Current and Emerging Strategies for Osteoporosis

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I have nothing to disclose.

Outline
- Osteoporosis screening and diagnosis
- Nonpharmacologic strategies
- Pharmacologic therapy
  - Whom to treat
  - FDA-approved medications
  - Common patient questions
  - Combination therapy

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

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
- Falls

National Osteoporosis Foundation, 2008

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

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

National Osteoporosis Foundation, 2008

United States Preventive Services Task Force, 2011
DXA Scanning

- Assesses 2-dimensional BMD
  - 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”)
  - T-score -1.0 to -2.5
- Osteoporosis
  - T-score ≤ -2.5

For use in postmenopausal women and men age ≥ 50

What about premenopausal women and men <50?

- Diagnosis more complicated
- ISCD:
  - “Low BMD for age” when Z-score ≤ -2.0
  - Don’t diagnose osteoporotic by BMD alone
- Example of diagnostic challenge: Adolescent girl who has not attained peak bone mass

Approach to Osteoporosis Treatment

1) Evaluate for secondary causes of bone loss/fracture
2) Institute nonpharmacologic strategies
3) Select pharmacologic therapy

Simonelli et al., J Clin Densitom, 2008
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: PTH, testosterone in men
- Consider: 24h urinary Ca, SPEP/UPEP
- As clinically indicated: Celiac Abs, 24h urinary free cortisol/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

IOM Dietary Reference Intakes

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<thead>
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<th>AGE</th>
<th>CALCIUM (mg) (RDA)</th>
<th>CALCIUM (mg) (UL)</th>
<th>VITAMIN D (IU) (RDA)</th>
<th>VITAMIN D (IU) (UL)</th>
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<td>2000</td>
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</table>

Institute of Medicine, 2010
Vitamin D: The Controversy

- IOM: 25(OH)D ≥ 20 ng/mL adequate
  - 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

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
  - Estrogen therapy
  - Calcitonin
  - Denosumab
- Anabolic agents
  - Parathyroid hormone (PTH)

Bone Resorption

Bisphosphonates cause osteoclast apoptosis

From Bob Josse, HealthPlexus 2010

Oral Bisphosphonates

- Alendronate, risedronate, ibandronate
  - Alendronate and risedronate: ↓ risk of spine, nonvertebral, hip fractures
  - Ibandronate: ↓ 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
  - ↓ risk spine, nonvertebral, hip fxs
  - Given w/in 90 days of hip frx: ↓ mortality
- Side effect: transient flu-like symptoms
- Potential complication (of any antiresorptive): 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**
  - ↓ risk spine fractures (not NVF)
  - ↓ risk breast cancer
  - ↑ risk venous thromboembolism
- **Estrogen or estrogen/progestin therapy**
  - ↓ risk spine, nonvertebral, hip fxs
  - Other concerns
- **Calcitonin**
  - ↓ risk spine fracture (not NVF)
  - Analgesic benefit in pts with vertebral fxs?


**Denosumab**

- Monoclonal antibody to RANK-ligand
- ↓ 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


**Teriparatide (PTH Therapy)**

- Sole anabolic agent currently available
  - ↑ bone formation
- ↓ 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: 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

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)
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. (~10 yrs?)

“My friend told me this medication actually causes fractures.”

Atypical Femur Fractures

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

Minimal or no trauma
+/- prodromal dull pain

X-ray findings:
- Subtrochanteric
- Transverse
- Thick cortices

Neviaser, J Orthop Trauma, 2008; Shane, J Bone Miner Res, 2014

Atypical Femur Fractures

- Pathogenesis: stress fractures
  - Suppression of targeted remodeling at the stress fracture site impairs normal healing
- More common with long-term BP exposure
- Risk is very low:
  - 3.2 to 50 cases per 100,000 person-years
  - Treating 1000 women for 3 years would prevent 100 fx, including 10 hip fx, and could cause 1 atypical femur fx
- D/C BP, Ca/D, consider teriparatide

Shane, J Bone Miner Res, 2014; Black, N Engl J Med, 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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Combination therapy

- Avoid concurrent use of 2 antiresorptives
- Concurrent or sequential therapy with PTH?
  - PTH (teriparatide) is . . .
    ▫ Highly effective, particularly at spine
    ▫ Anabolic in action
    ▫ Daily subQ injection
    ▫ Expensive
  - Can we optimize its use by making it more effective or less burdensome (or both)?

- PaTH Study: Daily alendronate + daily PTH
  - Concurrent alendronate blunts PTH effects
  - A course of PTH should be followed by BP (or another antiresorptive)
- DATA Trial: Denosumab q 6 mo + daily PTH
  - 2 years of concurrent therapy increased BMD more than either agent alone

DATA Study

<table>
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<th>Lumber Spine</th>
<th>Total Hip</th>
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Leder, J Clin Endocrinol Metab, 2014
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