Chapter 3: Osteoporosis

INTRODUCTION

- *Osteoporosis* is a bone disorder characterized by low bone density, impaired bone architecture, and compromised bone strength predisposing to fracture.

PATHOPHYSIOLOGY

- Bone loss occurs when resorption exceeds formation, usually from high bone turnover when the number or depth of bone resorption sites greatly exceeds the ability of osteoblasts to form new bone. Accelerated bone turnover can increase the amount of immature bone that is not adequately mineralized.
- Men and women begin to lose bone mass starting in the third or fourth decade because of reduced bone formation. Estrogen deficiency during menopause increases osteoclast activity, increasing bone resorption more than formation. Men are at a lower risk for developing osteoporosis and osteoporotic fractures because of larger bone size, greater peak bone mass, increase in bone width with aging, fewer falls, and shorter life expectancy. Male osteoporosis results from aging or secondary causes.
- Age-related osteoporosis results from hormone, calcium, and vitamin D deficiencies; decreased production or function of cytokines; decreased body water; less exercise; and other factors that result in accelerated bone turnover and reduced osteoblast formation.
- Drug-induced osteoporosis may result from systemic corticosteroids, excessive thyroid hormone replacement, antiepileptic drugs (eg, phenytoin, phenobarbital), depot medroxyprogesterone acetate, and other agents.

CLINICAL PRESENTATION

- Many patients are unaware that they have osteoporosis and only present after fracture. Fractures can occur after bending, lifting, or falling or independent of any activity.
- The most common fractures involve vertebrae, proximal femur, and distal radius (wrist or Colles fracture). Vertebral fractures may be asymptomatic or present with moderate to severe back pain that radiates down a leg. Pain usually subsides after 2–4 weeks, but residual back pain may 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.

DIAGNOSIS

- The FRAX tool uses the following risk factors to predict the percent probability of fracture in the next 10 years: age, race/ethnicity, sex, previous fragility fracture, parent history of hip fracture, body mass index, glucocorticoid use, current smoking, alcohol (≥3 drinks per day), rheumatoid arthritis, and select secondary causes with femoral neck or total hip bone mineral density (BMD) data optional.
- The Garvan calculator uses four risk factors (age, sex, low-trauma fracture, and falls) with the option to also use BMD. It calculates 5- and 10-year risk estimates of any osteoporotic/fragility fracture and hip fracture. This tool corrects some disadvantages of FRAX because it includes falls and number of previous fractures, but it does not use as many other risk factors.
- Physical examination findings may include bone pain, postural changes (ie, kyphosis), and loss of height (>1.5 in [3.8 cm]).

- Laboratory testing: complete blood count, serum creatinine, calcium, phosphorus, electrolytes, alkaline phosphatase, albumin, thyroid-stimulating hormone, total testosterone (for men), 25-hydroxyvitamin D, and 24-hour urine concentrations of calcium and phosphorus.
- Measurement of central (hip and spine) BMD with dual-energy x-ray absorptiometry (DXA) is the diagnostic standard. Measurement at peripheral sites (forearm, heel, and finger) with DXA or quantitative ultrasonography is used only for screening and for determining need for further testing.
- A T-score compares the patient's BMD to the mean BMD of a healthy, young (20- to 29-year-old), sex-matched, white reference population. The T-score is the number of standard deviations from the mean of the reference population.
- Diagnosis of osteoporosis is based on low-trauma fracture or femoral neck, total hip, and/or spine DXA using World Health Organization (WHO) T-score thresholds. Normal bone mass is T-score above −1, low bone mass (osteopenia) is T-score between −1 and −2.4, and osteoporosis is T-score at or below −2.5.

TREATMENT

- Goals of Treatment: The primary goal of osteoporosis care is prevention. Optimizing peak bone mass when young reduces the future incidence of osteoporosis. After low bone mass or osteoporosis develops, the objective is to stabilize or improve bone mass and strength and prevent fractures. Goals in patients with osteoporotic fractures include reducing pain and deformity, improving function, reducing falls and fractures, and improving quality of life.
- **Figure 3-1** provides an osteoporosis management algorithm for postmenopausal women and men ages 50 and older.

FIGURE 3-1

Algorithm for the management of osteoporosis in postmenopausal women and men aged 50 and older.

(BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; FRAX, World Health Organization Fracture Risk Assessment Tool.)

image

Nonpharmacologic Therapy

- All individuals should have a balanced diet with adequate intake of **calcium** and **vitamin D** (**Table 3-1**). Achieving daily calcium requirements from calcium-containing foods is preferred.

  ✔ Consumers can calculate the amount of calcium in a food serving by adding a zero to the percentage of the daily value on food labels. One serving of milk (8 oz or 240 mL) has 30% of the daily value of calcium; this converts to 300 mg of calcium per serving.

  ✔ To calculate the amount of vitamin D in a food serving, multiply the percent daily value of vitamin D listed on the food label by 4. For example, 20% vitamin D = 80 units.
- Protein is required for bone formation; the recommended dietary allowance (RDA) is 0.8 g/kg body weight per day for adults, increasing to 1–1.2 g/kg body weight in older adults.
- Alcohol consumption should not exceed 1–2 drinks per day for women and 2–3 drinks per day for men.
- Ideally, caffeine intake should be limited to 2 or fewer servings per day.
- Smoking cessation helps optimize peak bone mass, minimize bone loss, and ultimately reduce fracture risk.
- Weight-bearing aerobic and strengthening exercises can decrease risk of falls and fractures by improving muscle strength, coordination, balance, and mobility.
- Fall prevention programs that are multifactorial can decrease falls, fractures, other injuries, and nursing home and hospital admissions.

- Vertebroplasty and kyphoplasty involve injection of cement into fractured vertebra(e) for patients with debilitating pain from compression fractures. Although intended to stabilize damaged vertebrae, reduce pain, and decrease opioid intake, recent research demonstrated only short-term benefit with no major pain relief and the potential for post-procedure complications.

TABLE 3-1

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–6 months	200[b]	1000	400[b]	1000
7–12 months	260[b]	1500	400[b]	1500
Children				
1–3 years	700	2500	600	2500
4–8 years	1000	2500	600	3000
9–18 years	1300	3000	600	4000
Adults				
19–50 years	1000	2500	600[b,c]	4000
51–70 years (men)	1000	2000	600[b,c]	4000
51–70 years (women)	1200	2000	600[b,c]	4000
>70 years	1200	2000	800[b,c]	4000

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

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

[c]Guidelines recommend 800–1000 units or 1000–2000 units for adults with osteoporosis.

PHARMACOLOGIC THERAPY

General Approach

- Combined with adequate calcium and vitamin D intakes, alendronate, risedronate, zoledronic acid, and denosumab are the prescription medications of choice because they reduce both hip and vertebral fracture risks.

- Abaloparatide, bazedoxifene/conjugated equine estrogens, ibandronate, raloxifene, romosozumab, and teriparatide are second-line alternatives because they decrease vertebral but not hip fracture risks.
- Calcitonin is last-line therapy.
- Estrogen and testosterone are not used for osteoporosis treatment but can have a positive bone effect when prescribed for other conditions.

Antiresorptive Therapy

Calcium Supplementation

- Calcium generally maintains or increases BMD slightly, but its effects are less than those of other therapies. There are insufficient data to support using calcium and vitamin D supplementation to reduce fracture incidence. Because the fraction of calcium absorbed decreases with increasing dose, maximum single doses of 600 mg or less of elemental calcium are recommended.
- **Calcium carbonate** is the salt of choice because it contains the highest concentration of elemental calcium (40%) and is typically least expensive. It should be ingested with meals to enhance absorption in an acidic environment.
- **Calcium citrate** (21% calcium) has acid-independent absorption and need not be taken with meals. It may have fewer GI side effects than calcium carbonate.
- **Tricalcium phosphate** contains 38% calcium, but calcium-phosphate complexes could limit overall calcium absorption. It may be useful in patients with hypophosphatemia that cannot be resolved with increased dietary intake.
- Constipation is the most common calcium-related adverse reaction; treat with increased water intake, dietary fiber (given separately from calcium), and exercise. Calcium carbonate can sometimes cause flatulence or upset stomach. Calcium causes kidney stones rarely.
- Calcium can decrease the oral absorption of some drugs including iron, tetracyclines, quinolones, bisphosphonates, and thyroid supplements.

Vitamin D Supplementation

- **Vitamin D** supplementation using 700–800 units per day has been shown to significantly reduce the incidence of both hip and nonvertebral fractures with small increases in BMD.
- Supplementation is usually provided with daily nonprescription cholecalciferol (vitamin D_3) products. Higher-dose prescription ergocalciferol (vitamin D_2) regimens given weekly, monthly, or quarterly may be used for replacement and maintenance therapy. The RDAs in **Table 3-1** should be achieved through food and supplementation.
- Current guidelines recommend treating patients with osteoporosis to a 25-hydroxyvitamin D concentration of at least 30 ng/mL (mcg/L; 75 nmol/L) or 30–50 ng/mL.
- Because the half-life of vitamin D is about 1 month, recheck the vitamin D concentration after about 3 months of therapy.
- Medications that can induce vitamin D metabolism include 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.

Bisphosphonates

- Bisphosphonates (**Table 3-2**) mimic pyrophosphate, an endogenous bone resorption inhibitor. Therapy leads to decreased osteoclast maturation, number, recruitment, bone adhesion, and life span. Incorporation into bone gives bisphosphonates long biologic half-lives of up to 10 years.

- Bisphosphonates consistently increase BMD and reduce fracture risk, with differences in sites of fracture reduction among agents. Ibandronate is not a first-line therapy because of the lack of hip fracture reduction data.
- BMD increases are dose dependent and greatest in the first 12 months of therapy. After discontinuation, the increased BMD is sustained for a prolonged period that varies per bisphosphonate.
- **Alendronate**, **risedronate**, and **IV zoledronic acid** are Food and Drug Administration (FDA) indicated for postmenopausal, male, and glucocorticoid-induced osteoporosis. **IV and oral ibandronate** are indicated only for postmenopausal osteoporosis. Weekly alendronate, weekly and monthly risedronate, and monthly oral and quarterly IV ibandronate therapy produce equivalent BMD changes to their respective daily regimens.
- Oral bisphosphonates must be administered correctly to optimize clinical benefit and minimize adverse GI effects. Each oral tablet should be taken in the morning with at least 6 oz (180 mL) of plain water (not coffee, juice, mineral water, or milk) at least 30 minutes (60 minutes for oral ibandronate) before consuming any food, supplements, or medications. An exception is delayed-release risedronate, which is administered immediately after breakfast with at least 4 oz (120 mL) of plain water. The patient should remain upright (sitting or standing) for at least 30 minutes after alendronate and risedronate and 1 hour after ibandronate to prevent esophageal irritation and ulceration.
- If a patient misses a weekly dose, it can be taken the next day. If more than 1 day has elapsed, that dose is skipped. If a patient misses a monthly dose, it can be taken up to 7 days before the next scheduled dose.
- The most common bisphosphonate adverse effects include nausea, abdominal pain, and dyspepsia. Esophageal, gastric, or duodenal irritation, perforation, ulceration, or bleeding may occur. The most common adverse effects of IV bisphosphonates include fever, flu-like symptoms, and local injection-site reactions.
- Rare adverse effects include osteonecrosis of the jaw (ONJ) and subtrochanteric femoral (atypical) fractures. ONJ occurs more commonly in patients with cancer receiving higher-dose IV bisphosphonate therapy and other risk factors including glucocorticoid therapy and diabetes mellitus.
- The optimal duration of bisphosphonate therapy is unknown. Some experts recommend considering a bisphosphonate holiday (defined as disruption of therapy during which medication effects exist with a plan for medication reinstitution) in postmenopausal women after 5 years of oral bisphosphonates or 3 years of IV bisphosphonates if no significant fracture history, hip BMD T-score is above –2.5, and fracture risk is not high. In women with a high fracture risk or lower hip BMD T-scores, continuing oral bisphosphonates for 10 years or IV bisphosphonates for 6 years should be considered. A bisphosphonate holiday should last for ≤5 years with BMD and patient assessment done every 2–4 years.

TABLE 3-2

Medications Used to Prevent and Treat Osteoporosis

Drug	Brand Name	Dose	Comments
Antiresorptive Medications—Nutritional Supplements			
Calcium	Various	*Adequate daily intake:* IOM: 200–1200 mg/day, varies per age); supplement dose is difference between required adequate intake and dietary intake. Immediate-release doses should be <500–600 mg.	Recommend food 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 to create a serving size and desired amount of elemental calcium. Give calcium carbonate with meals to improve absorption.
Vitamin D	Over the	Adequate daily intake: IOM: 400–800	Vegetarians and vegans need to read label to determine if a plant-based

D_3 (cholecalciferol) D_2 (ergocalciferol)	counter. Tablets, 400, 1000, and 2000 units Capsule, 400, 1000, 2000, 5000, and 10,000 units Gummies, 300, 500, 1000 units Drops 300, 400, 1000, and 2000 units/mL or drop Solution, 400 and 5000 units/mL Spray 1000 and 5000 units/spray Creams and lotions 500 and 1000 units per ¼ teaspoonful Prescription. Capsule, 50,000 units Solution, 8000 units/mL	units/day to achieve adequate intake; NOF: 800–1000 units orally daily; if low 25(OH) vitamin D concentrations, malabsorption, or altered metabolism higher doses (>2000 units daily) might be required. *Vitamin D deficiency:* 50,000 units orally once to twice weekly for 8–12 weeks; repeat as needed until therapeutic concentrations.	product. Slight advantage of D_3 over D_2 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 unknown.
Antiresorptive Prescription Medications			
Bisphosphonates			
Alendronate	Fosamax Fosamax Plus D Binosto (effervescent tab)	Treatment: 10 mg orally daily or 70 mg orally weekly Prevention: 5 mg orally daily or 35 mg orally weekly	Generic available for weekly tablet product. 70 mg dose is available as a tablet, effervescent tablet, oral liquid or combination tablet with 2800 or 5600 units of vitamin D_3. Administered in the morning on an empty stomach with 6–8 ounces of plain water. Do not eat and remain upright for at least 30 minutes following administration. Do not coadminister with any other medication or supplements, including calcium and vitamin D.
Ibandronate	Boniva	Treatment: 150 mg orally monthly, 3	Generic available for oral product.

		mg IV quarterly Prevention: 150 mg orally monthly	Administration instructions same as for alendronate, except must delay eating and remain upright for at least 60 minutes.
Risedronate	Actonel Atelvia (delayed-release)	Treatment and prevention: 5 mg orally daily, 35 mg orally weekly, 150 mg orally monthly	Generic available for immediate-release product. 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.
Zoledronic acid	Reclast	Treatment: 5 mg IV infusion yearly Prevention: 5 mg IV infusion every 2 years	Can premedicate with acetaminophen to decrease infusion reactions. Contraindicated if CrCl <35 mL/min Also marketed under the brand name Zometa (4 mg) for treatment of hypercalcemia and prevention of skeletal-related events from bone metastases from solid tumors with different dosing.
RANK Ligand Inhibitor			
Denosumab	Prolia	Treatment: 60 mg SC every 6 months	Administered by a healthcare practitioner. Correct hypocalcemia before administration. Also marketed under the brand name Xgeva (70 mg/mL) for treatment of hypercalcemia and prevention of skeletal-related events from bone metastases from solid tumors with different dosing.
Estrogen Agonist/Antagonist and Tissue Selective Estrogen Complex			
Raloxifene	Evista	60 mg orally daily	Generic available
Bazedoxifene with conjugated equine estrogens (CEE)	Duavee	20 mg plus 0.45 mg CEE orally daily	For postmenopausal women with a uterus; no progestogen needed. Bazedoxifene monotherapy available in some countries.
Calcitonin (salmon)	Fortical	200 units (1 spray) intranasally daily, alternating nares every other day.	Generic available. Also available as an SC injection. Refrigerate nasal spray until opened for daily use, then room temperature. Prime with first use.
Formation Medications			
Recombinant human parathyroid hormone (PTH 1–34 units)			
Teriparatide	Forteo	20 mcg SC daily for up to 2 years	First dose sitting or lying. Refrigerate before and after each use. Use new needle with each dose. Inject thigh or stomach. Discard after 28 days or if cloudy.
Human parathyroid hormone–related peptide (PTHrP[1–34]) analog			
Abaloparatide	Tymlos	80 mcg SC 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 SC 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. Inject in abdomen, thigh, or upper arm; preferably each injection at a different site.

IOM, Institute of Medicine; IV, intravenously; NOF, National Osteoporosis Foundation; NSAID, nonsteroidal anti-inflammatory drug; SC, subcutaneously.

Data from product prescribing information.

Denosumab

- **Denosumab** (Prolia) is a RANK ligand inhibitor that inhibits osteoclast formation and increases osteoclast apoptosis. It is indicated for treatment of osteoporosis in women and men at high risk for fracture, for glucocorticoid-induced osteoporosis, 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.
- Over 3 years, denosumab significantly decreased vertebral fractures, nonvertebral fractures, and hip fractures in postmenopausal women with low bone density. Continued increases in BMD occur with long-term treatment with no plateau in BMD effects over 10 years.
- Denosumab is administered as a 60-mg subcutaneous (SC) injection in the upper arm, upper thigh, or abdomen once every 6 months.
- Adverse reactions not associated with the injection site include back pain, arthralgia, and infection. ONJ and atypical femoral shaft fracture occur rarely. Denosumab is contraindicated in patients with hypocalcemia until the condition is corrected.
- After 5–10 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

- **Raloxifene** (Evista) is an estrogen agonist/antagonist that is an estrogen agonist on bone receptors but an antagonist at breast receptors, with minimal effects on the uterus. It is approved for prevention and treatment of postmenopausal osteoporosis and for reducing the risk of invasive breast cancer in postmenopausal women with and without osteoporosis.
- **Bazedoxifene** is an estrogen agonist/antagonist that is an agonist at bone and antagonist at the uterus and breast; however, it has no breast cancer prevention effects. The proprietary product Duavee is combined with **conjugated equine estrogens** (CEE), making it a tissue-selective estrogen complex. It is approved for prevention of postmenopausal osteoporosis and vasomotor menstrual symptoms.
- Raloxifene and bazedoxifene decrease vertebral but not hip fractures. The drugs increase spine and hip BMD, but to a lesser extent than bisphosphonates. Data for both drugs support beneficial effects for up to 7–8 years of use. However, the benefit is lost after discontinuation, and bone loss returns to age- or disease-related rates.
- Hot flushes are common with raloxifene but decreased with bazedoxifene/CEE. Raloxifene rarely causes endometrial thickening and bleeding; bazedoxifene decreases these events making progestogen therapy unnecessary when combined with CEE. Leg cramps and muscle spasms are common with these agents. Thromboembolic events are uncommon (<1.5%) but can be fatal. Bazedoxifene/CEE has all of the contraindications and precautions for estrogens as a class.

Calcitonin

- **Calcitonin** is an endogenous hormone released from the thyroid gland when serum calcium is elevated. Salmon calcitonin is used clinically

because it is more potent and longer lasting than the mammalian form.

- Calcitonin is indicated for osteoporosis treatment for women at least 5 years past menopause. An FDA Advisory Committee Panel voted against continued use for postmenopausal osteoporosis, but it can be used if alternative therapies are not appropriate.
- Only vertebral fractures have been documented to decrease with intranasal calcitonin therapy. Calcitonin does not consistently affect hip BMD. No calcitonin data exist for men. Intranasal calcitonin may provide some pain relief in patients with acute vertebral fractures, but such use should be short-term (4 weeks) and not in place of other more appropriate analgesic or osteoporosis therapy.

Hormone Therapies

- Hormone therapies (**estrogen** and **testosterone**) are not recommended solely for osteoporosis but have positive bone effects when used for other indications. Estrogen therapy can be a good choice for women going through early menopause when protection against bone loss is needed in addition to reduction of vasomotor symptoms, reserving other osteoporosis therapy until treatment is reassessed closer to the average age of menopause.
- Estrogen with or without a progestogen significantly decreases fracture risk and bone loss in women. Oral and transdermal estrogens at equivalent doses and continuous or cyclic regimens have similar BMD effects. Effect on BMD is dose dependent, with some benefit seen with lower estrogen doses. When estrogen therapy is discontinued, bone loss accelerates and fracture protection is lost.
- Testosterone is used to treat hypogonadism in men, but an osteoporosis medication should be added when risk for osteoporotic fracture is high. No fracture data are available, but some data support minor bone loss prevention for testosterone use in men and women.

Formation Medications

Parathyroid Hormone Analogs

- **Abaloparatide** (Tymlos) is an analog of parathyroid hormone-related peptide (PTHrP), and **teriparatide** (Forteo) and **PF708** (approved with Forteo [teriparatide injection] as the reference drug) are analogs of parathyroid hormone (PTH); these agents are indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as multiple risk factors for fracture, history of osteoporotic fracture, or failure or intolerance to other therapies. Teriparatide is also FDA approved for men with idiopathic or hypogonadal osteoporosis who are at high risk for fracture, men intolerant to other osteoporosis medications, and patients with glucocorticoid-induced osteoporosis.
- Teriparatide increases bone formation with a minor increase in bone resorption for a net anabolic effect when administered intermittently (ie, subcutaneously once daily). Abaloparatide has a greater anabolic effect with less activation of bone resorption and remodeling than teriparatide. Both medications improve bone mass.
- Two years of teriparatide or abaloparatide reduces vertebral and nonvertebral fracture risk in postmenopausal women. Observational teriparatide data suggest a similar fracture benefit in men, whereas no data are available regarding abaloparatide use in men. Discontinuation of PTH analog therapy results in decreased BMD, which can be alleviated with subsequent antiresorptive therapy.
- Transient hypercalcemia can occur and is less common with abaloparatide than teriparatide (3.4% vs 6.4%, respectively). Because of an increased incidence of osteosarcoma in rats, both medications contain a box warning against use in patients at increased risk for osteosarcoma; this adverse effect has not occurred in people. PTH analogs should not be used in patients with hypercalcemia, metabolic bone diseases other than osteoporosis, metastatic or skeletal cancers, or premenopausal women of childbearing potential.

Formation and Antiresorptive Medication

Romosozumab

- **Romosozumab** (Evenity) is a humanized monoclonal antibody that binds to sclerostin to prevent inhibition of bone formation and decrease bone resorption, an activity that differentiates this medication from other anabolic therapies. It indicated for postmenopausal women at high risk for fracture defined as multiple risk factors for fracture, a history of osteoporotic fracture, or failure or intolerance to other therapies.

- After 1 year of therapy in postmenopausal women, vertebral fractures decreased by 73%, with a nonsignificant decrease in nonvertebral fractures of 25%; lumbar spine and hip BMD statistically increase after 1 year of treatment. To prevent BMD loss after discontinuation, 1 year of denosumab or alendronate after romosozumab resulted in BMD continuing to increase at both sites.

- The most common adverse effects are headache and arthralgia; hypercalcemia occurs in <1% of patients. Mild injection site irritation occurs in 6%–8% of patients. Romosozumab antibodies may occur in 10%–20% of patients but are generally not neutralizing and do not reduce efficacy. Serious cardiovascular events have been reported, and the labeling contains a boxed warning of an increased risk of myocardial infarction (MI), stroke, and cardiovascular death. Romosozumab should not be used within 1 year of an MI or stroke, and benefit–risk evaluation should be conducted in patients with or at risk for these conditions. Rare cases of ONJ and atypical femoral fractures have been reported.

- Therapy should be limited to 12 monthly doses. If osteoporosis therapy remains warranted, continued therapy with an antiresorptive agent should be considered.

Sequential and Combination Therapy

- 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. 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 increases but may be especially useful for patients who have fractured or continue to lose bone mass while on antiresorptive therapy.

  ✔ Small increases in BMD can occur after switching from an oral bisphosphonate to denosumab. This sequential therapy can be used during a bisphosphonate drug holiday or for bisphosphonate treatment failures (ie, no BMD changes or fracture).

- Combination therapy is rarely used because of no documented fracture benefit, increased cost, concern for dual suppression of bone turnover, and potential for more adverse effects. When raloxifene is used for breast cancer prevention, another antiresorptive agent is sometimes prescribed, especially if hip fracture risk is high.

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

- Glucocorticoids decrease bone formation through decreased proliferation and differentiation as well as enhanced apoptosis of osteoblasts. They also increase the number of osteoclasts, increase bone resorption, decrease calcium absorption, and increase renal calcium excretion.

- All glucocorticoid doses and formulations have been associated with increased bone loss and fractures; however, risk is much greater with oral prednisone doses ≥5 mg daily (or equivalent) and oral therapy vs inhaler or intranasal therapy.

- Bone losses are rapid, with up to 12%–15% loss over the first year; the greatest decrease occurs in the first 6 months of therapy. Bone loss is about 2%–3% per year after the first year.

- Perform an initial BMD assessment prior to or within 6 months of glucocorticoid initiation for adults ≥40 years of age and for adults <40 years of age with a history of fragility fracture or other risk factors. Repeat BMD testing is recommended every 2–3 years during osteoporosis therapy for those taking very high glucocorticoid doses (≥30 mg prednisone per day or a cumulative dose >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.

- All patients starting or receiving systemic glucocorticoid therapy (any dose or duration) should practice a bone-healthy lifestyle and ingest 1000–1200 mg elemental calcium and 600–800 units of vitamin D daily to achieve therapeutic 25-hydroxyvitamin D concentrations. Use the lowest possible corticosteroid dose and duration.

- Treatment guidelines divide recommendations for prescription medication use by fracture risk and age. Alendronate, risedronate, zoledronic acid, denosumab, and teriparatide are FDA approved for glucocorticoid-induced osteoporosis.

- Standard osteoporosis therapy doses are used. Oral bisphosphonates are recommended first-line, although IV bisphosphonates can be used in nonadherent patients or those 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 as first-line therapy due to limited safety data in this population. Raloxifene does not have an FDA indication for this use, but there are clinical data documenting improved BMD at the lumbar spine in patients taking glucocorticoids.

EVALUATION OF THERAPEUTIC OUTCOMES

- Assess medication adherence and tolerability at each visit.
- Ask patients about possible fracture symptoms (eg, bone pain, disability) at each visit. Assessment of fracture, back pain, and height loss can help identify worsening osteoporosis.
- Obtain a central DXA BMD measurement after 1–2 years or 3–5 years after initiating a medication therapy to monitor response. Repeat a central DXA every 2 years until BMD is stable, at which time the reassessment interval can be lengthened. More frequent monitoring may be warranted in patients with conditions associated with high rates of bone loss (eg, glucocorticoid use).

See Chapter 108, Osteoporosis, authored by Mary Beth O'Connell, Jill S. Borchert, Erin M. Slazak, and Joseph P. Fava for a more detailed discussion of this topic.