The Skeletal Response to Aging: There’s No Bones About It!

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Interrelationship of Intestinal, Skeletal, and Renal Systems to the Overall Maintenance of Normal Calcium Homeostasis

Dietary Ca (800 mg/d)

Absorption (500 mg)  Resorption (500 mg)  Formation (500 mg)

Blood Calcium

Filtration (8000 mg/d)  Reabsorption (7800 mg/d)

600 mg lost in stool  800 mg output  200 mg lost in urine

Secretion (300 mg)

600 mg lost in stool
Functions of the Human Skeleton

- Protects soft tissues and organs from injury
- Provides sites for insertion of muscles
- Capable of repair in response to injury
- Storehouse for 99% of body’s calcium, 80% of phosphorus, and substantial amounts of magnesium, sodium, and carbonate
- Third line of defense in maintaining acid-base balance
Distribution of Cortical and Cancellous Bone in a Long Bone

<table>
<thead>
<tr>
<th>% of total skeleton</th>
<th>% of total activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical</td>
<td>80</td>
</tr>
<tr>
<td>Cancellous</td>
<td>20</td>
</tr>
</tbody>
</table>

Growth plate
Metaphysis
Diaphysis

Cortical bone
Cancellous bone
Bone Modeling

- Denotes sites of bone resorption
- Denotes sites of bone formation
OSTEOCLAST

DEMOLITION CREW
OSTEOBLASTS
(Laying down collagen)

CARPENTER
MINERALIZATION

CEMENT CREW

Ca P
Summary of Bone Remodeling

A. Pre-osteoclasts
B. Osteoclasts Forming New Bone
C. Osteoid
D. New Bone

Lining Cells
Osteoblasts
Osteoclasts
Pre-osteoblasts
Osteocytes
The Role of Parathyroid Hormone in Normal Calcium Homeostasis

• Major calcium-sensing glands in body
• Secrete parathyroid hormone in response to low circulating calcium
• Parathyroid hormone increases serum calcium by:
  1) Promoting bone resorption
  2) Diminishing urinary calcium excretion
  3) Indirectly promoting increased dietary calcium absorption via increased renal production of 1,25(OH)$_2$D
Secretion and Metabolism of Human PTH

Intact PTH 1-84

C-terminal fragments (inactive)

N-terminal fragments (active)
Physiological Action of Parathyroid Hormone in Raising Blood Calcium Concentration
Cutaneous Production and Systemic Activation of Vitamin D

UV Irradiation

Skin (Vitamin D)

Liver
Calcidiol

Kidney
Calcitriol
Physiological Action of 1,25(OH)$_2$D in Raising Blood Calcium Concentration
Central Role of PTH and Vitamin D in the Homeostatic Control of Calcium and Phosphate

**Initial Plasma Condition**

- **A. Low Circulating Calcium**
  - $\text{Ca}$

- **B. Low Circulating Phosphate**
  - $\text{P}$

**Physiological Adjustment**

- $25\text{OHD}_3$ (+)
- $1,25(\text{OH})_2\text{D}_3$ (+)
- $\text{PTH}$

**Final Plasma Condition**

- Urinary Ca ↓
- Urinary P ↑
- $\text{Ca}$
- $\text{P}$
- PTH
- $1,25(\text{OH})_2\text{D}_3$
- $25\text{OHD}_3$
- Urinary Ca ↓
- Urinary P ↑
Change in Bone Mineral Density versus Age in Normal Men and Women

Bone Mass

Age

Active Growth
Slow Loss
Rapid Loss
Continuing Loss

MENOPAUSE

♂
♀
Model for the Proposed Changes in Calcium Homeostasis and Bone Turnover with Age

Aging

- Decreased 25OHD
- Decreased 1α-hydroxylase
- Intestinal resistance to 1,25(OH)₂D
- Decreased bone formation

Decreased production of 1,25(OH)₂D

- Decreased calcium absorption
- Secondary hyperparathyroidism
- Bone loss
Osteoporosis

Patient at age 50...

and 25 years later

Definition of Osteoporosis

“A systematic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures.”

<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimate</th>
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</thead>
<tbody>
<tr>
<td>Osteoporosis-related fractures</td>
<td>1,500,000</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>184,000</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>26,000</td>
</tr>
<tr>
<td>Cervical and endometrial cancer</td>
<td>15,000</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>317,000</td>
</tr>
</tbody>
</table>

*Cancer Facts and Figures 1996*
Osteoporosis is Pervasive

• Afflicts 25 million Americans
• 15% of women and 5% of men will experience a hip fracture in their lifetime
• Hip fractures occur as frequently as breast cancer
• Total cost of osteoporosis is estimated at about $14 billion each year

### Annual Costs of Various Chronic Diseases

<table>
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<tr>
<th>Condition</th>
<th>Cost ($ Billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>13.8</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>11.2</td>
</tr>
<tr>
<td>Asthma</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Medical, Nursing Home and Social Costs of Osteoporotic Fractures

- $60 billion in 1995
- $30 billion in 2020
- $15 billion in 1995

Established Risk Factors for Osteoporosis

**Genetic**

- Female
- Caucasian or Asian races
- Thin body habitus
- Low peak bone mass
- Family history of fractures
Established Risk Factors for Osteoporosis

**Medical**

- Menopause
- Menstrual dysfunction or early menopause
- Glucocorticoids, thyroid, anticonvulsants, benzodiazepines and GnRH use
Established Risk Factors for Osteoporosis

**Nutritional**

- Low calcium intake
- Vitamin D deficiency
- Excessive caffeine intake
- Excessive dietary sodium
- Reduced alkali intake
Established Risk Factors for Osteoporosis

**Lifestyle**

- Excessive smoking
- Excessive alcohol
- Lack of exercise
- Slipping, falling as a result of loose rugs, cords, etc.