Osteoporosis Evaluation and Treatment

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Objectives
- Explain when to initiate screening
- Describe nonpharmacologic strategies for better bone health
- Identify candidates for pharmacologic therapy
- Answer patients’ questions about potential risks of osteoporosis medications

Osteoporosis Has Tremendous Medical and Economic Impact
- Mortality after hip fracture ~25% at 1 yr
  - Of survivors, only 50% recover pre-fracture functional status
- 1.5 million fractures per year in US
- Direct cost $18 billion

Osteoporosis Definition

- A chronic, progressive disease characterized by
  - low bone mass,
  - microarchitectural deterioration of bone,
  - bone fragility and a consequent increase in fracture risk
- Decreased bone quality as well as quantity

(National Osteoporosis Foundation, 2008)

“Osteopenia” Definition

- Preferred term is “low bone mass”
- Bone mineral density (BMD) lower than that considered normal but not low enough to be classified as “osteoporosis”
- May be useful for epidemiologic studies, but not a disease

Risk Factors for Osteoporosis

**Non Modifiable**
- Increasing age
- Female gender
- White or Asian race
- Family history
- Previous osteoporotic fracture

**Modifiable**
- Low BMI
- Current smoking
- Alcohol (≥3/day)
- Immobilization
- Glucocorticoids
- Sex hormone deficiency
  - Amenorrhea
  - Menopause

Risk Factors for Falls

- Cognitive impairment
- Frailty
- Impaired vision
- Residential facility
- History of falls
Screening for Osteoporosis

**National Osteoporosis Foundation:**
- Women age ≥ 65 and men age ≥ 70
- Younger postmenopausal women, and men age 50-69, with additional risk factors
- Adults with a condition or taking a medication associated with bone loss
- Adults who fracture after age 50

(National Osteoporosis Foundation, 2008)

**Screening for Osteoporosis**

**US Preventive Services Task Force:**
- Women age ≥ 65
- Younger women whose risk is equal to that of a 65 y.o. white woman who has no additional risk factors
- 9.3% ten-year risk for any osteoporotic fracture, by the US FRAX algorithm
- Current evidence insufficient to assess benefits vs. harms in men

(United States Preventive Services Task Force, 2011)

**DXA Scanning**

- Dual-energy X-ray absorptiometry (DXA) assesses areal (2-dimensional) BMD at key regions of interest
  - Lumbar spine, total hip, femoral neck
- Same machine, by same operator, for optimal longitudinal assessment
- Reports BMD (g/cm²), T-scores, Z-scores
  - T-scores: compared to sex-matched reference population of young adults
  - Z-scores: age- and sex-matched

**WHO Definitions - 1994**

- **Normal** = BMD within one SD of a “young normal” adult (T-score +1.0 to -1.0)
- **Low bone mass (“osteopenia”)** = BMD between 1 and 2.5 SDs below “young normal” adult (T-score -1.0 to -2.5)
- **Osteoporosis** = BMD 2.5 or more SDs below “young normal” adult (T-score ≤ -2.5)

*For use in postmenopausal women and men age ≥ 50*

(WHO, 1994)
What about premenopausal women and men <50?

- Diagnose with care!
- ISCD:
  - Use race-adjusted Z-scores, with low BMD for chronological age defined as Z-score ≤ -2.0
  - Diagnosis of osteoporosis not made on densitometric criteria alone
- Example of diagnostic challenge: Adolescent girl who has not attained peak bone mass

(Simonelli et al., J Clin Densitom, 2008)

Other Limitation of WHO Definition

- Does not recognize that a presumptive diagnosis of osteoporosis can be made by a low-trauma (fragility) fracture regardless of the patient’s BMD

Approach to Osteoporosis Treatment

1) Evaluation for secondary causes of osteoporosis and/or fracture
2) Institution of nonpharmacologic strategies
3) Selection of pharmacologic therapy

Secondary Causes of Osteoporosis and/or Fracture

- Vitamin D deficiency
- Calcium deficiency
- Malabsorption (e.g., celiac disease, gastric bypass surgery)
- Hypogonadism
- Thyrotoxicosis
- Primary hyperparathyroidism
- Anorexia nervosa
- Multiple myeloma
- Rheumatoid arthritis
- Medications
  - Glucocorticoids
  - Aromatase inhibitors
  - Depo-Provera
  - Thyroid hormone excess
  - Thiazolidinediones
  - Phenytoin
  - Androgen deprivation therapy
How extensive a laboratory work-up does a patient need?

- Depends on degree of suspicion
  - Pre-menopausal women, men deserve more
  - Severe (e.g., multiple fractures, very low Z-scores)
- **Basic**: Serum Ca, alb, Cr, 25(OH)D, TSH, CBC, LFTs
- **Next level**: 24-hour urinary Ca, PTH, SPEP/UPEP, testosterone in men
- **As clinically indicated**: Celiac disease antibodies, 24-hour urinary free cortisol or dexamethasone suppression test

Nonpharmacologic Strategies

- Calcium
- Vitamin D
- Weight-bearing & resistance exercise
- Smoking cessation
- Alcohol moderation
- Fall prevention measures
  - Home safety evaluation
  - Medication review
  - Hip protectors

New IOM Dietary Reference Intakes

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<th>AGE</th>
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<th>CALCIUM (mg) (UL)</th>
<th>VITAMIN D (IU) (RDA)</th>
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(Institute of Medicine, 2010)

Vitamin D: The Controversy

- IOM: 25-hydroxyvitamin D level of ≥ 20 ng/mL adequate for bone health
  - Based on rigorous RCT evidence
  - Population-based recommendation
- Others insist ≥ 30 ng/mL optimizes Ca absorption, suppresses PTH, protects against fractures/falls
- More than 600-800 IU daily may be needed to achieve ≥ 20 (or ≥ 30) ng/mL
  - Malabsorption, obesity

(Institute of Medicine, 2010; Endocrine Society, 2011)
Do calcium supplements cause heart attacks?

- 2008, 2010: Secondary analysis of calcium supplementation RCT, and subsequent meta-analysis, both suggested increase in CV events with calcium supplementation
- Limitations
  - CV outcomes not primary outcomes
  - Event frequency low
  - Non-uniform adjudication of outcomes
- Other studies show no increased risk
- Calcium + vitamin D does reduce fracture risk in older adults

(Tolland, BMJ, 2008; Bolland, BMJ, 2010; Chapuy, NEJM, 1992; Boonen, JCEM, 2007)

Pharmacologic Therapy

NOF recommends osteoporosis medication for postmenopausal women and men ≥ 50 with
- An osteoporotic hip or vertebral fracture
- T-score at the femoral neck or spine ≤ -2.5 after secondary causes excluded
- Low bone mass (T-score < -1.0 but > -2.5) and FRAX 10-year risk of
  - major osteoporotic fracture ≥ 20%, or
  - hip fracture ≥ 3%

(Tosteson, Osteoporos Int, 2008)

FRAX

- Estimates 10-year absolute fracture risk
- Especially for those in low bone mass (“osteopenia”) range
  - Example: 80 y.o. w/ prior fracture and taking prednisone, 52 y.o. with no risk factors, both with femoral neck T-score -2.0
- Applies to postmenopausal women and men ≥ 50 y.o., who are treatment naïve

(Kanis, Osteoporos Int, 2008)

FRAX

(www.sheffield.ac.uk/FRAX)
Pharmacologic Therapy

- **Antiresorptive agents**
  - Bisphosphonates (oral or IV)
  - Raloxifene
  - Hormone therapy
  - Calcitonin
  - Denosumab
- **Anabolic agents**
  - Parathyroid hormone (PTH)

Oral Bisphosphonates

- **Alendronate, risedronate, ibandronate**
  - Alendronate and risedronate: Decreased risk of spine, nonvertebral, hip fractures
  - Ibandronate: Decreased risk spine fracture
- **Side effect: esophagitis**
  - Full glass of water, do not lie down
- **Inefficiently absorbed**
  - Take on empty stomach

IV Bisphosphonates

- **Zoledronic acid**
  - Once yearly infusion
  - Decreased risk spine, nonvertebral, hip fxs
  - Given within 90 days after hip fracture: Decreased risk of new spine and nonvertebral fxs, and decreased mortality
- **Side effect: transient flu-like symptoms**
- **Potential complication: osteonecrosis of the jaw**
  - Risk 1-10/100 with IV therapy at cancer doses; ~1/100,000 with oral therapy for osteoporosis

Raloxifene, Estrogen, Calcitonin

- **Raloxifene**
  - Decreased risk spine fractures (not NVF)
  - Decreased risk breast cancer
  - Increased risk venous thromboembolism
- **Estrogen or estrogen/progestin therapy**
  - Decreased risk spine, nonvertebral, hip fxs
  - Other concerns
- **Calcitonin**
  - Decreased risk spine fracture (not NVF)
  - Analgesic benefit in pts with vertebral fxs?

(Black, 1996; Cummings, 1998; Harris, 1999; McClung, 2001; Chesnut, 2004)
(Ettinger, JAMA, 1999; Rossouw, JAMA, 2002; Anderson, JAMA, 2004; Chesnut, Am J Med, 2000)
Denosumab

- Monoclonal antibody to RANK-ligand
- Decreased risk of spine, nonvertebral, hip fractures
- SubQ injection q 6 months
- Expensive
- Can be used in renal failure
  - But be careful that you are treating osteoporosis, not CKD-MBD

(Cummings, N Engl J Med, 2009)

Teriparatide (PTH Therapy)

- Sole anabolic agent available
  - Increases bone formation
- Decreased risk of spine and nonvertebral fractures
- Daily subQ injection
- Approved for 2 years of use
- Consider in severe disease, especially spine > hip
- Follow course with a bisphosphonate


You start Ms. O, a 70 y.o. woman with osteoporosis, on alendronate.

“How long will I take this medication?”

Duration of Bisphosphonate Therapy

- FLEX trial: After 5 years of alendronate (ALN), randomized to continued ALN vs. placebo
  - ALN group had continued reduction in clinical (but not radiographic) vertebral fx
  - Those in ALN group with femoral neck T-scores ≤ -2.5 had continued nonvertebral fx risk reduction

(Black, JAMA, 2006; Schwartz, J Bone Miner Res, 2010)
Duration of Bisphosphonate Therapy

- HORIZON-PFT extension trial: After 3 years of zoledronic acid (ZOL), randomized to continued ZOL vs. placebo
  - Those with 3 years on, 3 years off had a small but significant decline in BMD
  - Those with 6 years ZOL had fewer radiographic vertebral fractures (but no difference in other fracture types)

(Black, ASBMR abstract, 2010)

Duration of Bisphosphonate Therapy

- No formal guidelines
- One reasonable approach:
  - Discuss with pt after ~5 yrs
  - Repeat DXA
  - If FN (or other?) T-score at that point is ≤ -2.5, or if very high risk of fracture (e.g., hx of hip or vertebral fracture), continuing therapy may be beneficial.

Atypical Femur Fractures

Recent reports, some in setting of long-term bisphosphonate therapy

Xray findings:
- Subtrochanteric
- Transverse
- Thick cortices
Atraumatic
- Fx before fall
- +/- prodromal pain

(Neviaser, J Orthop Trauma, 2008)
**Atypical Femur Fractures**

Is the connection to bisphosphonate therapy real? Should it change practice?

- Danish registry study:
  - Similar associations between ALN use and atypical femur fracture, typical hip fracture
- Post-hoc analysis of RCT data:
  - 12 fractures in 10 (of 14,195) women
  - 2.3 per 10,000 person-years
  - Wide confidence intervals, not stat sig


**Atypical Femur Fractures**

- If relationship is real, risk is very low:
  - Treating 1000 women for 3 years would prevent 100 fxs, including 10 hip fxs, and could cause 1 atypical femur fx
- ASBMR Task Force:
  - Causal association not established
  - But, risk may ↑ with ↑ duration of med use
- Thoughtful decision-making about duration of therapy

(Black, N Engl J Med, 2010; Shane, J Bone Miner Res, 2010)

**Monitoring response to therapy**

- The challenge: Not all patients’ BMD will increase on therapy.
  - Treatment failure?
- Women adherent to ALN but with no change or a ≤ 4% decrease in BMD still had fracture reduction compared to those taking placebo.
- Bisphosphonates also appear to improve bone quality, geometry.

(Chapurlat, Osteoporos Int, 2005)
Monitoring response to therapy

- One reasonable approach:
  - Educate patient that while BMD helps decide whether to treat, it’s less useful for assessing treatment response.
  - If repeating DXA, look for meaningful loss in BMD, and be prepared to explain this to patient.
  - Meaningful loss → reassess adherence, secondary causes

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Thank you for your attention!