OSTEOPOROSIS
A REVIEW

Osteoporosis: Definition and Clinical Perspective

- Osteoporosis is a skeletal disease characterized by low bone mass and deterioration of bone microarchitecture.
- These abnormalities increase bone fragility and substantially raise the risk of fractures.

Global Burden of Osteoporosis

- Osteoporotic fractures are a major cause of disability and loss of independence in older adults.
- Osteoporosis affects both women and men, although it is more commonly recognized in older women.
- Approximately one-third of osteoporotic fractures occur in older men.
- The mortality rate during the first year after hip fracture is approximately 24%, with persistent impairment in mobility and function.

PATHOPHYSIOLOGY

Bone Development and Remodeling

- Skeletal development during childhood and adolescence depends primarily on new bone formation and bone modeling.
- After skeletal maturity, bone maintenance depends mainly on continuous bone remodeling.
- Remodeling involves removal of older or damaged bone followed by formation of new bone.
- Osteoclasts are responsible for bone resorption, whereas osteoblasts produce new bone tissue.
- Balanced activity between these cell types is essential for maintaining bone strength and structural integrity.
- Disruption of this balance can result in progressive bone loss and increased fracture susceptibility.

Cellular Regulation of Bone Remodeling

- Bone remodeling is regulated by several interconnected cellular and molecular signaling pathways.
- The Wnt–LRP4/5/6–sclerostin pathway plays an important role in regulating osteoblast activity and bone formation.
- The osteoprotegerin–RANK–RANKL system is a major regulator of osteoclast differentiation and bone resorption.
- .

RISK FACTORS

Determinants of Peak Bone Mass

- Osteoporosis may result from failure to achieve optimal peak bone mass, excessive bone loss later in life, or both.
- Peak bone mass is usually reached during early adulthood by the end of the second decade of life.
- Genetic factors have a major influence on both peak bone mass and the subsequent rate of bone loss.
- Adequate calcium intake and regular physical activity contribute importantly to optimal skeletal development.
- Sex hormones :estrogen,progestron,testosterone, growth hormone, and other endocrine factors also regulate bone acquisition and maintenance.

Major Risk Factors for Osteoporosis

- **Premature menopause before the age of 40 years** is an important risk factor because of prolonged **estrogen deficiency.**
- **Hypogonadism**, **low BMI below 20**, **weight loss**, and **nutritional deficiencies** can adversely affect skeletal health.
- **Vitamin D and calcium deficiencies** may further compromise bone mineralization and bone strength.
- **Immobility** and **chronic diseases** such as **inflammatory bowel disease**, **rheumatoid arthritis**, and **chronic kidney or liver disease** are also associated with bone loss.
- Current **smoking** and **high alcohol** consumption, particularly approximately **three or more drinks per day**, increase the risk of osteoporosis.
- **Medication**:glucocorticoid,aromatase inhibitors: anastrozole and letrozole,androgen deprivation :leuprolide bicalutamide

Medication-Associated Bone Loss

- Several commonly used medications can accelerate bone loss or increase fracture risk.
- Glucocorticoid therapy is a well-established cause of secondary osteoporosis.
- Aromatase inhibitors such as anastrozole and letrozole reduce estrogen activity and can adversely affect bone health.
- *Androgen-deprivation therapies*, including agents such as leuprolide and bicalutamide, may also increase skeletal fragility.

CLINICAL PRESENTATION

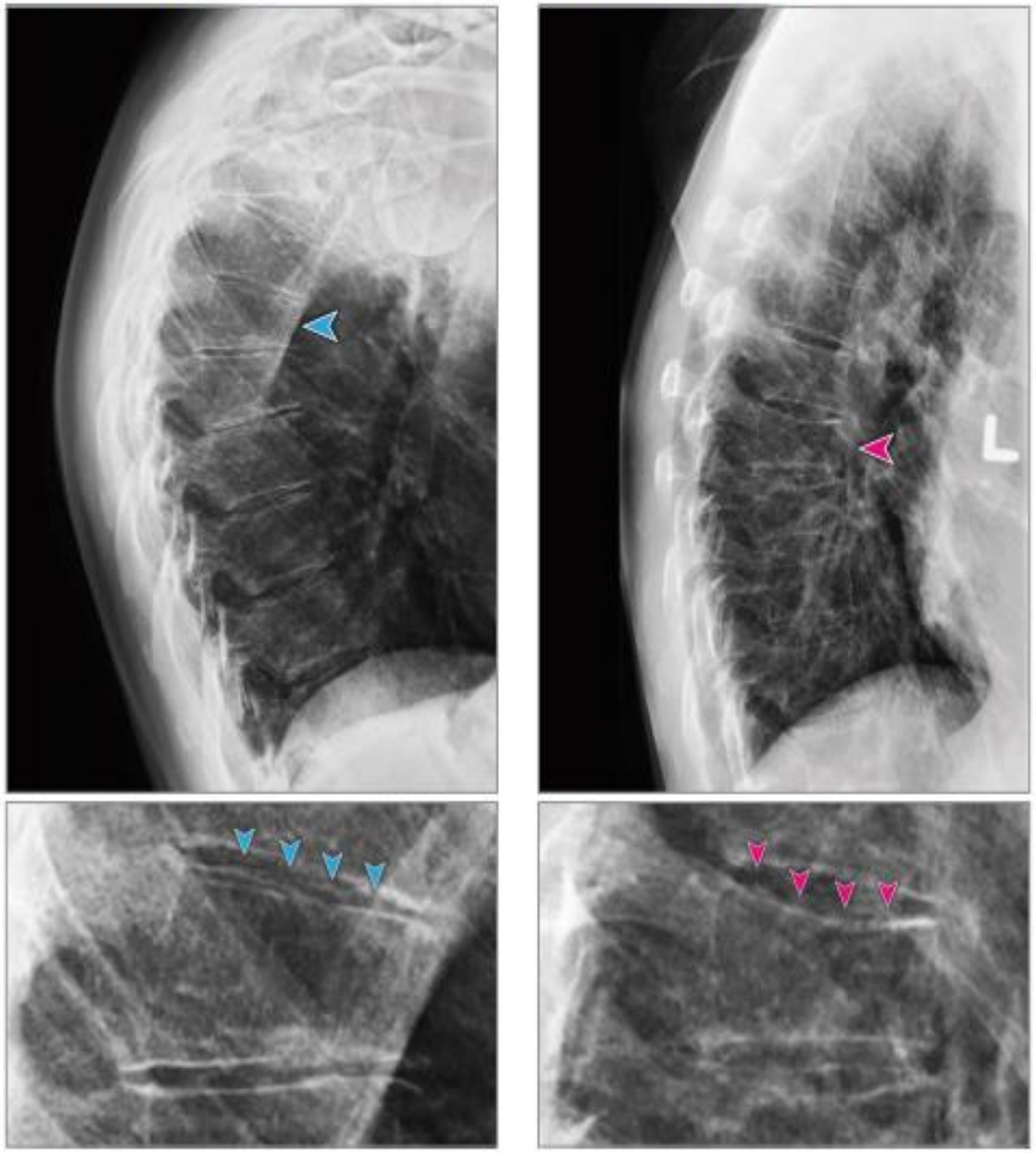
Clinical Presentation of Osteoporosis

- Osteoporosis is frequently asymptomatic until a fracture occurs.
- Clinical presentation may include a painful fracture or an asymptomatic vertebral fracture detected on imaging.
- Approximately two-thirds of vertebral fractures remain clinically undiagnosed.
- Common osteoporotic fracture sites include the hip, spine, shoulder, forearm, and pelvis.
- Fractures involving the hands, feet, and craniofacial bones are generally not considered typical osteoporotic fractures.

Figure 1. Radiographic Images of the Thoracic Spine

A Lateral thoracic spine radiograph of nonfracture deformity (top) and close-up (bottom)

B Lateral thoracic spine radiograph of fracture deformity (top) and close-up (bottom)



A, Nonfracture deformity is shown with the wedge-shaped vertebral body (arrowheads) and without superior end plate depression (arrowheads). B, Fracture deformity is shown with the wedge-shaped vertebral body (arrowheads) and with a depressed superior end plate (arrowheads).

Vertebral Fractures: Clinical Clues

- **Progressive loss of height** can suggest vertebral compression and cumulative **vertebral deformity**.
- Increased horizontal distance between the **occiput and the wall** may indicate **kyphotic** spinal deformity.
- **Vertebral height loss** can also reduce the space between the **lower ribs and the pelvis**.

Fracture Trauma and Osteoporosis

- **Osteoporotic fractures were traditionally defined as fragility fractures occurring after minimal trauma.**
- **A typical example is a fracture resulting from a fall from standing height or a similarly low-energy event.**
- **Fractures caused by extreme trauma or local pathology, such as malignancy, should instead be excluded from osteoporosis-related risk assessment.**

ASSESSMENT AND DIAGNOSIS

BMD, DXA and Clinical Diagnosis

- Most clinical guidelines recommend assessment of osteoporosis risk factors in postmenopausal women and men older than 50 years.
- A previous fracture is one of the strongest clinical predictors of future fracture.
- A history of at least one fall during the previous year also substantially increases fracture risk.
- DXA provides a standardized measurement of BMD and remains central to fracture-risk assessment.
- A T-score of −2.5 or lower is classified as osteoporosis when compared with the BMD of young healthy adults.

FRAX: Individualized Fracture Risk Assessment

- FRAX is the most widely used clinical fracture-risk assessment tool.
- It estimates the 10-year probability of hip fracture and major osteoporotic fracture.
- The calculation incorporates age, sex, BMI, and selected clinical risk factors.
- Relevant factors include previous fracture, parental history of hip fracture, current smoking, and high alcohol intake.
- FRAX also considers secondary osteoporosis, rheumatoid arthritis, and prolonged glucocorticoid exposure.
- Other fracture prediction tools include the Garvan Fracture Risk Calculator and QFracture.

SCREENING

Who Should Undergo BMD Screening?

- The recommended age for universal BMD screening varies among international clinical guidelines.
- Some guidelines recommend targeted screening of individuals with clinical risk factors for osteoporosis.
- Other approaches recommend fracture-risk assessment in all individuals older than 50 years to identify those at increased risk.
- The Bone Health and Osteoporosis Foundation recommends BMD testing in postmenopausal women aged 50 to 64 years who have clinical risk factors.
- Similar targeted screening is recommended for men aged 50 to 69 years when risk factors such as previous fracture or frequent falls are present.
- Universal BMD screening is recommended for women aged 65 years or older and men aged 70 years or older under these US recommendations.

*Without RF : Women > 65 y

men >70 y

*With RF: women >50 y

men >50 y

Table 1. Assessments Used in the Evaluation and Management of Osteoporosis

	Description	When should this test be used?	Other considerations
Laboratory investigations			
Blood testing	• Measure serum calcium, phosphate, alkaline phosphatase, and creatinine levels and assess thyroid function	Prior to initiating therapy to assess for • Potential secondary causes of osteoporosis (eg, hyperparathyroidism or chronic liver disease) • Potential contraindications to treatment when considering pharmacotherapy (eg, kidney dysfunction) in individuals with osteoporosis (if levels were not measured within prior year)	• Clinical guidelines vary in the extent of testing recommended
Test individuals at risk for vitamin D deficiency	• Measure serum 25-hydroxyvitamin D (25[OH]D) level	• When treating individuals at risk for vitamin D deficiency, including those with malabsorption, liver disease, chronic kidney disease, reduced sun exposure, and after gastric bypass surgery	• Routine follow-up (3 mo after initiation of supplementation) is not recommended for those without risk factors for vitamin D deficiency
Fracture risk assessment tools			
Fracture Risk Assessment Tool (FRAX)[a]	• All 3 tools predict probability of fracture over 1-10 y (depending on the tool used) based on clinical risk factors (with or without measurement of femoral neck for bone mineral density)	• All 3 tools assess absolute fracture risk in adults who are not currently receiving treatment for osteoporosis • Most guidelines recommend assessing fracture risk when ≥50 y of age in both postmenopausal females and in males	• Takes into consideration competing risk of mortality • Bone mineral density is an optional input variable
QFracture (assesses the risk of osteoporotic fracture)			• Bone mineral density is not an input variable
Garvan Fracture Risk Calculator			• Includes the number of falls and prior fractures • Bone mineral density is an optional input variable
Imaging			
Imaging of lateral spine	• Vertebral fracture assessment using conventional radiography or dual-energy x-ray absorptiometry	• To identify the presence of a vertebral fracture in individuals with signs or symptoms of acute vertebral fractures or of occult vertebral fractures (such as height loss and kyphosis)	• A confirmed vertebral fracture on imaging (even if the patient is asymptomatic or it is a remote fracture) is associated with a high fracture risk
Dual-energy x-ray absorptiometry	Areal bone mineral density assessment is • Expressed in g/cm^2 • Expressed as a T score (SDs above or below peak bone mass)	• To assess bone mineral density in both postmenopausal females and in males aged ≥50 y as part of the fracture risk assessment or for monitoring the response to osteoporosis therapy	• Patients are considered to have normal bone mass when the T score is ≥−1.0 • Patients are considered to have low bone mass (osteopenia) when the T score is between −1.0 and −2.5 • Patients are considered to have osteoporosis when the T score is ≤−2.5
Trabecular bone score	• Unitless texture measure derived from dual-energy x-ray absorptiometry images of the lumbar spine, which are only available when specific software is available for the densitometer	• The trabecular bone score can be entered in the FRAX prediction algorithm to assess fracture risk in adults • When available on the bone mineral density report, the trabecular bone score is useful in individuals close to the treatment threshold (indicates when the results are most likely to alter clinical management)	• Adding the trabecular bone score to FRAX improves fracture prediction

[a] Calibrated using individual population-specific fracture and mortality data by country. The country-specific tool is available at https://www.fraxplus.org.

TREATMENT OF OSTEOPOROSIS

Treatment Strategy: General Principles

- The primary goal of osteoporosis treatment is to prevent fragility fractures and preserve functional independence.
- Management should combine lifestyle interventions, fall prevention, adequate nutrition, and pharmacologic therapy when indicated.
- Maintaining a BMI above 20 is recommended because low body weight is associated with increased skeletal fragility.
- Cigarette smoking should be avoided, and excessive daily alcohol consumption should be minimized.

Exercise and Fall Prevention

- Exercise is an important component of fracture prevention because it improves bone health, muscle strength, balance, and physical function.
- Recommended programs include balance, strength, resistance, flexibility, and endurance exercises.
- Progressive resistance training for at least 8 months has been associated with improved femoral neck BMD in adults at increased fracture risk.
- Balance and functional exercises reduce the rate of falls by approximately 24% in community-dwelling adults.

Calcium and Vitamin D: Nutritional Foundations

* calcium in men : 19-70 y : 1000 mg/d

>71 : 1200 mg/d

*Calcium in women: 19-50 y : 1000 mg/d

>51 y : 1200 mg/d

*Vit D : UNTIL 70 : 600 u/d

>70 : 800 u/d

Calcium and Vitamin D Supplementation Evidence

- Routine calcium or vitamin D supplementation does not consistently reduce fracture risk in community-dwelling adults without established osteoporosis or nutritional deficiency.
- Combined calcium and vitamin D supplementation did not significantly reduce hip or other fracture risk in this population.
- Recent meta-analyses found no meaningful improvement in BMD or fracture risk with vitamin D supplementation in adults without established osteoporosis.

Safety and Monitoring of Calcium and Vitamin D

-Excessive calcium supplementation may cause adverse effects such as nephrolithiasis and may potentially increase cardiovascular risk.
Evidence regarding cardiovascular effects is inconsistent, with one large randomized trial showing no increased cardiovascular risk and another meta-analysis suggesting increased risk.
-Routine vitamin D testing is not recommended by the Endocrine Society for otherwise healthy individuals.
-Vitamin D measurement is appropriate in patients at increased risk of deficiency, including those with chronic kidney or liver disease, malabsorption, limited sun exposure, or previous bariatric surgery.
-Testing is also recommended in patients with osteoporosis, fractures, or metabolic bone diseases such as osteomalacia.

PHARMACOTHERAPY

Table 2. Pharmacological Fracture Prevention Therapies

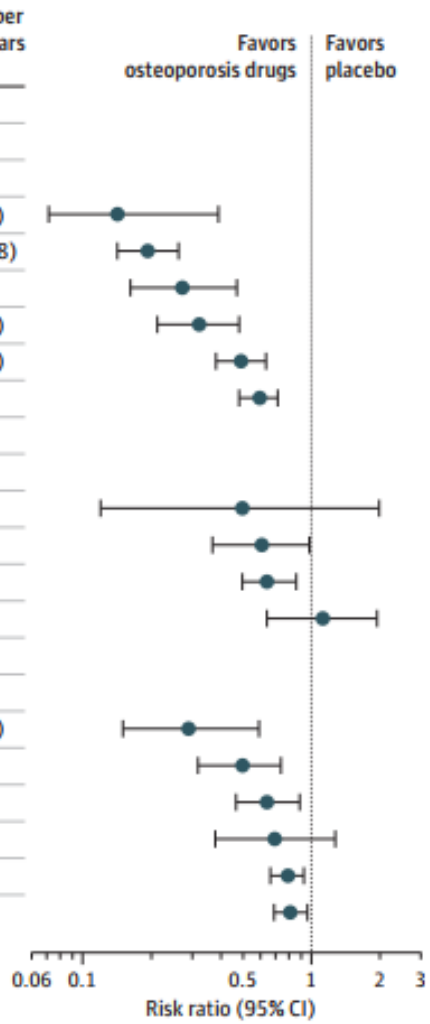
	Drug	Dosage	Mechanism of action	Contraindications	Potential adverse effects
Antiresorptive agents					
Oral bisphosphonate	Alendronate	70 mg/wk	• Direct osteoclast inhibition	Creatinine clearance <30-35 mL/min, hypocalcemia, or esophageal abnormalities (eg, esophagitis or peptic ulcer disease)	Dyspepsia (20%-30% of patients), myalgia (4% of patients), osteonecrosis of the jaw (<0.1% of patients), and atypical femoral fracture (0.02%-0.1% of patients)
	Risedronate	35 mg/wk			
	Ibandronate	150 mg/mo			
Intravenous bisphosphonate	Zoledronic acid	5 mg every 12-18 mo (administered intravenously)	• Direct osteoclast inhibition	Creatinine clearance <30-35 mL/min or hypocalcemia	Headache, myalgia, or fever (30% of patients); transient elevated level of creatinine (2% of patients); kidney failure (rare); hypocalcemia (<1% of patients); osteonecrosis of the jaw (<0.1% of patients); and atypical femur fracture (0.02%-0.1% of patients)
	Ibandronate	3 mg every 3 mo (administered intravenously)			Esophageal abnormalities are not a consideration with the intravenous formulation
RANKL inhibitor	Denosumab	60 mg every 6 mo (administered subcutaneously)	• Reduces osteoclast differentiation and activity due to inhibition of RANKL	Hypocalcemia	Eczema (3% of patients), cellulitis (0.3% of patients), osteonecrosis of the jaw (<0.1% of patients), and atypical femur fracture (0.02%-0.1% of patients)
					Increased risk of vertebral fracture if denosumab dosing is delayed by >1 mo or interrupted
Selective estrogen receptor modulator	Raloxifene	60 mg/d (administered orally)	• Estrogen receptor agonist on bone	Venous thromboembolism, stroke, or cardiovascular disease	Hot flashes (10% of patients), leg cramps (7% of patients), peripheral edema (5% of patients), and deep vein thrombosis (0.9% of patients)
Anabolic agents					
Parathyroid hormone analog	Teriparatide	20 µg/d for 1.5-2 y (administered subcutaneously)	• Stimulation of parathyroid hormone receptor • Increases bone remodeling (formation is greater than resorption)	Creatinine clearance <30 mL/min, bone malignancy, increased risk for osteosarcoma, or hypercalcemia	Nausea (20% of patients), headache (13% of patients), hypercalcemia (3%-6% of patients), and leg cramps (3% of patients)
	Abaloparatide	80 µg/d for 1.5-2 y (administered subcutaneously)			
Sclerostin inhibitor	Romosozumab	210 mg/mo for 12 mo (administered subcutaneously)	• Inhibits the sclerostin-activating Wnt signaling pathways • Increases bone formation • Reduces bone resorption	Myocardial infarction or stroke (within past 12 mo) or hypocalcemia	Injection site reactions (5% of patients), serious cardiovascular events (2.5% of patients treated with romosozumab vs 1.9% treated with alendronate), osteonecrosis of the jaw (rare[a]), and atypical femur fracture (rare[a])

Abbreviation: RANKL, receptor activator of nuclear factor κB ligand.

[a] There were 2 cases of osteonecrosis of the jaw and 3 cases of atypical femur fracture reported in 5621 participants who received romosozumab in the large romosozumab vs placebo trials.

Figure 2. Efficacy of Osteoporosis Medication Use for the Prevention of Vertebral, Hip, and Any Clinical Fractures

	No. of fractures/No. of participants		Risk difference per 1000 person-years (95% CI)[a]
	Placebo	Treatment	
Fracture location			
Vertebral fracture			
Drug class			
Abaloparatide	30/711	4/690	-36 (-52 to -21)
Teriparatide	122/1510	22/1504	-69 (-112 to -28)
Romosozumab	59/3322	16/3321	-13 (-18 to -8)
Denosumab	264/3691	86/3702	-48 (-58 to -39)
Bisphosphonates	799/7970	406/8932	-56 (-84 to -33)
Raloxifene	308/4177	315/6385	-28 (-57 to -1)
Hip fracture			
Drug class			
Teriparatide	4/544	4/1093	-4 (-12 to 4)
Denosumab	43/3906	26/3902	-4 (-8 to 0)
Bisphosphonates	160/8305	103/8329	-6 (-11 to -1)
Raloxifene	18/2576	26/3902	1 (-3 to 5)
Any clinical fracture			
Drug class			
Abaloparatide	34/821	10/824	-29 (-45 to -14)
Teriparatide	94/1716	61/2254	-27 (-56 to -7)
Romosozumab	90/3591	58/3589	-9 (-15 to -2)
Raloxifene	339/4461	526/6978	-6 (-18 to 6)
Bisphosphonates	1134/9280	964/10 283	-24 (-42 to -7)
Denosumab	293/3906	238/3902	-14 (-25 to -3)



[a]The data are from a systematic review and network meta-analysis conducted by Ayers et al.[47]

Pharmacologic Treatment: Overview

- **Pharmacologic therapies for osteoporosis can be classified as antiresorptive, anabolic, or agents with combined effects on bone remodeling.**

Bisphosphonates: First-Line Therapy

- **Oral alendronate and risedronate are considered first-line antiresorptive therapies because of their efficacy, tolerability, and cost-effectiveness.**

Bisphosphonates: Safety and Renal Considerations

- During the first 2 years of treatment, serious adverse events such as osteonecrosis of the jaw and atypical femoral fractures are not higher than with placebo.
- Longer exposure is associated with an increased risk of osteonecrosis of the jaw and atypical femoral fractures.
- The risk of atypical femoral fracture decreases substantially after discontinuation, falling by approximately 50% during the first year and 80% by 3 years.

Bisphosphonate Duration and Rare Complications

- **Osteonecrosis of the jaw** becomes more frequent with bisphosphonate exposure exceeding approximately **2 years**.
- Reported rates range from approximately **0.2 to 10 cases per 10,000 patient-years** compared with placebo.
- **Atypical femoral fractures** are associated particularly with treatment **lasting 3 years or longer**.
- The estimated incidence increases from approximately **2.5 per 10,000 patient-years after 3 to 5 years to 13 per 10,000 patient-years after more than 8 years** of treatment.
- The risk of atypical femoral fracture is higher among **women who self-report Asian race or ethnicity**.

Denosumab: Mechanism and Efficacy

. Denosumab is a monoclonal antibody that binds RANKL and inhibits osteoclastogenesis and osteoclast activity.

. Although follow-up studies suggest sustained efficacy for up to 10 years, the certainty of evidence for very long-term fracture prevention remains low.

Denosumab: Safety and Discontinuation

- Hypocalcemia may occur after denosumab administration, particularly in patients with vitamin D deficiency or advanced kidney dysfunction.
- A major clinical concern is rapid bone loss and increased vertebral fracture risk after denosumab discontinuation or significant dosing delays.
- In one post hoc analysis, vertebral fracture rates increased from 1.2 to 7.1 per 100 participant-years after treatment discontinuation.
- Current guidelines therefore recommend continuing denosumab indefinitely or transitioning to a bisphosphonate when denosumab is stopped.

Denosumab Discontinuation: High-Risk Patients

- **Delaying a scheduled dose by more than approximately 1 month can also increase the risk of vertebral fractures.**
- **Longer duration of denosumab therapy is also associated with greater vertebral fracture risk after stopping treatment.**
- **Alendronate or intravenous zoledronic acid can be used after discontinuation to reduce the risk of rebound vertebral fractures.**

ANABOLIC THERAPY: Teriparatide and Abaloparatide

- Teriparatide and abaloparatide are contraindicated in hyperparathyroidism because they may worsen hypercalcemia. and in individuals with skeletal malignancy or conditions that have increased osteosarcoma risk, such as prior skeletal radiation Or Paget disease of bone

- postmarketing surveillance studies have shown no excess osteosarcoma risk in people taking these medications, and therefore this risk no longer appears as a blackbox Warning
- Transient hypotension infrequently occurs with the first dose of teriparatide or abaloparatide.
- Other potential adverseevents include nausea, dizziness, palpitations, headache,myalgia, and hypercalcemia.
- Loss of bone mass occurs after discontinuation, so the use of antiresorptive therapy, such a bisphosphonates or denosumab, should be prescribed after discontinuation of teriparatide and abaloparatide.

Romosozumab

- Romosozumab is a monoclonal antibody that binds and inhibits sclerostin,anosteocyte-secretedinhibitor of theWnt-signaling pathway,and thereby markedly increases bone formation and moderately reduces bone resorption.

  After 12 months of treatment with romosozumab, an antiresorptive therapy, such as bisphosphonates or denosumab, should be prescribed. After discontinuing romosozumab, further increases in bone mass typically occur with denosumab, and maintenance of bone mass occurs with alendronate.

RECOMMENDED THERAPEUTIC STRATEGIES

Who Should Receive Pharmacotherapy?

- Most guidelines recommend pharmacologic treatment for postmenopausal women and men aged 50 years or older with osteoporosis based on BMD.
- Treatment is also recommended for individuals with a high fracture risk, regardless of whether their BMD is in the osteopenic or normal range.
- A history of hip, vertebral, or multiple fractures is an important indication for pharmacologic therapy.
- Oral or intravenous bisphosphonates are appropriate first-line treatments for most patients at high fracture risk.

Table 3. Summary of Guideline Recommendations for Management of Osteoporosis[a]

	Bone Health and Osteoporosis Foundation guideline,[3] 2022	UK Osteoporosis guideline,[6] 2022	Endocrine Society guideline updates,[78,79] 2019 and 2020	American Association of Clinical Endocrinologists/ American College of Endocrinology clinical practice guidelines,[5] 2020
Target population	• Postmenopausal females and males ≥50 y of age	• Postmenopausal females and males ≥50 y of age	• Postmenopausal females	• Postmenopausal females ≥50 y
Measurement of bone mineral density (BMD)	• Postmenopausal females aged 50-64 y and males aged 50-69 y with risk factors for osteoporosis • Females aged ≥65 y • Males aged ≥70 y	• FRAX assessment without BMD should be performed in postmenopausal females and in males ≥50 y of age • FRAX assessment with BMD should be performed in individuals at intermediate risk (close to the age-dependent treatment threshold) or in individuals at high or very high risk (if a baseline BMD measurement is needed for a subsequent monitoring purpose)		• Postmenopausal females aged 50-64 y with clinical risk factors for osteoporosis or history of fractures • Postmenopausal females aged ≥65 y
FRAX (a fracture risk assessment tool)	• Country specific	• Country specific	• Country specific	• Country specific
Treatment initiation	• In postmenopausal females and males aged ≥50 y with • Hip or vertebral fracture (regardless of T score) • Fracture of the pelvis, proximal humerus or distal forearm with T score between −1 and −2.5 • T score ≤−2.5 at the femoral neck, total hip, or lumbar spine or 33% radius • T score between −1 and −2.5 and a 10-y probability of ≥20% for major osteoporotic fractures or ≥3% for hip fractures (based on the country-specific[b] FRAX tool)	Postmenopausal females and males aged ≥50 y with • Prior or recent fragility fracture (particularly in older people) • A 10-y probability of high or very high fracture risk based on the country-specific[b] FRAX tool; intervention threshold increases with age until 70 y (after which it is constant)	• Postmenopausal females at high fracture risk with • Hip or vertebral fracture • Recent fracture (within 2 y) • T score ≤−2.5 for femoral neck BMD, total hip, or lumbar spine or distal radius • T score of −1 to −2.5 and a 10-y probability of ≥20% for major osteoporotic fractures or ≥3% for hip fractures (based on the country-specific[b] FRAX tool)	• Postmenopausal females with • Low bone mass (osteopenia) and a history of fracture of the hip or spine • T score ≤−2.5 for femoral neck BMD, total hip, or lumbar spine or one-third radius • T score of −1 to −2.5 and a 10-y probability of ≥20% for major osteoporotic fractures or ≥3% for hip fractures (based on the country-specific[b] FRAX tool)
Monitoring after initiation of treatment	• Measurement of BMD every 2 y	• No specific recommendation	• Measurement of BMD every 1 to 3 y	• Measurement of BMD every 1 to 2 y until stable
Interruption of bisphosphonate treatment (drug holiday)	• In those at modest risk of fracture (no recent fracture or T score >−2.5) after 3 y of intravenous or 5 y of oral bisphosphonate • Reassess fracture risk and BMD level every 2 to 3 y	• After 3 y of treatment with intravenous bisphosphonate or 5 y of treatment with oral bisphosphonate, reassess fracture risk and reconsider treatment every 1.5-3 y • Pause treatment for those at lower risk	• In those at low to moderate fracture risk, consider bisphosphonate interruption after 3 to 5 y of therapy	• For oral bisphosphonates, consider a bisphosphonate holiday after 5 y of treatment or 6 to 10 y in very high risk • For zoledronate, consider a bisphosphonate holiday after 3 y in patients at high risk and up to 6 y in those at very high risk

[a] The 2024 US Preventive Services Task Force[3,4] recommendations are to screen postmenopausal females aged 65 years or older for BMD level to prevent osteoporotic fractures and screen postmenopausal females younger than 65 years who are at increased risk of osteoporosis (as determined by a clinical risk assessment tool). The current evidence is insufficient to assess the balance of benefits and harms of BMD screening in men.

[b] Calibrated using individual country population-specific fracture and mortality data. When using FRAX to calculate absolute fracture risk, it is important to use the country-specific tool, which is easily identified on the website (https://www.fraxplus.org).

DURATION AND SEQUENCE OF THERAPY

Bisphosphonate Duration and Drug Holidays

- **Interruption of bisphosphonate therapy should be considered because of concerns regarding rare adverse effects with prolonged exposure.**
- **A drug holiday may be considered after approximately 3 years of intravenous bisphosphonate therapy or 5 years of oral therapy.**
- **The benefits of continuing bisphosphonate treatment beyond 5 years are not completely established.**
- **In an RCT of 1099 participants, continuing alendronate after 5 years reduced clinically recognized vertebral fractures compared with discontinuation.**
- **However, radiologically confirmed vertebral fracture rates did not differ significantly between continuation and discontinuation groups.**
- **Therefore, the decision to continue or interrupt treatment should be based on the patient's residual fracture risk rather than treatment duration alone.**

Drug Holiday in Low-to-Moderate Risk Patients

- A **bisphosphonate drug holiday** is appropriate for patients with **low or moderate** fracture risk who have not sustained a fracture during treatment.
- The optimal duration of a bisphosphonate interruption has not been clearly established.
- Available evidence suggests that fracture rates generally do not increase during the **first 1 to 2 years after discontinuation.**
- Fracture risk may **begin to increase approximately 2 to 5 years after stopping treatment**.
- Patients should therefore undergo periodic **reassessment** during a drug holiday rather than remaining untreated indefinitely.
- Resumption of therapy should be considered if fracture **risk increases substantially or a new fracture occurs.**

Management of Persistent High Fracture Risk

- Patients who remain at high fracture risk after 3 to 5 years of bisphosphonate therapy may require continued or intensified treatment.
- Intravenous bisphosphonate therapy can be continued for approximately 3 additional years in selected high-risk patients.
- Oral bisphosphonate therapy can be extended for approximately 5 additional years when clinically appropriate.
- Switching to denosumab is another option for patients who remain at high fracture risk after initial bisphosphonate therapy.
- Teriparatide, abaloparatide, or romosozumab may be considered when fracture risk remains particularly high despite previous treatment.

Sequencing of Osteoporosis Therapies

- **Anabolic therapy** produces **smaller improvements** when administered **after previous antiresorptive** treatment than when used in treatment-naive patients.
- **Transitioning** from **denosumab directly to teriparatide** or **abaloparatide** is associated with transient **bone loss** and should generally be avoided.
- **Switching from denosumab to romosozumab** may help prevent transient bone loss, although available evidence remains limited.

Combination Therapy and Repeated Anabolic Courses

- The clinical value of combining anabolic and antiresorptive agents also remains uncertain.
- Combination treatment is substantially more expensive than treatment with an individual agent.
- Combined therapy may also increase treatment burden and potentially increase adverse events.
- Therefore, combination therapy is generally reserved for selected patients with very high fracture risk.
- There is currently no indication for combining two antiresorptive agents as routine osteoporosis therapy.

MONITORING

Clinical Monitoring During Therapy

- **Regular clinical assessment** is recommended throughout osteoporosis treatment.
- Follow-up should assess changes in **body weight** and **height** because these may indicate progressive skeletal deterioration or vertebral fractures.
- Clinicians should specifically ask about new **fractures** and **falls** during follow-up visits.
- **Adverse effects** and **medication tolerability** should be systematically evaluated.
- **Adherence to pharmacologic** and **lifestyle** interventions should also be assessed regularly.

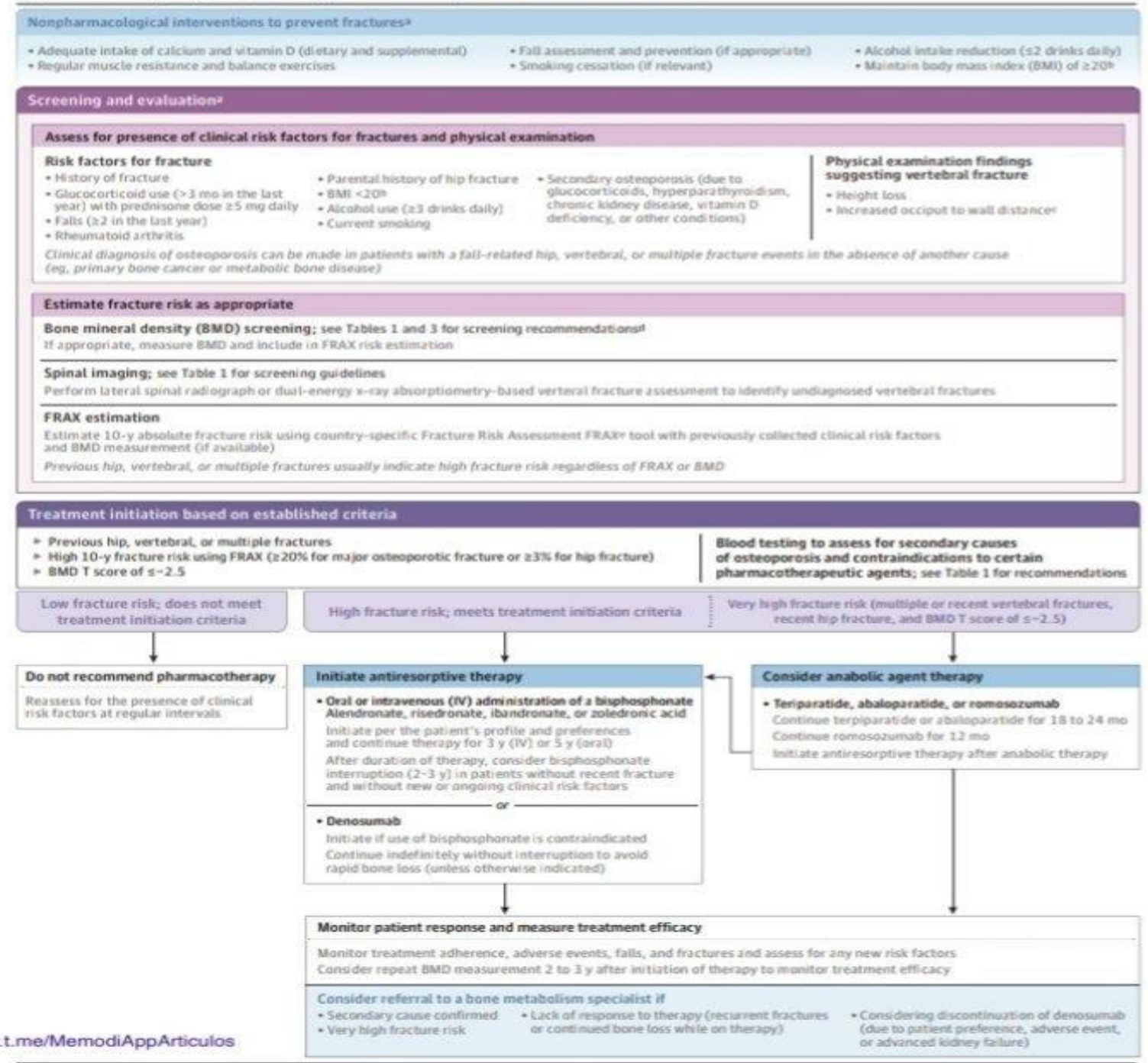
Monitoring BMD Response

- **Repeat BMD measurement** can generally be performed **after** approximately **2 to 3 years of pharmacologic therapy.**

Reassessment of Fracture Risk

- Fracture risk should be reassessed periodically according to the patient's baseline risk and treatment status.
- In patients who are not receiving treatment, FRAX-based reassessment can be performed after approximately 3 to 10 years.
- The appropriate reassessment interval depends on the individual's initial fracture risk.
- Patients with higher baseline risk generally require closer clinical follow-up.
- A new fracture, significant height loss, recurrent falls, or substantial clinical changes should prompt earlier reassessment.

Figure 3. Screening, Diagnosis, and Management of Osteoporosis and Fracture Prevention



Box. Commonly Asked Questions About the Management of Osteoporosis

Bisphosphonates are typically discontinued after 3 to 5 years. When should a bisphosphonate be resumed, and for how long, after a drug holiday?

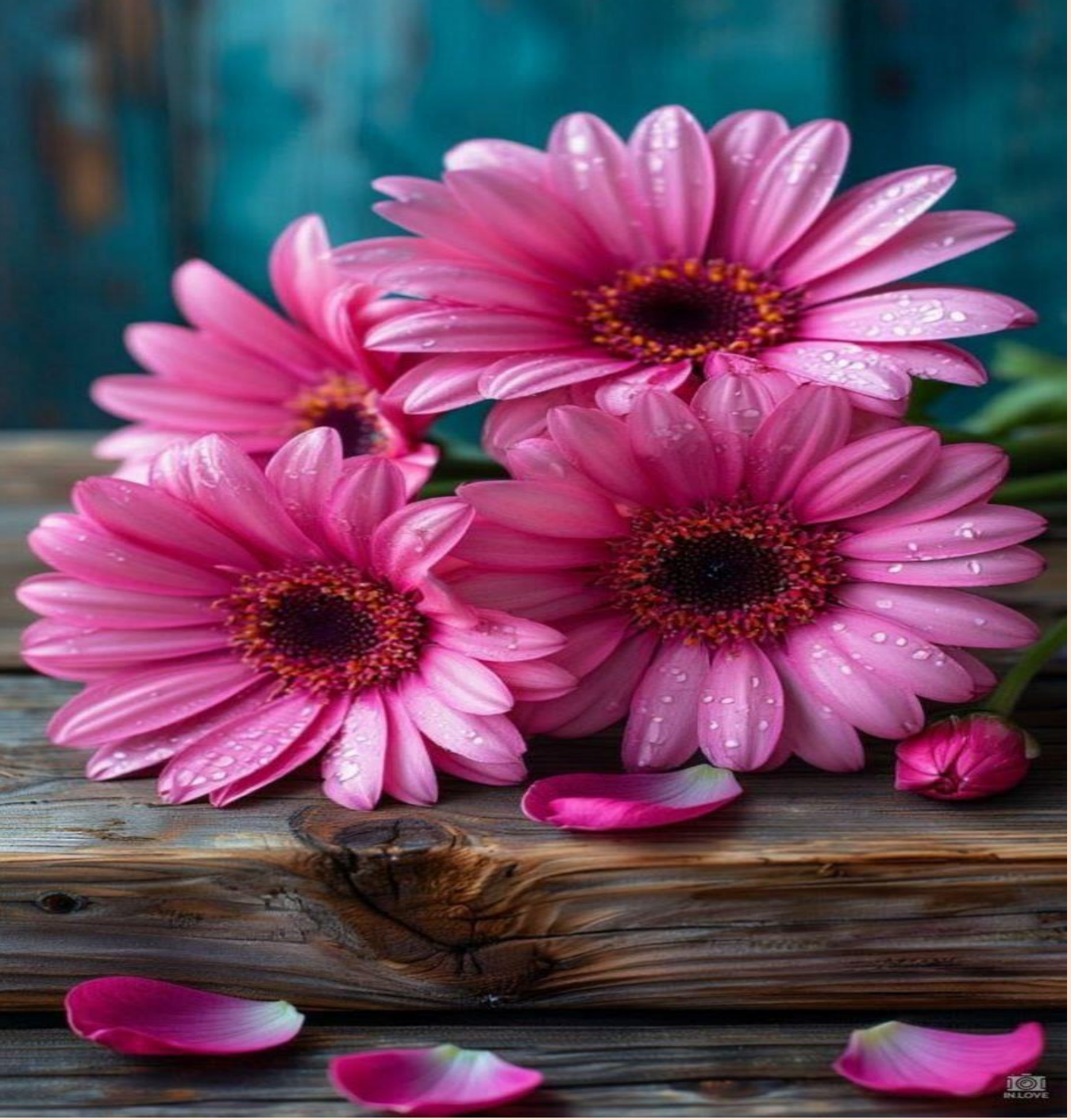
Typically, after 3 to 5 years of treatment, bisphosphonates are discontinued for approximately 2 to 3 years. Bisphosphonates can be resumed if new fractures or risk factors occur. The Fracture Risk Assessment Tool can be used to calculate absolute fracture risk after a drug holiday. When resuming bisphosphonates, the duration of therapy is similar to the initial recommendations.

Should monitoring with dual-energy x-ray absorptiometry (DXA) be performed in people who had a T score of less than −2.5?

The guidelines recommend repeated measurement of bone mineral density (BMD) in patients who initiate bisphosphonate therapy even if the initial T score is less than −2.5. Data from trials with antiresorptive and anabolic therapies show an inverse relationship between the BMD level attained with therapy and the subsequent fracture risk. A clinically meaningful reduction in fracture risk is expected when the increase in BMD level exceeds the measurement error reported by the DXA facility where the BMD test was performed (https://iscd.org/official-positions-2023/).

Should patients with a BMD level within the range for osteopenia (ie, a T score of −1.0 to −2.5) or within the normal range (ie, a T score >−1.0) ever be treated with medications for osteoporosis?

Patients with fall-related hip, vertebral, or multiple fractures are at high subsequent fracture risk even if their T score is not in the range for osteopenia. The use of osteoporosis drugs is associated with significant reductions in fracture risk even when a patient's T score is greater than −2.5 (high evidence certainty).



Thank you for listening