Osteoporosis

Prof René Rizzoli M.D.

Division of bone diseases
WHO collaborating center for osteoporosis prevention
Department of rehabilitation and geriatrics
University hospitals
Geneva, Switzerland
Osteoporosis Definition

A systemic skeletal disease characterized by low bone mass and microarchitectural deterioration, with a consequent increase in bone fragility with susceptibility to fracture.

Osteoporosis: a 2-Stage Disease

- With
- Without Fracture
Epidemiology
Fractures by Age and Gender

## Lifetime risk of fragility fracture in the Swedish population at the age of 50 years (%)

<table>
<thead>
<tr>
<th>Location</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal femur</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>Distal forearm</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Vertebral (clinical)</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Proximal Humerus</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Any</td>
<td>46 %</td>
<td>22 %</td>
</tr>
</tbody>
</table>

From Kanis et al 2000
Osteoporotic Fractures in Women: Comparison With Other Diseases

- **Annual incidence all ages**: 1,500,000
- **Annual estimate women 29+**: 228,000
- **Annual estimate women 30+**: 184,300
- **1996 new cases, all ages**: 750,000

**Vertebral fractures**: 250,000
**Hip fractures**: 250,000
**Forearm fractures**: 250,000
**Other site fractures**: 250,000

SWITZERLAND 2000, 2025 and 2050

Source: U.S. Census Bureau, International Data Base.
Projected burden of osteoporotic hip fractures worldwide

Number of hip fractures: **1990: 1.66 million; 2050: 6.26 million**

Adapted from Cooper C., Melton U, *Osteoporosis Int* 2:285-289, 1992
If the prevalence of hip fracture continues to rise at current rates, it may well be that in the next few decades, orthopaedists will do little else but treat this problem.

Degree of dependence

Normal aging

Hip fracture

Vertebral fracture

Forearm fracture

Age (years)
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 Results in More Cost Than Many Other Diseases

- Annual cost of acute hospitalization in Switzerland in 1992: 600 million Swiss francs (US$350 million)*
  - Number of bed days (men and women)
    - 701,000 for osteoporosis
    - 891,000 for COPD
    - 533,000 for stroke
    - 328,000 for myocardial infarction
    - 201,000 for breast cancer

**Mortality after Major Types of Osteoporotic Fracture in Men and Women: an Observational Study**

Center et al, Lancet 1999

5 - Year Prospective Cohort Study

<table>
<thead>
<tr>
<th>Fracture</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal Femur</td>
<td>2.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Vertebral</td>
<td>1.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Other Major</td>
<td>1.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Other Minor</td>
<td>0.8</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Survival after Hip Fracture

Trombetti et al, Osteoporos Int 2002

- Expected survival in the general population
- Hip fractured Women
- Hip fractured Men

Survival probability vs Time after hip fracture (years)
Risk of Death For Hip Fracture in Women Similar to Other Diseases

• A 50 year old woman’s lifetime risk of dying from a hip fracture is equal to her risk of dying from breast cancer and greater than her risk of dying from endometrial cancer
  – Hip Fracture: 2.8%
  – Breast Cancer: 2.8%
  – Endometrial Cancer: 0.7%

Diagnosis
DXA: Principle

- Two attenuation profiles:
  - Low energy X-ray attenuation
  - High energy X-ray attenuation
- Multiply high energy profile by ‘k’ factor (ratio of soft tissue attenuation at low- & high-energy)
- BMD along scan = Low-energy profile - k-corrected high energy profile
## Noninvasive Measurement of Bone Mass

<table>
<thead>
<tr>
<th>Technique</th>
<th>Site</th>
<th>Precision</th>
<th>Cost Response to Therapy</th>
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</thead>
<tbody>
<tr>
<td>SXA</td>
<td>Forearm</td>
<td>++</td>
<td>±</td>
</tr>
<tr>
<td></td>
<td>Heel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXA</td>
<td>Spine</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Hip</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Tot. Body</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>QCT</td>
<td>Spine</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Forearm</td>
<td>++</td>
<td>+(+)</td>
</tr>
<tr>
<td>US</td>
<td>Heel</td>
<td>±</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ Fingers</td>
<td></td>
<td></td>
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</table>
### Medicare Coverage for BMD Tests

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Site</th>
<th>Fee Schedule Medicare *</th>
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<tbody>
<tr>
<td>DXA</td>
<td>Axial</td>
<td>$ 128</td>
</tr>
<tr>
<td>pDXA</td>
<td>Appendicular</td>
<td>$ 40</td>
</tr>
<tr>
<td>RX Absorptiometry</td>
<td>Appendicular</td>
<td>$ 38</td>
</tr>
<tr>
<td>QUS</td>
<td>Appendicular</td>
<td>$ 53</td>
</tr>
<tr>
<td>SXA</td>
<td>Appendicular</td>
<td>$ 40</td>
</tr>
<tr>
<td>QCT</td>
<td>Axial</td>
<td>$ 185</td>
</tr>
<tr>
<td>pQCT</td>
<td>Appendicular</td>
<td>$ 40</td>
</tr>
</tbody>
</table>

* Medicare Allowable Charge = 80% of the Costs

JAMA 288:1889-1897,2002
Example for $T$-score = -2.0, 60 year old and $Z$-Score = -0.5
Diagnosis of Osteoporosis Using Central DXA

WHO-Definition

<table>
<thead>
<tr>
<th>Condition</th>
<th>T-score</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>$\geq -1$</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>$&lt;-1$ and $&gt;-2.5$</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>$\leq -2.5$</td>
</tr>
<tr>
<td>Severe Osteoporosis</td>
<td>$\leq -2.5$ with Fracture</td>
</tr>
</tbody>
</table>

Mainly for Spine and Hip in Women
Pathophysiology
Osteoporosis Pathogenesis and Management

Fracture

Fracture Treatment

Rehabilitation

-> To Restore Independence
-> To Reduce Disabilities
Prevention Subsequent Fracture
Osteoporosis Pathogenesis and Management

Osteoporosis
- Low Peak Bone Mass
- Sex Hormone Deficiency
- Age
- Nutritional Insufficiency

Mechanical Incompetence

Fracture

Fracture Treatment

Rehabilitation
- To Restore Independence
- To Reduce Disabilities

Prevention Subsequent Fracture
Osteoporosis Pathogenesis and Management

- Falls
  - Sway
  - Walking
  - Muscle Strength
  - Neuro-muscular Impairment

- Mechanical Overload

- Osteoporosis
  - Low Peak Bone Mass
  - Sex Hormone Deficiency
  - Age
  - Nutritional Insufficiency

- Mechanical Incompetence

Fracture

Fracture Treatment

Rehabilitation
  - To Restore Independence
  - To Reduce Disabilities

Prevention Subsequent Fracture
Determinants of Fracture Risk

1. Age
2. Prevalent Fracture
3. Baseline BMD
4. Baseline Turnover
5. Changes in BMD
6. Changes in Turnover
7. Fall-related Risk
Type I collagen epitopes and Cathepsin K cleavage sites

Deoxypyridinoline
Pyridinolines

Garnero et al., JBC, 1998
Sassi et al., Bone, 2000
Pathogenesis of Osteoporotic Fracture

- **LOW PEAK BONE MASS**
- **POSTMENOPAUSAL BONE LOSS**
- **AGE-RELATED BONE LOSS**

**LOW BONE MASS**

- Nonskeletal factors (propensity to fall)
- Poor bone quality (architecture)

- Other risk factors
Rizzoli et al., J Mol Endocrinol 2001
Tracking of Bone Mineral Mass Accrual

Age (years)

Bone Mineral Mass

10  20
Heredity

Gender

Mechanical Forces

Peak Bone Mass

Hormones

Risk Factors

Nutrition
- Coupled and balanced
- Coupled but imbalanced
- Uncoupled but balanced
- Uncoupled and imbalanced
Estrogen Deficiency

- TNF
- IL-6
- IL-1
- GM CSF

Increased Bone Turnover

Bone Loss
Effects of OVX in Mice overexpressing sTNFR1-IgG3 Fusion Protein and in Negative Littermate
MALNUTRITION IN ELDERLY

- Calcium Deficiency
  - > PTH
  - > Bone Resorption

- Vitamin D Deficiency

- Protein Deficiency
  - > IGF-1
  - > Sensitivity to IGF-1
  - > Bone Formation

OSTEOPOROSIS
Management

• Indication to treatment

• Treatment possibilities
Osteoporosis Preventive Strategies

**Present Situation**

- **Higher Risk Population Modification**
- **Target very High Risk**

**Whole Population Modification**

**BMD (SD units)**

-4 -3 -2 -1 0 1 2 3

**Subjects Number**
10-Year Risk:

<table>
<thead>
<tr>
<th>Factors</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ten-Year Fracture Risk

Risk Factors

Age
General Management

- Treatment of any Disease Causing Bone Loss
- Ensure Dietary Calcium Intake $\geq 1000$ mg /d
- Ensure Adequate Dietary Protein Intake
- Correct or Prevent Vitamin D Insufficiency (800 IU/d)
- Promote Weight-Bearing Physical Exercise
- Reduce Falling Risk
- Reduce Fall Consequences (Hip Protectors)
Risk Factors Associated with Falls

1. Impaired Mobility, Disability
2. Impaired Gait and Balance
3. Neuromuscular or Musculoskeletal Disorders
4. Age
5. Impaired Vision
6. Neurological, Heart Disorders
7. History of Falls
8. Medication
9. Cognitive Impairment

After Myers et al., Bone 1996
The Hip Protector

The hip protector
**Prevention of Hip Fracture in Elderly People with Use of Hip Protector**


1725 Elderly, 82 yrs, 650 with Hip Protectors vs 1075 Controls

<table>
<thead>
<tr>
<th></th>
<th>Hip Protectors</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Fracture</td>
<td>21.3</td>
<td>46.0</td>
</tr>
<tr>
<td>(*/1000 person-years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative Hazard</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Hip Fracture *</td>
<td>0.39</td>
<td>2.43</td>
</tr>
<tr>
<td>(*/100 Falls)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arms Fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(*/1000 person-years)</td>
<td>16.4</td>
<td>19.9</td>
</tr>
<tr>
<td>(*/100 Falls) *</td>
<td>0.68</td>
<td>0.81</td>
</tr>
</tbody>
</table>

* According to Use of the Protector
Therapeutic Agents Used in Osteoporosis

**Anticatabolic Agents**
- Estrogens ± Progestagens
- SERMs
- Bisphosphonates
- Calcitonin
- Calcium

**Anabolic Agents**
- (Fluoride)
- Parathyroid Hormone
- Growth Hormone
- IGF-I

**Complex Action**
- Vitamin D and Derivatives
- Anabolic Steroids
- (Ipriflavone)
- Tibolone
Mean Distance From the Equality Line for Spine BMD

Häuselmann & Rizzoli, 2003
Morphometric Vertebral Fractures: Summary of Relative Risk and 95% Confidence by Therapy

Relative Risk

- Alendronate
- Alpha-Calcidiol
- Calcitonin 200 IE
- Calcitriol
- Calcium
- Etidronate
- Fluoride
- HRT
- Raloxifene 60 mg
- Risedronate
- 1-34 PTH 40 µg
- 1-34 PTH 20 µg

Häuselmann & Rizzoli, 2003
Hip Fracture: Summary of Relative Risk and 95% Confidence Intervals by Therapy

- **Alendronate**
- **Calcitonin**
- **Calcium and Vit. D**
- **Fluoride**
- **Raloxifene**
- **Risedronate 2.5 and 5 mg**
- **Risedronate 5mg**

Häuselmann & Rizzoli, 2003
Fracture:

Hip

Vertebrae

All

Placebo HRT

Hormone Replacement Therapy and Fracture Risk

WHI Study, Cauley et al, 2003
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Reduction in Fracture Risk (Randomized Controled Trials)</th>
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<tbody>
<tr>
<td></td>
<td>Vertebral Fracture</td>
</tr>
<tr>
<td>Fracture</td>
<td></td>
</tr>
<tr>
<td>Estrogens</td>
<td>+</td>
</tr>
<tr>
<td>Cyclic Etidronate</td>
<td>±</td>
</tr>
<tr>
<td>Alendronate</td>
<td>++</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>+</td>
</tr>
<tr>
<td>Risedronate</td>
<td>++</td>
</tr>
<tr>
<td>Nasal Calcitonin</td>
<td>+</td>
</tr>
<tr>
<td>Calcium-Vitamin D</td>
<td>?</td>
</tr>
<tr>
<td>Fluoride Salts</td>
<td>±</td>
</tr>
<tr>
<td>Tibolone</td>
<td>?</td>
</tr>
<tr>
<td>PTH</td>
<td>++</td>
</tr>
<tr>
<td>Strontium Ranelate</td>
<td>++</td>
</tr>
</tbody>
</table>
SOTI: CUMULATIVE INCIDENCE OF PATIENTS WITH NEW VERTEBRAL FRACTURE

Risk of vertebral fracture: - 41%

Over 3-year: Relative Risk = 0.59, 95% CI [0.48; 0.73]

Kaplan-Meier; RR: Cox model

Meunier PJ et al., NEJM 2004
Factors Influencing Treatment Decision

- Advancing age
- Lower BMD
- Presence of Fracture
- Risk factors or disease causing continued bone loss
- Leanness
- Family history

Adapted from E. Seeman (2004)
Fractures are not Unavoidable Expenses to Pay as a Consequence of Increased Life-Expectancy

Because of

- **Better Identification of Risk Factors for Osteoporosis**
- **Early Diagnosis, before the First Fracture**
- **A Larger Use of Preventive and Therapeutical Strategies, whose Efficacy has been Demonstrated in Randomized Controlled Trials, with Fracture Incidence as Primary End-Point**
1. Aim of Therapy

≠ Treatment of Osteoporosis

= Treatment of Patients with Osteoporosis

2. Never Too Late