American College of Physicians
DC Chapter Scientific Meeting:
Osteoporosis

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Disclosures

• None
Outline

• Define osteoporosis, its prevalence and pathophysiology
• Define the risk factors and diagnostic criteria for osteoporosis
• Bone density testing interval
• Compare the advantages and disadvantages of treatments used for osteoporosis
• Examine key clinical data from recent clinical trials of osteoporosis treatment
Definition of Osteoporosis

- Current NIH definition: Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to increased risk of fracture\(^1\)
- Images from 3-D micro-CT bone scans\(^2\)

Osteoporosis: Prevalence

- Osteoporosis and low bone mass affect almost 54 million U.S. women and men >50
- 12 million Americans have osteoporosis; 80% of these cases are in women
- 2 million fractures in US each year
  - 1,500,000 spine; 260,000 hip; 250,000 wrist
  - 1/3 are hospitalized
  - Most common musculoskeletal condition requiring hospitalization in Medicare enrollees
  - Direct costs $12-$18 billion per year in 2002
1. The cycle of bone remodeling is carried out by osteoclasts and osteoblasts.

2. Bone remodeling is initiated by contraction of the lining cells and the recruitment of osteoclast precursors.

3. Precursors fuse to form multinucleated, active osteoclasts that mediate bone resorption.

4. Osteoclasts remove bone by acidification and proteolytic digestion.

5. Osteoblasts move in to cover the excavated area and secrete osteoid, which is eventually mineralized into new bone.
World Health Organization (WHO)
Osteoporosis Guidelines

T-Score

WHO, Guidelines for Preclinical Evaluation and Clinical Trials in Osteoporosis, 1998
BMD, Osteoporotic Fracture Rate, and Number of Women With Fractures in the National Osteoporosis Risk Assessment

Fracture Resistance Depends on Bone Strength

Reducing and stabilizing bone turnover and thereby increasing bone density are important in fracture risk reduction.

Increased bone turnover

- Vitamin D insufficiency increases bone turnover

- Decreased bone mass

  - Increased cortical porosity

  - Disrupted trabecular connectivity

  - Decreased mineralization

- Reduced bone strength/Increased fracture risk
Please answer the questions below to calculate the ten year probability of fracture with BMD.

**Questionnaire:**

1. Age (between 40-90 years) or Date of birth

   Age: 55

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

2. Sex

   - Male
   - Female

3. Weight (kg)

   56

4. Height (cm)

   165

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 more units per day

    - No
    - Yes

12. Femoral neck BMD

    T-score: -2.6

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**BMI: 20.5**

The ten year probability of fracture (%) with BMD

- Major osteoporotic: 11
- Hip fracture: 2.10

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Weight Conversion:

- pound: 125

  125 pound = 56.7 kg

Height Conversion:

- inch: 65

  65 inch = 165.1 cm
FRAX - WHO Fracture Risk Assessment Tool

Country: US(Caucasian)  Name / ID: 

Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: 55  Date of birth:  
   Y:  M:  D:  

2. Sex  Male  Female

3. Weight (kg)  56

4. Height (cm)  165

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 more units per day  No  Yes

12. Femoral neck BMD  
   T-score  -2.6

BMI  20.5
The ten year probability of fracture (%) with BMD

- Major osteoporotic  20
- Hip fracture  3.1

Weight Conversion:
pound: 125  convert
125 pound = 56.7 kg

Height Conversion:
inches: 65  convert
65 inch = 165.1 cm

http://www.shef.ac.uk/FRAX/index.htm

Please answer the questions below to calculate the ten year probability of fracture with BMD.
Trabecular Bone Score (TBS): Novel Assessment of Fracture Risk

- TBS is a textural index that evaluates pixel gray-level variations in the lumbar spine DXA image, providing an indirect index of trabecular microarchitecture.

- High TBS value is associated with better bone structure, whereas low TBS values indicate worse bone structure.

Prospective studies have confirmed TBS predicts fracture risk.

Each SD decline in TBS confers 35% increase in fracture risk.

Fracture prediction improved when BMD and TBS used in combination compared to either alone.

Determine how the BMD testing interval relates to the timing of the transition from normal BMD or osteopenia to the development of osteoporosis before a hip or clinical vertebral fracture occurs.

4957 women, 67 years of age or older, who did not have osteoporosis at baseline and who were followed longitudinally for up to 15 years in the SOF.

BMD testing interval was defined as the estimated time during which osteoporosis developed in 10% of women before they had a hip or clinical vertebral fracture.
Unadjusted Cumulative Incidence of Osteoporosis According to Baseline T-Score

- Advanced osteopenia: T score, -2.00 to -2.49 (N=1351)
- Moderate osteopenia: T score, -1.50 to -1.99 (N=1478)
- Mild osteopenia: T score, -1.01 to -1.49 (N=1386)
- Normal BMD: T score, -1.00 or higher (N=1255)

Table 2. Interval between Baseline Testing and the Development of Osteoporosis in 10% of Study Participants, According to the Result of Baseline Testing.*

<table>
<thead>
<tr>
<th>Result of Baseline Test</th>
<th>Interval between Baseline Testing and Development of Osteoporosis†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
<td>no. of years (95% CI)</td>
</tr>
<tr>
<td>Normal BMD</td>
<td>17.4 (11.5–26.3)</td>
</tr>
<tr>
<td>Mild osteopenia</td>
<td>16.5 (13.6–20.2)</td>
</tr>
<tr>
<td>Moderate osteopenia</td>
<td>4.6 (4.1–5.1)</td>
</tr>
<tr>
<td>Advanced osteopenia</td>
<td>1.0 (0.8–1.1)</td>
</tr>
</tbody>
</table>

* Osteoporosis was defined as a T score of −2.50 or lower at the femoral neck or total hip. Normal BMD was defined as a T score of −1.00 or higher, mild osteopenia as a T score between −1.01 and −1.49, moderate osteopenia as a T score between −1.50 and −1.99, and advanced osteopenia as a T score between −2.00 and −2.49.
Antiresorptive Therapy for Osteoporosis
Osteoporosis: Treatment Goals and Strategies

• Treatment Goals
  ➢ Fracture prevention is the primary objective
  ➢ Provide early fracture benefit and sustained protection
  ➢ Maintain bone strength

• Treatment Strategies

Nonpharmacologic
  • Dietary+supplementation
    ➢ Calcium: IOM recommendations
      • 1000 mg daily <50 years of age
      • 1200 mg daily >50 years of age
    ➢ Vitamin D: IOM recommendations
      • 600 units daily <70 years of age
      • 800 units daily >70 years of age
  • Physical exercise

Pharmacologic
  Bisphosphonates
    • Risedronate
    • Alendronate
    • Ibandronate
    • Zoledronic acid
  Anabolic
    • Teriparatide
  Other
    • Hormone therapy
    • Raloxifene
    • Calcitonin
    • Denosumab
## Medications for Postmenopausal Osteoporosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reduction in Fracture Risk</th>
<th>Side Effects</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate, bisphosphonate, oral</td>
<td>Vertebral, non-vertebral, hip</td>
<td>Esophagitis, myalgias, ONJ, atypical fractures</td>
<td>Treatment &amp; prevention</td>
</tr>
<tr>
<td>Risedronate (oral)</td>
<td>Vertebral, non-vertebral, hip</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Ibandronate (oral/IV)</td>
<td>Vertebral</td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td>Zoledronic acid (IV)</td>
<td>Vertebral, non-vertebral, hip</td>
<td>Fever, myalgias, ONJ, atypical fractures</td>
<td>Same</td>
</tr>
<tr>
<td>Raloxifene, SERM, oral</td>
<td>Vertebral</td>
<td>Hot flashes, DVT, nausea, leg cramps</td>
<td>Treatment &amp; prevention</td>
</tr>
<tr>
<td>PTH (1-34), anabolic, SQ</td>
<td>Vertebral, non-vertebral</td>
<td>Hypercalcemia, nausea, leg cramps</td>
<td>Treatment</td>
</tr>
<tr>
<td>Calcitonin (nasal)</td>
<td>Vertebral</td>
<td>Nasal stuffiness, nausea</td>
<td>Treatment</td>
</tr>
<tr>
<td>Estrogens (oral, transdermal)</td>
<td>Vertebral, non-vertebral</td>
<td>DVT,</td>
<td>Prevention</td>
</tr>
</tbody>
</table>
HORIZON Pivotal Fracture Trial Overview

• 3-year, randomized, double-blind, placebo-controlled trial
• Annual infusion of zoledronic acid 5 mg or placebo
• Calcium 1000–1500 mg/d; vitamin D 400–1200 IU/d
**Morphometric Vertebral Fracture Results (Stratum I)**

Relative risk reductions (95% confidence intervals) vs placebo

*P < .0001, based on logistic regression with treatment and baseline fracture status in the model using log-likelihood type approach

Cumulative Risk of Hip Fracture (Strata I + II)

- Placebo (n = 3861)
- ZOL 5 mg (n = 3875)

Relative risk reduction (95% confidence interval) vs placebo:
P = .0032

40% (15%, 57%)

HORIZON Recurrent Fracture Trial

- Double blind, randomized, placebo-controlled trial
- Annual infusion of zoledronic acid 5 mg or placebo
- Calcium 1000-1500 mg/d; vitamin D 800-1200 IU/d
# Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Zoledronic acid</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture - # (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>139 (13.9)</td>
<td>92 (8)</td>
<td>0.65 (0.5-0.84)</td>
<td>0.001</td>
</tr>
<tr>
<td>Nonvertebral</td>
<td>107 (10.7)</td>
<td>79 (7.6)</td>
<td>0.73 (0.55-0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hip</td>
<td>33 (3.5)</td>
<td>23 (2)</td>
<td>0.70 (0.41-1.19)</td>
<td>0.18</td>
</tr>
<tr>
<td>Vertebral</td>
<td>39 (3.8)</td>
<td>21 (1.7)</td>
<td>0.54 (0.32-0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death - # (%)</td>
<td>141 (13.3)</td>
<td>101 (9.6)</td>
<td>0.72 (0.56-0.93)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Bone Safety/Adverse Events with Bisphosphonates

- GI side effects well described
- Atrial fibrillation (discounted)
- Esophageal cancer (very weak association)

**Osteonecrosis of the jaw**
- Exposed bone that does not heal for 6 weeks or more
- Increased risk with recent extraction or dental surgery
- Increased risk with poor dental hygiene
- Increased risk with underlying malignancy and/or radiation exposure to jaw region
- Estimated incidence 1/10,000-1/250,000 with oral bisphosphonates
- Higher risk in those receiving monthly IV bisphosphonates (~4-6% incidence)
# Risk of Atypical Femoral Fracture Associated with Bisphosphonate Use

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Women</th>
<th>Cases of Atypical Fracture</th>
<th>Age-Adjusted Relative Risk (95% CI)</th>
<th>Age-Adjusted Absolute Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of Atypical Fracture</td>
<td>Crude Incidence</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cases</td>
<td>no./10,000 patient-yr</td>
<td></td>
</tr>
<tr>
<td>Bisphosphonate use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1, 437,820</td>
<td>13</td>
<td>0.09</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Ever</td>
<td>83,311</td>
<td>46</td>
<td>5.5</td>
<td>47.3 (25.6–87.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0005 (0.0004–0.0007)</td>
</tr>
<tr>
<td>Duration of use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.0 yr</td>
<td>15,672</td>
<td>3</td>
<td>1.9</td>
<td>18.4 (5.3–64.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0002 (0.0000–0.0004)</td>
</tr>
<tr>
<td>1.0–1.9 yr</td>
<td>21,406</td>
<td>4</td>
<td>1.9</td>
<td>17.0 (5.7–50.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0002 (0.0000–0.0004)</td>
</tr>
<tr>
<td>≥2.0 yr</td>
<td>46,233</td>
<td>39</td>
<td>8.4</td>
<td>67.0 (35.8–125.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0008 (0.0006–0.0011)</td>
</tr>
<tr>
<td>Time since last use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.0 yr</td>
<td>83,311</td>
<td>42</td>
<td>5.0</td>
<td>42.9 (22.9–80.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0005 (0.0004–0.0007)</td>
</tr>
<tr>
<td>1.0–1.9 yr</td>
<td>70,036</td>
<td>1</td>
<td>0.1</td>
<td>3.5 (1.0–11.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001 (0.0000–0.0000)</td>
</tr>
<tr>
<td>≥2.0 yr</td>
<td>75,583</td>
<td>3</td>
<td>0.4</td>
<td>3.2 (1.0–10.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001 (0.0000–0.0001)</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval.
• Randomized, double blind, placebo-controlled trial
• Denosumab 60 mg SQ twice yearly or placebo
• Calcium 1000 mg/d; vitamin D 400-800 IU/d
Bone Resorption Dependent on RANK Ligand - Primary Cytokine Mediator of Osteoclast Activity

RANK Ligand Is Essential for Osteoclast Formation, Function, and Survival

- Growth Factors
- Hormones
- Cytokines

RANKL → RANK → Pre-Fusion Osteoclast → Multinucleated Osteoclast → Mature Osteoclast

CFU-M = colony forming unit macrophage

Osteoprotegerin (OPG) Modulates Effects of RANKL and Decreases Bone Resorption by Acting as Decoy Receptor

Alterations of the RANK Ligand/OPG ratio are critical in the pathogenesis of bone diseases that result from increased bone resorption\(^1\)\(^-\)\(^3\)

- **RANKL**
  - Promotes OC activation

- **OPG**
  - Inhibits OC activation

Osteoclast Activity


OC = osteoclast
Mechanism of Action for Denosumab

Osteoclast Activation
- Denosumab
- OPG
- RANKL
- RANK

Growth Factors, Hormones, Cytokines

Osteoclast Formation, Function and Survival Inhibited by Denosumab
- CFU-M
- Pre-Fusion Osteoclast
- Multinucleated Osteoclast
- Mature Osteoclast

Denosumab: Changes in Bone Mineral Density and Fracture Rates

Anabolic Therapy for Osteoporosis
EFFECT OF PARATHYROID HORMONE (1-34) ON FRACTURES AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

ROBERT M. NEER, CLAUDE D. ARNAUD, JOSE R. ZANCHETTA, RICHARD PRINCE, GREGORY A. GAICH, JEAN-YVES REGINSTER, ANTHONY B. HOOSMAN, ERIK F. ERIKSEN, SOPHIA ISH-SHALOM, HARRY K. GENANT, OUHONG WANG, AND BRUCE H. MITLAK

New Vertebral Fractures (%)

Vertebral Fractures at 21 Months

* p≤ 0.001 for comparison with PBO
NEJM, 344, 19: 1436
EFFECT OF PARATHYROID HORMONE (1-34) ON FRACTURES AND BONE MINERAL DENSITY IN POSTMENOPAUSAL WOMEN WITH OSTEOPOROSIS

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Nonvertebral Fractures at 19 Months

* p=0.04 for comparison with PBO
** p=0.02 for comparison with PBO
§ p=0.01 for comparison with PBO
NEJM, 344, 19: 1437
Combination Anabolic and Antiresorptive Therapy: Teriparatide and Denosumab in Postmenopausal Osteoporosis

- PTH monotherapy had greater BMD gains than combination ALN or ALN alone
- BMD change PTH plus ZOL equivalent to PTH or ZOL alone
- PTH plus denosumab increased BMD more than PTH or denosumab alone with less effect on bone formation markers
- No fracture endpoint

Lancet. 2013 Jul 6;382(9886):50-6
Conclusions

• Osteoporosis is a condition resulting in an increased risk of skeletal fractures due to a reduction in the density and strength of bone

• Bisphosphonates and monoclonal antibodies against RANKL are the mainstays of pharmacologic treatment for osteoporosis

• Osteoporosis develops in <10% of older, postmenopausal women during screening intervals set 5 years apart for moderate osteopenia (−1.50 to −1.99) and 1 year for advanced osteopenia (−2.00 to −2.49)

• DXA may never need to be repeated for those with T scores >−1.5 at baseline assessment