Updates in Screening and Treatment of Osteoporosis

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I have no conflicts of interest

Overview

- Risk assessment and evaluation
- Prevention
- Pharmacologic treatment
  - Recommended therapies
  - New treatment harms
  - When to start and stop drug therapy
- New drugs
- (Under-diagnosis and under-treatment)

Normal bone

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

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 density measurement:
Dual energy x-ray absorptiometry (DXA)

- Absolute mineral (calcium) content using x-rays
  - Not used clinically
- **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></td>
<td>-1.0</td>
<td>-2.5</td>
</tr>
<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>
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</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
  – “Earlier” for postmenopausal women with fracture, family history, smoker, weight<127, certain meds
• Usually covered by insurance

How Often to Screen?

• No evidence based guidelines available (until ACP May 2017)
• Study of Osteoporosis Fractures
  – 4597 women: BMD baseline, 2, 6, 10, 16 y
  – Estimate time for ≥10% to develop osteoporosis

Risk of Osteoporosis by BMD Result at Age 65

<table>
<thead>
<tr>
<th>Baseline BMD Result</th>
<th>Time to ≥10% to Develop Osteoporosis</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 Interval

• BMD results greater than –1.49 at age 65
  – Repeat screening at age 80 (15 years)
• BMD results of –1.50 to –1.99 at age 65
  – Repeat screening at age 70 (5 years)
• BMD results –2.00 to –2.49
  – Repeat screening at age 67 (2 years)
Medical Evaluation of Osteoporosis

- 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

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

Osteoporosis prevention

- Lifestyle
  - Smoking cessation
  - Avoid excess alcohol intake
  - Physical activity: modest effect on BMD – but 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..."
- Systematic review and MA 2016: No significant increase

**Rational use of Calcium and Vitamin D**

- Vitamin D 600 - 1000 IU per day
- Calcium
  - Ensure adequate intake (1000-1200 mg)
  - Dietary intake preferred
  - Small doses with meals if needed
  - Focus on adherence (calcium poorly tolerated)

**Pharmacologic therapy**
**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><strong>Calcitonin</strong></td>
</tr>
<tr>
<td>Alendronate</td>
<td></td>
</tr>
<tr>
<td>Risedronate</td>
<td></td>
</tr>
<tr>
<td>Ibandronate</td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td></td>
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<tr>
<td>Teriparatide</td>
<td></td>
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<tr>
<td>Abaloparatide</td>
<td></td>
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<tr>
<td>Denosumab</td>
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</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)

**NNT and Fractures Prevented for 3 Years of Anti-resorptive Treatment**

Among older women with prevalent VF or T-score<-2.5

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. Needed to Treat</th>
<th>No. of Events Prevented per 1000 Patients Treated</th>
<th>(3 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Fracture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any nonvertebral, including hip</td>
<td>35</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Any vertebral fracture (nonpelvis)</td>
<td>34</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Any fracture</td>
<td>130</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Compare to 3 years of statin to prevent one major cardiovascular event^2^: NNT= 95

**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 &lt; -1.5 – -2.0</td>
<td>1.06 (0.77, 1.46)</td>
</tr>
<tr>
<td>T &lt; -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>0.66 (0.73, 1.01)</td>
</tr>
</tbody>
</table>


Cummings, JAMA 1998
FIT Trial

• 1/5 women taking alendronate lost BMD during first year
  – Still had 50% fracture reduction
  – 92% regained lost BMD 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

Treatment Summary

• 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.
    ▪ Oral bisphosphonate is first line
    ▪ IV Zoledronic acid annually if intolerant of oral
    ▪ Denosumab if poor renal function (CrCl <35)
  – Anabolic therapy with teriparatide or abaloparatide (PTH/PTHrP analogs)
    ▪ Increase BMD more than antiresorptive treatment
    ▪ No significant difference in fracture prevention in published trials

Harms of therapy
A New Side Effect of Potent Bisphosphonates?

Osteonecrosis of the Jaw

- Associated with potent bisphosphonate use:
  - 94% treated with IV bisphosphonates
  - 4% of cases were being treated for osteoporosis, most treated for cancer
  - 60% caused by tooth extraction. Other risk factors unknown. Infection?
- Dental exam recommended before Rx, but no need to stop for dental procedures
- Risk is low: 1/10,000 treated for 10 years

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

Atypical Femoral 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
- 10 year risk about 1/200

Perspective on risk

- 1000 women treated for 3 years with zoledronic acid
  - Prevent
    - 71 vertebral fractures
    - 11 hip fractures
    - 18 other fractures
  - Cause 0.1 atypical femoral fractures
- 110 hip fractures prevented for every 1 atypical femoral fracture
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 (AFFs)
- FIT Long-term Extension (FLEX) study
  - 1099 women with ALN in FIT for 5 years
  - Randomized to ALN or PBO for 5 additional yrs

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>

2017 NOF 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
"New" treatments

Other Anti-resorptive Agents

• Less effective than bisphosphonates
  – Calcitonin (poor quality studies)
  – Raloxifene (prevents vertebral fractures only; use for breast cancer prevention?)

• Hormone replacement

• Denosumab (antibody to RANKL)
  – SQ q 6 months, not cleared by kidneys
  – Effective, but expensive.

The Future?: Anabolic Agents
Teriparatide and Abaloparatide

• PTH and PTH-rp analogs
  – Teriparatide
  – Abaloparatide approved April 28, 2017

• Romosozumab pushed back to 2018: ARCH trial

• Daily SQ injections x 2 years decreases vertebral and nonvertebral fractures. **No hip fracture reduction.**

• Sequencing: Combination PTH and anti-resorptive drug less effective than PTH alone in increasing BMD

• Anabolics must be followed by anti-resorptive

• Expensive, daily injections
  – Reserve for severe OP: Fragility fracture plus very low BMD

2017 ACP Guideline Recommendations

• Strong recommendations
  – Women with osteoporosis: 1st line therapy = alendronate, risedronate, zoledronic acid, or denosumab
  – Don’t use hormone therapy or raloxifene

• Weak recommendations
  – Treat for 5 years
  – Treat men with osteoporosis to prevent vertebral fractures
  – Recommend against bone density monitoring during 5 year treatment
  – For women with high FRAX risk, informed consent to decide whether to treat
**Controversies**

- Sequencing of therapies
  - Value of starting with anabolic therapy?
- Length of treatment / length of drug holiday
- Defining exceptionally high risk
  - Population warranting treatment with expensive new drugs

**Take Home Points**

- Aggressive screening and treatment = fewer fractures; screen all women by 65 years
  - NNT, context, FRAX may help
- Interval screening defined by baseline BMD
  - Wait 15 years / age 80 if T-Score > -1.5
- 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

**Under-diagnosis and under-treatment**

Thank you!

**Questions?**
**Risk for fractures**

- **Lifetime risk for osteoporotic fractures**
  - Women: 50%
  - Men: 20%

- **US Hospitalizations for women ages ≥ 55 years between 2000 and 2011**
  - Osteoporotic fractures: 4.9 million
  - Stroke: 3.0 million
  - MI: 2.9 million

*Harvey et al, 2008; Singer et al, Mayo CP, 2015*

**Under Recognition of Osteoporosis**

- Osteoporosis (like hypertension) is silent until something bad happens. Under-diagnosed and under-treated
  - Women with fracture or BMD<2.5: only 20-30% are evaluated and treated!
  - 12 months after hip fracture: 2% had DXA, 15% treated with appropriate drug

- Implications: Ask about fracture history, note vertebral fractures, use chart reminders for DXA

*Soloman, Mayo Clin Proc, 2005; Shibli-Rahhal, Osteo Internat, 2011*

**More Bad News: Adherence with Treatment is Poor**

- 30-50% persistence after one year
  - Multiple practice settings (similar to other preventive treatments)

- Why?
  - Oral burdensome: fasting, remain upright for 30 minutes
  - Parenteral: daily injections; infusion at doctors office
  - Upset stomach and heartburn; infusion reactions
  - Asymptomatic until fracture

*Clowes, JCEM, 2004*
Adverse Publicity: Effect on Oral Bisphosphonate Use in USA

More concerns...

- 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
- Atypical femoral fractures (AFF)
  - Subtrochanteric fracture (with atypical features)
  - Likely real...

Does Dosing Interval Matter?

- Poor quality data:
  - Daily to weekly may improve compliance
  - Weekly to monthly may not
- Yearly dosing available: zoledronic 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…

Summary of Bisphosphonate¹ and Denosumab² Fracture Reductions (up to 5 Years)*

- Zoledronic acid or Denosumab

Also reductions ~25% in non-vertebral fractures

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 IU/d
  - Recommends serum levels 20-50 ng/ml
  - Non-skeletal benefits not established, harms minimized

IOM Report, 2010

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: PTH [1-34]

- 1st 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 10% 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
Abaloparatide: PTHrP analog

- 2nd treatment that is anabolic — Approved April 28, 2017
- 80 mcg daily subcutaneously for ≤ two years
- Effects:
  - Increased bone density in spine by 11% and hip by 4% vs placebo over 18 months
  - Reduced incidence of vertebral fractures (86%) and non-vertebral fragility fractures (43%) in women with pre-existing vertebral fractures
  - Studies too small to evaluate effect on hip fractures
- Adverse reactions: hypercalciuria, nausea, hypercalcemia, orthostatic hypotension, tachycardia, injection site reactions