Osteoporosis
Evaluation and Treatment

Anne Schafer, MD
Assistant Professor of Medicine
Division of Endocrinology & Metabolism
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No conflicts of interest
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 $\geq 65$ and men age $\geq 70$
• 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 $\geq 65$
• 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>VITAMIN D (IU) (RDA)</th>
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(Institute of Medicine, 2010)

Vitamin D: The Controversy

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

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

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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)
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

(Black, 1996; Cummings, 1998; Harris, 1999; McClung, 2001; Chesnut, 2004)
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?
  (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

(Teunis, 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.
“My friend told me this medication actually causes fractures of the femur.”

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 Orthp 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)
“How will we know whether the medication is working?”

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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