Osteoporosis Overview

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Objectives

- Review pathophysiology of osteoporosis
- Describe diagnostic technologies for osteoporosis
- Explain risk assessment
- Define screening recommendations
- Identify options in pharmacologic intervention
- Explore osteoporosis treatment guidelines

Introduction

- Osteoporosis affects >10 million individuals in the US
  - 10.8 million women, 2.5 million men
- Estimated that 2 million osteoporosis-related fractures occur each year
  - 300,000 hip fractures
  - 500,000 vertebral fracture, only about ½ recognized clinically at time of event
  - 400,000 wrist fractures
  - 150,000 pelvic fractures
  - >100,000 proximal humerus fractures
- Untreated osteoporosis may result in disability and premature death

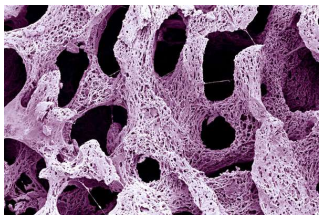
"Around the world, one in three women and one in five men over the age of fifty will suffer a broken bone due to osteoporosis."
- International Osteoporosis Foundation

Bone Remodeling

- Bone loss due to age-related changes
  - Decreased sex hormone
- Intrinsic factors
  - Peak skeletal mass and density primarily determined by genetic factors
  - Multiple hormones – estrogens, androgens, vitamin D, PTH, growth factors, IL, prostaglandins, TNFs
    - Mechanical loading, hormonal or cytokine factors stimulate Wnt pathway activation and decrease RANKL secretion.
      - **RANKL** is the final common path in osteoclast development and activation
      - **Sclerostin** is an osteocyte protein which is an inhibitor of Wnt activation
  - Chronic disease
- Extrinsic factors
  - Exercise, nutrition (calcium, vitamin D, calories, protein), medications, smoking, excessive alcohol intake, other drugs of abuse, pollution, use of triclosan, COPD, excess vitamin B, hormonal therapies utilized among transgender population

Pathophysiology

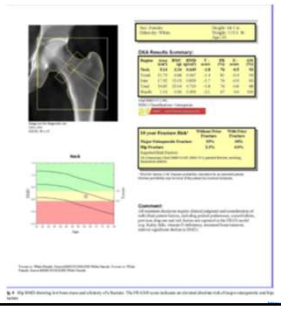
- Though the process of remodeling maintains bone health, over time, the process results in osteoporosis due to disordered skeletal architecture
- Currently the only clinical tool generally available (DXA) measures mass not architecture



https://www.clinicaladvisor.com/slideshow/slides/osteoporosis-diagnosis-prevention-treatment/

Diagnosis - DXA

- DXA: standard for measuring bone density
  - Provides T-score which compares patient's result to gender and race matched young adult population.
    - Mean value is given score of 0 and the range as SD from mean
    - T-score <-2.5 in the lumbar spine, femoral neck, or total hip is defined as osteoporosis



Diagnosis - FRAX

- FRAX often accompanies the DXA report
  - FRAX evaluates risk factors to assess risk
    - Age, BMD at femoral neck, gender, BMI, fracture history, hip fracture in a parent, steroid use, RA, alcohol intake (3 or more drinks/day), oral glucocorticoid intake, smoking, other secondary causes (type 1 DM, osteogenesis imperfecta, untreated long-standing hypothyroidism, hypogonadism or premature menopause, chronic malnutrition or malabsorption, chronic liver disease)
  - The program then calculates the estimated risk over a 10-year time frame for major osteoporosis related fractures (clinical spine, hip, wrist, and proximal humerus) as well as hip fracture.

10-year Fracture Risk[1]	Without Prior Fracture	With Prior Fracture
Major Osteoporotic Fracture	19%	30%
Hip Fracture	2.3%	4.0%

Reported Risk Factors:
US (Caucasian), Neck BMD=0.649, BMI=19.4, parental fracture, smoking, rheumatoid arthritis

[1] FRAX® Version 3.08. Fracture probability calculated for an untreated patient. Fracture probability may be lower if the patient has received treatment.

http://www.shef.ac.uk/FRAX/tool.jsp?locationValue=9

Who do I screen?
The Bone Health and Osteoporosis Foundation

Indications for Bone Mineral Density Testing

- Women aged ≥65 and men aged ≥70; regardless of clinical risk factors
- Younger postmenopausal women, women in the menopausal transition, and men aged from 50 to 69 with clinical risk factors for fracture
- Adults who have a fracture at or after age 50
- Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids at a daily dose >5 mg prednisone or equivalent for >3 months associated with low bone mass or bone loss

USPSTF recommendations being updated. Currently include:
- Grade B: Women 65 years and older
- Grade B: Postmenopausal women younger than 65 years at increased risk of osteoporosis
- Grade I: Men

Supportive Treatment

Risk Factor Evaluation

- Evaluate for secondary causes of osteoporosis AND factors that may contribute to falls
- Medications
  - Glucocorticoids, PPI, thyroid replacement, hypnotics, anxiolytics, diuretics
- Smoking
- Safety – rugs, cords, shoes, lighting, visual impairment
- Diet – nutrients, calories, protein

Exercise

- Most important during bone formation to achieve maximum bone mass
- Weight bearing is preferred to prevent further bone loss, though doesn't typically result in bone formation
- Non-weight bearing may still provide benefit in fall prevention

Calcium & Vitamin D

Calcium and Vitamin Requirements

Age	Calcium (milligrams per day)	Vitamin D (IU per day)
1–3 years	500	200
4–8 years	800	200
9–13 years	1300	200
14–18 years	1300	200
19–30 years	1000	200
31–50 years	1000	200
51–70 years	1200	400
Over 70 years	1200	600

Table 7. OTC Calcium and Vitamin D Products

Formulation	Commercial Products	Elemental Calcium	Administration
Calcium carbonate	Caltrate, OsCal, Rolaids, Tums, Viactiv	40%	Take with food
Calcium citrate	Calcitrate, Citracal	21%	Recommended for patients on acid suppressive therapy or elderly; can take on an empty stomach
Calcium gluconate	Cal-G, Cal-GLU	9%	Requires multiple doses

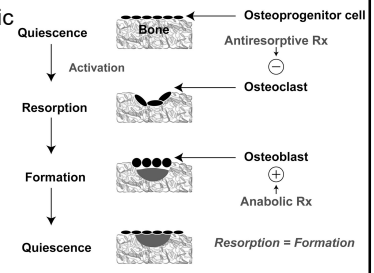
Source: Reference 19.

*Calcium citrate is absorbed best

Pharmacologic Treatment Options

Medication Classes

- Antiresorptive vs. Anabolic
  - Antiresorptive
    - Estrogen
    - SERMS
    - Bisphosphonates
    - Calcitonin
    - RANKL inhibitor
  - Anabolic
    - PTH analogues
    - Sclerostin inhibitor



The Journal for Nurse Practitioners 2015;11(10):1011-1017DOI: (10.1016/j.nurpra.2015.08.010)

Estrogen

- WHI data showed reduction of hip and spine fracture by 35%, all clinical fractures by 24%
- Beneficial effect greatest among those who start replacement early and continue treatment
- In women with intact uterus, recommended to combine with progestin – though this does not impact osteoporosis
- WHI data also show increased risks 29% MI, 40% Stroke, 100% VTE, 26% breast cancer, dementia, decreased colon cancer
- *USPSTF suggested that estrogen therapy/hormone therapy not be used for disease prevention.
- Suspected MOA – inhibit osteoclasts directly, but majority of estrogen effects are mediated through osteoblasts to decrease bone resorption

SERMS

- raloxifene, (tamoxifen), bazedoxifene

- Effect on bone density is somewhat less than that seen with standard doses of estrogen
  - Reduces vertebral fracture by 30-50%
  - No data confirming reduction in nonvertebral fractures
- Benefits – reduction in invasive breast cancer, no effect on heart disease, no increased risk of uterine cancer or benign uterine disease
- Risks – increases hot flashes/menopausal symptoms, DVT, stroke death
- MOA – estrogenic effect on skeleton

Bisphosphonates

- alendronate, risedronate, ibandronate, zoledronic acid

- Alendronate
  - Reduces vertebral fracture risk by ~50%, multiple vertebral fractures by up to 90%, and hip fractures by up to 50%
- Risedronate
  - Reduces vertebral fracture risk by 40-50%, nonspine fractures by 40%
- Ibandronate
  - Reduces vertebral fracture risk by ~40%, no overall effect on nonvertebral fractures
- Zoledronic acid – associated with acute phase reaction in ~25% of patients
  - Reduces vertebral fractures by 70%, nonvertebral fractures by 25%, and hip fractures by 40%

Bisphosphonates

- Adverse events
  - MSK & joint pains
  - Renal toxicity
  - Hypocalcemia
  - Osteonecrosis of the jaw (ONJ)
    - Usually follows a dental procedure in which bone is exposed
    - May be prevented with oral antibiotic rinse or oral systemic antibiotics
  - Atypical femoral fracture (AFF)
    - Subtronchanteric femoral region or across the femoral shaft distal to lesser trochanter
    - If found early (lateral hip/groin pain) with stress reaction/fracture, teriparatide can help heal and preclude need for surgical repair
- MOA – impair osteoclast function and reduce osteoclast number, in part by inducing apoptosis

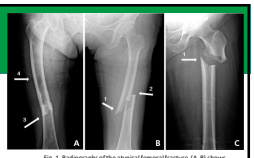


Fig. 1. Radiographs of the atypical femoral fracture. (A, B) shows atypical femoral fracture in femoral shaft region, and (C) in the subtrochanteric area. The radiographic features of atypical femoral fractures: (1) medial spike; (2) transverse fracture pattern (3) localized periosteal thickening of the lateral cortex; (4) generalized thickening of the femoral cortices.
https://www.sciencedirect.com/science/article/pii/S2405525516300524

Calcitonin

- Small reduction in new vertebral fractures, no proven effectiveness against nonvertebral fractures
- May have analgesic effect on bone pain
- Concern of increase incidence of cancer
- FDA Advisory Committee has voted to remove osteoporosis indication
- MOA – suppresses osteoclast activity by direct action on the osteoclast calcitonin receptor. Osteoclast cannot maintain contact with underlying bone

RANKL Inhibitor

- Denosumab

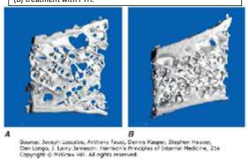
- Reduces vertebral fracture by 70%, hip fracture by 40% and nonvertebral fracture by 20%
- May increase risk of ONJ and atypical femur fracture similarly to bisphosphonates
- Can cause hypersensitivity reactions, hypocalcemia, skin reactions
- When discontinued (~5-10 years), rebound increase in bone turnover and acceleration of bone loss
  - Use of bisphosphonates may prevent rebound, duration of therapy is not clear & variable
- MOA – antibody to RANKL (final common effector of osteoclast formation, activity, and survival)

PTH analogues

- teriparatide, abaloparatide

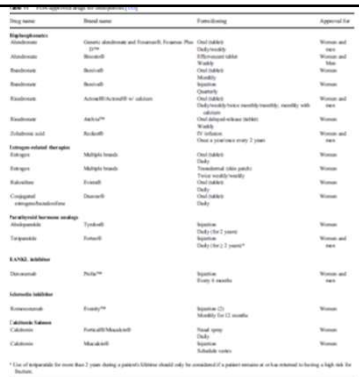
- Side effects – muscle pain, weakness, dizziness, headache, nausea, osteosarcoma in rodents
- MOA
  - Teriparatide – direct action on osteoblast activity increasing bone tissue and restoration of bone microarchitecture
    - Reduces vertebral fractures by 65%, nonvertebral fractures by 40-50%
  - Abaloparatide – analogue of PTHrP which also binds the PTH receptor. Results in similar bone formation but lesser bone resorption stimulus
    - One study comparing teriparatide and abaloparatide showed slightly higher fracture reduction with abaolparatide

Effect of PTH treatment on bone microarchitecture. Paired biopsy specimens from a 64-year-old woman before (A) and after (B) treatment with PTH.



Sclerostin Inhibitor
- Romosozumab

- Reduces vertebral fractures by 73%, nonvertebral fracture reduced depending on study from no significance to >40%
- One study showed increase in cardiovascular side effects – warning on label
- MOA – antibody that blocks the osteocyte production of sclerostin. Results in increased bone formation and decline in bone resorption



Ineffective Treatments

- Testosterone – can increase bone density, but no data indicating improvement in any fracture endpoints
- Fluoride – BMD increases, but fracture risk increased in nonvertebral sites
- Strontium (approved in Europe) – reduces risk of vertebral & nonvertebral fractures, but increased risk of cardiovascular disease and severe skin reactions
- Growth hormone – no consistent or substantial positive effects

Rx Treatment Considerations

General Guidelines

- Begin pharmacologic treatment in
  - BMD T-score ≤ -2.5
  - Low-trauma fracture in setting of BMD in low bone mass or osteoporosis range
  - Consider (in postmenopausal women) with fracture or multiple risk factors regardless of BMD/T-score
  - Based on FRAX – typically ≥20% 10-year major fracture probability and ≥3% 10-year hip fracture probability

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Who/how to treat

Endocrine Society's 2019 Endocrine Society Clinical Practice Guideline

Fracture risk	Fracture history	T-score	FRAX score	Treatment
Low risk	No previous spine or hip fracture	>-1.0	Below treatment threshold	Reassess fracture risk in 2-4 years
Moderate risk	No previous spine or hip fracture	-1.0 to -2.5	Below treatment threshold	Reassess fracture risk in 2-4 years
High risk	Prior spine or hip fracture	≤-2.5	Above treatment threshold	Initial treatment with bisphosphonate. Initial treatment with denosumab as alternative to reduce fracture risk
Very high risk	Multiple spine fractures/hip fracture	≤-2.5		Teriparatide or abaloparatide treatment up to 2 years Romosozumab for 1 year Following anabolic, treatment with antiresorptive to maintain gains

Recent fracture and/or very low BMD

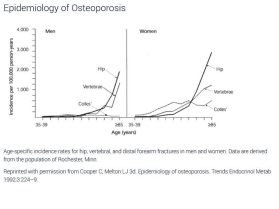
- Consider more aggressive therapy with anabolic (e.g. teriparatide) + antiresportive (e.g. denosumab) treatment
  - Combination
    - Coadministration of agents
  - Sequential
    - Evidence showing greatest benefit starting with anabolic therapy and following with an antiresorptive agent
- Research into definite guidelines for either combination/sequential treatment is ongoing

Bisphosphonate Holiday

- Sustained antifracture benefit, but may decrease risk of ONJ & AFF
- May be appropriate for patients at modest risk for fracture
  - T-score >-2.5
  - No recent fracture
  - 3 years on IV/5 years oral
- Temporary suspension (up to 5 years)
- Patients who continue to demonstrate high fracture risk, continue up to 10 years oral/6 years IV
  - T score ≤-2.5
  - Recent fracture

Men with osteoporosis

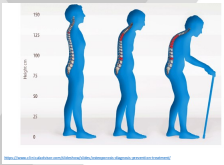
- FDA approved treatment
  - Bisphosphonates – alendronate, risedronate, zoledronic acid
  - Teriparatide
  - Denosumab
- Androgen deficiency
  - Consider testosterone



Age-specific incidence rates for hip, vertebral, and distal forearm fractures in men and women. Data are derived from the population of Rochester, Minn.

Reprinted with permission from Cooper C, Melton LJ 3d. Epidemiology of osteoporosis. Trends Endocrinol Metab 1992;3:224–9.

Monitoring Treatment Response



Serial BMD measurement

- DXA assessment is gold standard
- Biological changes in BMD are small compared to inherent error of the test itself
  - BMD changes of less than 3-6% of hip and 2-4% at spine may be due to precision error of testing itself
- Follow-up BMD should be done after 1 year of initial therapy or change in therapy
- Longer intervals once an effective treatment is established
- BHOF recommends repeating BMD every 2 years in adults ages 65 and older

Medicare Coverage of Bone Density Screening

https://www.medicare.gov/coverage/bone-mass-measurements

- Covers this test once every 24 months (or more often if medically necessary) if you meet one of more of these conditions:
  - You're a woman whose doctor determines you're estrogen-deficient and at risk for osteoporosis, based on your medical history and other findings.
  - Your X-rays show possible osteoporosis, osteopenia, or vertebral fractures.
  - You're taking prednisone or steroid-type drugs or are planning to begin this treatment.
  - You've been diagnosed with primary hyperparathyroidism.
  - You're being monitored to see if your osteoporosis drug therapy is working.

Research

- Recommendations for anabolic and/or antiresorptive agent selection/duration
- Several on new denosumab-like agents
- Atenolol for prevention of osteoporosis
  - https://www.centerwatch.com/clinical-trials/listings/278156/atenolol-for-the-prevention-of-osteoporosis-apo/?page=2&query=osteoporosis&rnk=6
- Addition of magnesium to bisphosphonate
  - https://www.centerwatch.com/clinical-trials/listings/303450/magnesium-effect-with-antiosteoporotic-drugs/?page=2&query=osteoporosis&rnk=10
- Denosumab vs. romosozumab
  - https://www.centerwatch.com/clinical-trials/listings/295785/anabolic-therapy-in-postmenopausal-osteoporosis/?page=7&query=osteoporosis&rnk=21
- Zoledronic acid vs zoledronic acid + Vit D; Ibandronate vs. ibandronate + Vit D
  - https://www.centerwatch.com/clinical-trials/listings/156813/efficacy-of-zoledronic-acid-in-osteoporosis/?page=7&query=osteoporosis&rnk=35
  - https://www.centerwatch.com/clinical-trials/listings/159510/efficacy-of-oral-ibandronate-in-osteoporosis/?page=7&query=osteoporosis&rnk=42
- Should low turnover, age-related osteoporosis be diagnosed and treated differently from estrogen deficiency related osteoporosis
  - https://www.centerwatch.com/clinical-trials/listings/289415/novel-precision-medicine-approach-to-treatment-of-osteoporosis-based-on-bone-turnover/?page=7&query=osteoporosis&rnk=63

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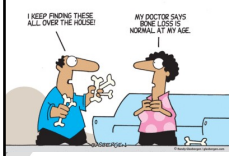

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