those taking high-glucocorticoid doses (30 mg of prednisone or more per day or a cumulative dose greater than 5 g in the past year), a fracture 18 months or more after starting osteoporosis therapy, medication adherence or absorption concerns, or other risk factors for osteoporosis. VFA is also suggested for patients receiving 5 mg or more prednisone or equivalent daily for 3 months or more.[37]

TABLE 112-9

Classification of Fracture Risk in Patients Treated with Glucocorticoids

Fracture Risk	Adults ≥40 Years Old	Adults <40 Years Old
Low	FRAX[a] 10-year risk of major osteoporotic fracture <10% FRAX[a] 10-year risk of hip fracture ≤1%	None of the risk factors listed below for moderate- or high-fracture risk
Moderate	FRAX[a] 10-year risk of major osteoporotic fracture 10%-19% FRAX[a] 10-year risk of hip fracture >1% and <3%	Hip or spine BMD Z-score <−3.0, or rapid bone loss (≥10% at the hip or spine over 1 year) and continuing glucocorticoid therapy with ≥7.5 mg/day for ≥6 months
High	History of osteoporotic fracture, or hip or spine BMD T-score ≤−2.5 in men ≥50 years old and postmenopausal women, or FRAX[a] 10-year risk of major osteoporotic fracture ≥20%, or FRAX[a] 10-year risk of hip fracture ≥3%	Prior osteoporotic fracture

[a]If glucocorticoid treatment is >7.5-mg prednisone or equivalent per day, the FRAX risk score should be multiplied by 1.15 for major osteoporotic fracture and by 1.2 for hip fracture and then used to determine overall fracture risk.

Date from Reference 82.

All patients using glucocorticoids should practice a bone-healthy lifestyle and minimize glucocorticoid exposure when possible.[82-84] All patients starting or receiving glucocorticoid therapy (any dose or duration) should consume 1,000 to 1,200 mg elemental calcium and 600 to 800 units of vitamin D daily or more to achieve therapeutic 25(OH) vitamin D concentrations. Minimizing fall risk is important. Osteoporosis prevention counseling should occur for all patients using this medication for three months or more regardless of dose. Glucocorticoids should be used at the lowest dose and for the shortest duration possible. Upon discontinuation of glucocorticoid therapy, fracture risk decreases and BMD increases, though they might not increase to baseline levels.[84]

Alendronate, risedronate, zoledronic acid, denosumab, and teriparatide are approved by FDA for GIO.[84] The current guidelines from the American College of Rheumatology divide recommendations for prescription osteoporosis medication use in GIO by fracture risk and age (see Tables 112-9 and 112-10).[82] Therapy recommendations are based on comparative efficacy, potential for toxicity, and cost.

TABLE 112-10

Therapy to Prevent or Treat Glucocorticoid-Induced Osteoporosis in Adults Beginning Long-Term Glucocorticoid Treatment (≥2.5-mg Prednisone or Equivalent Per Day for ≥3 Months)

Patient Population	Low-Fracture Risk	Moderate-Fracture Risk	High-Fracture Risk
All	Optimize calcium and vitamin D intake; bone-healthy lifestyle	Optimize calcium and vitamin D intake; bone-healthy lifestyle	Optimize calcium and vitamin D intake; bone healthy lifestyle
Adults age ≥40 years	No prescription osteoporosis therapy	Oral bisphosphonate alternatives: IV bisphosphonate, teriparatide, denosumab, or raloxifene[b]	Oral bisphosphonate alternatives: IV bisphosphonate, teriparatide, denosumab, or raloxifene[b]
Adults age <40 years	No prescription osteoporosis therapy	Oral bisphosphonate alternatives: IV bisphosphonate, teriparatide, or denosumab	Oral bisphosphonate alternatives: IV bisphosphonate, teriparatide, or denosumab
Women of childbearing potential[c,d]	No prescription osteoporosis therapy	Oral bisphosphonate alternative: teriparatide	Oral bisphosphonate alternatives: teriparatide, IV bisphosphonate, or denosumab

IV, intravenous.

[a]Listed in order of preference; abaloparatide and romosozumab were not yet approved during guideline development.

[b]Recommended only for postmenopausal women when other alternative therapies cannot be used.

[c]Women of childbearing potential who do not intend to become pregnant during the osteoporosis treatment period and are using effective birth control or are not sexually active.

[d]Fetal risks from osteoporosis medications during pregnancy.

Data from Reference 82.

Oral bisphosphonates are recommended first-line, though intravenous bisphosphonates can be used in patients who are not adherent or unable to take the oral preparations. Teriparatide is recommended for patients who cannot use a bisphosphonate, and denosumab is recommended if neither a bisphosphonate nor teriparatide can be used. Denosumab is not recommended first-line for GIO due to limited safety data in this population. Consideration should be given to potential risk of infection in patients taking immunosuppressive agents or biologic therapies. Raloxifene does not have an FDA indication for GIO, but does have some clinical data documenting improved BMD at the lumbar spine in patients taking glucocorticoids.[84] It is recommended only in postmenopausal women if no other osteoporosis medications can be used. Standard osteoporosis therapy doses are used. The recommendations are similar for women of childbearing potential who do not plan to become pregnant and are using effective contraception or are not sexually active.[82]

Patients receiving glucocorticoids are considered high risk, and, therefore, a bisphosphonate drug holiday is generally not considered after 5 years. Bisphosphonate treatment for 7 to 10 years is recommended if patients continue glucocorticoid use. Since glucocorticoids can cause hypogonadism, sometimes hormone therapy will be prescribed. The hormonal therapy for correcting hypogonadism symptoms most likely will have some positive bone effects as well.

Cancer Treatment–Induced Bone Loss

3 Cancers, some associated treatments and metastatic bone disease can cause bone loss and osteoporosis.[59,63] Medications used to treat hormone-responsive cancers—such as aromatase inhibitors and androgen deprivation therapy, and some cytotoxic chemotherapies—are associated with a reduction in BMD. Chemotherapy-induced ovarian failure can enhance bone loss. Glucocorticoids used as chemotherapy, chemotherapy premedication, and/or treatment for chemotherapy-induced nausea and vomiting also increase bone loss in patients with cancer.

Central DXA screening is advocated for patients at high risk for osteoporosis, which would include certain chemotherapies and cancers.[59] Patients with at least 1 risk factor should be offered BMD testing with central DXA. In patients on medications that cause bone loss or whose BMD is near the threshold of treatment with FRAX, BMD testing should be offered every 2 years or more frequently considering the results of the BMD and anticipated bone loss, but not more than annually. FRAX can be used to estimate the risk for osteoporotic fracture; however, it has not been validated in patients with cancer. When using FRAX, secondary osteoporosis can be checked "yes" when premature menopause and/or hypogonadism caused by chemotherapy and cancer are present, though fracture risk is likely still underestimated in this group.[86]

Certain osteoporosis medications are used to prevent bone loss or treat osteoporosis due to chemotherapy, cancer, and metastases. Bisphosphonates and denosumab decrease chemotherapy-induced bone loss and in some trials, reduce fractures.[59] Most research has been conducted in women with breast cancer and men with prostate cancer. Raloxifene decreases the risk of invasive breast cancer in high-risk women.[2,34] Due to risk of osteosarcoma, teriparatide and abaloparatide are specifically contraindicated in patients with bone metastases or prior radiation to the skeleton. Zoledronic acid and denosumab are used for cancer-related hypercalcemia and skeletal-related events.[63] They are marketed with different product names for these indications since dosages are much higher than for osteoporosis. For additional information see Chapter 150, "Supportive Care in Cancer."

EVALUATION OF THERAPEUTIC OUTCOMES

Monitoring of Patient-Centered Care Plan

10 Assessment of adherence and tolerability of medication should be performed during each encounter patients have with the healthcare system. Having patients repeat back instructions for medication administration will help identify administration problems and enable timely correction. Assessment of fracture, back pain, and height loss can help identify worsening osteoporosis.

The role of routine monitoring of BMD via central DXA is controversial and recommendations vary since change in BMD is only one component of fracture risk.[2,87] Nonetheless, decreases in BMD while on treatment are associated with increases in fracture risk compared to stable or increased BMD. Since BMD continues to decrease with aging, no change from baseline can be an acceptable response. However, BMD is considered a failure if BMD significantly decreases while on treatment. This treatment failure could indicate nonadherence, a lack of response, or the presence of secondary causes contributing to continued bone loss.[2] To minimize test variability, BMD testing should be performed on the same DXA machine. A statistical change needs to be greater than the least significant change for that specific piece of equipment based on local data with the team of technicians.

The AACE/ACE guidelines recommend central DXA every 1 to 2 years after medication initiation until BMD is stable at which time the interval for reassessment could be lengthened.[2] The Endocrine Society guidelines recommend waiting 3 years for zoledronic acid, 5 years for other bisphosphonates, and 5 to 10 years for denosumab.[39] Financial support for testing at intervals less than 2 years might not be provided by insurance plans. In patients with conditions associated with higher rates of bone loss (eg, glucocorticoid use and certain chemotherapy agents), more frequent monitoring might be warranted.

Like central DXA, BTM can be used to identify nonadherence and lack of response to therapy.[2] The markers are measured 3 to 6 months after therapy initiation and compared to baseline values.[2,88] Significant changes need to be greater than the least significant change for that test.[2] Because no consensus on result interpretation and high-test variability exists, these tests are not routinely ordered.

Osteoporosis Services

10 Despite the availability of effective therapies, many patients (approximately 70%) are not being evaluated or do not receive appropriate

osteoporosis therapy.[2] In fact, the proportion of patients receiving osteoporosis medication following a hip fracture has decreased. People of color receive even fewer DXA screenings and less medication therapy, and have poorer results after a fracture.[3] To combat this trend, many institutions are implementing an Own the Bone program or a fracture liaison service, which is generally an interprofessional, multifaceted program to increase treated patient numbers, enhance adherence, and improve osteoporosis treatment outcomes. All providers and programs should work to decrease health disparities in osteoporosis prevention and treatment.[3] Communicating risk is important for people to understand their risk for and consequences of fractures, especially in relation to other medical conditions.[2] Community pharmacists and other healthcare professionals can provide osteoporosis screenings using the FRAX tool to estimate fracture risk in the community, especially at health fairs. Osteoporosis prevention and treatment services have been clinically successful in community pharmacies and in ambulatory care settings. At 1 year, only 26% to 56% of patients still use their osteoporosis medications. Thus, all healthcare professionals should identify and resolve barriers to optimal medication initiation and adherence. The main reasons for nonadherence are medication cost, fear of adverse effects, resistance to medication use, and perceived lack of medication need. Routine follow-up with healthcare professionals and enhanced risk-benefit communication tools could improve treatment and adherence rates. Databases can be used to identify patients after a low-trauma fracture who have not had a DXA screening or osteoporosis medication started. Patient medication assistance programs can be used to decrease cost.

To improve patient care, the US Centers for Medicare and Medicaid Services have created this quality measure—the percent of women 50 to 85 years old with a recent fracture that is screened or treated within 6 months.[1,44,89] Financial incentives tied to these measures could help bridge the gap in quality of care.

CONCLUSION

Osteoporosis prevention begins at birth and continues throughout life by practicing a bone-healthy lifestyle (adequate calcium and vitamin D intake, exercise, no smoking, minimal alcohol use, and fall prevention). Generally, osteoporosis occurs in postmenopausal women and older men; however, the disease can occur in all ages because of secondary causes such as genetics, diseases, and medications. FRAX tool can be used for screening and to assist in identifying patients at high risk for fracture requiring treatment. Central DXA can be used for osteoporosis screening, diagnosis, and monitoring.

Alendronate, risedronate, zoledronic acid, and denosumab are first-line therapies for those with high fracture risk since these medications decrease hip, nonvertebral, and vertebral fractures. Abaloparatide, romosozumab, and teriparatide are the only medications that can build bone; however, cost, subcutaneous administration, and lack of hip fracture prevention limit their use. Although medications decrease fracture risk, prescribing of osteoporosis medications and patient adherence to them is suboptimal. All healthcare professionals need to be actively involved with people of all ages to provide osteoporosis education and counseling, prevent osteoporosis development across the lifespan, treat osteoporosis, and improve medication adherence to prevent osteoporotic fractures.

ABBREVIATIONS

25(OH) vitamin D	25-hydroxyvitamin D/calcidiol
APC	adenomatous polyposis coli
ATPase	adenosine triphosphatase
BMD	bone mineral density
BMP	bone morphometric proteins
BSAP	bone-specific alkaline phosphatase
BTM	bone turnover markers

Ca^{++}	Calcium
Cbfa1	core-binding factor alpha 1
Cbl	E3 ubiquitin ligase
CEE	conjugated equine estrogens
Csk1α	casein kinase 1α
CKD-MBD	chronic kidney disease-mineral and bone disorder
CrCl	creatinine clearance
CTX	c-terminal type 1 collagen telopeptide
Dkk-1	Dickkoff-1
DPD	deoxypyridinoline
DSH	disheveled cytoplasmic protein
DXA	dual-energy x-ray absorptiometry
EAA	estrogen agonist antagonist
FAK	focal adhesion kinase
FDA	US Food and Drug Administration
FGF	fibroblast growth factor
FRAX	World Health Organization fracture risk assessment tool
GFR	glomerular filtration rate
GI	gastrointestinal
GIO	glucocorticoid-induced osteoporosis
GSK-3β	glycogen synthase kinase-3β
ICTP	carboxy-terminal telopeptide of type I collage
IGF	insulin-like growth factor
IOM	Institute of Medicine
LGR4	leucine-rich repeat-containing G protein
LRP5/6	lipoprotein-receptor related protein

m-CSF	macrophage-colony stimulating factor
MMP	matrix metalloproteases
NF-Kβ	nuclear factor kappa β
NHANES	National Health and Nutrition Examination Survey
NTX	n-terminal type 1 collagen telopeptide
OCN	osteocalcin
ONJ	osteonecrosis of the jaw
OPG	osteoprotegerin
P13K	phosphatidyl inositol 3-kinase
pDXA	peripheral dual-energy x-ray absorptiometry
PICP	procollagen type 1 carboxy(C)-terminal propeptide
PINP	procollagen type 1 amino(N)-terminal propeptide
PPARγ	peroxisome proliferator-activated receptor gamma
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related protein
QCT	quantitative computed tomography
QUS	quantitative ultrasound
RANK	receptor activator of nuclear factor-kappa β
RANKL	receptor activator of nuclear factor-kappa β ligand
RDA	recommended dietary allowances
runX2	runt-related transcription factor
Scr	nonreceptor tyrosine kinase
sFRP	secreted frizzled related proteins
TBS	trabecular bone score
TCF/LEF	T-cell-specific transcription factor 4/lymphoid enhancer factor 1
TGF-β	tissue growth factor-β

TNF-α	tumor necrosis factor-α
TRACP5b	tartrate-resistant acid phosphatase isoenzyme 5
TRPV6	transient receptor potential cation channel subfamily V member 6
TSEC	tissue selective estrogen complex
UL	upper limits
USP	United States Pharmacopeia
USPSTF	United States Preventive Services Task Force
VDR	vitamin D receptor
VFA	vertebral fracture assessment
WIFI	Wnt inhibitory factor 1
WISE	Wnt modulator insurface estoderm
WHO	World Health Organization
Wnt	wingless tail ligands

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SELF-ASSESSMENT QUESTIONS

1. Which of the following statements is correct about the epidemiology of osteoporosis?

   A. The disease affects women and men equally.

   B. Vertebral fractures are the most prevalent and the largest component of osteoporosis healthcare expenditures.

   C. The disease affects all race and ethnic groups equally.

   D. Adults with low bone density also experience osteoporotic fractures.

2. Which statement is true about bone physiology and pathophysiology?

A. Osteoblasts secrete osteoprotegerin that binds to immature and mature osteoclasts to cause bone resorption.

B. Bone loss due to menopause is predominantly from increasing bone resorption.

C. Parathyroid hormone prevents RANKL from binding to the Wnt signaling pathway.

D. Sclerostin binds to RANKL and thereby stops bone formation.

3. Which statement is correct about calcium and vitamin D homeostasis?

A. Calcium undergoes predominantly a passive absorption process from the stomach to achieve the serum calcium concentration.

B. Vitamin D increases calcium absorption from the small intestine.

C. Vitamin D is converted to 25(OH) vitamin D in the kidneys.

D. Guidelines consider 25(OH) vitamin D concentrations less than 50 ng/mL (mcg/L; 125 nmol/L) to be deficient.

4. The FRAX tool can be used to calculate fracture risk in which of the below patients to determine whether osteoporosis therapy is needed or should be continued?

A. A 68-year-old postmenopausal woman with a T-score of -2.1 at the femoral neck.

B. A 72-year-old woman currently receiving denosumab.

C. A 70-year-old man with a T-score of -2.7 at the femoral neck.

D. A 58-year-old woman with a 3-year history of osteoporosis secondary to glucocorticoid therapy.

E. A 66-year-old woman with a low-trauma vertebral fracture on abaloparatide.

5. A 65-year-old woman with osteoporosis has adjusted her diet but cannot achieve the recommended daily calcium intake. She has hypertension and hypercholesteremia. Her daily medications include alendronate, amlodipine, and atorvastatin. Her current dietary calcium intake is approximately 700 mg daily. Which of the following calcium supplement regimens is the BEST recommendation? Note doses listed represent elemental calcium content.

A. Calcium carbonate 500 mg daily

B. Calcium carbonate 1,200 mg daily in divided doses

C. Calcium citrate 250 mg twice daily

D. Calcium citrate 1,200 mg daily in divided doses

6. A 66-year-old woman with osteoporosis asks for recommendations for calcium and vitamin D daily intakes. According to the American Association of Clinical Endocrinology guidelines, which daily calcium and vitamin D intake would you recommend she achieve through diet and/or supplements?

A. Calcium 1,000 mg and vitamin D 600 units

B. Calcium 1,000 mg and vitamin D 800 units

C. Calcium 1,200 mg and vitamin D 600 units

D. Calcium 1,200 mg and vitamin D 1,000 units

E. Calcium 1,500 mg and vitamin D 2,000 units

7. In which of the following postmenopausal women should bisphosphonate therapy be recommended? A postmenopausal woman with a

   A. T-score lumbar spine −0.9

   B. T-score lumbar spine −2.1, T-score femoral neck −1.9, and 10-year probability of major osteoporotic fracture of 12%

   C. T-score lumbar spine of −2.3 and 10-year probability of hip fracture of 3.2%

   D. T-score femoral neck of −2.3 and 10-year probability of major osteoporotic fracture of 18%

8. Which oral medication is a first-line therapy option for osteoporosis in a postmenopausal woman with high fracture risk?

   A. Romosozumab

   B. Alendronate

   C. Ibandronate

   D. Raloxifene

9. A patient with osteoporosis is being treated with alendronate to prevent hip and spine fractures. What is the minimum timeframe alendronate should be continued before considering a drug holiday for a patient with high fracture risk?

   A. 1 year

   B. 3 years

   C. 5 years

   D. 6 years

10. Which instruction for administration should be given to a patient on delayed release risedronate?

    A. Take after breakfast

    B. Remain upright for at least 60 minutes after taking

    C. Take with at least 4–8 ounces (120–240 mL) of water

    D. May take together with your multivitamin tablet

11. A health professional identifies a 70-year-old postmenopausal woman who has not refilled her risedronate prescription for the last 6 months. The practitioner discusses her adherence with her. She responds that she is concerned about osteonecrosis of the jaw (ONJ). What is the health professional's BEST response?

    A. ONJ is only associated with intravenous bisphosphonate medications.

    B. ONJ only happens in patients with cancer taking high-dose bisphosphonates.

    C. Because of the risk of ONJ, the healthcare team will consider changing your risedronate to denosumab.

    D. ONJ is rare with this medication. You are more likely to have a hip fracture.

12. A 53-year-old postmenopausal woman is in the community pharmacy participating in an osteoporosis health fair. The pharmacist calculates her FRAX scores and finds she has a 1.2% risk for hip fracture and a 14% risk for any osteoporotic fracture. She has a strong family history of breast cancer. What should the pharmacist recommend?

    A. Practice a bone-healthy lifestyle and get a central DXA when your hip fracture FRAX score is greater than 3% or your major osteoporotic fracture

risk is greater than 20%.

B. Since you have osteoporosis, schedule a visit with your healthcare provider to get an osteoporosis prevention medication ordered.

C. Ask your healthcare provider for a central DXA, and if you have only spine but not hip osteoporosis, raloxifene could be a good medication for you.

D. Get a central DXA in 5 years since you don't have osteoporosis.

13. A 70-year-old man with symptomatic hypogonadism is diagnosed with osteoporosis. He is at high risk for hip fracture. Which of the following is the BEST initial treatment?

A. Risedronate and testosterone

B. Ibandronate and testosterone

C. Alendronate alone

D. Ibandronate alone

E. Testosterone alone

14. A 38-year-old premenopausal woman with a 15-year history of inflammatory bowel disease for which she takes prednisone 7.5 mg daily is in clinic today to discuss her DXA results. Her Z-scores are lumbar spine −2.8 and femoral neck (right) −2.6. Besides a bone health lifestyle, what would you recommend/do today?

A. All osteoporosis medications are contraindicated, so she should add daily running to her bone healthy lifestyle.

B. Data support denosumab but not bisphosphonates to prevent fractures in premenopausal women. Denosumab has no fetal toxicity risks.

C. Add calcium and vitamin D supplements to achieve adequate intakes to prevent bone loss. They are safe during pregnancy.

D. If she uses birth control, she could start a bisphosphonate. No long-term effects exist for a future baby.

15. A 60-year-old woman is initiated on alendronate. She has been receiving prednisone for rheumatoid arthritis. She asks the pharmacist why her doctor started this medication. Your BEST answer is?

A. Because of your age but not due to your medications, the doctor prescribed alendronate to prevent postmenopausal osteoporosis.

B. The prednisone you are taking for arthritis causes bone loss and fractures that can be prevented with this medication. Bone loss also decreases with aging.

C. Your doctor should have prescribed romosozumab.

D. The osteoporosis medication is not needed.

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** 43 million adults have low bone mass. In one study, 5.3% of adults with low bone mass had osteoporotic fractures, just a bit lower than the percentage of those with osteoporosis having a fracture (6.8%). Women have a higher incidence of osteoporosis; however, mortality after a hip fracture is greater in men. Non-Hispanic White and Mexican American women have more osteoporosis and osteoporotic fractures than non-Hispanic Black women. Hip fractures consume the greatest amount of osteoporosis healthcare expenditures. See the "Introduction" and "Epidemiology" sections.

2. **B.** Bone loss due to menopause is predominantly due to increased bone resorption from increased RANKL and decreased osteoprotegerin. Osteoblasts control bone resorption by producing RANKL that works to increase maturation of osteoclasts and also increase their actions on bone.

They also secrete osteoprotegerin that binds to RANKL to stop bone resorption. Parathyroid hormone stimulates Wnt activity to increase bone formation. Sclerostin inhibits bone formation by binding to LRP 5/6. See "Bone Physiology" section and Fig. 112-2A-C.

3. **B.** Calcium absorption is an active process requiring 1,25(OH) vitamin D, and occurs in the duodenum and jejunum. Vitamin D is converted to 25(OH) vitamin D in the liver and to 1,25(OH) vitamin D in the kidneys. 25(OH) vitamin D concentrations greater than 30 ng/mL (mcg/L; 75 nmol/L) are usually considered in the normal range, insufficiency is usually described as 20 to 30 ng/mL (mcg/L; 50-75 nmol/L), and deficiency is usually described as less than 20 ng/mL (mcg/L; 50 nmol/L). Certain laboratories can have different cut off points, for example, deficiency less than 13 ng/mL (mcg/L; 32 nmol/L). See the "Calcium Homeostasis, Vitamin D, and Parathyroid Hormone" and "Vitamin D supplementation" sections.

4. **A.** Per US guidelines and practices, FRAX should be used to calculate fracture risk in patients with low bone mass (T-score between −1 and −2.5) to determine if prescription osteoporosis medications are needed. FRAX should not be used for patients on current therapy, who already have osteoporosis diagnosed or if a patient has had a low-trauma fracture. See the "Risk Factor Assessment," "Diagnosis of Osteoporosis," "Drug Treatment of Choice," and "Glucocorticoid-induced Osteoporosis" sections.

5. **A.** The goal for a woman this age is 1,200 mg of calcium per day. She is receiving 700 mg through her diet, which leaves a need for 500 mg daily from supplements. This patient is not taking any acid-suppression therapy where calcium citrate would be the preferred salt since it does not require acid for absorption. The calcium citrate option here is also twice a day, increasing medication burden. Calcium carbonate is inexpensive and has a higher percentage of elemental calcium. See "Nonpharmacologic Therapy" (Calcium), "Pharmacologic Therapy" (Calcium Supplementation), and Table 112-5 sections.

6. **D.** Calcium goals are different between men and women 51 to 70 years old. For this woman, 1,200 mg elemental calcium would be recommended. The American Association of Clinical Endocrinologists recommends 1,000 to 2,000 units of vitamin D for patients with osteoporosis or at high risk for osteoporosis, which would include all older adults. The National Osteoporosis Foundation recommends 800 to 1,000 units of vitamin D daily and the Institute of Medicine recommends 600 units daily for this age group. See the "Pharmacologic Therapy" (Calcium Supplementation, Vitamin D Supplementation) sections and Table 112-5.

7. **C.** Therapy for osteoporosis is indicated for those with a low-trauma fracture, a T-score <−2.5, or low bone mass (T-score between −1 and −2.5) and a 10-year risk of major osteoporotic fracture of greater than or equal to 20% or hip fracture of greater than or equal to 3%. See the "Diagnosis of Osteoporosis" section and Fig. 112-3.

8. **B.** Medications recommended first line for treatment of osteoporosis with high fracture risk are those that reduce the risk of hip fracture. These medications include alendronate, risedronate, zoledronic acid, and denosumab. Alendronate and risedronate are orally available medications. The other medications might be used if high risk for breast cancer (raloxifene) or very high fracture risk (romosozumab). Ibandronate does not have hip fracture prevention data. See the "Pharmacologic Therapy" (Bisphosphonates, Denosumab, and Romosozumab) sections and Fig. 112-3.

9. **C.** Drug holidays are used only for bisphosphonate medications because they reside in bone for long durations after discontinuation and have some activity. For the other medication classes, bone effects begin to return to baseline after discontinuation. The minimum time at which a drug holiday from oral bisphosphonates can be considered is after 5 years of therapy. The minimum time at which a drug holiday from zoledronic acid is considered is after 3 years of therapy. The fracture risk of the patient will be considered (longer treatment durations for patients at very high risk of fracture, such as those on zoledronic acid for 6 years). See the "Pharmacologic Therapy" (Bisphosphonates) section.

10. **A.** Delayed-release risedronate is the only oral bisphosphonate that can be taken after food (breakfast). Alendronate, regular release risedronate, and ibandronate need to be taken 30 minutes before breakfast. All oral bisphosphonates should be ingested with 6 to 8 ounces (180-240 mL) of water only (oral delayed-release risedronate can be taken with 4 ounces (120 mL). Patients need to remain upright for at least 30 minutes (60 minutes for ibandronate) to prevent oral bisphosphonate gastrointestinal adverse effects. Oral bisphosphonates have minimal absorption <1%, so they should not be taken with any other medications or supplements nor with any foods or beverages except plain water. See Tables 112-7 and 112-8.

11. **D.** Osteonecrosis of the jaw (ONJ) is a rare adverse effect seen with oral and intravenous bisphosphonates, denosumab, and romosozumab but not with raloxifene and conjugated equine estrogens with bazedoxifene. In osteoporosis, the incidence is 0.001% to 0.01%. The incidence is higher with larger doses of intravenous bisphosphonates used in cancer patients (also increased from radiation and glucocorticoid therapy use) but can occur with lower oral and injectable doses for osteoporosis. Denosumab can prevent hip fractures but does have ONJ as a rare adverse effect. She

might have problems with insurance coverage for denosumab, which could be explored. The magnitude of the risk of ONJ and the benefit of therapy should be conveyed to the patient to determine if it alleviates her concerns. You can use an osteoporosis decision aid to help her understand the risks. See the "Pharmacologic Therapies" (Bisphosphonates, Denosumab, Estrogen Agonists/Antagonists Mixed Estrogen Agonists/Antagonists and Tissue Selective Estrogen Complexes) sections and Tables 112-6 and 112-8.

12. **C.** A FRAX major osteoporotic fracture risk score greater than 8.4% for a postmenopausal woman under 65 years old should get a central DXA. Younger postmenopausal women are at greater risk for a vertebral fracture. With her family history of breast cancer, she could be a candidate for raloxifene as long as she does not have osteoporosis at the hip. Since her FRAX suggests a DXA, she should not wait for 5 years. With normal FRAX scores (<8.4%) and no other risks, getting a repeat DXA in 5 years could be acceptable. FRAX scores are screening data. Central DXA would be needed for a diagnosis. Practicing a bone healthy lifestyle is good for everyone including this woman, but she needs to get a DXA now. See the "Risk Factor Assessment." "Monitoring of Patient-Centered Care Plan," and "Pharmacologic Therapy" sections, Fig. 112-3, and Table 112-8.

13. **A.** If a man has both symptomatic hypogonadism and osteoporosis with a high risk of fracture, he would be prescribed both testosterone and a first line osteoporosis medication, one of the infrequent times combination therapy is advocated. The provider might start one medication first to check for tolerance and then add the next medication. Testosterone has a positive effect on bone but is generally insufficient alone to prevent osteoporosis and osteoporotic fractures. An older man has a high risk for hip fracture, requiring a first-line medication such as alendronate, risedronate, zoledronic acid, and denosumab. Ibandronate does not decrease hip fracture risk. See sections "Pathophysiology" (Male Osteoporosis), "Pharmacologic Therapy" (Hormone Therapies [Testosterone]), and (Sequential and Combination Therapy) sections.

14. **C.** This woman is categorized as low fracture risk since her Z-scores are above –3.0 and she hasn't had a fragility fracture. The American College of Rheumatology does not recommend any prescription therapy for patients on glucocorticoids with low fracture risk. Due to secondary causes or medications, premenopausal women can develop osteoporosis. Glucocorticoids are the medications that cause the most medication-induced osteoporosis. Bisphosphonates stay in bone for long durations and could have an impact on the fetus during pregnancy, so childbearing status needs to be determined and considered. If a woman does not become pregnant while on therapy and needs bone loss and fracture prevention, the benefit of a bisphosphonate or denosumab could be considered greater than the risk; however, the woman needs to be educated about all benefits, risks, and unknown fetal toxicities to make this decision about a future pregnancy. Data on osteoporosis medications for fracture prevention in children, and premenopausal and pregnant women are limited or nonexistent. Calcium and vitamin D are assumed safe during pregnancy. They have some effects on decreasing bone density. In premenopausal women, only the Z-score is evaluated and if <–2.0 she is labeled as bone mass below the expected range for age, not as having osteoporosis (unless she has had the required number of fragility fractures) per International Society of Bone Densitometry guidelines. The T-scores will be used with FRAX to determine her osteoporosis risk and medication choices. FRAX scores need to be increased by 1.15 for major osteoporotic fracture and by 1.2 for hip fracture for interpretation. (see the "Nonpharmacologic Therapy" (Calcium, Vitamin D, and Phytoestrogens), "Special Populations" (Premenopausal Women, and Glucocorticoid-Induced Osteoporosis)] sections. See Tables 112-7 and 112-8.

15. **B.** Glucocorticoids can cause bone loss, osteoporosis, and osteoporotic fractures and require osteoporosis medications to prevent these conditions. Bisphosphonates are used to prevent glucocorticoid-induced bone loss. Bisphosphonates are also used to prevent postmenopausal osteoporosis, so this medication would be used for both indications. Teriparatide has evidence to help prevent osteoporosis while on glucocorticoids but no data exist yet for romosozumab. See the "Medication-Induced Secondary Causes of Osteoporosis" and "Glucocorticoid-Induced Osteoporosis" sections