Bone and Calcium Homeostasis in the Elderly

René Rizzoli MD

Division of Bone Diseases
[WHO Collaborating Center for Osteoporosis Prevention]
Department of Rehabilitation and Geriatrics
Geneva University Hospitals and Faculty of Medicine
Geneva, Switzerland
Incidence of Major Osteoporotic Fractures
(Spine, Hip, Humerus, Forearm)

Incidence of major osteoporotic fractures (per 100,000)

Age categories (years)

Men

Women

Lippuner et al
Fracture Pathophysiology and Management

Falls

Mechanical Overload

Bone Fragility (Osteoporosis)

Mechanical Incompetence

Fracture

Fracture Treatment

Rehabilitation

- To Restore Independence
- To Reduce Disabilities

Prevention Subsequent Fracture
Determinants of Bone Strength

Microarchitecture
- Bone Remodeling
- (Size + Geometry -> Mineral Mass)

Tissue Properties
- Mineralization
- Collagen (structure, cross-links)
- Microdamage

Bone Remodeling

Bone Strength

or

Structural Properties

Material Properties
Femoral Neck areal BMD

Vertebral Volumetric BMD

Women

Pre-/Postmenopausal Women

Men

Lippuner et al

Riggs et al 2004
**Effect of Sex and Age on bone Microstructure**

**Noninvasive In vivo Assessment**

*Khosla et al 2006*

### Percent change between ages 50 and 90 years

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
<th>(p) (W vs. M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV/TV</td>
<td>(-14.6^\dagger)</td>
<td>(-9.8^\dagger)</td>
<td>0.783</td>
</tr>
<tr>
<td>TbN</td>
<td>(-10.5^\ddagger)</td>
<td>(-8.2^\ddagger)</td>
<td>0.411</td>
</tr>
<tr>
<td>TbTh</td>
<td>(-6.9)</td>
<td>(-4.1)</td>
<td>0.794</td>
</tr>
<tr>
<td>TbSp</td>
<td>(17.1^\dagger)</td>
<td>(9.3^\ddagger)</td>
<td>0.079</td>
</tr>
<tr>
<td>CTh</td>
<td>(-50.7^*)</td>
<td>(-44.8^*)</td>
<td>0.195</td>
</tr>
<tr>
<td>Cort vBMD</td>
<td>(-22.2^\ddagger)</td>
<td>(-17.6^\ddagger)</td>
<td>0.009</td>
</tr>
</tbody>
</table>
10-Year Fracture Risk: age & BMD

For a given BMD, risk increases with age.

Kanis et al, 2001
Change of Bone Mass with Age

Women

Children

Men

Young adult

"Old age"

Increased by TE + E2

Decreased by E2

Endosteal resorption

Periosteal apposition

Adapted from Seeman E., J Appl Physiol. 2003;
Decreased Bone Strength

1. Reduced Periosteal Formation

2. Increased Resorption and Reduced Formation in each Remodeling Unit (BMU)

3. High Remodeling Rate
Rate of Bone Mass Change =

Activation Frequency x [Wall Thickness - Erosion Depth]

New BMU Initiated x

Wall Thickness Erosion Depth
Aaron et al. 1987

Erosion Depth

Wall Thickness

Age
Pathophysiology of Bone Loss in Women

Negative BMU Balance

Bone loss

Remodeling rate

Resorption in BMU

Formation in BMU

Bone mineral content

Menopause

Aging

Ca-deficiency

Vitamin D deficiency

Serum CTX (CrossLaps) in Relation with Age
The OFELY Cohort Study

Garnero et al., Clin Chem 2001
EUROPE: Percent of older population with Severe 25(OH)D Deficiency (< 30 nmol/l)

Vitamin D deficiency within Europe is highest in the South

Men tend to have Higher 25(OH)D levels than women

SENeca study of 11 countries; winter season; Lancet 1995
Severe Vitamin D Deficiency in Swiss Hip Fracture Patients (n = 222)

% with severe deficiency

% supplemented

- home
- assisted living
- nursing home

Bischoff-Ferrari HA, Dawson-Hughes B, Theiler R, Bone 2007
Vitamin D Levels in Response to Whole Body Exposure to UVB (54 mJ/cm²)

Aging: Reduction of 7-dehydrocholesterol in the Skin
Vitamine D: Threshold for Neuromuscular Function

- 4,100 Ambulatory Adults in NHANES III, aged 60 to 90 yrs

8-Foot walk

Repeated sit-to-stand

NHANES: national health and nutrition education survey
Calcium Metabolism in Elderly

- Calcium Intake
- Vitamin D Intake and Endogenous Production
- Intestinal Calcium Absorption
- Adaptation to a Low Calcium Diet
- Renal Tubular Reabsorption of Calcium
Effect of Dietary Calcium and Age on Jejunal Calcium Absorption in Humans Studied by Intestinal Perfusion

Ireland et al., J Clin Invest 1973

![Graph showing the effect of dietary calcium and age on jejunal calcium absorption.](image)
Age-dependent alterations in Ca$^{2+}$ homeostasis: role of TRPV5 and TRPV6

Monique van Abel, Sylvie Huybers, Joost G. J. Hoenderop, Annemiete W. C. M. van der Kemp, Johannes P. T. M. van Leeuwen, and René J. M. Bindels
Decreased Synthesis of 1,25-(OH)2 Vitamin D3

Chronic Kidney Disease:

• **Stage 2 & 3** (GFR 31-89 ml/min x 1.73 m2)

• **Stage 4 & 5** (GFR < 31 ml/min x 1.73 m2)
Vitamin D and Fracture Risk

- **Dietary calcium intake**
  - **Calcium absorption**
    - **Plasma calcium**
      - **Bone formation**
        - **BONE LOSS**
          - **FRACTURES**

- **Vitamin D intake and synthesis**
  - **Estrogen deficiency**
    - **PTH secretion**
      - **Bone turnover and resorption**
        - **FRACTURES**

- **Neuro-muscular functions**
  - **Falls**
Relationship between PTH and 25-OH-D

2/3 of patients show a blunted PTH response

Bone 35: 312, 2004
PTH

↓ osteoblast apoptosis

↑ osteoblast number/function

↓ bone lining cells

↑ cbfa1 (pre-OB)

↑ osteoclast

↑ bone resorption

↑ bone mass/strength

↑ serum Ca++

RANKL

↓ OPG
### Vitamin D Anti-fall Efficacy

#### Primary Analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Pfeifer et al, 2000</td>
<td>0.47 (0.20–1.10)</td>
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<tr>
<td>Bischoff et al, 2003</td>
<td>0.68 (0.30–1.54)</td>
</tr>
<tr>
<td>Gallagher et al, 2001</td>
<td>0.53 (0.32–0.88)</td>
</tr>
<tr>
<td>Dukas et al, 2004</td>
<td>0.69 (0.41–1.16)</td>
</tr>
<tr>
<td>Graafmans et al, 1996</td>
<td>0.91 (0.59–1.40)</td>
</tr>
<tr>
<td>Pooled (Uncorrected)</td>
<td>0.69 (0.53–0.88)</td>
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Pooled corrected OR=0.78; 95% CI [0.64, 0.92]

Subgroup analysis for 800 IU vitamin D per day:
pooled OR=0.65 [0.40, 1.00]

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Hip Fracture Risk in relation to Total Estimated Vitamin D Intake

Estimated mean daily intake of Vitamin D in the treatment group:
Total intake = (trial intake + baseline intake) x compliance

- Compliance: 85% 47% 59% 76% 84% 100%

Bischoff-Ferrari 2007
*: WHI intend-to-treat, **:hip and forearm, ***: WHI compliant
Age-related Changes in Serum IGF-I in Healthy Women

Rosen, Endocrine 2000

IGF-I (ng/ml)

Age (years)

10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-89
Marginal Protein Intake Results in Reduced Plasma IGF-I Levels and Skeletal Muscle Fiber Atrophy in Elderly Women

Castaneda et al., J Nutr Health & Ageing 2000

12 Healthy Elderly Women (66-79 yrs), Protein Intake 0.45 vs 0.92 g/kg, Weight Maintaining Diet, 10 wks

<table>
<thead>
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<th>Changes (%)</th>
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<tr>
<td><strong>Protein Intake:</strong></td>
</tr>
<tr>
<td>0.92 g/kg</td>
</tr>
<tr>
<td><strong>IGF-I</strong></td>
</tr>
<tr>
<td><strong>Type I Fiber</strong></td>
</tr>
<tr>
<td><strong>Cross-sectional Area (CSA)</strong></td>
</tr>
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</table>

Changes CSA vs Changes IGF-I: $r^2 = 0.70$, $p < 0.03$
Low Serum IGF-I and Osteoporotic Fractures in Postmenopausal Women
Garnero et al., Lancet, 2000

435 Women (65 yrs) Followed-up for 5 years,
21 Vertebral, 37 Non Vertebral Fractures

Hip BMD-Adjusted Relative Risk of Fracture (95% CI)
Baseline Serum IGF-I

RR for 1 SD Decrease  1.5 (1.0 - 2.2)
RR for concentration < Median  2.9 (1.4 - 6.3)
\[ \phi = \frac{\text{Vertebral Compressive Force (Load)}}{\text{Vertebral Strength (Resistance)}} \]

\[ \phi \geq 1 \]

Bouxsein et al 2006
It’s Never Too Late!