Updates in Osteoporosis

Jeffrey A. Tice, MD
Associate Professor of Medicine
Division of General Internal Medicine,
University of California, San Francisco

I have no conflicts of interest

What’s New in Osteoporosis

• Risk factors and absolute risk
• Screening intervals
• Calcium and vitamin D?
• Newish treatments
• Rare harms
• When to stop bisphosphonates

What Would You Do? Mrs. C…

• 66 WF recently moved to Switzerland. No previous fracture. Sister had breast cancer, 3 drinks/d, healthy. No meds. Exam normal.
• About 5’7” and weighs 130
• Hip BMD T-score -2.2
• No contraindication to treatment
• What tests would you order? How would you manage her?
What is osteoporosis?

A disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk. *World Health Organization (WHO)*, 1993

- Normal bone
- Osteoporosis

What About Trauma?

- Even non-osteoporotic bone will fracture with extreme trauma
- There is no threshold for skeletal fragility
- The weaker the bone the less trauma required to fracture…

Traditional Risk Factors for Fracture

- The Big Three:
  - Older age
  - Postmenopausal female
  - Caucasian/Asian
- Other important risk factors
  - Family history of fracture
  - Low body weight (<127 in women)
  - Smoker, >3 drinks/d
  - Certain drugs (steroids, AIs) and diseases
  - Previous fracture (especially hip or spine)
- Bone mineral density (BMD)

Bone Mineral Density (DXA)
Interpretation of DXA Scans: Really Confusing

- Absolute mineral (calcium) content using x-rays
- Relative to young adult reference population
- T-score is the number of standard deviations above or below average 30 year old
  - T > -1.0 “normal”
  - -1.0 to -2.5 “low bone mass” (was called “osteopenia”)
  - T < -2.5 “osteoporosis”
- Low BMD increases fractures risk in both women and men

Risk of Fractures Over 10 Years in Women

<table>
<thead>
<tr>
<th>AGE</th>
<th>T-Score = -1.0</th>
<th>T-Score = -2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>6 %</td>
<td>11 %</td>
</tr>
<tr>
<td>60</td>
<td>8 %</td>
<td>16 %</td>
</tr>
<tr>
<td>70</td>
<td>12 %</td>
<td>23 %</td>
</tr>
<tr>
<td>80</td>
<td>13 %</td>
<td>26 %</td>
</tr>
</tbody>
</table>

BMD Does Not Fully Explain The Effect of Age on Fracture Risk

Calculating Absolute Fracture Risk: FRAX

http://www.shef.ac.uk/FRAX/tool.jsp

Who Should Have a DXA?

- Guidelines for general population
  - All women > 65, men > 70
  - Postmenopausal with fracture, family history, smoker, weight < 127, certain meds
- Usually covered by insurance (Medicare pays $128)
What About Interval Screening?

- Recommendations of q 2 y as interval to measure change
- No evidence based guidelines available
- 4597 women in Study of Osteoporosis Fractures: BMD baseline, 2, 6, 10, 16 y
- Estimated interval to transition from normal to low bone mass, to osteoporosis

Risk of Osteoporosis in 15 years by BMD Result at Age 65

<table>
<thead>
<tr>
<th>BMD Result Femoral Neck</th>
<th>Time to 10% BMD &lt; −2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal &gt; −1.0</td>
<td>16.8 y</td>
</tr>
<tr>
<td>T = −1.01 to −1.49</td>
<td>17.3 y</td>
</tr>
<tr>
<td>T = −1.50 to −1.99</td>
<td>4.7 y</td>
</tr>
<tr>
<td>T = −2.00 to −2.49</td>
<td>1.1 y</td>
</tr>
</tbody>
</table>

Implications for Screening

- BMD results of more than −1.49 at age 65
  - Defer repeat screening to age 80
- BMD results of −1.50 to −1.99 at age 65
  - Repeat screening BMD at 5 years
- BMD results −2.00 to −2.49
  - Repeat screening BMD at 2 years

Medical Evaluation

- History and physical to identify underlying problems
- Basic lab tests:
  - Vitamin D level
  - Serum calcium, kidney and thyroid function
- Additional tests only if indicated
  - PTH, SPEP/UPEP, anti-TTG IgA

Jamal et al, Osteo Inter, 2005
Under Recognition of Osteoporosis

- Among women with fracture or BMD<-2.5 only 20-30% are evaluated and treated!
- 12 months after hip fracture at the VA: 2% had DXA, 15% treated with appropriate drug
- Implications for providers: Ask about fracture history, note vertebral fractures, use chart reminders for DXA

Shibli-Rahhal, Osteo Internat, 2011

Summary: Osteoporosis
Risk Factors and Evaluation

- Osteoporosis (like hypertension) is silent until something bad happens. Under recognized.
- Routine assessment of risk factors and screening DXA at 65. Extensive lab testing wasteful.
- Everyone should receive lifestyle and nutritional counseling
- Calculation of absolute risk (FRAX) helps clinicians and patients

Solomon, Mayo Clin Proc, 2005

What Would You Do? Mrs. C…

- 66 WF recently moved to Switzerland. No previous fracture. Sister had breast cancer, 3 drinks/d, healthy. No meds. Exam normal.
- About 5’7” and weighs 130
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- No contraindication to treatment
- What tests would you order? How would you manage her?

FRAX Calculation:

- Age: 66
- Date of birth: M: 6
- Height: 1.70
- Weight: 58.97
- Previous fracture: No
- Parent fractured hip: No
- Glucocorticoids: No
- Rheumatoid arthritis: No

Bone mineral density (BMD) T-score: -2.2

- Major osteoporotic fracture: 13%
- Hip fracture: 3.1%
Who Should Be Treated?

- Preventive measures for everyone:
  - Adequate calcium, vitamin D, and exercise
- When to offer osteoporosis medications:
  - Anyone with hip or spine fracture
  - T-score < -2.5
  - “Low bone mass” and 10 year fracture risk >20% or hip fracture risk >3%

2013 National Osteoporosis Foundation Guidelines

What Can Be Done To Prevent Osteoporosis?

Prevention for everyone

- Smoking cessation, avoid excess alcohol intake
- Physical activity: modest transient effect on BMD – reduces fracture risk
- Calcium and vitamin D

Calcium and Vitamin D

- Chapuy, 1992: 800 IU D; 1200 mg Ca
  - Older women in long-term care
  - 30% decrease in hip fracture
- Porthouse, 2005: 800 IU D; 1000 mg Ca
  - Independent women >70 with 1+ risk factor
  - No benefit on hip or other fractures
- MA 25 studies: 14% fewer fractures together, no benefit alone
News Flash: Calcium Kills!!!

• Pooled 15 calcium trials: cardiovascular events increased 30%
  – Not 1° endpoint; trials with vitamin D excluded
  – Calcium + vitamin D in WHI did not increase risk
• Little supporting scientific data
  – No effect on other surrogates (coronary calcium on CT)
  – Dairy calcium not implicated
• ASBMR Task Force: “the weight of the evidence is insufficient to conclude that calcium supplements cause adverse CV events…”

Bockman, ASBMR, 2010

How Much Is Enough for Skeletal Health?
The Institute of Medicine

• Calcium
  – 1200 mg/d for women >50, men >70
• Vitamin D
  – Recommends daily intake 600-800 IU/d, no more than 4,000/d
  – Recommends serum levels 20-50 ng/ml
  – Non-skeletal benefits not established, harms minimized

How Much Is Enough for Skeletal Health?
The Institute of Medicine

Rational use of Calcium and Vitamin D

• Vitamin D 600 - 1000 IU per day
• Calcium
  – Ensure adequate intake (1000-1200 mg)
  – Focus on adherence

How Much Is Enough for Skeletal Health?
The Institute of Medicine

Pharmacologic therapy
Treatment Summary

- FRAX® to identify patients at risk: bone mineral density, age and previous fractures are the strongest independent predictors of fracture risk.
- Treatments significantly decrease fracture risk:
  - “Antiresorptive” therapy: modest BMD increase, yet decreases fracture risk faster and to a larger extent than predicted by the relatively small change in BMD.
  - Anabolic therapy with teriparatide (PTH analog) increases BMD more than antiresorptive treatment, but it is not yet clear that fracture protection is greater.

FDA-Approved Therapeutic Options in the USA

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>Treated</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Calcitonin</td>
</tr>
<tr>
<td>Risedronate</td>
<td>PTH (teriparatide)</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Denosumab</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td></td>
</tr>
</tbody>
</table>

Bisphosphonate efficacy

- Bind to bone and prevent absorption and remodeling
  - Resides in bone for decades
- Four approved agents: alendronate, risedronate, ibandronate, and zoledronic acid
  - First line therapy
  - No head-to-head fracture studies
- What we know: fracture risk reduced 30-50% if
  - Existing vertebral fracture OR
  - Low BMD (T-score < -2.5)
  - May not be useful if higher BMD (“low bone mass”)

Effect of Alendronate on Non-spine Fracture Depends on Baseline BMD

<table>
<thead>
<tr>
<th>Baseline hip BMD</th>
<th>Relative Hazard (±95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T -1.5 to -2.0</td>
<td>1.06 (0.77, 1.46)</td>
</tr>
<tr>
<td>T -2.0 to -2.5</td>
<td>0.97 (0.72, 1.29)</td>
</tr>
<tr>
<td>T &lt; -2.5</td>
<td>0.69 (0.53, 0.88)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.86 (0.73, 1.01)</td>
</tr>
</tbody>
</table>

Cummings, Jama, 1998
**Risedronate HIP Study: Two Groups**

Group 1
- 5445 age <80; hip BMD T-score < -3.0
- 39% decreased hip fracture risk

Group 2
- 3886 age >80; risk factors for hip fx
- No significant effect on hip fracture risk

**Monitoring Bone Density**

- Yearly or every 2 years?
- Patients more satisfied with yearly monitoring.
- Does loss in year 1 predict continued loss and warrant change in therapy?

**FIT Trial**

- 18% taking alendronate lost BMD during first year
- Women who lost BMD on therapy had 50% fracture reduction
- 92% who lost BMD regained it by next measurement

**DEXA to monitor bisphosphonate therapy**

- BMD after 1 year of therapy does not accurately predict what will happen over time or reflect fracture reduction
- Effective treatment for osteoporosis should not be changed because of loss of BMD during the first year of use
A New Side Effect of Potent Bisphosphonates?

Associated with potent bisphosphonate use:
- 94% treated with IV bisphosphonates
- 4% of cases have OP, most have cancer
- 60% caused by tooth extraction. Other risk factors unknown. Infection?

Dental exam recommended before Rx, but no need to stop for dental procedures

Osteonecrosis of the Jaw

Atypical Subtrochanteric Fractures?

Rare case reports in long-term bisphosphonate users (and others)
- Transverse not spiral, cortical thickening, minimal trauma
- Often bilateral, preceding pain, abnormal x-ray or bone scan
- ASBMR Task Force (2011)
  “Causation not established”
  “Risk factors uncertain”
  “Mechanism unknown”

How Long to Use Bisphosphonates?

Prolonged use (decades) common
- Long half-life suggests that life-long treatment may not be necessary
- What happens when you stop?
- FIT Long-term Extension (FLEX) study
  - Women given ALN in FIT for 5 yr.
  - Randomized to ALN or PBO for 5 yr.

Woo et al; Ann Intern Med, 2006
ADA Guidelines, 2011

Black; Jama, 2006
### New Fractures During FLEX

<table>
<thead>
<tr>
<th></th>
<th>PBO (N = 437)</th>
<th>ALN (N = 662)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-spine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>20%</td>
<td>19%</td>
<td>1.0 (0.8, 1.4)</td>
</tr>
<tr>
<td>Hip</td>
<td>3%</td>
<td>3%</td>
<td>1.1 (0.5, 2.3)</td>
</tr>
<tr>
<td><strong>Vertebral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>11%</td>
<td>10%</td>
<td>0.9 (0.6, 1.2)</td>
</tr>
<tr>
<td>Painful</td>
<td>5%</td>
<td>2%</td>
<td>0.5 (0.2, 0.8)</td>
</tr>
</tbody>
</table>

### Implications of Bisphosphonate Trials

- Bisphosphonates reduce risk of spine, hip and non-spine fracture in women with existing spine fracture or low BMD (T-score < -2.5)
- May not reduce risk of non-spine fracture in women without spine fracture or BMD < -2.5, even if at high risk.
- Intermittent dosing, even yearly, effective
- Best data of any approved treatment for osteoporosis
- After 5 years of treatment, some may stop
  - BMD > -2.5 and no hip or vertebral fractures

### Other Anti-resorptive Agents

- Less effective than bisphosphonates
  - Calcitonin (poor quality studies)
  - Raloxifene (prevents vertebral fractures only; use for breast cancer?)
- Hormone replacement
- Denosumab (antibody to RANKL)

### The Future: Anabolic Agents

**Teriparatide (rhPTH) Summary**

- The only FDA approved anabolic agent
- Increases spine, hip and total body BMD
- Decreases vertebral and nonvertebral fractures
- Combination PTH and antiresorptive drug less effective than PTH alone in increasing BMD
- PTH followed by alendronate is promising
- Reserve for very high risk population
Conclusions: Treatment

- Bisphosphonates: treatment of choice in selected individuals
  - Spine/hip fracture or T<2.5. Benefit for others less clear.
  - Duration of therapy? 3-5 years then off?
- Other agents available but expensive and unclear when to use
- New diagnostic tests and better treatments on the way…

Take Home Points

- Absolute risk estimates help with decisions
- Aggressive screening and treatment = fewer fractures; start for all women by 65 years
- Interval screening defined by baseline BMD
- Bisphosphonates: treatment of choice
  - Use for spine/hip fracture or T<2.5
  - Adherence counseling. Intermittent dosing.
  - Duration of therapy? 5 years then off?
  - No role for interim monitoring with DEXA

Denosumab

- Monoclonal antibody to RANKL
- 60 mg subcutaneous injection every 6 months
- 9% increase in spinal BMD after 3 years in the pivotal FREEDOM trial; 4%-5% increase in hip BMD
- Reduction in fracture risk after 3 years:
  - 68% decrease in new vertebral fractures
  - 40% decrease in hip fractures
  - 20% decrease in nonvertebral fractures
- 8-year data: continued increase BMD, reduced bone turnover, good safety

Questions?
Thank you!
**Teriparatide: rhPTH [1-34]**

- Only treatment that is anabolic—stimulates bone formation rather than inhibiting bone resorption
- 20 mcg daily subcutaneously for ≤ two years
- Effects:
  - Increased bone density in spine by 9% and hip by 3% vs placebo over 18 months
  - Reduced incidence of vertebral fractures (85%) and non-vertebral fragility fractures (53%) in women with pre-existing vertebral fractures
  - Studies too small to evaluate effect on hip fractures
- Adverse reactions: arthralgia, pain, nausea

**New and Emerging Therapies**

- Denosumab
- SERMs: lasofoxifene, bazedoxifene
- Strontium
  - strontium ranelate
  - strontium malonate
- Anti-sclerostin antibody
- Cathepsin K inhibitor – odanacatib
- Cyclic analog of PTH (1-31)
- Calcium receptor antagonist – “calcilytic”

**Drugs to Treat Osteoporosis**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cost per year</th>
<th>Effect on Fracture Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vertebral</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>$976</td>
<td>✓</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>$1517*</td>
<td>✓</td>
</tr>
<tr>
<td>Brand alendronate</td>
<td>$1103</td>
<td>✓</td>
</tr>
<tr>
<td>Generic alendronate</td>
<td>$108</td>
<td>✓</td>
</tr>
<tr>
<td>Risedronate</td>
<td>$1110</td>
<td>✓</td>
</tr>
<tr>
<td>Ibandronate (oral)</td>
<td>$1024</td>
<td>✓</td>
</tr>
<tr>
<td>Ibandronate (IV)</td>
<td>$1938</td>
<td>✓</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>$1249</td>
<td>✓</td>
</tr>
<tr>
<td>Denosumab</td>
<td>$1650</td>
<td>✓</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>$9786</td>
<td>✓</td>
</tr>
</tbody>
</table>

✓: antifracture efficacy proven in clinical trial  --: antifracture efficacy not proven in clinical trial