OSTEOPOROSIS: PREVENTION, TREATMENT AND NEW DIRECTIONS

Micol S. Rothman, MD
Clinical Director, Metabolic Bone Program
Diabetes, Endocrinology and Metabolism
University of Colorado Hospital
LEARNING OBJECTIVES

- Participants should be able to:
- 1) Understand the role of lifestyle and dietary modifications in the prevention of osteoporosis.
- 2) Know the FDA approved therapies for osteoporosis and their risks and benefits as well what is in the pipeline.
OSTEOPOROSIS PREVALENCE

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

Adapted from IOF Slide, www.nof.org
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?
# DEFINITIONS

<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.
HOW CAN WE DETERMINE INDIVIDUAL RISK?

- 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: 

1. Age (between 40-90 years) or Date of birth
   Age: 52
   Date of birth: Y: M: D: 

2. Sex
   Male

3. Weight (kg) 56.7

4. Height (cm) 160.02

5. Previous fracture
   No

6. Parent fractured hip
   No

7. Current smoking
   No

8. Glucocorticoids
   No

9. Rheumatoid arthritis
   No

10. Secondary osteoporosis
    No

11. Alcohol 3 or more units per day
    No

12. Femoral neck BMD (g/cm²)
    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 ➔ kg
125 ➔ Convert

Height Conversion
Inches ➔ cm
63 ➔ 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
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
Based on her FRAX score, you suggest she take calcium, Vitamin D and do weight bearing exercise.

She wants to know:
- How much calcium?
- How much D?
- What kind of exercise is best?
NON PHARMACOLOGIC THERAPY

Basic building blocks:

- Calcium supplements
- Vitamin D
- Exercise
Fig 3 Random effects models of effect of calcium supplementation on cardiovascular events and death.

Bolland MJ et al. BMJ 2010;341:bmj.c3691
### VITAMIN D AND CALCIUM SUPPLEMENTATION TO PREVENT FRACTURES IN ADULTS

**CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION**

<table>
<thead>
<tr>
<th>Population</th>
<th>Community-dwelling postmenopausal women at doses of &gt;400 IU of vitamin D$_3$ and &gt;1000 mg of calcium</th>
<th>Community-dwelling postmenopausal women at doses of ≤400 IU of vitamin D$_3$ and ≤1000 mg of calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Men or premenopausal women</td>
<td></td>
</tr>
<tr>
<td>Recommendation</td>
<td>No recommendation. Grade: I statement</td>
<td>Do not supplement. Grade: D</td>
</tr>
</tbody>
</table>

**Preventive Medications**

Appropriate intake of vitamin D and calcium are essential to overall health. However, there is inadequate evidence to determine the effect of combined vitamin D and calcium supplementation on the incidence of fractures in men or premenopausal women.

There is adequate evidence that daily supplementation with 400 IU of vitamin D$_3$ and 1000 mg of calcium has no effect on the incidence of fractures in postmenopausal women.

There is inadequate evidence regarding the effect of higher doses of combined vitamin D and calcium supplementation on fracture incidence in community-dwelling postmenopausal women.

**Balance of Benefits and Harms**

Evidence is lacking regarding the benefit of daily vitamin D and calcium supplementation for the primary prevention of fractures, and the balance of benefits and harms cannot be determined.

Evidence is lacking regarding the benefit of daily supplementation with >400 IU of vitamin D$_3$ and >1000 mg of calcium for the primary prevention of fractures in postmenopausal women, and the balance of benefits and harms cannot be determined.

Daily supplementation with ≤400 IU of vitamin D$_3$ and ≤1000 mg of calcium has no net benefit for the primary prevention of fractures.

**Other Relevant USPSTF Recommendations**

The USPSTF has made recommendations on screening for osteoporosis and vitamin D supplementation to prevent falls in community-dwelling older adults. These recommendations are available at www.uspreventiveservicestaskforce.org.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to www.uspreventiveservicestaskforce.org.
## IOM 2010 RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Life Stage Group</th>
<th>Recommended Daily Calcium (mg)</th>
<th>Recommended Daily D (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-18 (including pregnant/lactating)</td>
<td>1300</td>
<td>600</td>
</tr>
<tr>
<td>Pregnant and lactating 19-50</td>
<td>1000</td>
<td>600</td>
</tr>
<tr>
<td>19-50</td>
<td>1000</td>
<td>600</td>
</tr>
<tr>
<td>51-70 female</td>
<td>1200</td>
<td>600</td>
</tr>
<tr>
<td>70+ female</td>
<td>1200</td>
<td>800</td>
</tr>
</tbody>
</table>
PTH AND VITAMIN D:

Where did the target of 30mg/ml come from?

Adults< 50 400-800 (IU) of vitamin D daily

Adults> 50 800-1,000 IU of vitamin D daily

Experts disagree on the safe upper limit for vitamin D.

It is difficult to get too much vitamin D unless a person is taking a prescription dose of the vitamin. In that case, healthcare providers can easily monitor a person’s vitamin D level with a blood test.
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

- Suggest she get 1200mg of calcium daily, best through dietary sources.
- Vitamin D 600-1000 IU

- Exercise:
  - 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](http://www.nof.org)
A 76 year old woman is admitted to the hospital with a hip fracture.

She went through menopause at age 51, and did not take hormone therapy.

She smoked 1PPD for 52 years, quit about 10 years ago.

Due to COPD, she is prescribed steroids intermittently and is currently on long term inhaled steroids.

She was prescribed oral alendronate about 2 years ago. She took it intermittently for about 6 months, but had some GI upset with it, so stopped it on her own.

In addition to some blood work and lifestyle counseling, what are her options for osteoporosis therapy?
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.

Nursing home patients with recent hip, wrist or humeral fracture:
- 4430 patients eligible, 11.5% received medication.

3,347 VA patients post hip fracture:
- 14.5% received osteoporosis therapy within 12 months of fracture.

Shibli-Rahhal et al. Osteoporosis International 2011
WHAT ARE HER OTHER OPTIONS?

Bone resorption
- Anti-resorptive therapy
- Bisphosphonates
- SERMs/Estrogen
- RANK-L inhibitor

Bone formation
- Anabolic therapy
- Teriparatide

www.surgeongeneral.gov
## FDA-APPROVED THERAPIES: FRACTURE REDUCTION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vertebral</th>
<th>Hip</th>
<th>Non-vertebral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>Not approved for treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitonin</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Alendronate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risedronate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoledronate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

www.nof.org
### 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

Silverman Osteoporosis International 2012
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
- Recent estimates: 1-20/1000 depending on study

What to tell patients

- 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)

Shannon et al J American Geriatrics Society 2011
Zhang et al Rheum Dis Clin N Am 2011
J Clinical Densitometry January-March 2012
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
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)

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
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.
Risk of vertebral fracture was reduced by 68% at 3 y 2.3% in the denosumab group, versus 7.2% in the placebo group. Hip fracture (secondary) was reduced by 40%, other non-vert fx reduced by 20%.

www.nejm.org
Cummings et al 2009
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.
ANABOLIC: TERIPARATIDE

- Parathyroid Hormone injections
- Parathyroid hormone given as a daily injection acts to increase osteoblast activity.

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

**Cons**
- Daily injection
- Cost
- Osteosarcoma risk (rats) 2 year black box warning (recent data suggest risk in humans low over long term)
Glucocorticoid Induced Osteoporosis

Treatment – Vertebral Fracture Reduction

428 women and men with GIOP, on ≥ 5 mg/d prednisone for ≥ 3 months
RCT: Alendronate (n=214) vs Teriparatide (n=214) for 18 months

Bone Mineral Density

<table>
<thead>
<tr>
<th></th>
<th>Alendronate</th>
<th>Teriparatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine</td>
<td>7.2%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Hip</td>
<td>2.4%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

P < .001

Vertebral Fractures

<table>
<thead>
<tr>
<th></th>
<th>Absolute Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spine</td>
<td>10</td>
</tr>
<tr>
<td>Hip</td>
<td>1</td>
</tr>
</tbody>
</table>

P < .004

CASE #2

- Patient is not tolerating oral bisphosphonate
- If creatinine clearance is >35 mg/ml, consider IV.
- Could also consider denosumab.
- Given high risk of fracture and steroid exposure could consider teriparatide as well.
WHAT IS IN THE PIPELINE?

- **Sclerostin inhibitor**
  - (produced by osteocytes, inhibits bone formation)
- **Cathepsin-K inhibitor**
  - (Protease involved in resorption)
- **Oral calcium sensing receptor antagonists**
  - (increase PTH transiently)
Think about patients risk for fracture when prescribing therapy or determining length of therapy.

Calcium and Vitamin D are still important for those with low BMD or risk factors, but more is not always better.

Discuss risks and benefits of therapy with patients.
How long should we treat with bisphosphonates?

Survival Curve for Time to First Nonvertebral Fracture and Time to First Clinical Vertebral Fracture
## Risk of Clinical Vertebral Fracture and Number Needed to Treat for 5 Years to Prevent One Clinical Vertebral Fracture in the Fracture Intervention Trial Long-Term Extension (FLEX) Study.

<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></td>
<td>Placebo Group</td>
<td>Alendronate Group‡</td>
<td></td>
</tr>
<tr>
<td>All women in study</td>
<td>no./total no. (%)</td>
<td>no./total no. (%)</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>

* The risks, risk differences, and numbers needed to treat were estimated from proportional-hazards models for the effect of treatment — first unadjusted, then adjusted for bone-mineral-density (BMD) categories, and finally adjusted for BMD categories and baseline prevalent vertebral fracture together. The 5-year risks (percentages) were derived from the proportional-hazards model and account for censoring. Confidence intervals were calculated with the use of the bootstrap method with 1000 replications. CI denotes confidence interval.

† The extension period began after 5 years of initial treatment.

‡ Included are patients who received the drug at a dose of 5 mg per day and those who received the drug at a dose of 10 mg per day.
“Thus, for clinicians, we believe that the current evidence base supports the following conclusions.

- Patients with low bone mineral density at the femoral neck (T score below −2.5) after 3 to 5 years of treatment are at the highest risk for vertebral fractures and therefore appear to benefit most from continuation of bisphosphonates.
- Patients with an existing vertebral fracture who have a somewhat higher (although not higher than −2.0) T score for bone mineral density may also benefit from continued therapy.
- Patients with a femoral neck T score above −2.0 have a low risk of vertebral fracture and are unlikely to benefit from continued treatment.
- We recognize that these conclusions, which are based on reductions in vertebral fractures, might change as additional data about long-term risks of bisphosphonate therapy become available.”

Black et al NEJM May 9, 2012