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)

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 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 = -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

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% 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 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

Prevention for everyone
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>Stop bone loss</td>
<td>Reduces vertebral fractures</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Calcitonin</td>
</tr>
<tr>
<td>Alendronate</td>
<td>Teriparatide</td>
</tr>
<tr>
<td>Risedronate</td>
<td>Abaloparatide</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>Denosumab</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td></td>
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<tr>
<td>Raloxifene</td>
<td></td>
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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 (yr)</th>
<th>No. of Events Prevented per 1000 Patients Treated (3 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any nonvertebral, including hip</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Hip</td>
<td>90</td>
<td>12</td>
</tr>
<tr>
<td>Vertebral fracture (morphometric)</td>
<td>14</td>
<td>71</td>
</tr>
<tr>
<td>Any fracture</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Compare to 3 years of statin to prevent one major cardiovascular event\(^1\) NNT= 95

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

Baseline hip BMD

| T < -1.5 | 1.06 (0.77, 1.46) |
| T < -2.0 | 0.97 (0.72, 1.29) |
| T < -2.5 | 0.69 (0.53, 0.88) |
| Overall | 0.86 (0.73, 1.01) |

Cummins, 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?

- 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

Osteonecrosis of the Jaw

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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

FLEX Change in Hip BMD:
% Change from FIT Baseline

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>

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

Questions?

Thank you!
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

Solomon, 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 doctor's 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)*

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/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