Bone Health Update

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Disclosure of Financial Relationships

• Scientific Advisory Council: Merck
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The Problem

• 50% women and 20% of men have an osteoporotic fracture after age 50
• 2 million fractures annually, 1 every 15 seconds
• 350,000 hip fractures with mortality of 20%
• Cost -- $19 billion annually
Topics

• Screening and rescreening interval
• Calcium and cardiovascular disease
• Vitamin D
• Alternatives to bisphosphonates
• Atypical fractures and bisphosphonate holidays
Who Should Have a Bone Density Test?

- **Screening**
  - All women age 65 and older\(^1,2\)
  - All men age 70 and older\(^1\)
- **Test younger postmenopausal women and men age 50-69\(^1\)**
  - Fracture after age 50
  - Risk factors for osteoporosis*
- **Monitoring:** ≥ 24 months (→ bone loss)

*Risk factors to consider include family history of osteoporosis, low body weight, smoking, premature menopause, other diseases and medications

WHO Diagnostic Criteria and NOF Treatment Guidelines

Normal Bone Density

Low Bone Mass (Osteopenia)

Osteoporosis

T-score

-1.0

-2.5

WHO Diagnostic Criteria

Therapy Decision

No pharmacologic treatment

Depends on the risk of fracture

Treat

## DXA Interval Time

### Patients w/o Osteoporosis, No Rx

Study Osteoporotic Fractures
~5000 women > 65 years followed ~ 15 years
Interval 10% transition to osteoporosis

<table>
<thead>
<tr>
<th>BMD Classification</th>
<th>T-score (total hip or fem neck)</th>
<th>Approximate Interval (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>-1.0 and higher</td>
<td>15</td>
</tr>
<tr>
<td>Mild Osteopenia</td>
<td>-1.0 to -1.5</td>
<td>15</td>
</tr>
<tr>
<td>Moderate Osteopenia</td>
<td>-1.5 to -2.0</td>
<td>5</td>
</tr>
<tr>
<td>Advanced Osteopenia</td>
<td>-2.0 to -2.5</td>
<td>1</td>
</tr>
</tbody>
</table>

Gourlay ML, NEJM, 2012
### NOF Guidelines for Treatment

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture</td>
<td>Hip or Spine</td>
</tr>
<tr>
<td>T-score (DXA)</td>
<td>T-score $\leq -2.5$ at spine, hip or femoral neck</td>
</tr>
</tbody>
</table>
| FRAX (osteopenia, low bone mass) | 10-year probability of a major fracture $\geq 20\%$  
10-year probability of a hip fracture $\geq 3\%$ |

National Osteoporosis Foundation.  
**Questionnaire:**

1. Age (between 40 and 90 years) or Date of Birth
   - Age: 78
   - Date of Birth: Y: _ _ M: _ _ D: _ _

2. Sex
   - Male
   - Female

3. Weight (kg)
   - 63.5

4. Height (cm)
   - 160.02

5. Previous Fracture
   - No
   - Yes

6. Parent Fractured Hip
   - No
   - Yes

7. Current Smoking
   - No
   - Yes

8. Glucocorticoids
   - No
   - Yes

9. Rheumatoid arthritis
   - No
   - Yes

10. Secondary osteoporosis
    - No
    - Yes

11. Alcohol 3 or more units/day
    - No
    - Yes

12. Femoral neck BMD (g/cm²)
    - T-Score
    - -2.2

**BMI: 24.8**

The ten year probability of fracture (%)

with BMD

- Major osteoporotic: 24
- Hip Fracture: 6.8
Calcium Recommendations

• Total calcium intake: (IOM, NOF, AACE, Endocrine Society)
  – Diet plus supplement = 1200 mg daily
• Upper intake: 2000 mg/day (IOM)
• More is not better
  – No added bone benefit
  – Excessive calcium intake (bringing total above 2000 mg/day) increases the risk of kidney stones and may increase CVD (still controversial)

IOM guidelines Nov 2010
Calcium and CVD Controversy

**CVD yes:**
- 2 meta analyses from New Zealand in BMJ\(^1,2\)
- Calcium vs placebo: MI ↑ 27%
- Calcium+/- D vs placebo: MI ↑ 24%, stroke ↑15%
  - Excluded 54% WHI subjects

**CVD no:**
- WHI calcium +/- D vs placebo\(^3\)
  - 11 year f/u; 36,282 women
  - No impact on CVD or all-cause mortality
- Nurses Health Study (prospective)\(^4\)
  - 24 yr f/u; 74,245 women, no impact on CVD or stroke

Meta-Analysis Study Issues

• Differences in
  – Trial selection, inclusion/exclusion
  – Patient inclusion/exclusion
  – Dose/duration calcium +/- vitamin D
  – Outcome definition
  – Analytical methods
Calcium

• 1200 mg daily in divided doses
  – 500-600mg at a time

• Diet or supplement

• Types of supplements
  – Calcium carbonate (with food)
  – Calcium citrate (with or without food)
Calcium in Foods

Nutrition Facts

<table>
<thead>
<tr>
<th></th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>20% (= 200 mg calcium)</td>
</tr>
<tr>
<td>1 cup of milk</td>
<td>30% (= 300 mg calcium)</td>
</tr>
<tr>
<td>1 string cheese</td>
<td>15% (= 150 mg calcium)</td>
</tr>
<tr>
<td>Total cereal</td>
<td>100% (=1000 mg calcium)</td>
</tr>
</tbody>
</table>

Add a zero to the % Daily Value
Metabolism and Function of Vitamin D

Vitamin D₃

Skin

Liver

25(OH)D₃

Prostate breast, colon, immune system

Kidney

1, 25(OH)₂D₃

Calcium homeostasis
Muscle health
Bone health

1, 25(OH)₂D₃

Regulation of cell growth (cancer prevention)

Immune function

Why Vitamin D Insufficiency is Increasing

• Downward trend in milk consumption
• Upward trend for sun protection/sun avoidance
• Upward trend in obesity
The 25(OH)D Continuum: Definitions

"deficiency"  "insufficiency"  "normal"

Goal > 30 ng/ml

Falls and Fractures

• Fall prevention:
  – Meta-analysis: mean serum level needed: 24 ng/mL

• Fracture prevention:
  – Meta-analyses
  – Nonvertebral fractures: 26.4 ng/mL
  – Hip fractures 29.6 ng/mL

• $25 \text{ hydroxyvitamin D level } \geq 30\text{ng/mL}$

Dawson-Hughes B, Osteoporosis Int, 2010
Vitamin D

- 53 trials
- 91,791 participants
- Vitamin D plus calcium
  - 16% reduction hip fracture
  - High risk → NNT ~ 10 to prevent 1 hip fracture
  - 5% reduction in any type fracture
  - Mortality not effected
- Vitamin D alone no impact on fractures

Avenell A, Cochrane Collaboration, 2014
Vitamin D Recommendations

- **Patient daily dose:**
  - IOM (2011): 600 (adults)-800 (> 70 yo) IU/day (target level 20 ng/mL)
  - NOF: 800-1000 IU (target level 30 ng/mL)
  - AACE: 1000-2000 IU (target level 30 ng/mL)
  - IOF: 800-1000 IU (target level 30 ng/mL)
  - Endo Society: 1500-2000 IU (target 30 ng/mL)
- **Daily dose:** at least 1000 IU/day (many need more ~ 1500 IU/day)
- **Upper limit intake:** 4000 IU/day (IOM)
## Osteoporosis Drugs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose*</th>
<th>Effect on Fracture Risk</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vertebra</td>
<td>Nonvertebral</td>
<td>Hip</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>200 IU IN/day</td>
<td>✓</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>60 mg/day</td>
<td>✓</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>150 mg/month</td>
<td>✓</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>3 mg every 3 months IV</td>
<td>✓</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Alendronate</td>
<td>70 mg/week</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Risedronate</td>
<td>35 mg/week ((Atelvia) 150 mg/month</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>5 mg every 12 months IV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>5 mg every 24 months IV</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>20 mcg/day SC</td>
<td>✓</td>
<td>✓</td>
<td>—</td>
</tr>
<tr>
<td>Denosumab</td>
<td>60 mg every 6 months SC</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</table>
# Non-skeletal Selection Issues

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pro</th>
<th>Con</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>Extended dosing interval</td>
<td>GI irritation oral; don’t use if GFR &lt; 30 mL/min (orals) or &lt; 35 mL/min (zoledronate)</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Breast cancer prevention</td>
<td>Exacerbate hot flashes DVT</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Extended dosing interval, not cleared by kidney</td>
<td>Eczema, skin infections, hypocalcemia (if no calcium)</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Osteoanabolic</td>
<td>Daily injection, refrigeration, expense, 24-month limit; nausea, leg cramps</td>
</tr>
</tbody>
</table>
Do They Work In Elderly?

- Pivotal trials compare those < 75 to ≥ 75 yo
  - Similar outcomes in women for zoledronic acid, denosumab and teriparatide
  - Healthy elderly in community

- Few studies in frail elderly or in LTC
  - Zoledronic acid is safe and maintains bone density in very frail elderly

¹Greenspan, Nace, Perera, Resnick, JAMA IM, 2015
Denosumab: Antiresorptive
Not a Bisphosphonate

- Denosumab, a fully human IgG2 antibody
- Novelty: reversible, biannual subcutaneous injection
- Decreased incidence of vertebral (68%), hip (40%) and nonvertebral fractures (20%)
- Indications: high risk postmenopausal women and men

Effect of Denosumab Retreatment on Lumbar Spine and Total Hip BMD

- **Lumbar Spine**
  - Discontinued Treatment: -2.4, -1.8
  - Retreatment 60 mg Q6M: 8.8, 9.0

- **Total Hip**
  - Discontinued Treatment: -2.8, -1.2
  - Retreatment 60 mg Q6M: 5.0, 3.9

*P = 0.004 at month 36 and < 0.001 at month 48 vs placebo

*P < 0.001 at month 48 vs placebo

Miller PD et al Bone 2009
Bisphosphonates: Adverse Events and Holidays

- How do they work
- Atypical fractures
- Osteonecrosis of the jaw
- Holidays
Bisphosphonates and Extended Dosing

Oral or IV Dose

Serum

Renal excretion

Concentrate at sites of bone resorption

Loss of resorptive function

Release and intracellular uptake during resorption

Duration of effectiveness is related to affinity and potency
Atypical Fractures of Femur

- Transverse fractures of femoral diaphysis
- May begin with stress reaction or stress fracture of lateral femoral cortex (A)
- Often bilateral
- Prodromal pain in thigh or groin in 70%
- Occur in untreated patients, but increased incidence in patients on oral bisphosphonates > 5 years

1 Shane E, et al. *J Bone Miner Res.* 2010;25:2267
2 Watts NB and Diab D, *J Clin Endocrinol Metab* 2010;95:1555-1655
3 Park-Wyllie JY, *JAMA.* 2011;305(8):783-789
Atypical Fractures

- Incidence: 50 cases/100,000 treated over 5 years\(^1\)
- Risk increases with prolonged use
- Prevent 100 hip fractures for 1 atypical femur fracture
- Mortality:
  - Conventional hip fracture: $\geq 20\%$ first year
  - Atypical fracture: no increased risk in mortality\(^2\)

\(^1\) Long term BP, ASBMR Task Force, JBMR 2016
\(^2\) Kharazmi M, JBMR, 2016
Osteonecrosis of the Jaw

- Extremely rare
- Incidence: 1/10,000-1/100,000
- Exposed bone
- Cancer patients on IV bisphosphonates
- Invasive dental procedures like tooth implant
- Conservative Rx


10-year Probabilities of AFF, ONJ and Other Adverse Outcomes

72-year-old woman with FN T-score -2.9; parent with a hip fracture

- **Fx Risk: Untreated**: 30%
- **Fx Risk: Treated**: 15%
- **Fatal MVA**: 0.11%
- **Murder**: 0.06%
- **ONJ**: 0.01%
- **AFF**: 0.50%

*Fracture risk typical of patient with osteoporosis.
“Millions of Americans are missing out on a chance to avoid debilitating fractures from weakened bones, researchers say, because they are terrified of exceedingly rare side effects from drugs that can help them.”

Reports of drugs’ causing jaw bone to rot and thigh bones to snap...

- Drugs fell by 50% from 2008-2012
- Treat 50 to prevent a fracture
- Treat 40,000 to see atypical fracture
Impact of FDA Safety Announcements on Bisphosphonate Use

- 22,598 hip fractures
- Claims data osteo meds 6 months post fracture
- US health plan

- 15% use in 2004 → 6% use 2013
- Atrial Fib 4% decrease
- Atypical Fx 4% decrease

Kim SC, JBMR, March 2016
What Happens When Therapy Stopped

• Risk of atypical fractures decreases rapidly within 1 year of stopping bisphosphonate

• Alendronate (after 5 years):
  – Bone loss in hip
  – More clinical vertebral fractures
  – More nonvertebral fractures if T-score < -2.5

• Zoledronic acid (after 3 years):
  – Small decreases in bone density
  – More vertebral fractures (x-ray)

“Time for a Holiday?”

• Bisphosphonate: Oral > 5y or IV > 3 y
  – Consider holiday if:
    • No fractures
    • BMD T-scores above -2.5
    • Not a high risk patient
  – If no holiday:
    • Reassess risks/benefits
    • Consider change in therapy (teriparatide, denosumab)
    • Recheck in 2-3 years

Monitoring A Drug Holiday (Data Free Zone)

• Repeat BMD at 2-3 years
  – If BMD decreased, likely bisphosphonate benefit diminished, restart therapy
  – Little data on bone turnover markers
• FRAX at 2-3 years (reassess fracture risk with current BMD and risk factors)
• New fracture – restart treatment

McClung M, AJM, 2013; 126: 13-20
ASBMR Task Force, JBMR, 2016
Meds on the Horizon

• Abaloparatide: PTHrP fragment
  – Anabolic agent that builds bone
  – Daily SC injection or patch

• Romosozumab: antibody to sclerostin
  – Sclerostin protein from osteocytes
  – Dual effect on bone, increasing bone formation and decreasing bone resorption
  – Monthly injection
Summary

• Screening:
  – Women > 65 years, men > 70 years
  – Rescreening if mod-severe osteopenia, no Rx

• Calcium:
  – Goal 1200 mg daily, divided dose, diet plus supplement

• Vitamin D: ~1000 IU daily

• Treatment:
  – Hip or vertebral fracture
  – BMD T-score below -2.5 at hip, spine, or radius
  – FRAX qualifications
Treatment options: in addition to fx reduction
  - Depends on contraindications, adverse events, route of administration

Atypical fractures: rare
  - Associated with bisphosphonate > 5 yrs
  - Thigh, hip, groin pain prodrome
  - Stop bisphosphonate and evaluate

Bisphosphonate holiday:
  - Consider in low risk patients after 5 yrs oral or 3 yrs IV
  - Reassess in 2-3 years