Skeletal Manifestations
of Metabolic Bone Disease

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The Three
Ages of
Women
Gustav Klimt
1905
Lecture Outline

Osteoporosis
- epidemiology
- diagnosis
- secondary causes

Osteomalacia

Renal Osteodystrophy

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Osteomalacia

Renal Osteodystrophy
Osteoporosis: Prevalence and Epidemiology

- **Osteoporosis**
  - 8 million women and 2 million men

- **Low bone mass**
  - Additional 34 million

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

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Osteoporotic Fractures and Incidence

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

- Hip
- Vertebral
- Wrist
- Other sites

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

American Heart Association, 1996
American Cancer Society, 1996
Riggs BL & Melton LJ 3rd, Bone, 1995;17(S suppl):505S-511S
Projected number of osteoporotic hip fractures worldwide

Total number of hip fractures:
1950 = 1.66 million
2050 = 6.26 million

Estimated no of hip fractures: (1000s)

Adapted from Cooper C et al, Osteoporosis Int, 1992; 2:285-289

All fractures are associated with morbidity

One year after a hip fracture:
- 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

- Men: 10-12,000,000
- Women: 23-32,000,000

National Osteoporosis Foundation, 2002
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Osteoporosis
epidemiology
diagnosis
secondary causes

Osteomalacia

Renal Osteodystrophy

Osteoporosis: Identifying the Problem

Healthy bone

Osteoporotic bone

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

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

Specialist will feed into machine
Interpretation of bone mineral density (BMD)

BMD of patient A is 0.72 g/cm²

-1 SD

BMD score: -1.0 (age-dependent)

-2.5 SD

BMD score: -2.5 (age-independent)

Age (yr)

59

0.72

BMD g/cm²
World Health Organization Osteoporosis Guidelines

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
• Postmenopausal women with fragility fracture
• Women and men on or starting steroids
• Postmenopausal women <65 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&lt;br&gt;Treat</td>
</tr>
</tbody>
</table>
| -1.5 to −2.5  | Intermediate risk<br>How do we regard these<br>p
                  | patients?                                     |
| Above −1.5    | Low risk<br>General preventive measures      |
**Fracture Rate Ratio Within One Year**
By T-Score from Peripheral Devices

Postmenopausal Women

<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>

Fracture Rate Ratio Within One Year

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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>

*(CI = 1.49-2.18)*
†(CI = 3.59-4.53)
*(CI = 2.14-3.40)*
†(CI = 6.84-11.57)


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

<table>
<thead>
<tr>
<th>BMD T-Scores (Peripheral)</th>
<th>Fracture Rate</th>
<th>No. of Women With Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;-1.0</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>1.0 to 0.5</td>
<td>10</td>
<td>350</td>
</tr>
<tr>
<td>0.5 to 0.0</td>
<td>15</td>
<td>300</td>
</tr>
<tr>
<td>0.5 to -1.0</td>
<td>20</td>
<td>250</td>
</tr>
<tr>
<td>0.0 to -0.5</td>
<td>25</td>
<td>200</td>
</tr>
<tr>
<td>-0.5 to -1.0</td>
<td>30</td>
<td>150</td>
</tr>
<tr>
<td>-1.0 to -1.5</td>
<td>35</td>
<td>100</td>
</tr>
<tr>
<td>-1.5 to -2.0</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>-2.0 to -2.5</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>-2.5 to -3.0</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>-3.0 to -3.5</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td>&lt; -3.5</td>
<td>60</td>
<td>0</td>
</tr>
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### What about the patient whose bone density is in the osteopenic range?

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</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>Above –1.5</td>
<td><strong>Low risk</strong></td>
</tr>
<tr>
<td></td>
<td><strong>General preventive measures</strong></td>
</tr>
</tbody>
</table>

### Other factors that contribute to fracture risk

- Age
- Prior fracture
For a given BMD, risk increases with age.

10-Year Fracture Risk: Age and BMD

Fracture Risk with Aging in Women


Wasnich RD, Osteoporos Int 1997;7 Suppl 3:68-72
Fracture Risk with Aging in Men

Age (Years)

Vertebrae
Hip
Wrist

Annual incidence per 100,000 men

Other factors that contribute to fracture risk

Age
Prior fracture

Wasnich RD, Osteoporos Int 1997;7 Suppl 3:86-7
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

The osteoporotic fracture does not often lead to diagnosis or therapy

Postmenopausal Women with Distal Radial Fracture

Siris et al. J Clin Endocrinol Metab 88: 2003
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Renal Osteodystrophy

The Causes of Low Bone Mass

Primary osteoporosis
(postmenopausal or age-related)

Secondary osteoporosis (caused wholly or in part by other diseases or medications such as glucocorticoids)

Other bone diseases
- osteogenesis imperfecta
- osteomalacia
Secondary Osteoporosis

Endocrine | Nutritional | Drug-induced | Immobilization | Others

Hyperparathyroidism
Hyperthyroidism
Hypogonadism
Cushing Syndrome
Diabetes Mellitus type 1

Glucocorticoids

Anticonvulsants
Rheumatoid Arthritis
Myeloma

Vitamin D deficiency
Malabsorption syndromes

Glucocorticoids Cause Bone Loss by Multiple Mechanisms

↓ Matrix synthesis

kidney ↑ Ca++ excretion

↓ Number and function of osteoblasts

bone Glucocorticoids gut ↓ Ca++ absorption

↓ LH/FSH
↓ Sex steroids

pituitary

Consequences:
early ↑ resorption
profound ↓ formation
bone loss

bone loss
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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
The 25-hydroxyvitamin D Continuum

- Osteomalacia
- Rickets
- Normal
- Osteoporosis

Osteomalacia and Rickets
Vitamin D Deficiency is Epidemic

Vitamin D Intakes

50 and older need 800-1,000 IU/d

Under 50 need 400-800 IU/d

Vitamin D is synthesized in skin on exposure to sunlight

Sunscreen blocks production of vitamin D in the skin
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Pathogenesis of Secondary Hyperparathyroidism and Renal Osteodystrophy

- $\uparrow$ phos
- $\downarrow$ calcitriol
- Resistance of bone to PTH
- $\downarrow$ calcium
- $\uparrow$ PTH
- $\downarrow$ Ca sensor
- $\downarrow$ Calcitriol receptors
Osteoporosis in 2008
Advances in Awareness, Diagnosis and Therapy