Osteoporosis

- Systemic skeletal disease
  - Low bone mass
  - Microarchitectural deterioration in bone tissue leads to
    - Increased bone fragility
    - Increased fracture risk

Types of osteoporosis

- ***Primary***: related to aging and loss of gonadal function
- ***Secondary***:
  - up to 30% of cases in postmenopausal women are estimated to be secondary
  - Causes: endocrine, hypogonadism, GI diseases, nutritional deficiency (Vitamin D), eating disorders, cancer with bone involvement, medications, etc.

Impact of osteoporosis

- 10.3% of non-institutionalized Americans >50 yo had hip osteoporosis in 2010
- 1.5 million Americans have osteoporotic fracture
- 40% of women and 10% of men will have a fracture of the hip, spine or wrist
- 40% regain pre-fracture independence
- 10-20% increased mortality at one year after a fracture
- 20% of patients with a fracture require long-term nursing care
- 500,000 hospitalizations annually
- 2.5 million office visits
- 180,000 nursing home admissions
- Health care costs in 2002 were $18 billion, projected to increase to $25 billion by 2025.

WHO diagnostic criteria for osteoporosis/osteopenia based on DEXA

- ***Normal***: spinal or hip BMD **within 1.0 SD below** the young adult female reference mean (T-score $\geq$-1.0)
- ***Low bone mass/osteopenia***: spinal or hip BMD **between -1.0 and -2.5 SDs below** the young adult female reference mean (T-score between -1.0 and -2.5)
- ***Osteoporosis***: spinal or hip BMD **$\geq$2.5 SDs below** the young adult female reference mean (T score $\leq$ -2.5)
- ***Severe/established osteoporosis***: BMD $\geq$2.5 SDs below the young adult female reference and presence of $\geq$1 fragility fractures

BMD: bone mineral density

DEXA: dual energy x-ray absorptiometry

SD: standard deviation

*not applicable to men <50, children and premenopausal women (International Society for Clinical Densitometry (2013) recommends using Z-scores: worse than -2.0 is less than expected for age)

Who should be screened?

- All women ≥ 65yo should have DEXA of hip and lumbar spine
  - 25% of this patient population has osteoporosis, but 25% of women age 65-85 have never had DEXA. In 2015, 73.8% (HMO) and 79.3% (PPO) had DEXA
- Risk assessment strategy in younger women is uncertain
  - Absolute risk of fracture for any given BMD is lower in younger women, despite rapid rates of bone loss during menopausal transition
  - Absolute 5-year probability of hip fracture is <1% until age 70, when it starts to increase exponentially
  - No data on benefits/harms of treatment beginning at age 50-64 and continuing over the next decades of life
  - Some guidelines encourage DEXA measurement for women age 50-64 only if they have risk factors for fracture (National Osteoporosis Foundation, International Society for Clinical Densitometry, American College of Endocrinology)

Women 50-64

- Osteoporosis self-assessment tool (**OST**)
  - Score= (weight in kg-age) X 0.2
- Studies have shown that an OST score <2 is an appropriate cut-off to select younger postmenopausal women for BMD testing
- USPSTF (2011): check BMD by DEXA in women <65yo who have a 10-year fracture probability (FRAX) the same or greater than that of a 65 yo white woman (i.e. ≥ 9.3% 10-year probability of major osteoporotic fracture-hip, clinical vertebral, distal forearm or humerus)
- Order DEXA only if there is intention for treatment if T-score is ≤2.5

FRAX clinical risk factors calculator available at www.shef.ac.uk/FRAX

- Age
- Sex
- Weight
- Height
- Previous fracture
- Parental history of hip fracture
- Smoking status
- Glucocorticoid use
- Rheumatoid arthritis
- Secondary osteoporosis
- ≥ 3 units of ETOH per day (1 unit: 9-10 oz. beer, 4 oz. wine, 1 oz. spirits, 2 oz. aperitif)
- Femoral neck BMD (g/cm2)

Risk factors from US Department of Health and Human Services: Bone health and osteoporosis: A report of the Surgeon General (2004)

- Excessive ETOH intake (> 4 drinks a day for men and >2 drinks a day for women)
- Excessive caffeine intake (>2.5 cups of coffee)
- Smoking (any amount)
- Family history of osteoporotic fracture
- Gonadal hormone deficiency
- Immobilization and inadequate physical activity
- Increasing age
- Low body weight <58 kg(128 lbs.)
- Low Calcium and Vitamin D intake
- Personal history of fracture
- White or Asian race

RISK FACTORS FOR OSTEOPOROTIC FRACTURE (NOF)

NONMODIFIABLE

- Personal history of fracture as an adult
- History of osteoporosis in a first degree relative
- Caucasian race
- Advanced age
- Dementia
- Poor health/frailty

MODIFIABLE

- Cigarette smoking
- Low body weight
- Estrogen deficiency: early menopause (age <45) or bilateral ovariectomies, prolonged (>1 yr) premenopausal amenorrhea
- Low calcium intake (lifelong)
- Alcoholism
- Impaired eyesight despite adequate correction
- Recurrent falls
- Inadequate physical activity
- Poor health/frailty

RISK FACTORS FOR SECONDARY OSTEOPOROSIS

Hypogonadism	Amenorrhea/oligomenorrhea
	Hyperprolactinemia
	Premature menopause
Endocrine and metabolic	Hyperparathyroidism or tumor secretion of PTH –rp
	Untreated/inadequately treated hyperthyroidism
	Cushing's syndrome
	Adrenal insufficiency
	Acromegaly
	Hypophosphatemia
	Hemochromatosis
	Porphyria
Gastrointestinal disorders	Malabsorption syndromes (celiac, IBD)
	Chronic obstructive jaundice
	Primary biliary cirrhosis
	Gastrectomy
	Pancreatic insufficiency
Eating disorders	Anorexia nervosa
	Bulimia
Chronic anemia	(sickle cell disease, thalassemia, hemophilia)
Cancers with diffuse bone involvement	
Chronic disorders	Autoimmune: Rheumatoid arthritis, Ankylosing spondylitis, SLE
	Renal failure/hemodialysis
	Liver failure
	Amyloidosis
	Systemic mastocytosis
	COPD

TPN or nutritional deficiencies	**Vitamin D,** Rickets, scurvy, etc.
Medications	Glucocorticoids (≥ of 5 mg prednisone / equivalent daily)
	Anticonvulsants
	Thyroxin (excessive dose)
	Heparin and Warfarin
	Cyclosporine, Tacrolimus
	GnRH analogues and antiestrogens
	Depo-Powera (chronic)
	Chemotherapy
	Lithium, Aluminum
	PPIs
CNS conditions	Epilepsy
	Multiple Sclerosis
	Parkinson's disease
	Spinal cord injury
	Stroke
HIV/AIDS	

Osteoporosis screening in men

- Prevalence of osteoporosis in men ≥65 yo is 5.6%
- Data on efficacy of pharmacotherapy is limited
- National Osteoporosis Foundation (NOF) recommends DEXA in men ≥70 and men 50-69 with risk factors
- Use the self-assessment tool: (weight in kg-age) x 0.2
- USPSTF: no recommendation because of insufficient evidence, but commented that men whose FRAX risk is ≥ to that of a 65 yo white woman would benefit from DEXA

How often to screen?

- Baseline T-score is important in deciding screening interval
- Most insurances require at least a 2 year interval to cover DEXA
- Study in older community dwelling women for 10% to develop osteoporosis
  - Normal BMD or mild osteopenia: (T-score between -1 and -1.5): 15 years
  - Moderate osteopenia (T scores between -1.5 and -2): 5 years
  - Advanced osteopenia (T scores between -2 and -2.5): 1 year
- Study in community dwelling older men for 10% to develop osteoporosis
  - Normal BMD/mild osteopenia: 0.2% develop osteoporosis in 15 years
  - Moderate osteopenia (T-score between -1.5 and -2): 8.5 years
  - Advanced osteopenia (T-score between -2 and -2.5): 2.7 years

When to stop screening patients who do not have osteoporosis?

- No clear guidelines
- Older women with T-scores better than -1.5 have a very low risk of disabling fracture before their estimated disk of death
- Older women with T-scores between -2 and -2.5 would benefit from re-screening if they have a high risk of disabling fracture before their estimated risk of death
- Assess competing co-morbidities and life expectancy

How should a patient's absolute risk be assessed?

- Clinical factors contribute to fracture risk beyond BMD
- A systematic review of studies in postmenopausal women concluded that no fracture risk assessment tool is optimal
- FRAX is the most commonly used in the US
  - Strengths: country specific models, reevaluation based on performance studies
  - Limitations:
    - no data from randomized controlled studies on benefit of pharmacotherapy for FRAX risk >3% for the hip and 20% for any major site
    - It only includes the femoral neck BMD (some patients have markedly lower spine BMD)
    - Does not nuance certain risk factors (e.g., how many fractures, severity and site prior fractures)
    - Fall history not included
    - It should be used to estimate fracture probability in treatment-naïve patients

What lifestyle measures are recommended for fracture prevention?

- Maintain a healthy body weight (BMI >20 mg/m2)
- Adequate dietary protein intake (0.8 g/kg body weight per day)
- Avoid smoking and excessive ETOH use
- Physical activity: weight-bearing exercises and muscle strengthening exercises (frequency, intensity and specific exercises are not recommended in the guidelines)- 30 minutes of daily walking and gentle resistance exercises for older adults
- Avoid falls (10-15% of falls in older adults result in fractures)
- Avoid certain medications/polypharmacy that can increase fall risk
- Consider PT for evaluation/treatment of gait, balance, lower extremity strengthening
- USPSTF: individualized decision making, physical activity, 800 iu Vitamin D supplementation in community-dwelling older adults at increased risk

What is the recommended intake of Calcium and Vitamin D?

- **Calcium**: Recommended daily allowance (RDA):
  - Women age 19-50: 1,000 mg/d
  - Women >50: 1,200 mg/d
  - Men age 19-70: 1,000 mg/d
  - Men >70: 1,200 mg/d
- Intake of Ca > 2,500 mg/d should be avoided
- Preferred sources are calcium-rich foods
- **Vitamin D:** RDA for women and men (corresponds to a serum level of 25-hydroxyvitamin D of 20 ng/mL and assumes minimal or no sun exposure):
  - Age 19-70: 600 IU/d
  - Age >70: 800 IU/d

Diagnosis of Osteoporosis in adults >50

- History of hip/clinical vertebral fracture not due to excessive trauma
- Existing vertebral fracture on X-ray (no symptoms)
- BMD by DEXA with T-score lower than -2.5
  - Measurements of sub-regions of the hip and lumbar spine (L1-L4)
  - Use total hip and femoral neck measurement to make the diagnosis (not Ward's area or greater trochanter sub-regions)
  - Spine bone density may increase with aging because of calcium deposition from DJD and abdominal aortic calcification
  - Use T-scores for postmenopausal women and men age >50 (for the hip, the T- score compares with a reference population of non-Hispanic white women age 20-29 from NHAES III-third National Health and Nutrition Examination Survey. For the L1-L4, the reference group is the manufactured specific database of young white women)
  - Use Z- scores in premenopausal women and men <50 (compares with average age-, sex- and race-matched people)

When should laboratory testing be considered to assess for secondary causes?

- Current evidence is insufficient to recommend routine lab testing in patients with osteoporosis to identify possible secondary causes
- Measurement of 25-OH-Vitamin D level is recommended in osteoporotic patients. There is no evidence that higher levels of D are superior to just ensuring the age-specific RDA (exception: patients with problems absorbing/metabolizing Vitamin D)
- If specific secondary causes are suspected, refer to specialist
  - GI for celiac disease, IBD, etc.
  - Endocrinology for hyperthyroidism, Cushing's syndrome, hyperparathyroidism, etc.
  - Rheumatology for autoimmune disease
  - Hematology/Oncology for multiple myeloma and cancers with bone involvement
  - Allergy/Immunology for systemic mastocytosis

Goals of treatment for fracture prevention

- Reduce risk of disabling clinical fractures, especially of the hip and vertebrae
- Change in BMD during treatment is less important (most of the reduction of fracture risk is *NOT* explained by a change in BMD)
- If fracture happens during treatment:
  - assess for adherence to treatment
  - review medication list for mediations that can decrease bone density
  - evaluate for secondary causes
  - assess for propensity to falls
  - refer to osteoporosis specialist

Which patients should take Calcium and Vitamin D supplementation?

- Best is to obtain Calcium and Vitamin D from dietary sources and only recommend supplementation if patients do not meet the levels
- Sun exposure: 30 min/day, 5 days a week
- Calcium supplements: make dose recommendations based on elemental Calcium content. Excessive intake can cause nephrolithiasis.
  - Calcium carbonate (elemental calcium equivalent)
    - 400 mg (161 mg)
    - 500 mg (200 mg)
    - 750 mg (300 mg)
    - 1000 mg (400 mg)
- Systematic review of trials of combined Calcium and Vitamin D supplementation reported a reduction in fracture risk in institutionalized elderly people (not significant in community-dwelling older adults)

Which patients are candidates for drug treatment?

- Postmenopausal women with osteoporosis (by DEXA or with evidence of radiographic vertebral fractures)- medications that reduce risk of fracture of hip and vertebrae:
  - Alendronate
  - Risedronate
  - Zoledronic acid
  - Denosumab
- Women and men >50 yo with recent low-trauma hip fracture:
  - Zoledronic acid Rx reduces the risk of clinical fractures
- Men with osteoporosis-medications that reduce risk of radiologic vertebral fracture (unclear role in preventing clinical or non-vertebral fracture)
  - Alendronate
  - Risedronate
  - Zoledronic acid

FRAX intervention thresholds

- NOF, American College of Endocrinology and the Endocrine Society endorse specific FRAX intervention thresholds and risk levels of
  - ≥3 % for hip fracture
  - ≥20% for any major osteoporotic fracture
- This is to add clinicians in deciding whether to recommend pharmacotherapy in adults ≥ 50 yo with osteopenia. It is unproven that pharmacologic Rx reduces risk of fracture
  - Systematic reviews of bisphosphonate trials in postmenopausal women with osteopenia reported no significant risk reduction of non-vertebral fractures
  - Pivotal trials of alendronate, risedronate and denosumab found no fracture risk reduction in postmenopausal women with osteopenia
- NBHA (National Bone Health Alliance): proposed changing diagnostic criteria for osteoporosis and recommends adults >50 yo be diagnosed with osteoporosis regardless of BMD if they have FRAX levels above 3% for the hip and 20% for any major site.
  - In the US, an estimated 4.3% of men and 15.4% of women ≥50 yo have osteoporosis based on BMD. The expanded NBHA definition would increase the estimate 3-fold in men and almost 2-fold in women
- ACP recommendations: Shared decision making between patient and physician in osteopenic women ≥ 65 yo at increased risk of fracture (weak recommendation, low quality evidence)

How to choose a specific pharmacologic agent?

- First line of treatment: **Bisphosphonates** (generic forms available for all)
- Ibandronate is rarely prescribed because there is no evidence from clinical trials that it reduces the risk of nonvertebral fractures.
- Contraindicated in patients with renal failure with CrCl of <35 ml/min/1.73m2
- Oral bisphosphonates: take with a glass of water on an empty stomach (contraindicated if achalasia, esophageal strictures, Barrett's esophagus but OK with GERD controlled with medications or remote hx of PUD)
- Common side effects:
  - GI irritation, musculoskeletal problems
  - Side effects of zoledronic acid: flu-like symptoms, bone pain (typically with the initial dose) and musculoskeletal symptoms.
- Rare side effects:
  - osteonecrosis of the jaw (exposed bone in the maxillofacial region that does not heal within 8 weeks)
  - Atypical femoral fractures (low-trauma subtrochanteric or femoral shaft fractures)

Bisphosphonates

- Alendronate: 10 mg/d or 70 mg/wk ($107/mo)
  - NNT to prevent one hip fracture: 91 (2-5 years)
- Ibandronate: 2.5 mg/d or 150 mg/mo ($153/mo)
  - NNT to prevent one vertebral facture 20 (3 years)
- Risedronate: 5 mg/d, 35 mg/wk, 75 mg/d in two consecutive days/mo or 150 mg/mo ($199/mo)
  - NNT to prevent one hip fracture 77 (3 years)
- Zoledronic acid 5 mg iv every year ($1,083 per dose=monthly cost $90)
  - NNT 91 (3 years) to prevent one hip fracture and 30 (2 years) to prevent one spine fracture (men)

Denosumab

- Biologic (human monoclonal antibody) treatment approved in postmenopausal osteoporosis
- Inhibits osteoclast formation and activity by blocking receptor activator of nuclear factor kappa B ligand
- BMD increase is higher than with Alendronate
- Decreases risk of vertebral and non-vertebral fractures NNT to prevent one spinal fracture 11 (1.5 yrs)
- 60 mg SQ twice a year (one dose=$881, monthly cost $146)
- Side effects: eczema, nausea, injection site reactions
- Rare side effects: osteonecrosis of the jaw, atypical femoral fractures
- Can be prescribed if Cr Cl <30-35 ml/min/1.73m2
- Check calcium level and correct hypocalcemia before starting Rx

Raloxifene

- Selective estrogen receptor modulator (SERM)
- 60 mg/d ($198/mo)
- Reduces risk of vertebral fractures in postmenopausal women with osteoporosis: NNT to prevent one fracture 29 (3 years)
- No risk reduction for non-vertebral fractures
- Not a first line agent
- Long term use
  - Increases risk of venous thromboembolic events
  - Decreases risk of breast cancer in high risk patients

Estrogen therapy of Combined hormone therapy (Estrogen+Progestin)

- Not recommended by the FDA for treatment of postmenopausal osteoporosis
- E+P is moderately beneficial in reducing risk of fractures in postmenopausal women, this benefit does not outweigh the harms (USPSTF: Menopausal hormone therapy for primary prevention of chronic conditions, Ann Intern Med 2013:158, 47-54)

CEE (0.45 mg)+Bazedoxifene (20 mg): FDA approved for osteoporosis prevention one tablet daily, monthly cost $215

Teriparatide

- Anabolic agent, recombinant human parathyroid hormone
- Treatment candidates: contraindications to bisphosphonates, hx of major fracture while on bisphosphonates, treatment-naïve patients with very low T-score (worse than -3.5)
- Reduces risk of vertebral and non-vertebral fractures in postmenopausal women with osteoporosis NNT to prevent one fracture is 11 (1.5 yrs)
- Does not reduce the risk of hip fracture
- 20 mcg/d SQ injection ($1,545)
- Efficacy and safety have not been evaluated beyond 2 years of Rx (FDA recommends a maximum of 2 year use)
- Common side effects: nausea, arthralgia, leg cramps, hypercalcemia and hypercalciuria
- Rare side effects: hypotension, hyperuricemia, angioedema, anaphylaxis
- Black box warning about risk of osteosarcoma (studies in rodents)

Abaloparatide

- Human parathyroid hormone peptide analogue
- 80 mcg/d SQ injection, max 2 years ($1,764 monthly cost)
- FDA approved for postmenopausal osteoporosis at high risk of fracture
- Efficacy and safety: similar to teriparatide

Calcitonin nasal spray

- Not first line of treatment because of low efficacy
- 200 units/spray, dose is one spray in one nostril QD
- Monthly cost $469
- Decreases incidence of vertebral compression fracture

Combination therapy?

- Not recommended
- Anti-fracture efficacy of combination regimens has not been adequately evaluated in randomized trials and safety has not been assessed

ACP recommendations

- Offer Rx with bisphosphonates (alendronate, risedronate, zoledronic acid) or denosumab to women with postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures.
- ACP recommends against hormone therapy or raloxifene in this group.
- Offer Rx with bisphosphonates to men with osteoporosis to reduce risk of vertebral fractures.

Should patients receiving pharmacotherapy be monitored with serial DEXA?

- Some organizations (NOF, American College of Endocrinology and the Endocrine Society) recommend spine and hip DEXA measurements evert 1-2 years until findings stabilize
- There is no data from randomized trials that this practice improved fracture prediction.
- Amongst women receiving alendronate and raloxifene and lost BMD by DEXA, they still had a lower risk of vertebral fractures.
- Not a good way to measure adherence to treatment
- ACP recommends against BMD monitoring during the 5-year drug treatment for osteoporosis in postmenopausal women.

Should patients receiving pharmacotherapy be monitored with serial bone turnover markers (BTMs)?

- BTMs measure collagen breakdown products and other molecules released from osteoclasts and osteoblasts during bone resorption and formation.
  - markers specific to bone formation: bone-specific alkaline phosphatase (BSAP), osteocalcin, and N-terminal propeptide of type I procollagen (PINP)
  - markers specific to bone resorption: N-terminal telopeptide of type I collagen (NTX), C-terminal telopeptide of type I collagen (CTX), and pyridinoline cross-links
- Some organizations (NOF, American College of Endocrinology and the Endocrine Society) recommend BTMs before and 3-6 months after starting antiresorptive therapy to monitor efficacy and patient adherence (evidence is insufficient for this recommendation)
- Limitations of BTM measurements: high within-patient variability, biologic variability, poor standardization of most essays.
- RCTs suggested that reductions in BTMs on antiresorptive Rx are associated with subsequent decrease in fractures, but the optimal reduction level is unclear.
- Insufficient data to support the use of BTMs for deciding whether/when to discontinue or restart bisphosphonate therapy, or for the assessment of risk of osteonecrosis of the jaw in bisphosphonate-treated patients undergoing invasive dental procedures.

How long should patients be treated and when to recommend a drug holiday?

- Ideal duration of Rx is controversial
- Long term risks (rare):
  - atypical femoral fractures
  - osteonecrosis of the jaw (ONJ) with bisphosphonates and denosumab
- Incidence of ONJ
  - patients with metastatic cancer on high dose bisphosphonates: 1-5%
  - patients on low dose bisphosphonates for osteoporosis: 0.001-0.01%.
- Risk factors for ONJ: poor oral hygiene, concomitant use of glucocorticoids and chemotherapy, smoking, diabetes, history of recent invasive dental procedure

How long should patients be treated and when to recommend a drug holiday?

- Atypical femoral fractures with bisphosphonates:
  - With little/no trauma
  - May be preceded by thigh/groin pain
  - May be bilateral
- Rare (lower incidence than hip fractures from osteoporosis): 1-5 of 100,000 bisphosphonate users
- Incidence increases with duration of Rx:
  - 1.8 per 100,000 patients per year with a 2 year exposure
  - 113 per 100,000 patients per year with an 8-10 year exposure
- Meta-analysis of studies: 1.7 fold risk increase of atypical femoral fractures with bisphosphonate use (range from 11 in case control studies to 1.5 in cohort studies)

How long should patients be treated and when to recommend a drug holiday?

American Society for Bone Mineral Research Task Force:

- Consider drug holiday after 5 years of oral bisphosphonates or 3 years of iv bisphosphonates if the patients
  - Have had no hip, spine or multiple other osteoporotic fractures during the treatment period
  - Hip BMD score is >-2.5 after the initial treatment period
  - They are not at high fracture risk
- Reassess these patients after 2-3 years drug holiday
- Bisphosphonates have long half-life in bones:
  - the reduction in fracture risk persists for years after discontinuation
  - no clear benefit of long-term use for prevention of non-vertebral fractures (RCTs suggest benefit in clinical or radiographic vertebral fracture)

How long should patients be treated and when to recommend a drug holiday?

- No guideline re. drug holiday for medications other than bisphosphonates
- BMD gains from denosumab, raloxifene, teriparatide wane rapidly after discontinuation
  - use of bisphosphonate is recommended when stopping teriparatide given rapid bone loss
  - "rebound fractures" when stopping denosumab (some experts do not recommend drug holiday for denosumab or start alternative treatment when discontinuing it)

ACP recommendations

- Women with osteoporosis should be treated with oral pharmacologic therapy (i.e., alendronate, risedronate, zoledronic acid or denosumab) for 5 years (weak recommendation, low quality evidence) or intravenous bisphosphonates for 3 years
- This should prevent fractures while minimizing potential harms of long-term exposure
- Decline in initiation of bisphosphonates in younger postmenopausal women and increase in initiation in older women with higher fracture risk
- Some patients may benefit from treatments of longer duration

When should consultation be considered?

- If uncertain whether a patient will benefit from pharmacotherapy for fracture prevention
- When to resume medication after drug holiday
- Which medication to use after drug holiday
- Intolerance to standard treatment
- If treatment failure is suspected
- If acute fracture-Orthopedic and Physical Medicine and Rehabilitation

Women age 65-85 who had a fracture

- 32.2% (PPO) and 40.7% (HMO) had DEXA or received Rx for medication within 6 months after the fracture
- 93% had contact with their PCP during the 6 months after the fracture
- 73% said that PCP knew about the fracture
  - management of osteoporosis was discussed in 63% cases
  - strategies to prevent further fracture were addressed in 55% cases.

Clinical guidelines

- ACP: www.annals.org/aim/article/2625385/treatment-low-bone-density-osteoporosis-prevent-fractures-men-women-clinical
- USPSTF 2011: www.annals.org/aim/article/746858/screening-osteoporosis-u-s-preventive-services-task-force-recommendation-statement or www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummarryFinal/osteoporosis-screening
- American Association of Clinical Endocrinologists: www.aace.com/files/postmenopausal-guidelines.pdf

Patient information

- National Institutes of Health patient handout: www.niams.nih.gov/health_info/bone/osteoporosis/osteoporosis_hoh_asp
- ACOG: www.acog.org/Patients/FAQs/Osteoporosis
- NOF: www.nof.org/patients/
- Mayo clinic: www.mayoclinic.org/diseases-conditions/osteoporosis/manage/ptc-20207963
- Medline plus: www.medlineplus.gov/osteoporosis.html