Normal and Abnormal Skeletal Metabolism; Pathophysiology of Osteoporosis

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The Three Ages of Women
Gustav Klimt
1905
Lecture Outline

Osteoporosis
  Epidemiology
  Pathophysiology
  Diagnosis
  Secondary causes

Osteomalacia

Osteoporosis: Definition

![Normal bone matrix and Osteoporosis comparison](image)
Lecture Outline

Osteoporosis

Epidemiology
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Osteomalacia

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
Osteoporotic Fractures and Incidence

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

Cost of Osteoporosis

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

Burge et al JBMR 2007, 465-475
Osteoporotic fractures: Comparison with other diseases

- Annual incidence x 1000
  - Osteoporotic Fractures
  - Heart Attack
  - Stroke
  - Breast Cancer

- Annual estimate women 20+
- Annual estimate women 30+
- 1996 new cases, all ages

- 1500000
- 513000
- 184300
- 228000

- 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)

American Heart Association, 1996
American Cancer Society, 1996
Riggs BL & Melton LJ 3rd, Bone, 1995;17(suppl):S05-S011S

Projected to reach 3.250 million in Asia by 2050

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

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

![Osteoporosis Affects Men Also](image)

National Osteoporosis Foundation, 2002

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Osteomalacia
Bone: the Ultimate Biomaterial

Bone Remodeling Sequence in Healthy Subjects

- **Oc**: Precursor
- **Osteoclast**
- **Mononuclear Cells**
- **Ob**: Precursors
- **Osteoblast**

**LC** = Lining Cells  **CL** = Cement Line  **OS** = Osteoid  **BRU** = Bone Remodeling Unit

- **3 WEEKS**
- **3 MONTHS**
Bone Remodeling Throughout the Life Cycle

Multiple Factors in the Pathogenesis of Fractures

- Inadequate peak bone mass
- Low bone density
- Heredity
- Menopause
- Increased bone loss
- Aging
- Trauma
- Fractures
Lecture Outline

**Osteoporosis**
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**Osteomalacia**

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
Strength of osteoporotic bone is impaired by:
- Loss of bone mass
- Reduction in bone quality:
  - Loss of horizontal struts
  - Loss of connectivity
  - Conversion of trabecular plates to rods
  - Resorption pits are "stress concentrators"
  - Unfavorable geometry
Comparison of Microarchitecture in Normal and Osteoporotic Bone

Resorption Cavities are Mechanical Stress Concentrators

The deeper resorption cavities in postmenopausal bone act to concentrate mechanical stress. Bone will tend to fracture at such sites, as will the cane at right.
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

Relationship Between BMD and Relative Risk of Fracture
Interpretation of bone mineral density (BMD)

BMD of patient A is 0.72 g/cm²
-1.0 (age-dependent)
-2.5 (age-independent)

BMD of patient A is 0.72 g/cm²

World Health Organization Osteoporosis Guidelines

Osteopenia

Osteoporosis

Normal

Peak bone mass

T-score

-3 -2.5 -2 -1 0 +1 +2 +3

3% 16% 50% 84% 97%
**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</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>
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</tr>
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<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

Postmenopausal Women

N = 212,000

* (CI = 1.49-2.18) † (CI = 3.59-4.53)

Hip Fractures

* (CI = 2.14-3.40) † (CI = 6.84-11.57)

Population 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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<td></td>
<td>Treat</td>
</tr>
<tr>
<td>-1.5 to –2.5</td>
<td>Intermediate risk</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>Low risk</td>
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<td></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
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

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)
Limitations of FRAX®

- Does not accommodate all known risk factors:
  - Falls, biochemical markers, QUS, etc.
- Lacks detail on some risk factors:
  - Dose response effects of glucocorticoids, smoking, prior fracture, etc.
- Depends on adequacy of epidemiological information
- Limited country models available
- Model relevant only for untreated patients
- Does not replace clinical judgment

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Osteomalacia
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
Glucocorticoids Cause Bone Loss by Multiple Mechanisms

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

Glucocorticoids

- ↑ Ca++ excretion
- ↓ Ca++ absorption

Consequences:
- Early ↑ resorption
- Profound ↓ formation
- Bone loss

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Osteomalacia
Osteomalacia

Extra Osteoid

Rickets
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

0 10 20 30 40 50 60 ng/ml

rickets/osteomalacia  
normal  
osteoporosis

26
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
Osteoporosis in 2010
Advances in Awareness, Diagnosis and Therapy