Updates in Osteoporosis

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I have no conflicts of interest

What’s New in Osteoporosis

- Risk stratification
- Under recognition and poor adherence
- New concerns about treatments
- When to start and stop drug therapy

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
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 pounds in women)
  - Smoker, >3 drinks/d
  - Certain drugs (steroids, AIs) and diseases (RA, celiac)
  - 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”
- Z-score is the number of SDs above or below others of the same age

Risk of Fractures Over 10 Years in Women

<table>
<thead>
<tr>
<th>AGE</th>
<th>T-Score</th>
<th>T-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>-1.0</td>
<td>-2.5</td>
</tr>
<tr>
<td>60</td>
<td>6 %</td>
<td>11 %</td>
</tr>
<tr>
<td>70</td>
<td>8 %</td>
<td>16 %</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)

2013 National Osteoporosis Foundation

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

- Normal > -1.0
- T = -1.01 to -1.49
- T = -1.50 to -1.99
- T = -2.00 to -2.49

NEJM 2012; 366: 225-33
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 (25OH-D)
  - Serum calcium, creatinine
- Additional tests only if indicated
  - TSH, 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

Soloman, Mayo Clin Proc, 2005

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

Shibli-Rahhal, Osteo Internat, 2011
What Can Be Done To Prevent Osteoporosis?

Prevention for everyone

• Little new data
• Smoking cessation, avoid excess alcohol intake
• Physical activity: modest transient effect on BMD – reduces fracture risk
• Fall prevention: targeted PT, home eval.
• 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

Rational use of Calcium and Vitamin D

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

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>Stops bone loss</td>
<td>Reduces vertebral fractures</td>
</tr>
<tr>
<td><strong>Estrogen</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Alendronate</strong></td>
<td><strong>Calcitonin</strong></td>
</tr>
<tr>
<td><strong>Risedronate</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Ibandronate</strong></td>
<td></td>
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<tr>
<td><strong>Zoledronic acid</strong></td>
<td></td>
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<tr>
<td><strong>Raloxifene</strong></td>
<td></td>
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<tr>
<td><strong>PTH (teriparatide)</strong></td>
<td></td>
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<tr>
<td><strong>Denosumab</strong></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 – -2.0</td>
<td>1.06 (0.77, 1.46)</td>
</tr>
<tr>
<td>T -2.0 – -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

McClung, NEJM, 2001
More Bad News: Adherence with Bisphosphonates is Poor

- 50-60% persistence after one year
  - Multiple practice settings (similar to other preventive treatments)
- Reasons for non-compliance
  - Burdensome oral administration (fasting, remain upright for 30 minutes)
  - Upset stomach and heartburn can occur
  - Asymptomatic until fracture
- Trials show clinician interest (but not tests) and regular nursing visits can improve compliance

Does Dosing Interval Matter?

- Poor quality data:
  - Daily to weekly may improve compliance
  - Weekly to monthly may not
- Yearly dosing available: zoleadronic acid
  - Extremely potent IV bisphosphonate
  - Fracture reduction after 3 annual injections: hip 40%, spine 60%, non-spine 25%
  - Precautions: acute phase reaction, renal insufficiency
- Don’t forget to discuss potential side effects…

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

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
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

Other Things to Worry About

- Atrial fibrillation (zolendronate and alendronate RCTs)
  - No association in other trials
  - Likely spurious
- Esophageal cancer
  - Case series (FDA author) and two conflicting cohorts,
  - Might be spurious
- Subtrochanteric fracture (with atypical features)
  - Likely real...

Osteonecrosis of the Jaw

- 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?
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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?

- Long half-life suggests that life-long treatment may not be necessary
- Ongoing concerns about excessive suppression of bone resorption
- FIT Long-term Extension (FLEX) study
  - 1099 women with ALN in FIT for 5 years
  - Randomized to ALN or PBO for 5 additional yrs

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>Non-spine</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>Vertebral</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>

2015 Update: Who to treat and when to stop

- NOF treatment thresholds
  - Existing hip or vertebral fracture: Yes!
  - T-score < -2.5: Yes!
  - Low bone mass + FRAX score above risk threshold (10 year risk > 3% hip; 20% any fracture): Probably not...

- Best data: alendronate and zoledronic acid
- After 3-5 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)
  – SQ q 6 months, not cleared by kidneys
  – Effective, but expensive. Less long term data

The Future: Anabolic Agents Teriparatide (rhPTH) Summary

• The only FDA approved anabolic agent
• Daily SQ rhPTH decreases vertebral and nonvertebral fractures. No hip fracture data.
• Combination PTH and antiresorptive drug less effective than PTH alone in increasing BMD
• PTH followed by alendronate is promising
• Expensive, daily injections
  – Reserve for severe OP

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: 3-5 years then off for most
  – No role for interim monitoring with DEXA

Be Skeptical of Wonder Drugs…
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

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 (65%) 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>
<th>Vertebral</th>
<th>Nonvert</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raloxifene</td>
<td>$976</td>
<td>✓</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>$1517*</td>
<td>✓</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Brand alendronate</td>
<td>$1103</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Generic alendronate</td>
<td>$108</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Risedronate</td>
<td>$1110</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Ibandronate (oral)</td>
<td>$1024</td>
<td>✓</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Ibandronate (IV)</td>
<td>$1938</td>
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<tr>
<td>Zoledronic acid</td>
<td>$1249</td>
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<td>Denosumab</td>
<td>$1650</td>
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<td>Teriparatide</td>
<td>$9786</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

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

### 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