Osteoporosis and Metabolic Bone Diseases

Mishaela R. Rubin, MD
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The Three Ages of Women
Gustav Klimt
1905
Lecture Outline

Osteoporosis
Definition and Epidemiology
Pathophysiology
Diagnosis
Treatment

Other Metabolic Bone Diseases
Osteoporosis: Definition

Over 2 million fractures/year in men and women over age 50

Osteoporosis: Prevalence and Epidemiology

Approximately ½ of women and ¼ of men > 50 yrs will suffer an osteoporosis-related fracture in their lifetime

Osteoporotic Fractures and Incidence

Burge et al JBMR 2007, 465-475
Cost of Osteoporosis

• $17 billion in direct medical costs
• >400,000 hospital admission
• 2.5 million physician visits
• >180,000 nursing home admissions

Osteoporotic fractures: Comparison with other diseases

- Annual incidence x 1000
- 1500000 annual incidence all ages
- 29 hip fractures
- 250000 forearm
- 250000 other sites
- 750000 vertebral
- 513000 annual estimate women 29+—Heart Attack
- 228000 annual estimate women 30+—Stroke
- 184300 1996 new cases, all ages—Breast Cancer
- 1530000 annual incidence all ages—American Heart Association, 1996
- 317000 annual estimate women 30+—American Cancer Society, 1996
- Riggs BL & Melton LJ 3rd, Bone, 1995;17(5 suppl):S505-S511S
Morbidity After Hip Fractures

- Death within one year: 20%
- Permanent disability: 30%
- Unable to walk independently: 40%
- Unable to carry out at least one independent activity of daily living: 80%

Cooper C, Am J Med, 1997;103(2A):12S-17S

Morbidity After Vertebral Fractures

- Back pain
- Loss of height
- Deformity (kyphosis, protuberant abdomen)
- Reduced pulmonary function
- Diminished quality of life:
  loss of self-esteem, distorted body image, dependence on narcotic analgesics, sleep disorder, depression, loss of independence
Osteoporosis Affects Men Also

National Osteoporosis Foundation, 2002

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Other Metabolic Bone Diseases
Bone: the Ultimate Biomaterial

Bone Remodeling Sequence in Healthy Subjects

- LC = Lining Cells
- CL = Cement Line
- OS = Osteoid
- BRU = Bone Remodeling Unit
Bone Remodeling Throughout the Life Cycle
Peak Bone Mass

Pathogenesis of Osteoporotic Fractures

- Aging
- Menopause
- Other Risk Factors
- Increased Bone Loss
- Low Peak Bone Mass
- Propensity To Fall
- Poor Bone Quality

Low Bone Density

FRACTURES
Osteoporosis: Quantity and Quality

A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture

NIH Consensus Development Conference on Osteoporosis, 2000

Determinants of Bone Strength

Bone strength

Bone density

Other bone qualities

- Rate of turnover
- Microarchitecture
- Bone size and shape
- Damage accumulation
- Mineralization
- Matrix quality
Comparison of Microarchitecture in Normal and Osteoporotic Bone

Normal

Osteoporotic

How Bone is Lost is Important

Osteoporotic

Young Normal
Lifestyle Risk Factors for Osteoporosis

- Low calcium intake
- Vitamin D insufficinency
- High caffeine intake
- Alcohol
- Smoking
- Falling
- Immobilization
- Thinness

Secondary Osteoporosis

Endocrine
- Hyperparathyroidism
- Hyperthyroidism
- Hypogonadism
- Cushing Syndrome
- Diabetes Mellitus type 1

Nutritional
- Vitamin D deficiency
- Malabsorption syndromes

Drug-induced
- Glucocorticoids
- Anticonvulsants

Immobilization
- Rheumatoid Arthritis
- Myeloma

Others
Medications Associated With Osteoporosis

- Glucocorticoids
- Cyclosporine
- Cytotoxic drugs
- Anticonvulsants
- Excessive thyroid hormone
- Heparin
- GnRH antagonists
- Progestin only birth control
- Aromatase Inhibitors

Glucocorticoids Cause Bone Loss by Multiple Mechanisms

- Matrix synthesis
- Number and function of osteoblasts
- LH/FSH
- Sex steroids

Consequences:
- early ↑ resorption
- profound ↓ formation
- bone loss

↑ Ca++ excretion
↓ Ca++ absorption
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Bone Density:
Dual energy X-ray absorptiometry (DXA)

- Gold standard for bone density measurement
- Measures central sites: spine and hip
- Extensive epidemiologic data
- Correlation with bone strength in-vitro
- Safe
- Correlates with fracture risk
BMD by DXA

- **BMD** in g/cm² - raw bone density

- **T-score**: Compared to "Young normal" adults (at peak bone mass) number of standard deviations below the mean of race and gender matched population

- **Z-score**: SDs from age-matched mean
**WHO Criteria for Osteoporosis in Women**

<table>
<thead>
<tr>
<th>T-Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>-1 and above</td>
</tr>
<tr>
<td>Low bone mass</td>
<td>-1 to -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>&lt; -2.5</td>
</tr>
<tr>
<td>Established osteoporosis</td>
<td>&lt; -2.5 and one or more fractures</td>
</tr>
</tbody>
</table>

Kanis JA et al, J Bone Miner Res, 1994;9:1137-1141

**Who Should Have a Bone Density Test: Screening Guidelines**

- Women ≥ 65 and men ≥ 70
- Postmenopausal women with fragility fracture
- Women and men on or starting steroids
- Postmenopausal women and men <70 with risk factors:
  - weight <127 lbs
  - early menopause
  - smoking
  - family history of fracture
  - medical causes
What about the patient whose bone density is in the osteopenic range?

<table>
<thead>
<tr>
<th>T-score</th>
<th>Therapy Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2.5 or below</td>
<td>High risk Treat</td>
</tr>
<tr>
<td>-1.5 to −2.5</td>
<td>Intermediate risk How do we regard these patients?</td>
</tr>
<tr>
<td>Above −1.5</td>
<td>Low risk General preventive measures</td>
</tr>
</tbody>
</table>

Fracture Rate Ratio Within One Year

By T-Score from Peripheral Devices

"Osteoporotic" Fracture

<table>
<thead>
<tr>
<th>T-score</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;−1.0</td>
<td>1.00</td>
</tr>
<tr>
<td>−1.0 to −2.5</td>
<td>1.80*</td>
</tr>
<tr>
<td>≤−2.5</td>
<td>4.03</td>
</tr>
</tbody>
</table>

Hip Fractures

<table>
<thead>
<tr>
<th>T-score</th>
<th>Relative Risk</th>
</tr>
</thead>
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<tr>
<td>&gt;−1.0</td>
<td>1.00</td>
</tr>
<tr>
<td>−1.0 to −2.5</td>
<td>2.70†</td>
</tr>
<tr>
<td>≤−2.5</td>
<td>8.90</td>
</tr>
</tbody>
</table>

N = 212,000

*CI = 1.49-2.18
†CI = 3.59-4.53

Postmenopausal Women

### Population BMD Distribution, Fracture Rates, and Number of Women With Fractures

![Graph showing BMD distribution, fracture rates, and number of women with fractures.]


### What about the patient whose bone density is in the osteopenic range?

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<tr>
<td>-2.5 or below</td>
<td>High risk</td>
</tr>
<tr>
<td></td>
<td>Treat</td>
</tr>
<tr>
<td>-1.5 to -2.5</td>
<td><strong>Intermediate risk</strong></td>
</tr>
<tr>
<td></td>
<td>Treatment is needed if other risk factors are present</td>
</tr>
<tr>
<td></td>
<td>Fractures</td>
</tr>
<tr>
<td></td>
<td>F. Hx of prior fx</td>
</tr>
<tr>
<td></td>
<td>Age (&gt;70)</td>
</tr>
<tr>
<td></td>
<td>Steroids</td>
</tr>
<tr>
<td>Above -1.5</td>
<td><strong>Low risk</strong></td>
</tr>
<tr>
<td></td>
<td>General preventive measures</td>
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Other factors that contribute to fracture risk

Age
Prior fracture

10-Year Fracture Risk: Age and BMD

For a given BMD, risk increases with age

Other factors that contribute to fracture risk

Age
Prior fracture

The Importance of One Vertebral Fracture as a Risk Factor for Another

*\(p<0.05\), vs. patients without prevalent vertebral fracture (increased risk of 12 times)

Lindsay R et al, JAMA 2001;285:320-323
How can we factor in risk factors and BMD to predict fracture risk?
FRAX WHO Risk Assessment Tool

• Developed by WHO to evaluate fracture risk

• Based on models that integrate the risks associated with clinical risk factors and BMD at the femoral neck

• Computer-driven:
  http://www.shef.ac.uk/FRAX/index.htm

• FRAX algorithms give the 10-yr probability of fracture
  10-yr probability of hip fracture
  10-yr probability of a major osteoporotic fracture
  (clinical spine, forearm, hip or shoulder fracture)

FRAX

1. Age  
2. Ht  
3. Wt  
4. Gender  
5. Previous Fracture  
6. Parent Fractured Hip  
7. Current Tobacco  
8. Glucocorticoid use  
9. Rheumatoid Arthritis  
10. Secondary Osteoporosis  
11. Alcohol 3 or more /day  
12. Femoral Neck T-score

Treatment recommended if 10 year probability of:

Major Osteoporotic Fracture > 20%
Hip Fracture > 3%
Limitations of FRAX

• Lacks detail on some clinical risk factors
• Relevant only for untreated patients
• Does not replace clinical judgment

Who Should Be Treated?

• Hip or vertebral fractures
• BMD T-score ≤ -2.5 at the femoral neck or spine
• BMD T-score > -1.0 and < -2.5 at the femoral neck or spine
  AND
  a 10-year hip fracture probability ≥ 3% or major osteoporosis-related fracture probability ≥ 20%
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Universal Recommendations

- weight-bearing exercise
- avoidance of smoking and alcohol
- calcium (1,200 mg/d) and vitamin D (800-1,000 IU/d)
Calcium

- 1200-1500 mg daily in divided doses (only 500-600 mg absorbed at a time) in both diet and supplements

- Calcium Carbonate
  - Take with food (need acid for absorption)
  - May cause gas, bloating
  - Less expensive

- Calcium Citrate
  - Take with or without food
  - Less GI upset
  - Slightly more expensive

Vitamin D

- At least 800 IU daily recommended

- Vitamin D3 (cholecalciferol) preferred

- Serum level of 25 (OH) vitamin D is a measure of vitamin D stores
Vitamin D Metabolism

Storage Form: Index of Vitamin D Sufficiency or Insufficiency

Role of Vitamin D

Essential for absorption of calcium from the GI tract

Calcitriol (1,25-dihydroxyvitamin D) is the biologically active form

Monitor serum 25-hydroxyvitamin D Should be > 30 ng/ml
25 (OH) Vitamin D
What is the lower limit of normal?

- > 10 ng/ml (crossed out)
- > 20 ng/ml
- > 30 ng/ml

Vitamin D Deficiency is Epidemic

Other Metabolic Bone Diseases

Osteomalacia
Renal osteodystrophy
Osteomalacia

Extra Osteoid

Rickets
The 25-hydroxyvitamin D Continuum

0 10 20 30 40 50 60 ng/ml

normal

osteoporosis

rickets/osteomalacia

Pathogenesis of Secondary Hyperparathyroidism and Renal Osteodystrophy

↑ phosphate
↓ calcitriol
↓ calcium
↑ PTH
Types of Renal Bone Disease

- Osteitis fibrosa cystica
- Osteomalacia
- Adynamic bone disease

Osteoporosis in 2010
Advances in Awareness, Diagnosis and Therapy