Optum Health Education™

Osteoporosis

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Disclosure

- Dr. Neil Braunstein has no financial relationships to disclose.

Learning Objectives:

1) Describe the screening recommendations for osteoporosis for different populations

2) Identify the diagnostic criteria for osteoporosis and osteopenia

3) Make evidence-based treatment decisions for osteoporosis based on patient characteristics and severity with awareness of potential adverse effects of therapy.

4) Describe monitoring recommendations for patients with osteoporosis

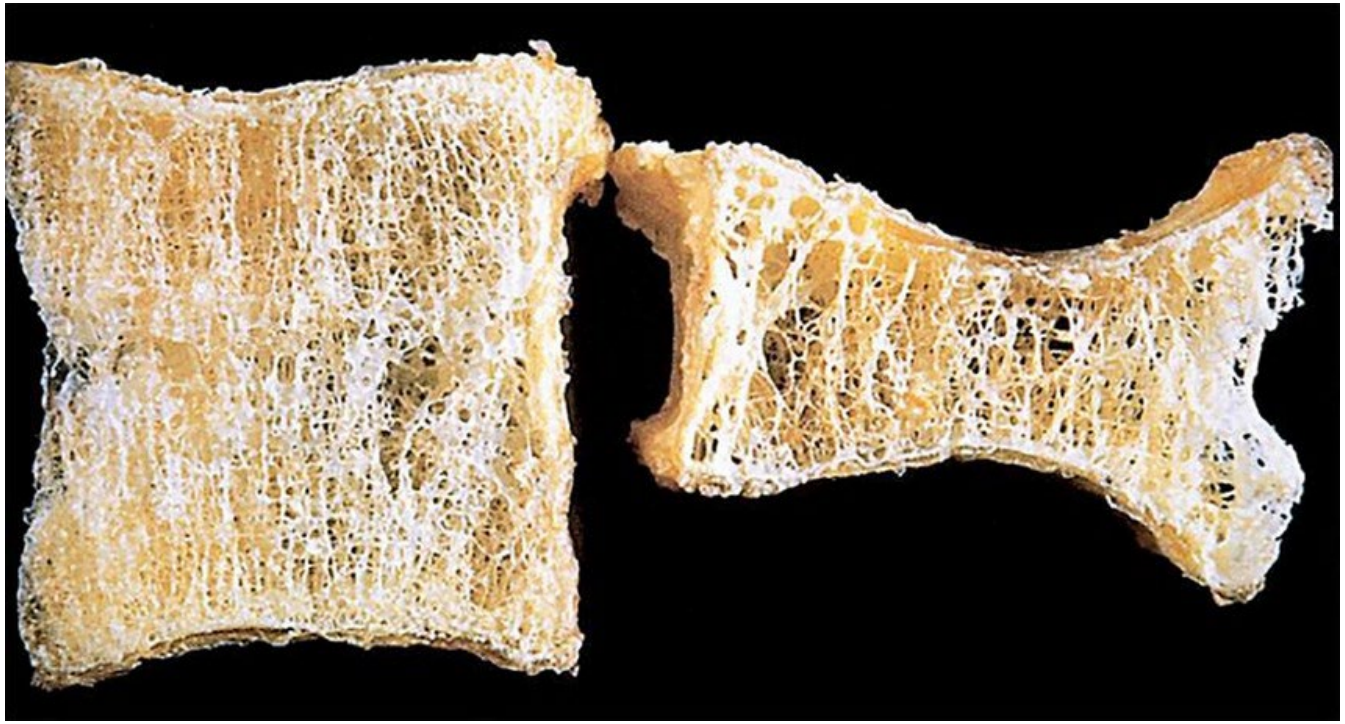
United States Impact of Osteoporosis

- Approximately 10 million Americans have osteoporosis and 44 million have osteopenia
- Half of adults aged 50 and older are at risk for an osteoporotic fracture
- Causes 2 million broken bones a year, yet 80% of those patients are not treated
- 50 % of women and 20% of men at least 50 years old will sustain an osteoporotic fracture
- 50% of patients with a hip fracture will never be able to walk without assistance and 25% will require long-term care
- Prevalence 12.6 % among adults aged 50 and over. Women 19.6%, Men 4.4%
- Projected direct cost of osteoporotic fractures in 2025 – $25.3 billion

OSTEOPOROSIS IS A MANAGEABLE CONDITION

LeBoff et al. Osteoporos Int 2022; 33:2049
NCHS Data Brief, March 2021
Burge et al. J Bone Miner Res 2007; 22:465
Riggs et al. Bone 1995; 17;505S

Osteoporosis: the evolution of a diagnosis



Journal of Internal Medicine, Volume: 277, Issue: 6, Pages: 650-661, First published: 02 April 2015, DOI: (10.1111/joim.12369)

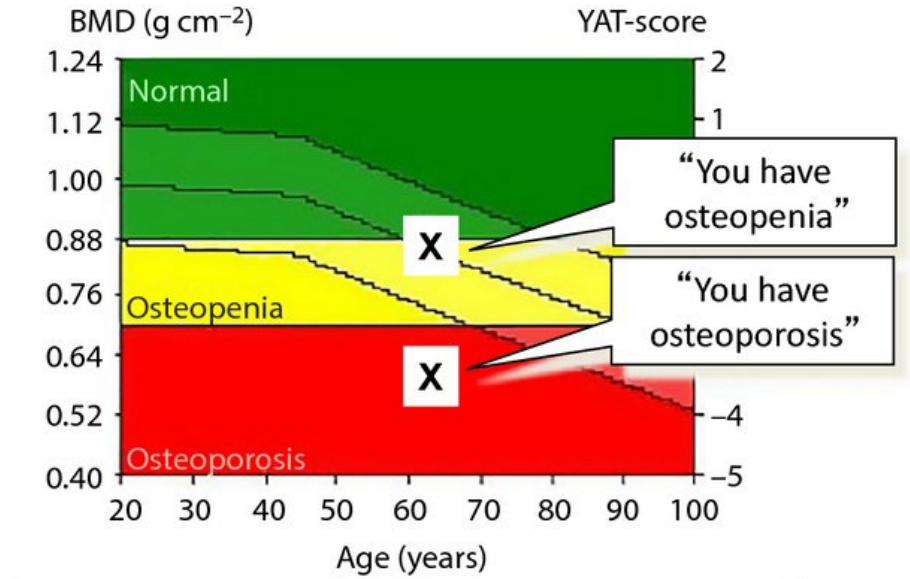
Screening

Dual-Energy X-ray Absorptiometry

- Best available method for diagnosis of osteoporosis in the absence of a fragility fracture
- Best method for monitoring changes in BMD over time
- Radiation exposure is similar to background radiation, only contraindication – pregnancy
- Care when comparing BMD on different instruments unless cross-calibration has been done
- BHOF guidelines: measure for the lowest T-score of the lumbar spine, total proximal femur or femoral neck
- Vertebral Fracture assessment by DXA can be done at the same time
- T-score is a comparison of the patient's bone density with healthy, young individuals of the same sex.
- Z-score is a comparison with the bone density of people of the same age and sex

Shuhart et al. J Clin Densitom 2023: 101435
Lewiecki et al. J Clin Endocrinol Metab 2006: 91:4215

Osteoporosis: the evolution of a diagnosis



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Fracture Risk Assessment Tool (FRAX)

- Developed in 2008 at the University of Sheffield, free online tool that estimates the 10 year probability of hip fracture and other major osteoporotic fracture for untreated patients between ages 40 and 90. https://frax.shef.ac.uk/FRAX/tool.aspx?country=9
- Answer 12 quick questions and input Femoral BMD by DXA
- Diagnostic, not recommended to monitor response and change of fracture rates for patients on therapy.
- Use of FRAX will increase number of older patients with low T-scores who are recommended for treatment and reduce the number of younger patients with low T-scores.
- US models indicate treatment is cost-effective if the threshold of 10-year hip fracture risk 2.4-4.9%
- Considered a positive screen when 10-year probability of fracture ≥ 3% at the hip and ≥ 20 % for major osteoporotic fracture.

Leslie et al. J Bone Miner Res 2014; 29:1074

Tosteson et al. Osteoporos Int 2008; 19:399

Optum | Screening for osteoporosis

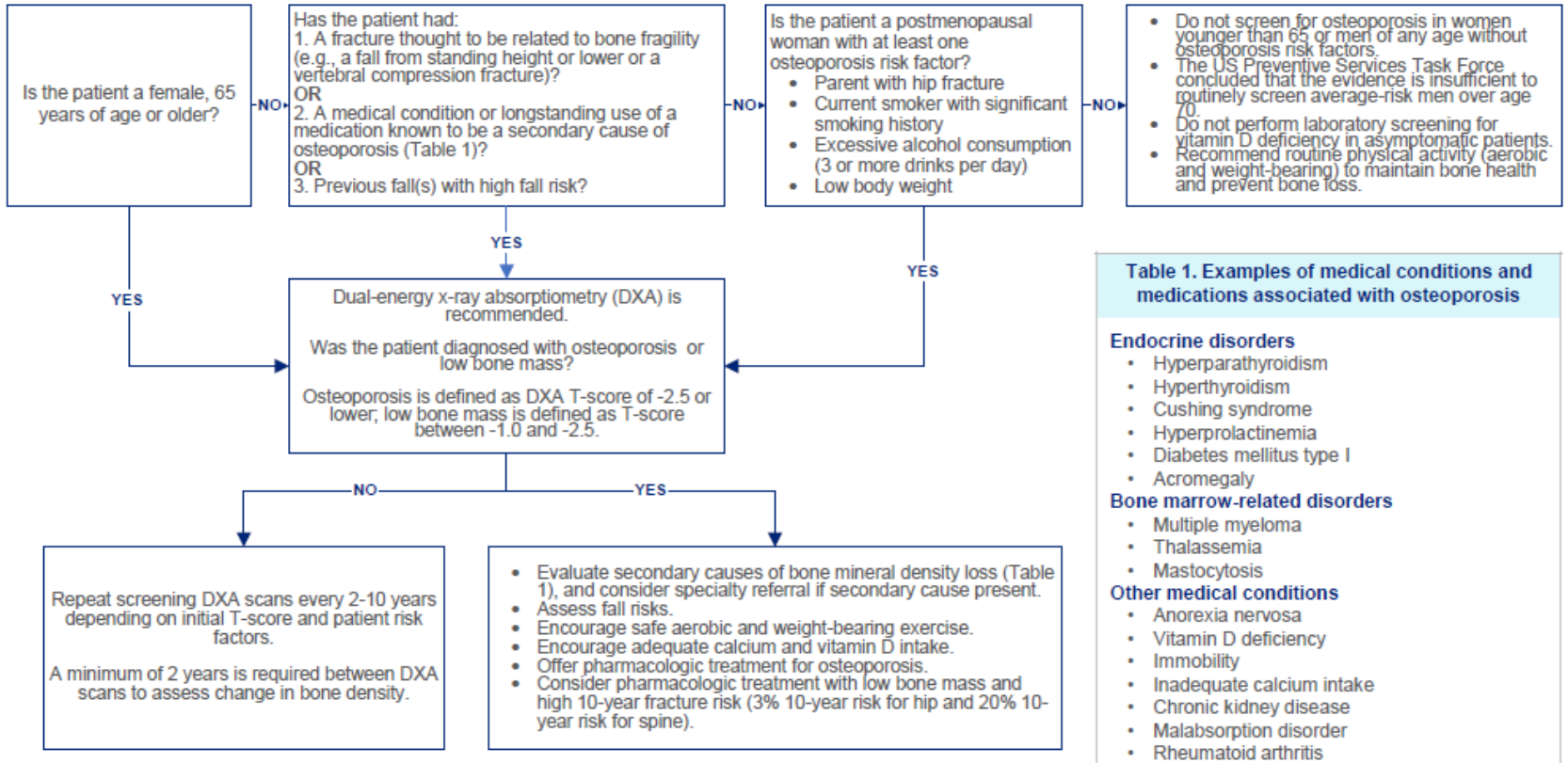


Table 1. Examples of medical conditions and medications associated with osteoporosis

Endocrine disorders
- Hyperparathyroidism
- Hyperthyroidism
- Cushing syndrome
- Hyperprolactinemia
- Diabetes mellitus type I
- Acromegaly

Bone marrow-related disorders
- Multiple myeloma
- Thalassemia
- Mastocytosis

Other medical conditions
- Anorexia nervosa
- Vitamin D deficiency
- Immobility
- Inadequate calcium intake
- Chronic kidney disease
- Malabsorption disorder
- Rheumatoid arthritis
- BMI less than 20 kg/m2
- Excessive alcohol use (3 or more drinks daily)
- Current smoker or significant smoking history

Medications
- Corticosteroids
- Medroxyprogesterone (Depo-Provera)
- Aromatase inhibitors
- Androgen deprivation therapy
- CYP450 inducing/inhibiting antiepileptic medicines
- GnRH agonists
- Proton pump inhibitors

References

1. US Preventive Services Task Force, Curry SJ, Krist AH, et al. Screening for Osteoporosis to Prevent Fractures: US Preventive Services Task Force Recommendation Statement. JAMA. 2018;319(24):2521-2531.
2. Shepstone L, Lenaghan E, Cooper C, et al. Screening in the community to reduce fractures in older women (SCOOP): a randomized controlled trial. Lancet. 2018;391(10122):741-747.
3. Kaiser Permanente. Osteoporosis Screening, Diagnosis, and Treatment Guideline. March 2022. Last accessed February 1, 2024: https://wa.kaiserpermanente.org/static/pdf/public/guidelines/osteoporosis.pdfast.
4. American College of Obstetricians and Gynecologists' Committee on Clinical Practice Guidelines–Gynecology. Osteoporosis Prevention, Screening, and Diagnosis: ACOG Clinical Practice Guideline No. 1. Obstet Gynecol. 2021;138(3):494-506.
5. Expert Panel on Musculoskeletal Imaging; Yu JS, Krishna NG, Fox MG, Blankenbaker DG, Frick MA, Jawetz ST, Li G, Reitman C, Said N, Stensby JD, Subhas N, Tulchinsky M, Walker EA, Beaman FD. ACR Appropriateness Criteria® Osteoporosis and Bone Mineral Density: 2022 Update. *J Am Coll Radiol.* 2022 Nov;19(11S):S417-S432.

Lifestyle Measures

- Adequate Calcium and Vitamin D intake: dietary intake of 1200mg calcium daily or if inadequate – supplement with 500-1000mg daily in divided doses at mealtime.
  - Calcium carbonate – cheapest, better absorbed with meals
  - Calcium citrate – first line for patients on PPIs and H2 blockers, OK fasting
- Vitamin D – Supplement 800 IU a day
- Exercise – Weightbearing exercise for at least 30 minutes on most days and muscle-strengthening and posture exercises 2-3 X a week
- Smoking Cessation
- Avoid heavy alcohol Use

Heaney et al. Osteoporosis Int 1999; 9:19

Brooke-Wavell et al. Br J Sports Med 2022

Diagnosis

Diagnosis of Osteoporosis

“The group recommends that postmenopausal women and men aged 50 years should be diagnosed with osteoporosis if they have a demonstrable elevated risk for future fractures. This includes having a T-score of less than or equal to −2.5 at the spine or hip as one method for diagnosis but also permits a diagnosis for individuals in this population who have experienced a hip fracture with or without bone mineral density (BMD) testing and for those who have osteopenia by BMD who sustain a vertebral, proximal humeral, pelvic, or, in some cases, distal forearm fracture. Finally, the term osteoporosis should be used to diagnose individuals with an elevated fracture risk based on the World Health Organization Fracture Risk Algorithm, FRAX.” from the National Bone Health Alliance Working Group

Siris et al. Osteoporos INT 2014: 25(5): 1439-1443

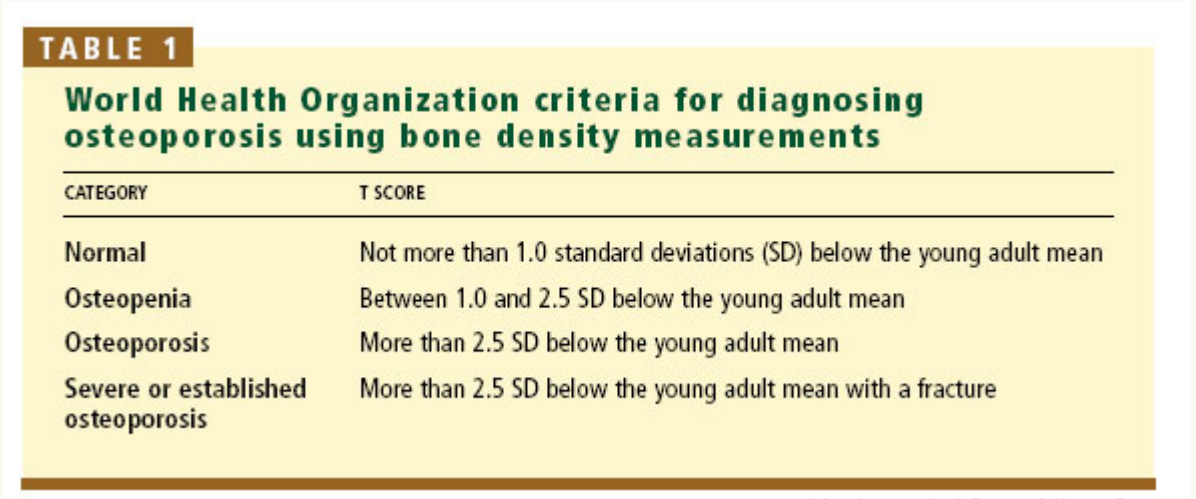


TABLE 1

World Health Organization criteria for diagnosing osteoporosis using bone density measurements

CATEGORY	T SCORE
Normal	Not more than 1.0 standard deviations (SD) below the young adult mean
Osteopenia	Between 1.0 and 2.5 SD below the young adult mean
Osteoporosis	More than 2.5 SD below the young adult mean
Severe or established osteoporosis	More than 2.5 SD below the young adult mean with a fracture

Kanis et al. J Bone Miner Res 1994: 9:1137-1141

Diagnosis of Osteoporosis in Premenopausal Women

- BMD alone not adequate in this population
- Low BMD Z-score < 2.0 with no history of fragility fracture have low BMD for chronologic age
- Fragility fracture or low BMD + an active condition or medication exposure known to cause bone loss = osteoporosis
- Always look for primary (genetic) and secondary (acquired condition or medication) causes in this population.

Osteoporosis in Men

- Mortality rate with hip and vertebral fractures is higher in men compared to women
- Men are less likely than women to receive evaluation and treatment
- Look for underlying medical conditions and medications contributing to bone loss

Kanis et al. Bone 2003: 32:468

Kiebzak et al. Arch Intern Med 2002; 162:2217

Treatment

Oral Bisphosphonates

- Should be first line therapy for most patients at high risk for fracture due to efficacy, cost effectiveness and long-term safety data. Inhibits bone resorption
- Confirmed to improve BMD, prevent vertebral and hip fractures in post menopausal women and men
- Do not use in combination with other osteoporosis medications
- Contraindications:
  - Esophageal Disorders
  - Inability to follow dosing recommendations
  - Bariatric surgery with anastomoses
  - CKD with GFR < 30-35

Yates et al. Osteoporosis Int 2013;24:253
Crandall et al. Ann Intern Med 2014: 161:711

Oral Bisphosphonates

- Best evidence recommendations: alendronate, risedronate

- Proper Oral administration:
  - Taken alone on an empty stomach first thing in the morning with 8oz of water – avoid esophageal retention
  - After taking, no food, medications or supplements for 30 minutes – impairs bioavailability. No calcium supplements for 1 hour
  - Remain upright for 30 minutes after taking – reduce reflux risk

- Pre-treatment evaluation:
  - Calcium
  - 25-hydroxyvitamin D
  - Creatinine

- Can be initiated 2 weeks post osteoporotic fracture. Do not discontinue if patient has a typical fragility fracture

- Approximate annual cost oral alendronate - $169

Molvik et al. Osteoporos Int 2015; 26;1251
Rozental et al. J Hand Surg Am 2009;34;59

IV Bisphosphonates

- For patients with intolerance or contraindication to oral bisphosphonates, recommend IV Zoledronic acid given the availability and fracture reduction in clinical trials
- Given as a 15-minute infusion once a year. 3 years of therapy has been shown to increase BMD and reduce fracture risk
- To avoid hypocalcemia, make sure vitamin D is sufficient
- Avoid if creatinine clearance ≤ 35
- Approximate annual cost zoledronic acid - $36

Black et al. N Engl J Med 2007; 356:1809

Adverse Effects of Bisphosphonates

- Esophageal reflux, esophagitis and esophageal ulcers are most common but rare if proper administration is followed.
  - Contraindicated in Barrett's esophagus
- IV can cause low-grade fever, myalgias and arthralgias 24-72 hours post infusion, mitigated with NSAIDS or acetaminophen
- Hypocalcemia – more common with IV administration. Risk is higher in patients with inadequate calcium and vitamin D
- MSK pain – rare but if persistent discontinue medication
- Osteonecrosis of the jaw – more commonly seen in higher doses for other indications, risk is 1 in 10,000-100,000 patient years. For dental procedures, bisphosphonates do not need to be stopped. If they are, D/C 2 months prior to procedure and resume after bone is healed
- Atypical femur fracture – rare (3.2-50 cases per 100,000 patient years, average duration 7 years). Stress fractures caused by over-suppression of bone turnover (frozen bone)

Liberman et al. N Engl J Med 1995; 333;1437
Lanza et al. Am J Gastroentrol 2000; 95:3112
Schussheim et al. Ann Intern Med 1999; 130;329
Adler et al. J Bone Miner Res 2016; 31:16
Ruggiero et al. J Oral Macillofac Surg 2022; 80:920
Odvina et al. J Clin Endocrinol Metab 2005; 90:1294

Bisphosphonate Holiday

Patient Category	Recommendation	Comment
High-risk: T-score still ≤−2.5 at the hip, previous fracture of the hip or spine or ongoing high-dose glucocorticoid therapy.	Drug holiday not justified.	Re-assess the need for therapy at regular intervals.
Moderate risk: Hip bone mineral density value is now >−2.5 (T-score), and no prior hip or spine fracture.	Consider drug holiday after 3-5 years of alendronate, risedronate, or zoledronic acid therapy. No information about ibandronate and drug holidays.	These patients should not be forced to take a drug holiday—decision should be an individual, informed choice with discussion of the potential benefits and risks.
Low risk: Did not meet current treatment criteria at the time of treatment initiation.	Discontinue therapy	Re-start when indications for therapy are met.

McClung et al. Am J Med 2013; 126:13.

Anabolic Therapies – PTH Analogs

- Teriparatide – PTH, Abaloparatide – PTHrP
- Intermittent short-term administration increases bone formation more than absorption
- Not recommended as routine first line therapy
  - Consider for high-risk patients t-score ≤ -3.0 or ≤ -2.5 with fracture
  - Inability to take bisphosphonate or failure of other therapies
- Contraindicated: Hyper PTH, hypercalcemic disorders, patients increased risk for osteosarcoma – Paget disease of bone
- Pre-treatment eval: DXA, serum calcium, phos, create, alk phos, albumin, 25-hydroxy D, 24-hour urine for calcium and creat
- Combination therapy not recommended
- Approximate annual cost – teriparatide - $38,400, Abaloparatide - $25,608

Rosen et al. J Clin endocrinol Metabl 2001; 86:957

Adverse Effects – PTH Analogs

- Hypercalcemia – only 3% required dose reduction. Measure serum calcium 1-3 months after starting therapy, consider reducing calcium supplementation
- Calciphylaxis, hypercalciuria, hypotension, tachycardia, severe muscle cramps, increased serum uric acid – gout. Minimal risk of osteosarcoma in humans
- For most patients limit duration of therapy to 2 years. Once therapy is completed recommend continuing treatment with an anti-resorptive to preserve or increase gains – prefer bisphosphonate

Black et al. N Engl J Med 2003; 349:1207
Neer et al. N Engl J Med 2001; 344:1434
Tashjian et al J Bone Miner Res 2002; 17:1151
Kakaria et al Ann Intern Med 2005; 142:310

Anabolic Therapy – Romosuzamab

- Monoclonal anti-sclerostin antibody - sclerostin inhibits bone formation. Enhances osteoblast function, improves bone mass and reduces fractures
- Treatment: 12 months monthly SC injections, followed by treatment with antiresorptive preferable bisphosphonate
- Adverse effects – Injection site reactions, rare osteonecrosis of the jaw, one atypical femur fracture
- Increased risk of serious cardiovascular events, not advised for patients with increased risk of MI or stroke
- Approximate annual cost - $23,772

Saag et al, N Engl J Med 2017: 377:1417

Li et al J Bone Miner Res 2008; 23:860

Denosumab

- Monoclonal antibody to the receptor activator of RANKL, inhibiting osteoclast formation
  - Decreases bone resorption, and reduces risk of fracture
- Pretreatment evaluation is the same as for bisphosphonates. Correct hypocalcemia and vitamin D deficiency prior to starting.
- Given as a SC injection once every 6 months, no adjustment for renal function
- BMD increases are slightly greater with denosumab compared to bisphosphonates, fracture rates not significantly different
- Cautions: Should not be considered as initial therapy. Should not be used in pre-menopausal women or for osteoporosis prevention. Do not use in combination.
- Approximate annual cost - $3,024

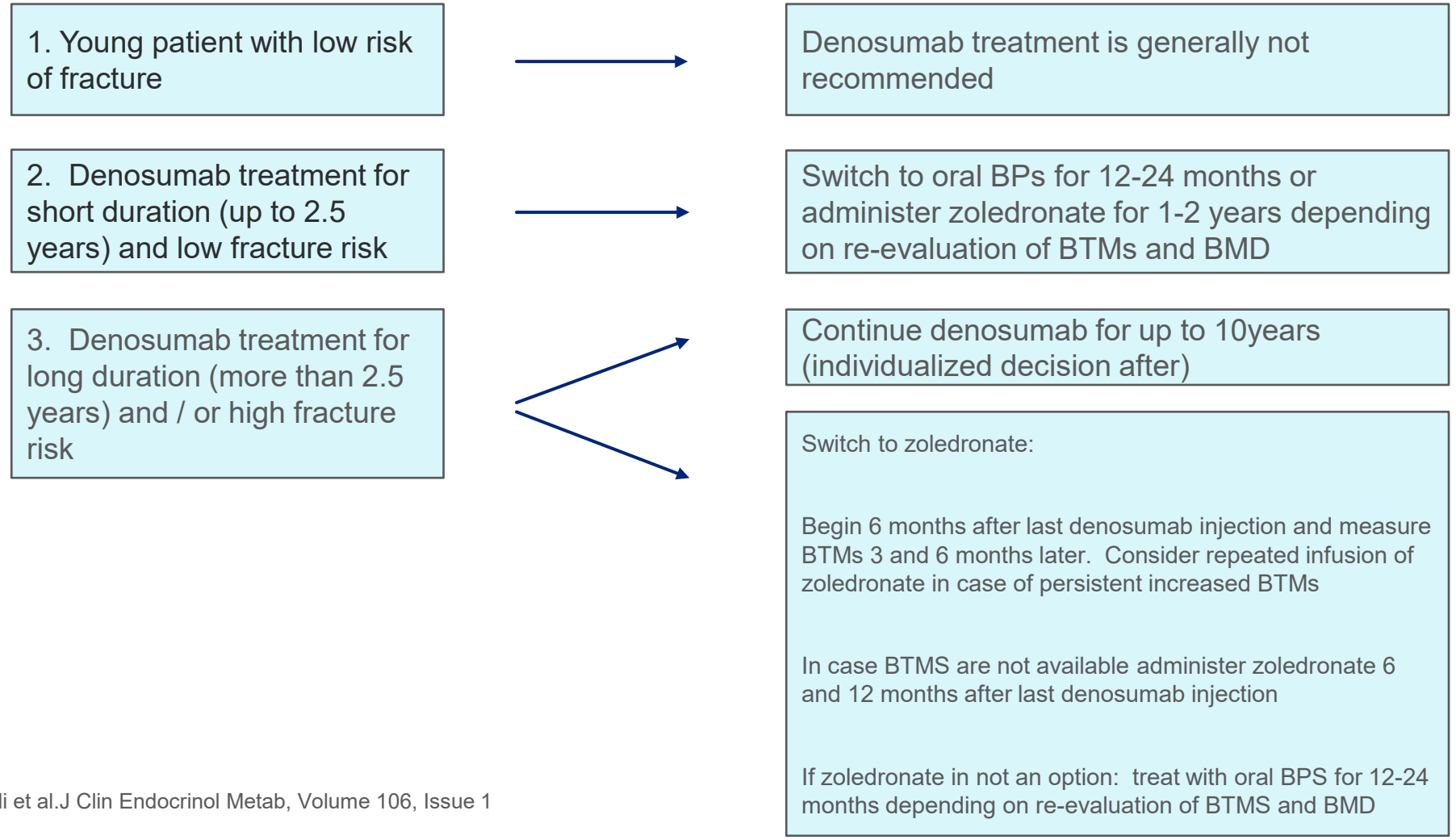
Cummings et al. N Engl J Med 2009; 361:756
Brown et al. J Bone Miner Res 2009; 24:153
Pedersen et al JAMA 2019: 2:e192416

Adverse Effects of Denosumab

- Increased risk of multiple vertebral fractures with delay or D/C of denosumab. If denosumab is stopped alternative osteoporosis medication must be given timely.
- Fractures have been seen as soon as 16 weeks after stopping denosumab. For patients on therapy > 3 years significant bone loss may occur even after alternative therapies are given
- Recommended that the possible need for indefinite treatment be discussed with patients prior to initiation
- Most common adverse effects, MSK pain, elevated cholesterol, cystitis. Watch for severe hypocalcemia in patients with impaired kidney function. ONJ and atypical fractures have been reported

Lyu et al Ann Intern Med 2020; 173:516
Yu et al. J Bone Miner Res 2020; 35:1009
Cosman et al. J Bone Miner Res 2022; 37:2112
Cowan et al. J bone Miner Res 2023; 38:650

Discontinuation of denosumab



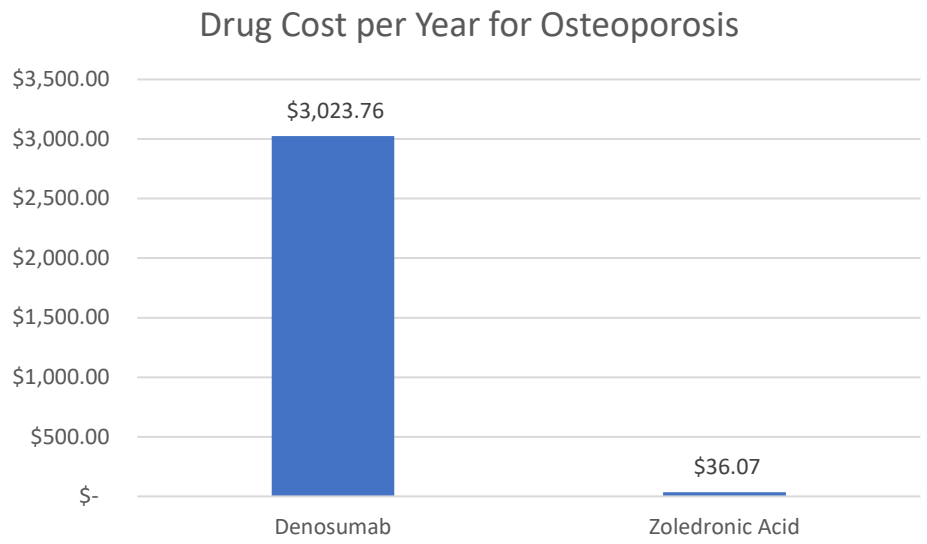
Tsourdi et al.J Clin Endocrinol Metab, Volume 106, Issue 1

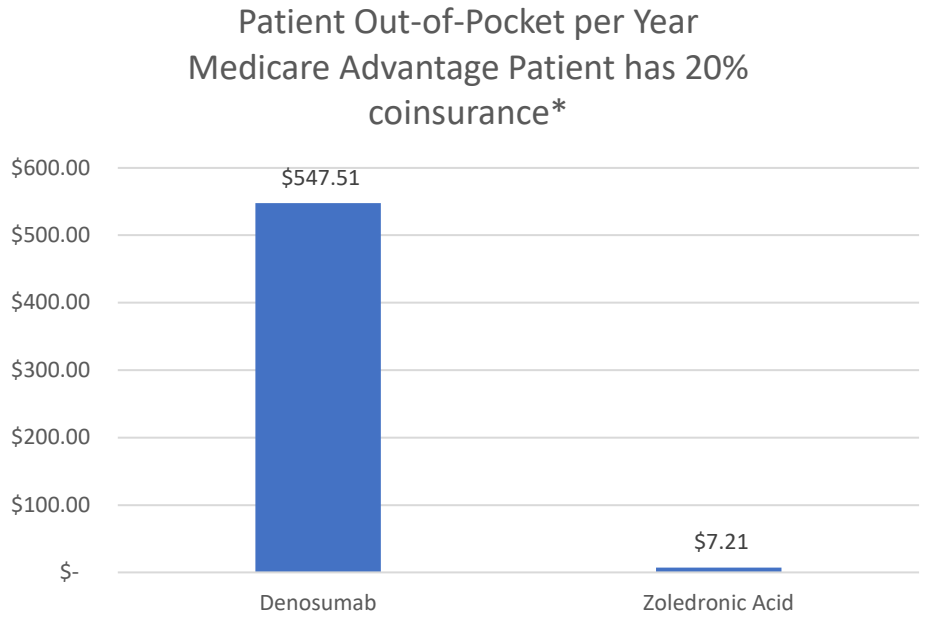
Effectiveness: Phase 3, randomized trials

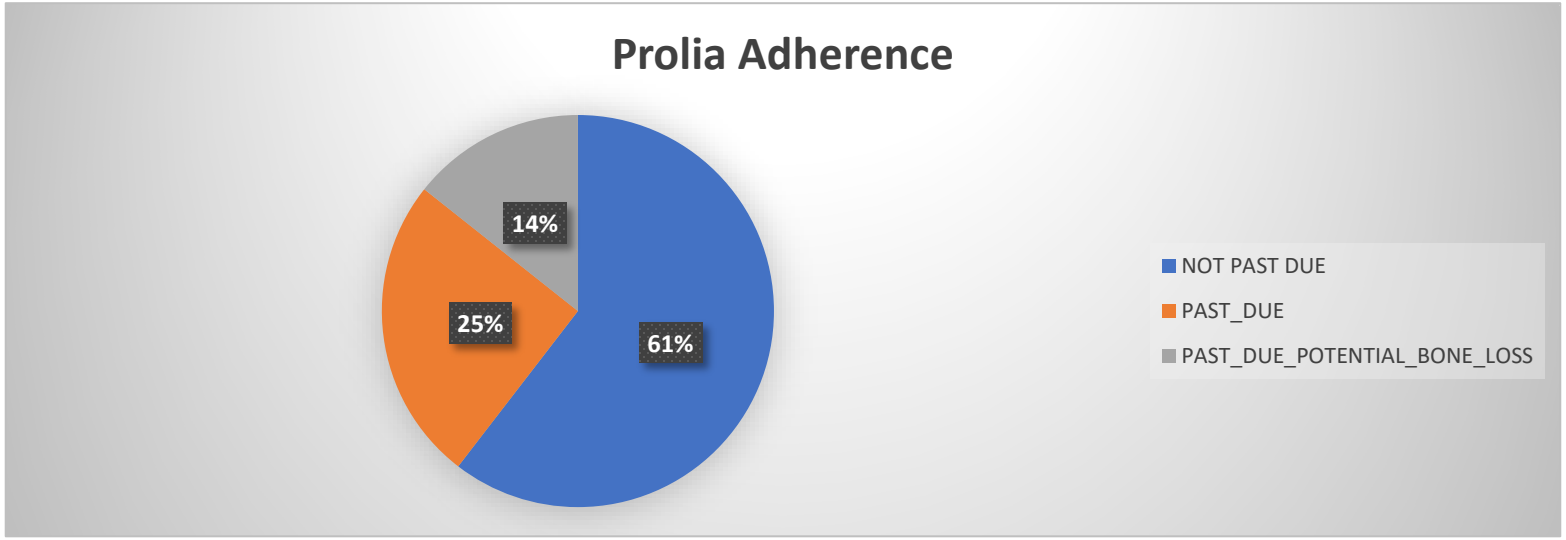
zoledronic acid	denosumab
7.6% absolute risk reduction	4.8% absolute risk reduction
• 7,736 patients • To prevent 1 vertebral fracture at yr. 3, NNT=13	• 7,808 patients • To prevent 1 vertebral fracture at yr. 3, NNT=21

https://www.novartis.com/us-en/sites/novartis_us/files/reclast.pdf
https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/prolia/prolia_pi.pdf

Cost and Adherence







Other osteoporosis therapies

- Selective estrogen receptor modulators – raloxifene has estrogen activity in bone, improves BMD and decreases risk of verterbral fracture
  - For postmenopausal women: reduction in breast cancer risk but increased risk of thromboembolic events. Bisphosphonates favored over SERMs due to greater efficacy.

- Calcitonin binds to osteoclasts and inhibits bone resorption. Limited to < 6 months due to increased risk of cancer with long term usage.
  - Inferior efficacy to bisphosphonates. Preferred route – nasal. Can be used for short-term pain relief after vertebral fracture. Switch to more effective agent after pain has abated

- Estrogen – not advised for direct treatment of osteoporosis due to risk of CHD, stroke, VTE and breast cancer.
  - If a women is receiving MHT for relief of menopausal symptoms, bone loss protection is similar to that seen with bisphosphonates

Crandall et al. Ann Intern Med 2014: 161:711

Ettinger et al. JAMA 1999; 282:637

Carstes et al. Calcif Tissue Int 1991; 49 Supple 2:S2

Knopp-Sihota et al. Osteoporos Int 2012; 23:17

Rossouw et al . JAMA 2002; 288:321

Ravn et al. Ann Intern Med 199; 131:935

ACP
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Treatments to Reduce Fractures in Postmenopausal Females With Primary Osteoporosis

Recommendations

RECOMMENDATION: ACP recommends that clinicians use bisphosphonates for initial pharmacologic treatment to reduce the risk of fractures in postmenopausal females diagnosed with primary osteoporosis (strong recommendation; high-certainty evidence).

RECOMMENDATION: ACP suggests that clinicians use the RANK ligand inhibitor (denosumab) as a second-line pharmacologic treatment to reduce the risk of fractures in postmenopausal females diagnosed with primary osteoporosis who have contraindications to or experience adverse effects of bisphosphonates (conditional recommendation; moderate-certainty evidence).

RECOMMENDATION: ACP suggests that clinicians use the sclerostin inhibitor (romosozumab, moderate-certainty evidence) or recombinant PTH (teriparatide; low-certainty evidence), followed by a bisphosphonate, to reduce the risk of fractures only in females with primary osteoporosis with very high risk of fracture (conditional recommendation).

RATIONALE: Bisphosphonates had the most favorable balance among benefits, harms, patient values and preferences, and cost among the examined drugs in postmenopausal females with primary osteoporosis and should be used as first-line treatment. Denosumab also had a favorable long-term net benefit, but bisphosphonates are much cheaper than other pharmacologic treatments and available in generic formulations. Evidence showed that the benefits of recombinant PTH (teriparatide) or the sclerostin inhibitor (romosozumab) may have outweighed harms compared with placebo in a select population of postmenopausal females (mean age >74 years) with osteoporosis and very high risk for fracture. Bisphosphonates were associated with higher risk for osteonecrosis of the jaw and atypical femoral fractures. Teriparatide may have resulted in no difference in risk of serious adverse events but probably increased the risk of withdrawal due to adverse events in RCTs after 36 months.

Patient Population

Postmenopausal females diagnosed with primary osteoporosis

Interventions Compared With Placebo

Special Circumstances

Glucocorticoid Induced Osteoporosis

- Glucocorticoids inhibit osteoblasts and stimulate osteoclasts, increase fracture risk even at doses as low as 2.5 – 7.5 mg / day
- Risk factors for fracture greater with age, larger dose and longer duration of therapy
- Any patient requiring treatment with a systemic glucocorticoid ≥ 3 months requires an evaluation.
- BMD for adults ≥ 40 taking any dose of glucocorticoid ≥ 3 months and for adults < 40 taking high dose of glucocorticoids ≥ 20 mg of prednisone for more than 1 month

van Staa et al. Osteoporos Int 2002; 13:777
Manolagas et al. J Bone Miner Res 1999; 14:1061
Angali et al. Bone 2006; 39:253

Glucocorticoid Induced Osteoporosis - Treatment

- All patients taking glucocorticoids for ≥ 3 months should receive calcium 1000-1200mg/day and 600–800 IU Vitamin D/day

- Pharmacologic therapy indicated:
  - postmenopausal women and men ≥ 50 with t-score ≤ - 2.5
  - postmenopausal women and men ≥ 50 with + FRAX and osteopenia
  - postmenopausal women and men ≥ 50 with – FRAX and osteopenia on ≥ 7.5 mg/day of prednisone for ≥ 3 months
  - premenopausal women and men < 50 with fragility fracture
  - premenopausal women and men < 50 with z score ≤ -3.0 or bone loss ≥ 4% a year on prednisone ≥ 7.5 mg/day for ≥ 3mo
  - premenopausal women and men on prednisone > 30 mg/ day for > 1 month

- Choice of therapy – first line oral bisphosphonate (alendronate, risedronate), second line IV bisphosphonate, consider PTH for severe osteoporosis (T-score < - 3.5 or < -2.5 with fracture)

- Denosumab only if other choices are not available.

Buckley et al. Arthritis Rheumatol 2017: 69:1521

MacLean et al. Ann Intern Med 2008: 148:197

Osteoporosis in Chronic Kidney Disease

- In this population, osteoporosis needs to be differentiated from CKD-MBD (mineral and bone disorder):
  - Abnormalities in calcium, phosphorus, PTH, fibroblast growth factor 23, vitamin D metabolism, bone turnover, mineralization, vascular and soft tissue calcification.

- If the eGFR ≥ 30 and no biochemical evidence of CKD-MBD, diagnosis and treatment is the same as patients with normal kidney function.

- If the eGFR < 30, BMD alone should not be used for diagnosis. If CKD-MBD is not present and the patient has fracture or is considered high risk, treatment can be considered with bisphosphonates (off-label), or denosumab (caution: hypocalcemia)

Moe et al. Kidney Int 2006; 69:1945

Jamal et al. Osteoporos Int 2012; 23:1191

Jamal et al. Curr Rheumatol Rep 2012; 14:217

Monitoring

Bone Turnover Markers

- Measure collagen breakdown products during bone resorption and formation
- Have random in-patient variability, biologic variability and poor standardization
- Have no role in selecting patients for therapy. Not recommended for routine use
- For select patients with concerns about adherence or absorption of anti-resorption therapy: measure fasting urinary NTX, serum CTX or serum PINP before and 3-6 months after therapy. A 30-50% reduction in markers shows proper adherence and efficacy
- Can also track rise of Bone Turnover Markers to determine need to end bisphosphonate drug holiday
- PTH analogs increase bone formation markers, followed by increasing markers of bone resorption. Romosozumab increases bone formation markers and reduces bone resorption markers

Hlaing et al Ann Clin Biochem 2014: 51:189

Ravn et al J Clin Endocrinol Metab 1999; 84:2363

Khosla et al. J Clin Endocrinol Metab 2012; 97:2272

DXA Monitoring

- Postmenopausal women and men –
  - After therapy, follow up DXA after 1-2 years
  - BMD stable or improved – next DXA in 2-5 years
  - BMD decreased or fragility fracture (all groups) – evaluate adherence, malabsorption, consider IV therapy, consider anabolic therapy

- Premenopausal women –
  - After therapy, follow up DXA in 1 year

- Glucocorticoid induced –
  - After therapy, follow up DXA in 1 year
  - BMD stable or improved – next DXA 2-3 years. If glucocorticoids are stopped can go to every 5 years

Rosen H et al. UpToDate, Wolters Kluwer (Accessed Dec 2023)
Becker C et al. UpToDate, Wolters Kluwer (Accessed Dec 2023)
Finkelstein J et al. UpToDate, Wolters Kluwer (Accessed Dec 2023)