Case 1: Monday morning, 8:15

- 68yoWF presents with mid-thoracic pain after lifting her ill husband out of his chair
- Height loss of 2.5” since youth
- PE with an apex of kyphosis, focal pain palpable at T10
- Labs all normal; plain X-ray with compression fracture at T10
- Does she have a diagnosis yet? What do you do?
Case 2

• 53yo WF requests BMD for health maintenance
• PMHx: GERD, treated HTN
• Menopause at age 49; no symptoms; never on HT
• PE: normal, weight 142#, no kyphosis, no bony pain, height 5’4” unchanged from high school
Case 2, cont

- BMD:
  - L₁₋₄ T-score –1.8
  - Total hip T-score –2
  - Femoral neck T-score –2.1

Now What?

Case 3

- 65yo WF presents for her yearly exam
- She’s not had any height loss, no personal history of fracture
- Smokes “6 cigarettes a day”
- Mom broke her hip at age 78
- Normal menstrual history; 3 pregnancies
- DXA: LS T-score -1.8, Fem Neck -2.1
Osteoporosis: Definition

- Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk for fracture.

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis and Therapy. JAMA 2001;285:785 - 795

Osteoporosis is Common Among US Women

- 10 million Americans have established osteoporosis, 80% of whom are women.

The Life Cycle of Bone

Resting

Activation

Resorption

Reversal

Formation --- Mineralization

Bone Lining Cells

Osteoclasts

Apoptotic Bodies

Osteoblasts

Osteoid

Bone Lining Cells

Activation

Osteoclasts

Apoptotic Bodies

Osteoblasts

Osteoid

Steve Moon, MS, Professor, School of Allied Medical Professions, OSU COM, Atwell Hall

Local Mechanism of Estrogen Effects on Bone Loss

PTH

Activation

Increase Resorption

Reduce OC Apoptosis

OB

ST

CSF

OC precursors

GM-CSF

Mono

IL-1

TNF

IL-6

E2
Normal  Moderate Osteoporosis

Severe Osteoporosis

Courtesy Dr. A. Boyde
## Hip Fractures

- Result in excess mortality of 10-20% within the first year
- Prognostic of further fracture – RR 2.5
- 20% of patients with hip fracture require long-term nursing home care
  - Decreased independence, depression, loss of quality of life
- Only 40% regain full independence follow hip fracture
- Account for 14% of all fractures but 72% of cost
  - In 2005 accounted for over 400,000 hospital stays
  - $12.5 billion annually

## NOF Screening Guidelines

### DXA:
- Women >65
- Men >70
- Postmenopausal women and men aged 50-69 based on risk factor profile
- Postmenopausal women and men over age 50 who have had a fragility fracture
- Screening of premenopausal women decided individually by clinician
- Only to be done at facilities using accepted quality assurance

### Vertebral Imaging:
- All women >70 and all men >80 with DXA T-score < -1.0
- Women >65 and men >70 if T-score ≤ -1.5
- In those with low trauma fracture in adulthood
- Those with height loss 1.5” or more
  - Or a documented height loss of > 0.8” based on reliable office measurement
- Recent or ongoing long term glucocorticoid treatment

* Can be VFA or lateral thoracic and lumbar spine plain x-ray

Uses of BMD by DEXA

- Diagnosis of Osteopenia or Osteoporosis
  - Postmenopausal women
  - Glucocorticoid use
  - Metabolic bone disease
  - Osteopenia on plain radiograph
  - Previous fragility fracture or loss of height
- Prognosis – fracture risk assessment
- Monitor therapeutic response

DXA of the hip

Permission by GE Healthcare

Scanning the Spine
Diagnosis – T-score
WHO criteria

- Normal - > -1
- Osteopenia - <-1 and >-2.5
- Osteoporosis - <-2.5
- “Severe” Osteoporosis - <-2.5 + Hx Fx

**Osteoporosis is also diagnosed in patients with a history of fragility fracture, regardless of BMD**

**Diagnosis**

**LS DXA:**

- L1-L3 – U or Y shaped
- L4 – H shaped
- L5 – “I on its side”

**DXA Results Summary:**

<table>
<thead>
<tr>
<th>Region</th>
<th>Area (cm²)</th>
<th>BMC (g)</th>
<th>BMD (g/cm²)</th>
<th>T-score</th>
<th>P-value</th>
<th>Z-score</th>
<th>AM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>12.81</td>
<td>13.95</td>
<td>1.087</td>
<td>1.5</td>
<td>117</td>
<td>1.7</td>
<td>121</td>
</tr>
<tr>
<td>L2</td>
<td>12.71</td>
<td>16.36</td>
<td>1.393</td>
<td>1.5</td>
<td>115</td>
<td>1.8</td>
<td>120</td>
</tr>
<tr>
<td>L3</td>
<td>16.37</td>
<td>19.97</td>
<td>1.220</td>
<td>1.2</td>
<td>113</td>
<td>1.5</td>
<td>116</td>
</tr>
<tr>
<td>L4</td>
<td>16.36</td>
<td>21.10</td>
<td>1.289</td>
<td>1.6</td>
<td>116</td>
<td>1.9</td>
<td>119</td>
</tr>
<tr>
<td>Total</td>
<td>59.28</td>
<td>71.38</td>
<td>1.204</td>
<td>1.4</td>
<td>115</td>
<td>1.7</td>
<td>119</td>
</tr>
</tbody>
</table>

Increase from L1 to L2; Increase from L2 to L3; also increase in L3 to L4, though this increase is often <50% seen in other increments and occasionally you may see a slight decline.
Total femur does not include hip joint

Should see just a small portion of lesser trochanter - this gives the lowest femoral neck T-score.
To achieve this positioning, internally rotate the femur 15-20 degrees

Total femur includes femoral neck, Ward’s area, trochanteric region and the shaft

DXA Pitfalls:
Report: “The LS bone density T-score is -3.3, falling into the range of osteoporosis.
The previous T-score was -2.1. Over the past 3 years there has been a 13% decline in bone density at the spine.”
### Osteoporotic Fracture Risk

<table>
<thead>
<tr>
<th>Personal History of Fx</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of Fx after age 50</td>
<td>White Race</td>
</tr>
<tr>
<td>Weight &lt;127#</td>
<td>Alcoholism</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>Low physical activity</td>
</tr>
<tr>
<td></td>
<td>Recurrent falls</td>
</tr>
<tr>
<td></td>
<td>Dementia</td>
</tr>
</tbody>
</table>

### National Osteoporosis Foundation guidelines for therapeutic management

- A hip or vertebral (clinical or morphometric) fracture
- T-score < -2.5 at the total hip, femoral neck or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between -1.0 and -2.5 at the FN, TH or LS) AND a 10-year probably of a hip fracture >3% or of a major osteoporotic fracture of >20% based upon FRAX
- Clinician’s judgement and/or patient preference may indicate treatment for people with 10-year fracture probabilities above or below these levels

FRAX Fracture Calculation Tool

http://www.shef.ac.uk/FRAX/tool.jsp

NOF Treatment Guidelines:
10 year probability
For major Osteoporotic Fx: 20%
10 year prob for Hip fracture: 3%

So, what about our 53yo with osteopenia on DXA, who seems to have no other risk factors for fracture?
Femoral neck T-score -2.1

http://www.shef.ac.uk/FRAX/tool.jsp
How about the 65 year old with the exact same T-score by DXA, who smokes 5 cigarettes a day?

Calcium and vitamin D

- **NOF and IOM Recs:**
  - Calcium:
    - Men 50-70: 1000mg cal/d
    - Women >50, men >70 consume 1200mg calcium/d
  - Increasing dietary calcium is preferred over calcium supplements

- **Vitamin D recommendations:**
  - NOF: adults > 50: 800-1000u/d
  - IOM: <70, 600 units/day; >70 800 units/day
  - Safe upper limit: 4000 units/day
  - Goal: > 30ng/mL serum level


www.ncbi.nlm.nih.gov Reference intakes for calcium and vitamin D
Osteoporosis: Treatment

Steven W. Ing, MD, MSCE
Assistant Professor of Internal Medicine
Fellowship Program Director
Division of Endocrinology, Diabetes and Metabolism
The Ohio State University Wexner Medical Center

Objectives

- Discuss FDA-approved drugs for treatment of osteoporosis
- Discuss safety
Case

- 60 year old healthy white woman
- Wrist fracture after fall from standing height within past year
- Mother had hip fracture
- L1-L4 T-score -3.0
- FN T-score -2.8
- Height loss → x-rays show T7, T10 fracture

Case: Patient’s Perception

- “I’ve heard so much bad about osteoporosis medications”
- “I could die from those drugs, but nobody dies from a broken bone.”

Patient’s Decision: “I would rather take my chances with having a broken bone than take the risks that come with one of those bad drugs.”
Case: Provider’s Perspective

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

http://www.shef.ac.uk/FRAX/tool.jsp?locationValue=9

Case: Provider’s Perspective
Non-Drug Measures

- Calcium & vitamin D
- PT/OT:
  - home safety assessment and modification
  - walking aid/assistive devices
  - weight-bearing, strengthening, balance exercises
- Meds: gradually withdraw psychotropics
- Correct visual impairment
- Alcohol moderation & cigarette cessation
FDA-Approved Drug Therapy

- bisphosphonate
- estrogen
- raloxifene
- calcitonin
- teriparatide
- denosumab

Bisphosphonate: Chemical Structure

R¹ OH group, binding to bone
R² Binding to bone
Antiresorptive potency
PO₄ Binding to bone
Bisphosphonate Mechanism

**Mevalonate Pathway**

- HMG CoA
- HMG CoA Reductase
- Mevalonate
- Mevalonate Pyrophosphate
- Isopentenyl Pyrophosphate + AMP → AppI
- Geranyl Pyrophosphate
- FPP-Synthase
- Farnesyl Pyrophosphate (FPP)
- Protein Prenylation
- Cholesterol Synthesis
- N-RPS

Thea L Rogers, Ingunn Holen

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Bisphosphonates

NEJM 2004;350(12):1172-1174
### Efficacy of Fracture Reduction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic</th>
<th>Spine</th>
<th>Non-spine</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>alendronate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>risedronate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ibandronate</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>zoledronate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>teriparatide</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>*</td>
</tr>
<tr>
<td>denosumab</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>calcitonin</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>estrogen</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>raloxifene</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### FDA-Approved Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Postmenopausal Osteoporosis</th>
<th>Glucocorticoid-induced Osteoporosis</th>
<th>Men</th>
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<tbody>
<tr>
<td></td>
<td>Prevention</td>
<td>Treatment</td>
<td>Prevention</td>
</tr>
<tr>
<td>alendronate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>risedronate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ibandronate</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>zoledronate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>teriparatide</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>denosumab</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>calcitonin</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>estrogen</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
Drug administration

- Fasting, first thing in the morning
- Plain water (8 oz)
- Wait ≥30 minutes before PO intake, meds
- Contact provider for upper GI symptoms

Balancing Benefits and Risks of Therapy

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Fractures</td>
<td>• Upper GI symptoms</td>
</tr>
<tr>
<td>↓ Mortality</td>
<td>• Acute phase reaction (IV)</td>
</tr>
<tr>
<td>↓ Cancers</td>
<td>• ONJ</td>
</tr>
<tr>
<td>↑ Quality of Life</td>
<td>• Atypical Femur Fracture</td>
</tr>
<tr>
<td>↓ Health Care Cost</td>
<td></td>
</tr>
</tbody>
</table>
Bisphosphonates May Decrease Mortality

<table>
<thead>
<tr>
<th></th>
<th>Mortality Rate per 100 per-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bisphosphonate</td>
</tr>
<tr>
<td>Women</td>
<td>0.8 (0.4-1.4)</td>
</tr>
<tr>
<td>Men</td>
<td>1.0 (0.3-3.9)</td>
</tr>
</tbody>
</table>

Center, JCEM 2011;96(4):1006-1014

What do Seniors Fear Most?

- 2007 Interview age 65+
- “What do you fear most?”
  - 26% Loss of independence
  - 13% Moving out of home into nursing home
  - 11% Giving up driving
  - 11% Loss of family & friends
  - 3% Death

In summary, many individuals who suffer fragility fracture do not associate their fracture with osteoporosis.”

Diagnosis of Osteoporosis Changes the Perception of Fracture Risk

“The odds of an individual responding, ‘yes’ to the question, ‘Do you think that breaking your ___ means that you are at increased risk for breaking a bone in the future?’ were higher for those that reported a diagnosis of osteoporosis (OR 22.9, p<0.001).”
Osteoporotic Fracture Should be Viewed as a “Bone Attack”

“I broke my ___ bone after I accidentally slipped and fell. Anyone could have fractured.”

“No drug is absolutely safe; all drugs have side effects. Safe in this sense means that the benefits of the drug appear to outweigh the risk.”

FDA Consumer 2002;36(4):19-24
Osteonecrosis of the Jaw

Exposed bone in mandible or maxilla for ≥ 6-8 weeks, no prior XRT to area

Site of prior dental surgery
IV BP in cancer patient
Chemo, steroid use
Longer duration of BP

Risk in oral bisphosphonate:
1 in 10,000 - 100,000 pt-yrs


Atypical Femur Fracture

• Treat 1000 women with BP x 5 years
• Prevent 35-50 non-vertebral fractures and
• 50-115 vertebral fractures
• May see 5 atypical femur fractures

ASBMR Task Force, JBMR 2010
Atypical Femur Fracture Incidence

Kaiser Study: 1,835,116 patients, age >45 yrs
188,814 used bisphosphonate (tracked with internal pharmacy records)
142 patients with AFF
128 with bisphosphonate exposure (14 w/o)

<table>
<thead>
<tr>
<th>BP Duration (years)</th>
<th># Cases</th>
<th>Incidence (per 100,000/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14</td>
<td>0.3 (0.3-0.4)</td>
</tr>
<tr>
<td>0.1-1.9</td>
<td>10</td>
<td>1.8 (1.5-2.0)</td>
</tr>
<tr>
<td>2.0-3.9</td>
<td>25</td>
<td>13.6 (10.3-17.0)</td>
</tr>
<tr>
<td>4.0-5.9</td>
<td>27</td>
<td>16.1 (14.7-17.6)</td>
</tr>
<tr>
<td>6.0-7.9</td>
<td>30</td>
<td>38.9 (26.5-51.3)</td>
</tr>
<tr>
<td>8.0-9.9</td>
<td>25</td>
<td>113.1 (69.3-156.8)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>11</td>
<td>107.5 (48.1-166.9)</td>
</tr>
</tbody>
</table>

Dell, et. al JBMR 2012;27(12)

Typical Hip Fracture Incidence

<table>
<thead>
<tr>
<th>Hip Fracture Incidence in PLA (per 100,000 pt-yr)</th>
<th>RR Hip Fracture in Active Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>750</td>
</tr>
<tr>
<td>Zolendronate</td>
<td>833</td>
</tr>
<tr>
<td>Risedronate</td>
<td>1390</td>
</tr>
</tbody>
</table>

Lancet 1996;348(9041):1535-41
NEJM 2007;356(18):1809-22
NEJM 2001;344(5):333-40
Alendronate FIT Long-term Extension (FLEX)

- Enrolled participants from Fracture Intervention Trial on ~5 years ALE
- Re-randomization to continue ALE (n=672) vs. switch to PLA (n=437)
- ALE x 10 yrs vs. stopping after 5 yrs
  - Clinical spine fractures ↓55%
  - Non-spine fractures ↓50% with T-score ≤ -2.5 at start of FLEX

Black et al, JAMA 2006;296:2927-2938
Schwartz et al, J Bone Miner Res 2010;25:976-982
### Bisphosphonate Holidays

**For mild-moderate fracture risk, consider “drug holiday” after 4-5 years of stability**

**For high fracture risk, consider drug holiday for 1-2 years after 10 years of treatment**

**Follow DXA (and bone markers) during a drug holiday**

**Restart therapy**
- Fixed period of time: e.g. 1-2 years
- BMD falls significantly
- Bone turnover markers increase
- Fracture occurs

Watts, Endocrine Practice 2010

---

**Bisphosphonate Holidays**

- Osteoporosis (FN T-score ≤ -2.5) after 3-5 years of BP at highest risk for fracture and appear to benefit most from continuation of BP
- Prevalent vertebral fracture (FN T-score ≤ -2.0) may benefit from continuation of BP
- FN T-score > -2.0 have low risk for fracture and unlikely to benefit from continuation of BP

Black NEJM 2012;366;2051-2054