OSTEOPOROSIS: AN UPDATE
GIM GRAND ROUNDS
APRIL 2014

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DISCLOSURES

- None
LEARNING OBJECTIVES

- Should be able to:
  1. Utilize the FRAX tool to risk stratify the patient with osteopenia
  2. Summarize the latest recommendations regarding calcium and Vitamin D
  3. Implement a drug holiday in the appropriate patient
  4. Identify the newest medications for osteoporosis
  5. Assess patient at high risk of fracture and treat accordingly
The lifetime risk of hip fracture is 1 in 6 for women.

Osteoporosis affects 200 million women worldwide
- 1/3 of women age 60-70
- 2/3 of women >80

Over 1.5 million fractures occur in the US each year.

About 20-25% of hip fractures occur in men.

The overall mortality is about 20% in the first 12 months after hip fracture and is higher in men than women.

In 2005, osteoporosis-related fractures were responsible for an estimated $19 billion in costs.

Adapted from IOF Slide, www.nof.org
CASE #1

- A 52 year old healthy woman comes to see you for concerns about her bone health.
- Her mother had rheumatoid arthritis and multiple compression fractures and the patient is worried about her own bone health.
- Current DXA shows her lowest site at the lumbar spine is -1.6 and femoral neck is -1.4.
- She takes calcium and Vitamin D and runs about 10 miles a week and skis all winter.
- What do you advise regarding her fracture risk and treatment choices?
<table>
<thead>
<tr>
<th>Condition</th>
<th>T score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>-1.0 or higher</td>
</tr>
<tr>
<td>Osteopenia (low bone mass)</td>
<td>-1.1 to -2.4</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>-2.5 and below</td>
</tr>
<tr>
<td>Severe osteoporosis</td>
<td>-2.5 and below, with a low trauma fracture</td>
</tr>
</tbody>
</table>
RISK FACTORS FOR FRACTURES

► Low Bone Density
  - Age
  - Gender
  - Estrogen deficiency
  - Ethnicity
  - Family history of fracture
  - Cigarette smoking
  - Low body weight
  - Low calcium intake (lifetime)
  - Excessive alcohol/caffeine
  - Reduced physical activity

► Falls
  - Cognitive impairment
  - Medications
  - Visual/proprioception
  - Obstacles

► History of Prior Fractures
PATHOGENESIS OF FRACTURE

- Low peak bone mass
- Post menopausal bone loss
- Age-related bone loss
- Other risk factors

Low bone mass → FRACTURE

- Propensity to fall
- Bone quality

Adapted from Melton LJ and Riggs BL. Osteoporosis: Etiology, Diagnosis and Management, Raven Press 1988, pp155-179.
ATTAINING GOOD PEAK BONE MASS IS KEY

Figure 6-2. Bone Mass Versus Age With Optimal and Suboptimal Bone Acquisition

Source: Based on Heaney et al. 2000.
HOW CAN WE DETERMINE INDIVIDUAL RISK?

- **FRAX**
- [http://www.shef.ac.uk/FRAX/](http://www.shef.ac.uk/FRAX/)

Developed to integrate risks factors to predict fracture with or without access to DEXA machine.
Calculation Tool

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: 52
   - Date of birth: Y: [ ] M: [ ] D: [ ]

2. Sex  Male  Female

3. Weight (kg)  56.7

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 per day  No  Yes

12. Femoral neck BMD (g/cm²)
   - T-Score: 1.4
   - T-Score: -1.4

BMI: 22.1

The ten year probability of fracture (%) with BMD:
- Major osteoporotic: 4.9
- Hip fracture: 0.4

Weight Conversion
- Pounds 125
- Re convert

Height Conversion
- Inches 63
- Re convert

01563804
Individuals with fracture risk assessed since 1st June 2011
WHO SHOULD BE TREATED WITH PHARMACOLOGICAL THERAPY?

- NOF guidelines

Postmenopausal women or men >50 with:

- Hip or vertebral fracture
- T-score of < -2.5 with no other risk factors
- T-score of -1.0 to -2.5 with any of the following:
  - a) other prior fractures, or
  - (b) secondary cause associated with high risk of fracture, or
  - (c) 10-year fracture risk as assessed by FRAX™ of 3% or more at the hip, 20% or more for major osteoporosis-related fracture (humerus, forearm, hip or clinical vertebral fracture)

www.nof.org
POST FRACTURE: INADEQUATE TREATMENT

- Most patients who have had fractures are not receiving treatment.
- Community based study women >65 with hip fracture, 13% receiving adequate treatment.\(^1\)
- Nursing home patients with recent hip, wrist or humeral fracture:\(^2\)
  - 4430 patients eligible, 11.5% received medication.

ISSUES WITH FRAX

- Consistency
  - 50 year old woman with low T-score
- Data for treating patients with higher BMD is lacking.
- Weighing of factors (i.e long term glucocorticoids, dose)
- Not all risk factors included
- Hip vs spine

Watts et al. J Clin Densitometry
Watts et al J BMR 2009
Collins G Current Osteoporosis Reports
NON PHARMACOLOGIC THERAPY

Basic building blocks:
- Calcium
- Vitamin D
- Exercise
Raised concern for risk for harm at:
>2000 mg Ca per day

<table>
<thead>
<tr>
<th>AGE</th>
<th>SUGGESTED CALCIUM</th>
<th>MAX</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-50 M/F</td>
<td>1000</td>
<td>2500</td>
</tr>
<tr>
<td>51-70 M</td>
<td>1000</td>
<td>2000</td>
</tr>
<tr>
<td>51-70 F</td>
<td>1200</td>
<td>2000</td>
</tr>
<tr>
<td>71+</td>
<td>1200</td>
<td>2000</td>
</tr>
</tbody>
</table>
Fig 3 Random effects models of effect of calcium supplementation on cardiovascular events and death.

Bolland M J et al. BMJ 2010;341:bmj.c3691

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### HOW TO GET ENOUGH CALCIUM?

- **Food sources are best:**
- **Each serving of dairy is about 300mg**
- **You get 250mg from a healthy diet.**

**Examples for getting the other 750mg**

<table>
<thead>
<tr>
<th>Product</th>
<th>Servings Per Day</th>
<th>Calcium (mg)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk (8 oz.)</td>
<td>X 300</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Yogurt (6 oz.)</td>
<td>X 300</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Cheese (1 oz. or 1 cubic inch)</td>
<td>X 200</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Fortified Foods &amp; Juices</td>
<td>X 80 - 1,000</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Estimated total from other foods</td>
<td></td>
<td>= 250</td>
<td></td>
</tr>
</tbody>
</table>

Note: Increase this amount if you get more than 250 mg of calcium from other foods.
WHAT KIND OF CALCIUM?

- If just intolerant, not allergic, try enzymes to add digestion
- Otherwise, supplements
- Look at the bottle for **elemental calcium**
  - Calcium carbonate needs to be taken with food
  - Calcium citrate can be taken without food and without acid
- You can only absorb about 500 mg of calcium at a time.
### IOM 2010 RECOMMENDATIONS

**VITAMIN D**

<table>
<thead>
<tr>
<th>AGE</th>
<th>RDA Vitamin D</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-70 male and female</td>
<td>600 IU</td>
<td>4000 IU</td>
</tr>
<tr>
<td>70 +</td>
<td>800 IU</td>
<td>4000 IU</td>
</tr>
<tr>
<td>Age</td>
<td>Suggested dose of Vitamin D</td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------</td>
<td></td>
</tr>
<tr>
<td>Infants 0-1</td>
<td>400-1000 IU</td>
<td></td>
</tr>
<tr>
<td>Children 1-18</td>
<td>600-1000 IU</td>
<td></td>
</tr>
<tr>
<td>Adults 19-50</td>
<td>600 IU</td>
<td></td>
</tr>
<tr>
<td>Adults 50+</td>
<td>600-800 IU</td>
<td></td>
</tr>
</tbody>
</table>

But they note that to raise blood level to >30 ng/dl may take 1500-2000 IU.
MIXED RESULTS ON FRACTURE RISK?

- Nursing home residents with a mean level of 14 with
  - 800 IU of D and 1200 mg of Calcium → 25% risk reduction in hip and non vertebral fractures.¹
- WHI² study compared
  - Vitamin D3 400 IU and Calcium 1000mg without improvement
  - However women who were most consistent with their Ca and D had a 29% risk reduction
- RECORD³ trial showed no improvement (levels went to 24.8 ng/dl)

¹ Chapuy et al BMJ 1994
² Jackson et al NEJM 2006
³ Grant A Lancet 2006
# Meta-analysis data on D for Fracture Prevention

## Table 2. Incidence of Fracture among 31,022 Participants, According to Vitamin D Treatment Dose and Actual Intake.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>No. of Participants</th>
<th>Hip Fracture</th>
<th>Any Nonvertebral Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Fractures</td>
<td>Relative Risk (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Intention-to-treat analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>15,495</td>
<td>586</td>
<td>1.00</td>
</tr>
<tr>
<td>Treatment</td>
<td>15,527</td>
<td>525</td>
<td>0.90 (0.80–1.01)</td>
</tr>
<tr>
<td>Treatment-dose analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>15,495</td>
<td>586</td>
<td>1.00</td>
</tr>
<tr>
<td>≤000 IU/day†</td>
<td>10,111</td>
<td>255</td>
<td>0.89 (0.74–1.07)</td>
</tr>
<tr>
<td>&gt;000 IU/day†</td>
<td>5,416</td>
<td>270</td>
<td>0.91 (0.78–1.06)</td>
</tr>
<tr>
<td>Actual-intake analysis‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>15,495</td>
<td>586</td>
<td>1.00</td>
</tr>
<tr>
<td>0–360 IU/day</td>
<td>3,935</td>
<td>100</td>
<td>1.00 (0.79–1.26)</td>
</tr>
<tr>
<td>361–637 IU/day</td>
<td>3,836</td>
<td>110</td>
<td>1.03 (0.83–1.29)</td>
</tr>
<tr>
<td>638–791 IU/day</td>
<td>3,790</td>
<td>164</td>
<td>1.01 (0.83–1.21)</td>
</tr>
<tr>
<td>792–2000 IU/day</td>
<td>3,966</td>
<td>151</td>
<td>0.70 (0.58–0.86)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>15,495</td>
<td>586</td>
<td>1.00</td>
</tr>
<tr>
<td>0–337 IU/day</td>
<td>3,353</td>
<td>84</td>
<td>1.01 (0.79–1.30)</td>
</tr>
<tr>
<td>338–360 IU/day</td>
<td>5,652</td>
<td>114</td>
<td>0.83 (0.66–1.05)</td>
</tr>
<tr>
<td>361–699 IU/day</td>
<td>2,640</td>
<td>180</td>
<td>1.14 (0.93–1.41)</td>
</tr>
<tr>
<td>700–2000 IU/day</td>
<td>3,882</td>
<td>147</td>
<td>0.71 (0.58–0.87)</td>
</tr>
<tr>
<td>Internal validation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–360 IU/day</td>
<td>18,153</td>
<td>639</td>
<td>1.00</td>
</tr>
<tr>
<td>361–637 IU/day</td>
<td>4,976</td>
<td>150</td>
<td>1.03 (0.84–1.26)</td>
</tr>
<tr>
<td>638–791 IU/day</td>
<td>3,865</td>
<td>168</td>
<td>1.02 (0.84–1.24)</td>
</tr>
<tr>
<td>792–2000 IU/day</td>
<td>4,028</td>
<td>154</td>
<td>0.70 (0.58–0.86)</td>
</tr>
</tbody>
</table>

* All analyses were adjusted for study, age group, sex, and type of dwelling. To limit false positive results and correct for multiplicity, we used a P value of 0.0125 to indicate significance.

† All trials included doses between 700 and 2000 IU per day.

‡ Among 21,241 participants from the eight trials that used vitamin D combined with any dose of calcium supplementation, a benefit was present only at the highest actual-intake level of vitamin D.

§ In the sensitivity analysis for adherence-adjusted dose without supplements outside the study protocol, 511 participants in the Women’s Health Initiative trial shifted from the highest actual-intake level (792 to 2000 IU per day) and 1336 shifted from the second-highest actual-intake level (638 to 791 IU per day) to the second-lowest adherence-adjusted intake level (338 to 360 IU per day). See the Supplementary Appendix for additional information.
Subgroup Benefits at the Highest Actual-Intake Level of Vitamin D (792–2000 IU per Day), as Compared with Control Group.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Treatment Group</th>
<th>Control Group</th>
<th>Hip Fracture</th>
<th>Any Nonvertebral Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of participants</td>
<td>no. of fractures</td>
<td>Treatment Group</td>
<td>Control Group</td>
</tr>
<tr>
<td>All</td>
<td>3966</td>
<td>15,495</td>
<td>151</td>
<td>586</td>
</tr>
<tr>
<td>65–74 yr</td>
<td>1018</td>
<td>7,521</td>
<td>13</td>
<td>128</td>
</tr>
<tr>
<td>75–84 yr</td>
<td>2603</td>
<td>5,989</td>
<td>130</td>
<td>332</td>
</tr>
<tr>
<td>≥85 yr</td>
<td>345</td>
<td>1,985</td>
<td>8</td>
<td>126</td>
</tr>
<tr>
<td>Type of dwelling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>3966</td>
<td>15,495</td>
<td>151</td>
<td>586</td>
</tr>
<tr>
<td>Community dwelling</td>
<td>2103</td>
<td>10,735</td>
<td>42</td>
<td>253</td>
</tr>
<tr>
<td>Institution</td>
<td>1863</td>
<td>4,760</td>
<td>109</td>
<td>333</td>
</tr>
<tr>
<td>Baseline 25-hydroxyvitamin D</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All†</td>
<td>412</td>
<td>2,220</td>
<td>11</td>
<td>177</td>
</tr>
<tr>
<td>&lt;30 nmol/liter</td>
<td>106</td>
<td>517</td>
<td>2</td>
<td>42</td>
</tr>
<tr>
<td>≥30 nmol/liter</td>
<td>306</td>
<td>1,703</td>
<td>9</td>
<td>135</td>
</tr>
<tr>
<td>Additional calcium intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2580</td>
<td>10,615</td>
<td>123</td>
<td>368</td>
</tr>
<tr>
<td>&lt;1000 mg</td>
<td>294</td>
<td>10,145</td>
<td>6</td>
<td>359</td>
</tr>
<tr>
<td>≥1000 mg</td>
<td>2286</td>
<td>470</td>
<td>117</td>
<td>9</td>
</tr>
</tbody>
</table>

* All analyses were adjusted for study, age group, sex, and type of dwelling. After Bonferroni adjustment, with a P value of less than 0.00625 considered to indicate statistical significance, there were no significant interactions between the highest actual-intake level of vitamin D and the four subgroups.
† Data on baseline 25-hydroxyvitamin D levels were available for a total of 4383 participants in nine trials.

**SOURCE OF VITAMIN D**

- Solar UV-B (sunlight without sunscreen)
  - Not recommended for all

- What foods have D naturally?
  - Salmon 400 IU/3.5 oz
  - Cod liver oil 400 IU/tsp
  - Egg yolks 20 IU

- What foods are fortified?
  - Milk 100 IU/serving
  - Cereal 100 IU/serving
  - Orange Juice 100 IU/serving
  - Yogurt 100 IU/serving

- Supplements
  - D2 or D3
HOW TO SUPPLEMENT

- If the level is <10, this is severe osteomalacia. Would not advise bisphosphonate and would treat aggressively with D to bring down OTH.
- If level is <20ng/mL, replete. Many will do this with 50,000 IU weekly for 6-12 weeks and then start a maintenance dose.
- The dose will depend on patient factors and how hard you think it will be to keep level up.
- If the level is 20-30ng/mL, many people treat with 600-2000 IU daily.
- D3 may be better than D2.

B. Dawson-Hughes from Up To Date
Micol Rothman, personal experience
Random-effects meta-analysis comparing the effects of daily and bolus supplementation of D3 with that of D2 on net changes in serum 25(OH)D concentrations.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>D3</th>
<th>D2</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Biancuzzo 2010-1 (7)</td>
<td>23.3</td>
<td>17.8</td>
<td>20</td>
</tr>
<tr>
<td>Biancuzzo 2010-2 (7)</td>
<td>32.2</td>
<td>25.3</td>
<td>18</td>
</tr>
<tr>
<td>Binkley 2011-1 (15)</td>
<td>23.3</td>
<td>33.8</td>
<td>16</td>
</tr>
<tr>
<td>Binkley 2011-2 (15)</td>
<td>22.3</td>
<td>18.3</td>
<td>15</td>
</tr>
<tr>
<td>Glendenning 2009 (16)</td>
<td>40.2</td>
<td>24.7</td>
<td>17</td>
</tr>
<tr>
<td>Heaney 2011 (17)</td>
<td>98.4</td>
<td>29.1</td>
<td>17</td>
</tr>
<tr>
<td>Holick 2008 (6)</td>
<td>23.3</td>
<td>17.8</td>
<td>20</td>
</tr>
<tr>
<td>Romagnoli 2008-1 (5)</td>
<td>70.2</td>
<td>20.8</td>
<td>8</td>
</tr>
<tr>
<td>Romagnoli 2008-2 (5)</td>
<td>65.4</td>
<td>30.3</td>
<td>8</td>
</tr>
<tr>
<td>Trang 1998 (4)</td>
<td>23.3</td>
<td>15.7</td>
<td>55</td>
</tr>
</tbody>
</table>

Total (95% CI) 194 150 100.0% 15.23 [6.12, 24.34]

Heterogeneity: Tau² = 162.74; Chi² = 47.10, df = 9 (P < 0.00001); I² = 81%

Test for overall effect: Z = 3.28 (P = 0.001)

Δ25(OH)D greater with D2  Δ25(OH)D greater with D3
EXERCISE FOR OSTEOPOROSIS

- Weight bearing exercise
  - High impact (running, jumping rope, stairs)
  - Low impact (elliptical, stair stepper, fast walking)

- Muscle strengthening

- Balance exercises

- Posture exercises

- www.nof.org
META-ANALYSIS: FRACTURE REDUCTION WITH EXERCISE

10 controlled exercise trials reported fractures
3 controlled exercise trials reported vertebral fractures

Exercise group
36/754 fractures
Control Group
73/670
Vertebral 19/103 vs 31/102

Kemmler Osteoporosis International 2013
CASE #1

- Her fracture risk is low and she does not require pharmacologic therapy at this time.
- She should continue her active lifestyle, make sure her calcium and D intake are at adequate.
- If she has no changes in medications, etc, it is reasonable to wait to rescreen her.
How often should we be doing bone density testing?

Women in this study were older, 67+
Applies to repeat studies, not screening
Everyone who had osteoporosis at baseline was not included
LACK OF SCREENING IS A BIG CONCERN AS WELL

Distribution Of Elderly Female Fee-for-Service Medicare Beneficiaries By Cumulative Number Of DXA Tests, 2002–08.

King A B, and Fiorentino D M Health Aff 2011;30:2362-2370

©2011 by Project HOPE - The People-to-People Health Foundation, Inc.
“Well, yes, we could fix it in Photoshop, but your arm would still be broken.”
CASE #2

- A 67 year old man comes to see you for concerns about his osteoporosis medication.
- He was placed on high dose prednisone and suffered a vertebral fracture 6 months ago.
- He has been taking oral alendronate for about 5 months, but reports some GI upset with it that last a day or two after he takes it.
- He does not currently smoke, but did smoke 1 PPD from age 18-60.
- DXA reveals lowest site is a T-score of -2.8 in his femoral neck.
WHAT ARE HIS OTHER OPTIONS?

Bone resorption

Antiresorptive therapy
Bisphosphonates
RANK-L inhibitor
(SERMs/Estrogen)

Bone formation

Anabolic therapy
Teriparatide

www.surgeongeneral.gov
### CURRENTLY FDA APPROVED THERAPIES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Vertebral fracture</th>
<th>Hip fracture</th>
<th>Non vertebral</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raloxifene</td>
<td>antiresorptive</td>
<td>+</td>
<td></td>
<td></td>
<td>$</td>
</tr>
<tr>
<td>Alendronate</td>
<td>antiresorptive</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>generic</td>
</tr>
<tr>
<td>Risedronate</td>
<td>antiresorptive</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>$</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>antiresorptive</td>
<td>+</td>
<td></td>
<td></td>
<td>$</td>
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<tr>
<td>Zoledronate</td>
<td>antiresorptive</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>$$$</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>anabolic</td>
<td>+</td>
<td></td>
<td>+</td>
<td>$$$$$$</td>
</tr>
<tr>
<td>Denosumab</td>
<td>antiresorptive</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>$$ $$</td>
</tr>
</tbody>
</table>
### BISPHOSPHONATES

<table>
<thead>
<tr>
<th></th>
<th>Alendronate</th>
<th>Risedronate</th>
<th>Ibandronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral Fractures</td>
<td>45%</td>
<td>39%</td>
<td>48%</td>
</tr>
<tr>
<td>Reduction vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non Vertebral Fractures</td>
<td>23%</td>
<td>20%</td>
<td>25%</td>
</tr>
<tr>
<td>Hip Fractures</td>
<td>53%</td>
<td>26%</td>
<td>None published</td>
</tr>
</tbody>
</table>

- Decrease breast cancer risk (observational)
- Skeletal metastases
- Decreased mortality?
- However, recent concerns surfaced on risks

Silverman Osteoporosis International 2012, Center JCEM 2011
OSTEONECROSIS OF THE JAW

- Definition: Exposed necrotic bone in maxillofacial region that fails to heal in 6-8 weeks
- Often follows an extraction or other invasive procedure (60%)
- Mandible: maxilla 2:1

- Initial report 2003, all high dose IV treatment for cancers
- 2006 Review of 368 cases
  - Myeloma, cancer 94.1%
  - Osteoporosis 4.1% (15)
  - Paget .8% (3)
- Recent estimates:
  - 1-20/1000 depending on study

Shannon et al J American Geriatrics Society 2011
Zhang et al Rheum Dis Clin N Am 2011
WHAT TO TELL PATIENTS ABOUT ONJ

► Dental exam and if extractions needed, try to have prior to starting to bisphosphonates
► Communication with dental colleagues
► Serum CTX is NOT useful
► No real consensus on stopping medication, how long to stop etc
► Bisphosphonates are one of many risk factors for ONJ (smoking, vascular disease, malnutrition)

► American Dental Association Guidelines November 2011

J Clinical Densitometry January-March 2012
JADA 2011; 142(11) 1243-1251
Atypical Femoral Fractures

FIGURE 1. Representative radiographs of femoral shaft fractures sustained from minimal trauma in patients taking alendronate. Although each radiograph demonstrates the pattern in its entirety, we have highlighted the following features. A, Fracture pattern pictured with an arch measuring 30 degrees to highlight transverse nature. B, The arrow pointing out the unicortical beak C, Hypertrophied cortices outlined.

Neviaser et al. J Orthop Trauma 2008
ATYPICAL FRACTURES

- Prevalence and rarity are disputed
- Many retrospective reviews, some without XR
- Reports from 5/10,000 patients years to 5.9/100,000 years
- May be higher with longer use of bisphosphonates
  2/100,000 with 2 years vs 78/100,000 for 8 years (ASMBR 2010)
- ? Risk may decrease fairly quickly when drug is stopped

Abrahamsen Bone 2012
ASBMR Task Force JBMR 2010
M McClung Snowmass Conference 2014
WHAT TO TELL PATIENTS?

► Weigh patients individual risk of typical fracture vs risk of side effects.
► Investigate complaints of thigh pain in patients on bisphosphonates.
► Consider risks and benefits of long term treatment.
HOW LONG TO TREAT WITH ALENDRONATE

# FLEX: NNT TO PREVENT ONE CLINICAL VERTEBRAL FRACTURE

<table>
<thead>
<tr>
<th>Femoral Neck BMD T Score at Start of Extension†</th>
<th>5-Yr Risk of Clinical Vertebral Fracture</th>
<th>Risk Difference (95% CI)</th>
<th>Number Needed to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Group</td>
<td>Alendronate Group‡</td>
<td>no./total no. (%)</td>
<td></td>
</tr>
<tr>
<td>All women in study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All BMD T scores</td>
<td>23/437 (5.5)</td>
<td>16/662 (2.5)</td>
<td>2.9 (0.3–5.4)</td>
</tr>
<tr>
<td>Less than or equal to −2.5</td>
<td>11/132 (9.3)</td>
<td>9/190 (4.5)</td>
<td>4.8 (0.8–9.2)</td>
</tr>
<tr>
<td>Greater than −2.5 and less than or equal to −2.0</td>
<td>9/126 (5.8)</td>
<td>3/185 (2.8)</td>
<td>3.0 (0.3–6.7)</td>
</tr>
<tr>
<td>Greater than −2.0</td>
<td>3/179 (2.3)</td>
<td>4/282 (1.1)</td>
<td>1.2 (0.2–2.8)</td>
</tr>
<tr>
<td>Women with no prevalent vertebral fracture at start of FLEX study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than or equal to −2.5</td>
<td>6/75 (8.0)</td>
<td>4/109 (3.8)</td>
<td>4.2 (0.6–9.1)</td>
</tr>
<tr>
<td>Greater than −2.5 and less than or equal to −2.0</td>
<td>3/82 (3.0)</td>
<td>1/121 (1.4)</td>
<td>1.6 (0.2–5.0)</td>
</tr>
<tr>
<td>Greater than −2.0</td>
<td>2/130 (1.8)</td>
<td>2/203 (0.9)</td>
<td>1.0 (0.1–2.6)</td>
</tr>
<tr>
<td>Women with prevalent vertebral fracture at start of FLEX study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than or equal to −2.5</td>
<td>5/57 (11.1)</td>
<td>5/81 (5.3)</td>
<td>5.8 (0.8–12.1)</td>
</tr>
<tr>
<td>Greater than −2.5 and less than or equal to −2.0</td>
<td>6/44 (11.1)</td>
<td>2/64 (5.3)</td>
<td>5.8 (0.8–13.6)</td>
</tr>
<tr>
<td>Greater than −2.0</td>
<td>1/49 (3.7)</td>
<td>2/79 (1.7)</td>
<td>2.0 (0.3–5.6)</td>
</tr>
</tbody>
</table>

HOW LONG TO CONTINUE TREATMENT?

- Editorial in same issue (NEJM 2012) suggests
  - Femoral neck T-score < -2.5
  - Patients with vertebral fractures and <-2.0
  - “may benefit from more than 3-5 years of treatment”
  - Those with T score above −2.0 are “unlikely to benefit from continued treatment.”
- This cannot be extrapolated to other medications.
- Osteoporosis is a chronic long term disease, like diabetes or hypertension.
- The reason some medications can be stopped is that they are still releasing into the bone, not because the patient is cured.
WHAT OTHER OPTIONS DO WE HAVE? DEanosumab

RANKL (expressed by osteoblasts) binds RANK receptor on osteoclast precursors to stimulate their differentiation. OPG (osteoprotegerin) is the endogenous receptor that acts as a decoy to inhibit this bone resorption. Denosumab is a human monoclonal antibody with specificity toward RANK.
Fracture risk reduction at 3 years:
Vertebral: 68%
Hip fracture (secondary): 40%,
Other non vertebral fracture: 20%.

Cummings SR et al. 

FREEDOM TRIAL 2009

7808 post menopausal women with T-score < -2.5

Vertebral fracture
2.3% in the denosumab group
7.2% in the placebo group.

Fracture risk reduction at 3 years:
Vertebral: 68%
Hip fracture (secondary): 40%,
Other non vertebral fracture: 20%.

Cummings SR et al. 
WHO IS DENOSUMAB APPROVED FOR?

- Post menopausal women and men with osteoporosis at high risk for fracture
- Men at high risk for fracture receiving androgen deprivation therapy for non metastatic prostate cancer.
- Women at high risk for fracture receiving aromatase inhibitor therapy.
- Given as a subcutaneous injection every 6 months
DENOSUMAB: PROS AND CONS

- **Advantages**
  - No renal adjustment
  - Convenience
  - ? Benefit to reversibility of suppression

- **Risks**
  - Hypocalcemia
  - ? Infection risk (skin)
  - Dermatitis
  - Remember still acts on osteoclasts: ONJ and atypical fracture reported
DENOSUMAB AFTER ALENDRONATE

506 women receiving alendronate for $\geq 6$ months average 34–range 6-192 months

Kendler et al JBMR 2010
ONSET AND OFFSET ARE DIFFERENT

SERUM CTX on and off estrogen and denosumab looks different!

JBMR 2012
Given in pulsatile fashion, PTH can be anabolic to bone.

TERIPARATIDE: PROS AND CONS

- **Advantages**
  - Only anabolic therapy available
  - Spine BMD and fracture risk improvement > alendronate (GIO)

- **Risks**
  - Daily injection
  - Cost
  - ? Osteosarcoma risk (rats) 2 year black box warning (recent data suggest risk in humans low over long term)
428 women and men with GIOP, on $\geq 5$ mg/d prednisone for $\geq 3$ months

RCT: Alendronate (n=214) vs Teriparatide (n=214) for 18 months

**Bone Mineral Density**

- Spine: 3.4% Alendronate vs 7.2% Teriparatide ($P < .001$)
- Hip: 2.4% Alendronate vs 3.8% Teriparatide ($P < .005$)

**Vertebral Fractures**

- 10 Teriparatide (10/10) vs 1 Alendronate (1/10) ($P < .004$)

CASE #2

- Patient is high risk and cannot tolerate oral medication
- Options would be:
  - IV bisphosphonates (make sure renal function OK)
  - Could consider denosumab or teriparatide
- In this patient, would repeat BMD in 1-2 years (depending on steroid dose/duration)
Use FRAX to help risk stratify patients with osteopenia, in addition to bone density.

Too much calcium may not be better

Still unclear as to the optimal amount, level of Vitamin D

Consider drug holidays in the appropriate patients after 5 years

Consider non bisphosphonate options in the appropriate patient.

High risk patients should be treated.
"I’m sorry, the results are quite clear. You’re bad only to the epidermis."
WHO SHOULD BE SCREENED FOR D DEFICIENCY?

- Osteoporosis
- Kidney disease
- Liver disease
- Malabsorption syndromes
- Hyperparathyroidism
- High risk populations
  - African American adults
  - Hispanic adults
  - Pregnant women
  - Adults with falls
  - Obese children and adults
- Medications:
  - Anti-seizure
  - Glucocorticoids
  - HAART
  - Anti-fungals
  - Colestyramine
- Granulomatous disorders

Endocrine Society Guidelines 2011