Controversies in Osteoporosis Screening and Treatment: An Evidenced Based Approach to Management

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Agenda

- Introduction
- Small group discussion 1
- Didactic: screening and FRAX
- Small group discussion 2
- Didactic: use of calcium and vitamin D
- Small group discussion 3
- Didactic: treatment of osteoporosis
- Wrap-up/evaluations/questions
Participants’ goals
Team-Based Learning

- Usually occurs in semester long course
- Teams: assigned, diverse, stable over course
- Before class: students read pertinent material
- In class:
  - Teams work on solving problems
  - Results simultaneously shared with entire class
  - Instructor fills in gaps in learning
- How used today:
  - Do case-based questions in small groups
  - Share results with large group
  - Didactic presentation to summarize learning points
Case 1: June is a 62 year old who woman tripped off of a curb and broke her ankle. What would you do?

A. Check a Vitamin D and calcium
B. Check a DEXA
C. Check a BMD using a peripheral scanner
D. Check a PTH level
E. Calculate a FRAX score.
2. Which of the following women does not need to be screened for osteoporosis?

A. A 65 year old woman with a BMI of 25 and average risk

B. A 62 year old woman with a BMI of 21 and a parental history of hip fracture

C. A 61 year old woman with a BMI of 26 on chronic glucocorticoid therapy for asthma

D. A 60 year old woman with a BMI of 23 who smokes.
Screening for Osteoporosis

Jamie Stern, MD, MPH
Rationale

- By 2012, approximately 12 million Americans older than 50 are expected to have osteoporosis.
- ½ of all postmenopausal women will have an osteoporosis related fracture during their lifetime.
Rationale

- Osteoporotic fractures are associated with:
  - Chronic pain and disability
  - Loss of independence
  - Decreased quality of life
  - Increased mortality
Major Risk Factors for Osteoporosis (NOF)

- Personal history of a fracture as an adult
- History of a fragility fracture in a first degree relative
- Low body weight
- Current smoking
- Use of corticosteroid therapy
DEXA Scanning

- Gives a measurement of bone mineral density at selected sites; usually both hip and spine are measures.

- Bone density is reported both as the standard deviations of bone mineral density compared to 30 y/o women and age matched controls.
  - T Score: SD from peak bone mass
  - Z Score: SD from age/gender matched control
DEXA Scan

- Classification
  - Normal: $> -1 \text{ SD}$
  - Osteopenia: $> -2.5 \text{ And } <-1 \text{ SD}$
  - Osteoporosis: $< -2.5 \text{ SD}$
Z Score

- Only used for children and adults less than age 40
- Helps when to think about secondary causes of osteoporosis. If the Z score is -2 SD or lower, secondary causes are less likely.
DEXA Scanning

- BMD cannot be used as the sole predictor of bone strength.

- National Osteoporosis Risk Assessment study revealed that 82% of 2259 postmenopausal women with a fracture had a T score above -2.5 and 67% had a T score greater than -2.0.
The USPSTF recommends screening for osteoporosis in women aged 65 years or older and in younger women whose fracture risk is equal to or greater than that of a 65 year old woman without additional risk factors. (B recommendation)

The current evidence for screening men is insufficient.
National Osteoporosis Foundation

- Recommends bone density testing for all women aged 65 and older and all men 70 and older
- It also recommends screening for postmenopausal women younger than 65 and men 50-69 if there is a concern for osteoporosis based on their risk factor profile.
The USPTF used the FRAX tool to estimate 10 year risk factors because:

- DEXA alone has multiple limitations.
- This tool relies on easily obtainable information.
- Its development was supported by a broad international collaboration and validated.
- It is freely accessible.
- Includes questions on DEXA results, but does not require this information.
Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian)  Name/ID: 

**Questionnaire:**

1. Age (between 40-90 years) or Date of birth
   - Age: ___________
   - Date of birth: Y: ___________ M: ___________ D: ___________

2. Sex
   - Male
   - Female

3. Weight (kg)

4. Height (cm)

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 per day
   - No
   - Yes

12. Femoral neck BMD (g/cm²)

- Select DXA
- Convert

**Weight Conversion**
- Pounds
- Kgs

**Height Conversion**
- Inches
- Cms

www.sheffield.ac.uk/FRAX/
Clinical Risk Factors Considered in FRAX

- Age - 40-90

- Previous Fracture - in adult life, occurring spontaneously or arising from trauma which, in a healthy person, would not have resulted in a fracture.

- Glucocorticoids - for more than 3 months at a dose of prednisone of 5mg/day or more
Clinical Risk Factors Considered in FRAX

- Secondary osteoporosis - Type I DM, osteogenesis imperfecta in adults, untreated long standing hyperthyroidism, hypogonadism, or premature menopause (<45 yrs), chronic malnutrition, malabsorption, chronic liver disease

- Alcohol - > 3 units/day
Based on the US FRAX tool, a 65 year old white woman with no other risk factors has a 9.3% 10 year risk for any osteoporotic fracture.

The USPSTF recommends using this threshold to screen women under the age of 65.
FRAX

• In the US, treatment for osteopenia becomes cost effective when the 10 year hip fracture risk is 3% or greater OR overall fracture risk is 20% or greater.

• This should not change the recommendations for treatment of osteoporotic women (T score <-2.5)
FRAX - 2 Uses

- Deciding which patients under the age of 65 should be screened with a DEXA
- Deciding which patients with osteopenia should be treated to prevent fracture.
Fine Points

• FRAX only applies to
  • previously untreated patients
  • patients older than 40 years of age

• Only incorporates the hip T score

• Applies to all ethnicities
Limitations of FRAX

- Question of accuracy of data
  - Relationships between risk factors and fracture risk constructed from data on 9 population cohorts around the world. Most databases have accurate data on hip fractures, but not other types.

- Question of generalizability
  - US FRAX data formulated from Olmstead County, Minnesota - white and well educated
Limitations of FRAX

- Recommendations may contradict NOF or other guidelines
  - example

- Some important risk factors for fractures are not included in this tool
  - 25 OH Vitamin D, physical activity, risk of falls
Screening Intervals

- The benefit of screening women whose initial DEXA was normal is unknown.

- A prospective study of 4,124 women aged 65 or older found that repeated BMD after 8 years did not predict subsequent fracture rate more than the original DEXA.
Case 2

Ms. D is a 62 year old woman who just moved from Pittsburgh, PA and is establishing care with you. She has no medical issues and is not taking any medications. In addition to other preventative measures, you want to address her bone health.

Question 3: Which of the following would you do (select all that apply)?

a. Order a DXA scan  
b. Order a 1,25-dihydroxyvitamin D level  
c. Order a 25-hydroxyvitamin D level  
d. Start calcium and vitamin D supplementation  
e. Encourage dietary calcium and weight bearing exercise
Case 2 continued

You decide to order a serum 25-OHD level and it is 22 ng/ml.

Question 4: How would you manage this?

a. Order 400 IU vitamin D qd
b. Order 1,000 IU vitamin D qd
c. Order 2,000 IU vitamin D qd
d. Order 50,000 IU vitamin D qweek for 8 weeks
e. Order a PTH level
Ms. C is a 68 year old woman with who was found to have a T-score of -2.7 on a recent DXA scan. Her 25-OHD level is 35 ng/ml. In addition to starting a bisphosphonate, you want to start calcium and vitamin D supplementation.

Question 5: How would you counsel her about calcium supplementation?

a. She should not take calcium supplementation because of her family history of MI
b. She should aim to take a total of 1,200 mg of calcium/day from diet plus supplementation combined

b. She should aim to take a total of 1,200 mg of calcium/day from diet plus supplementation combined

c. She should take 1,200 mg in calcium supplementation in addition to any dietary calcium intake

d. Doses of greater than 4,000 mg of calcium are associated with nephrolithiasis

e. Given her vitamin D level, she does not need to take calcium supplementation since she probably has adequate gut absorption
Use of Calcium/Vitamin D

Sonya Borrero, MD, MS
Background

- Until November 2010, most recent guidelines for calcium and vitamin supplementation were from 1997.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Calcium (mg)</th>
<th>Vitamin D (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-50</td>
<td>1000</td>
<td>200</td>
</tr>
<tr>
<td>51-70</td>
<td>1200</td>
<td>400</td>
</tr>
<tr>
<td>&gt;71</td>
<td>1200</td>
<td>600</td>
</tr>
</tbody>
</table>
Background

• Since 1997, abundance of data has emerged regarding effects of vitamin D on health outcomes from cancer prevention to increased immunity

• High prevalence of vitamin D deficiency reported in lay and medical literature

• Clinicians routinely ordering vitamin D doses higher than IOM 1997 recommendations
Background

- For calcium, recent widespread fortification in foods and use of supplementation

- The concept that “more is better” seems to have emerged for both calcium and vitamin D
Controversy: Calcium and MI risk

- Bolland et. al: BMJ 2010

- Meta-analysis of RCTs of calcium supplementation to assess whether calcium increases the risk of CV events

- 15 trials and 12,000 participants included (5 trials had patient-level data; 11 with trial-level data)
Patient-level data: Increased risk of MI

**Myocardial infarction**
- Hazard ratio 1.31 (95% CI 1.02 to 1.67), P=0.035

**Stroke**
- Hazard ratio 1.20 (95% CI 0.96 to 1.50), P=0.11

**Composite of myocardial infarction, stroke, or sudden death**
- Hazard ratio 1.18 (95% CI 1.00 to 1.39), P=0.057

**Death**
- Hazard ratio 1.09 (95% CI 0.96 to 1.23), P=0.18
**Trial-level data: Increased risk of MI**

**Relative risk of myocardial infarction (95% CI) and Weight (%)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baron 1999</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Grant 2005</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>Grant 2005 Vit D</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Prince 2006</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Reid 2006</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>Lappe 2007</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Reid 2008</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1.27 (1.01 to 1.59)</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2=0\% \, P=0.96$

**Relative risk of stroke (95% CI) and Weight (%)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reid 1993</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Baron 1999</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Grant 2005</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Grant 2005 Vit D</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Prince 2006</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Reid 2006</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Bonnick 2007</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Lappe 2007</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1.12 (0.92 to 1.36)</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2=0\% \, P=0.93$

**Relative risk of myocardial infarction, stroke, or sudden death (95% CI) and Weight (%)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reid 1993</td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Baron 1999</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Grant 2005</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>Grant 2005 Vit D</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Prince 2006</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>Reid 2006</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Lappe 2007</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Reid 2008</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1.12 (0.97 to 1.30)</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2=0\% \, P=0.91$

**Relative risk of death (95% CI) and Weight (%)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baron 1999</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Grant 2005</td>
<td></td>
<td>43</td>
</tr>
<tr>
<td>Grant 2005 Vit D</td>
<td></td>
<td>42</td>
</tr>
<tr>
<td>Prince 2006</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Reid 2006</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Bonnick 2007</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Reid 2008</td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1.07 (0.95 to 1.19)</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2=0\% \, P=0.84$

Favours calcium | Favours placebo
---|---
0.5 | 0.8 | 1 | 1.2 | 1.5 | 2 | 3

Controversy: Calcium and MI risk

- Patient-level data: Increased risk of MI in patients with dietary calcium intake above median of 805 mg/day; HR: 1.85 (1.28 to 1.67)

- Limitations:
  - CV outcomes were not primary outcomes
  - Event frequency was low
  - Many trials did not report baseline calcium intake
  - Renal function not considered as a covariate

- Other studies (including WHI) have had conflicting results
## IOM report: Summary of data

<table>
<thead>
<tr>
<th>Age group</th>
<th>Calcium (mg)</th>
<th>Vitamin D* (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RDA</td>
<td>UL</td>
</tr>
<tr>
<td>19-50</td>
<td>1000</td>
<td>2500</td>
</tr>
<tr>
<td>51-70 (men)</td>
<td>1000</td>
<td>2000</td>
</tr>
<tr>
<td>51-70 (women)</td>
<td>1200</td>
<td>2000</td>
</tr>
<tr>
<td>&gt;71</td>
<td>1200</td>
<td>2000</td>
</tr>
</tbody>
</table>
Most US adults getting adequate calcium from diet alone.

Data from NHANES 2003-2006 as analyzed by Bailey et al., 2010.
IOM report: Calcium supplementation

- When considering upper tolerable limits (UL), IOM did not consider MI data

- UL based on increased risk of nephrolithiasis
  - WHI data showed 17% increase in kidney stones among intervention group (HR: 1.75; 95% CI: 1.02-1.34)
  - Intervention: 1000 mg Ca + 400 IU vitamin D on top of baseline intake of about 1100 mg Ca (average total intake was 2100 mg)
IOM: Vitamin D Supplementation

- Recommendations based only on skeletal outcomes; not enough evidence to establish causality between vitamin D and extraskeletal outcomes

- Given concordance of 25OHD with relevant bone outcomes, used this measure to determine vitamin D recommendations

- Emphasized that 25OHD cut points have not yet been established by scientific consensus
  - PTH plateaus not necessarily helpful given variability of plateau points within and across individuals
IOM report: Vitamin D supplementation

![Graphs showing calcium absorption, BMD, risk of vitamin D deficiency and achieved 25OHD levels in relation to total vitamin D intake.](image-url)
## TABLE 7-3 Mean Vitamin D Intake and Mean Serum 25OHD Concentrations for the United States, 2005-2006, by Life Stage Groups

<table>
<thead>
<tr>
<th>Life Stage Group</th>
<th>Vitamin D Intake (IU/day)</th>
<th>Serum 25OHD Levels (nmol/L)</th>
<th>Adjusted for Sun Exposure (Reduced by 1/3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Food Alone(^a)</td>
<td>Total Intake(^b)</td>
<td>Mean(^c)</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>288 ± 8</td>
<td>364 ± 16</td>
<td>71.1 ± 2.0</td>
</tr>
<tr>
<td>4–8</td>
<td>256 ± 12</td>
<td>372 ± 16</td>
<td>70.5 ± 2.0</td>
</tr>
<tr>
<td>9–13</td>
<td>228 ± 8</td>
<td>300 ± 28</td>
<td>65.9 ± 2.2</td>
</tr>
<tr>
<td>14–18</td>
<td>244 ± 16</td>
<td>276 ± 20</td>
<td>60.1 ± 1.9</td>
</tr>
<tr>
<td>19–30</td>
<td>204 ± 12</td>
<td>264 ± 16</td>
<td>57.9 ± 2.0</td>
</tr>
<tr>
<td>31–50</td>
<td>216 ± 12</td>
<td>316 ± 12</td>
<td>58.5 ± 1.1</td>
</tr>
<tr>
<td>51–70</td>
<td>204 ± 12</td>
<td>352 ± 16</td>
<td>57.3 ± 1.8</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>224 ± 16</td>
<td>428 ± 28</td>
<td>58.9 ± 1.3</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>276 ± 16</td>
<td>336 ± 16</td>
<td>71.4 ± 1.9</td>
</tr>
<tr>
<td>4–8</td>
<td>220 ± 12</td>
<td>316 ± 24</td>
<td>70.5 ± 2.1</td>
</tr>
<tr>
<td>9–13</td>
<td>212 ± 24</td>
<td>308 ± 40</td>
<td>59.1 ± 1.6</td>
</tr>
<tr>
<td>14–18</td>
<td>152 ± 8</td>
<td>200 ± 20</td>
<td>57.6 ± 1.9</td>
</tr>
<tr>
<td>19–30</td>
<td>144 ± 12</td>
<td>232 ± 12</td>
<td>62.7 ± 2.8</td>
</tr>
<tr>
<td>31–50</td>
<td>176 ± 12</td>
<td>308 ± 20</td>
<td>57.6 ± 1.7</td>
</tr>
<tr>
<td>51–70</td>
<td>156 ± 16</td>
<td>404 ± 40</td>
<td>57.2 ± 1.5</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>180 ± 8</td>
<td>400 ± 20</td>
<td>56.5 ± 1.8</td>
</tr>
</tbody>
</table>

Data from NHANES 2003-2006 as analyzed by Bailey et al., 2010
IOM report: Vitamin D supplementation

- Given emerging evidence of potentially adverse consequences at lower 25OHD levels, took into account a study showing 5000 IUs/d achieved 25OHD levels of 100-150nmol/L and set UL at 20% below that.

Heaney et al., 2003
Melamed et al., 2008

All-cause mortality by 25OHD level in NHANESIII
What do we tell our patients?

- Encourage calcium from food sources
- Check 25OHD levels to ensure level >20 ng/mL and to motivate behavior
- Consider low dose calcium supplementation
- Vitamin D 1000 IUs daily
Case 4: Patty

Patty is a 62-year old patient who has a history of rheumatoid arthritis and asthma, for which she has frequently used oral steroids. She underwent menopause at 51 yo. She has no history of fractures or malignancy. Her femoral neck T-score is -2.0.

Based on her BMI of 27, her FRAX risk is:

- Major osteoporotic: 21%
- Hip fracture: 3.6%
Question 6

You want to reduce Patty’s risk of hip fracture. What is the most appropriate initial treatment:

A. Ibandronate 150mg PO monthly
B. Risedronate 35mg PO weekly
C. Calcitonin 1 spray intranasally daily
D. CEE 0.3mg/MPA 1.5mg (Prempro) daily
E. Teriperatide 20 mcg subcut daily
Patty has been talking to her friends and her dentist and heard that treatments for osteoporosis cause other bone problems (unusual fractures or jaw problems) and do not prevent or treat any other problems; she is worried about taking these medications. What do you tell her?

A. GI symptoms and bone aches are actually more common than unusual fractures while taking bisphosphonates

B. She is likely to get osteonecrosis of the jaw so if she needs any dental work done, she should not take bisphosphonates

C. Studies have shown that her risk of atypical femoral fractures will be much higher while taking bisphosphonates
Question 8

Patty asks, “How long will I have to take this medicine?”
You tell her:

A. For the rest of your life

B. Only for 5 years and then you won’t have to take it anymore

C. For 5 years, then you’ll stop taking it for 2 years, and then you’ll start again

D. For 5 years, then you’ll stop taking it and we’ll recheck your BMD yearly. When your BMD gets low (T score < 2.5), we’ll restart the med
Treatment of Osteoporosis

Briar Duffy, MD
Pharmacologic Interventions

- **Antiresorptive**
  - Bisphosphonates
    - Alendronate
    - Ibandronate
    - Risedronate
    - Zoledronic Acid
  - Calcitonin
  - Estrogen
  - Raloxifene

- **Anabolic**
  - Teriparatide
<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Evidence</th>
<th>Treatment Dose</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alendronate (Fosamax)</strong></td>
<td>Increase BMD at spine/hip Decrease fractures by 50% over 3 years</td>
<td>70mg/week or 10mg/day</td>
<td>Reflux Arthralgia/myalgia ? long bone fracture</td>
</tr>
<tr>
<td><strong>Risedronate (Actonel)</strong></td>
<td>Decreases spine/non-spine fractures by 40% over 3 years Prevent steroid-induced bone loss</td>
<td>150mg/month, 35mg/week, or 5mg/day</td>
<td>Same</td>
</tr>
<tr>
<td><strong>Ibandronate (Boniva)</strong></td>
<td>Reduces vertebral fractures by 62% Not been shown to reduce hip fracture</td>
<td>150mg/month PO or 3mg IV q3 months</td>
<td>Same IV: osteonecrosis of jaw</td>
</tr>
<tr>
<td><strong>Zoledronate (Zometa)</strong></td>
<td>Decreases spine fractures 70% over 3 years Decreases hip fractures 42% over 3 years</td>
<td>5 mg IV yearly</td>
<td>Same Flu-like sx 24-48 hrs Osteonecrosis of jaw</td>
</tr>
</tbody>
</table>
Osteonecrosis of the jaw

- 2003-2009: 2,408 cases published
- 88% associated with IV treatment
- 89% associated with treatment for cancer
- 67% preceded by tooth extraction
- More common in patients with previous invasive dental treatment

- What to do to ameliorate risk?
  - Invasive dental work before initiation of bisphosphonate
  - Stop bisphosphonate prior to dental work and restart several months later

Filleul O et al, J Cancer Res Clin Oncol, Aug 2010
Atypical (Subtrochanteric) femur fractures

- Only 2 to 4% of all hip fractures
- Case series have raised alarm about potential association of these with bisphosphonates
  - Does medication decrease ability of bone to repair microdamage?
Atypical fractures: observational data

- Case reports and small observational studies
  - Mixed results

- Large case-control study
  - 205,466 women who started bisphosphonate
  - Atypical fractures: 716 (0.35% of all women)
  - Use of bisphosphonates for > 5 years increased risk of atypical fracture (adjusted odds ratio, 2.74; 95% confidence interval, 1.25-6.02)
  - Typical fractures: 9723 (4.7%)
  - Use of bisphosphonates for > 5 years compared to transient use reduced risk of “typical” hip fracture (adjusted OR, 0.76; 95% CI, 0.63-0.93)

Park-Wyllie et al JAMA Feb 2011
Atypical fractures: RCT evidence

- 8835 total patients (FIT, FLEX and HORIZON-PFT trials)
  - 51,287 patient-years in the three studies

- 284 total hip/femur fractures
  - 12 subtrochanteric or diaphyseal fractures (4%) in 10 patients (2.3 per 10,000 patient-years)

- Hazard ratios:
  - FIT: 1.03 (95% CI: 0.06 to 16.46)
  - FLEX: 1.33 (95% CI, 0.12 to 14.67)
  - HORIZON-PFT: 1.50 (95% CI, 0.25 to 9.00)

- Wide CI: underpowered (very few atypical femoral fractures occurred)

- Population-based studies also show no increased risk

Black et al NEJM May 2010
Abrahamsen et al JBMR 2009
Atypical fractures, summary

- More likely to be caused by osteoporosis than by bisphosphonates
- Numbers of such fractures are reduced by high adherence to bisphosphonate therapy
- Epidemiology studies: overall incidence of such fractures has not increased since bisphosphonates were approved for the treatment of osteoporosis
- Typical fractures more common than atypical fractures, even with treatment
Duration of bisphosphonate treatment

- How long should we use bisphosphonates?
- If we gave “drug holiday,” could bone have time to repair microdamage?
Initial FLEX trial

- FLEX trial
  - Completed FIT alendronate arm (5 or 10mg/day)
  - 5 more years treatment with placebo vs alendronate 5mg/day vs alendronate 10mg/day

- Results:
  - Placebo group: decline in BMD
  - Continuation groups: lower risk of clinically recognized vertebral fractures (RR = 0.45, 95% CI 0.24-0.85)
  - No difference in non-vertebral fractures

Black et al JAMA Dec 2006
Post-hoc FLEX data

- If femoral neck T score still < -2.5 after FIT, those who continued treatment had reduced risk of non-vertebral fractures (RR = 0.50, 95% CI 0.26-0.96)
- No significant benefit if T score better than -2.5

Schwartz et al, JBMR May 2010
Duration of Treatment

- Currently no consensus on how long to treat patients with bisphosphonate therapy
- For some women, stopping after five years may be appropriate; there is a residual benefit both on BMD and fracture (non-vertebral > vertebral) as demonstrated by the FLEX Trial
Duration of Treatment

- Raised the question of a drug holiday in an effort to balance risks and benefits

- Drug holiday thoughts:
  - If T score still < -2.5, risk of drug holiday may be greater than benefit
  - If T score better than -2.5, consider holiday, check yearly DEXA. Persistent bone loss on at least two DEXA scans taken at least one year apart → restart of bisphosphonates
  - Drug therapy could be restarted at 3-5 years after discontinuation
  - Drug therapy could be restarted if bone turnover markers change rapidly 1-2 years after discontinuation
Duration of Treatment

- NEJM Editorial:
  - “many more common and equally devastating hip fractures are prevented by bisphosphonates than are potentially caused by the drugs”
  - “consider drug holidays with careful observation for most patients with osteoporosis who are receiving long-term therapy, particularly those whose bone-turnover markers [such as n-telopeptide] indicate substantially reduced levels”

E. Shane, NEJM May 13 2010
## Non-bisphosphonate therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence</th>
<th>Thoughts on appropriate use</th>
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<tbody>
<tr>
<td><strong>Raloxifene</strong>&lt;br&gt; SERM: estrogen agonist/antagonist</td>
<td>50% reduction vertebral fractures; no decrease non-vertebral fractures</td>
<td>• 50% reduction in breast cancer/5 years of tx&lt;br&gt;• Dosage: 60mg/day&lt;br&gt;• Side effects: Hot flashes, DVT</td>
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<tr>
<td><strong>Calcitonin</strong></td>
<td>Prevents spinal bone loss; unknown at hip</td>
<td>• Primary use: analgesia with compression fractures</td>
</tr>
<tr>
<td><strong>Teriparatide (Forteo)</strong>&lt;br&gt; anabolic effect</td>
<td>Severe (&lt;3.5 SD) or refractory disease</td>
<td>• Endocrinology only&lt;br&gt;• Daily injection</td>
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<tr>
<td><strong>Estrogen</strong></td>
<td>Reduction vertebral/non-vertebral fractures</td>
<td>• Use limited by other risks of HT (breast cancer)</td>
</tr>
<tr>
<td><strong>Nitroglycerin</strong></td>
<td>EARLY STUDIES: increased BMD at spine/hip and radius/tibia&lt;br&gt;No data on fracture</td>
<td>• Not approved for treatment/prevention of osteoporosis&lt;br&gt;• Stay tuned for fracture studies</td>
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</tbody>
</table>
Thank you!

Please fill out evaluation forms