Endocrine Physiology of Bone and Calcium Disorders

John P. Bilezikian, M.D.
Professor of Medicine and Pharmacology
Chief, Division of Endocrinology
Wednesday, February 21, 2007

Outline of Lecture

- Normal calcium homeostasis
- Useful indices of calcium metabolism
- Hypercalcemia
- Hypocalcemia
- Osteoporosis
Two Major Calcium-Regulating Hormones

- Parathyroid hormone
- 1,25-dihydroxyvitamin D
Regulation of Parathyroid Hormone

- Ionized calcium
- 1,25-dihydroxyvitamin D
Regulation of Parathyroid Hormone

- Ionized calcium
- 1,25-dihydroxyvitamin D
Major Functions of Parathyroid Hormone

- Regulation of serum calcium and phosphate
- Bone remodelling
- Regulation of 1,25-dihydroxyvitamin D levels
Two Major Calcium-Regulating Hormones

- Parathyroid hormone
- 1,25-dihydroxyvitamin D
## Major Functions of 1,25-dihydroxyvitamin D

- GI absorption of calcium and phosphate
- Bone remodelling
- Regulation of parathyroid hormone
Relationship between 25-hydroxyvitamin D and PTH


1,25(OH)₂D: Effect on Serum Calcium
HOW PTH AND 1,25(OH)_2D WORK TOGETHER TO CONTROL THE SERUM CALCIUM CONCENTRATION

Other Circulating Hormones that Influence Bone Metabolism

• Parathyroid hormone
• 1,25 (OH)_2 vitamin D
• Gonadal steroids
• Corticosteroids
• Thyroid hormone
• Growth hormone
Local Regulators of Bone Metabolism

- IGFs and IGF binding proteins
- TGF-β
- Bone morphogenic protein
- Platelet-derived growth factor, fibroblast growth factor
- Prostaglandins
- Interleukins (IL-1, IL-6)
- RANKL/osteoprotegerin

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Useful indices of calcium metabolism as gleaned from the multichannel autoanalyzer

“THE HOLY TRINITY”
Calcium
Phosphorous
Alkaline phosphatase
Useful Indices of calcium metabolism

- Calcium, phosphorus
- Dynamic markers of bone metabolism
  - Bone formation
  - Bone resorption
Bone turnover in the adult skeleton

- **Resorption**
- **Reversal**
- **Formation**
- **Resting phase**

**Useful Indices of calcium metabolism**

- **Calcium, phosphorus**
- **Dynamic markers of bone metabolism**
  - **Bone formation:**
    - Alkaline phosphatase (total and bone-specific), osteocalcin
  - **Bone resorption:**
    - N- or C- telopeptide of collagen and collagen crosslinks

**FROM:** Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism; 2nd Ed.
Useful Indices of calcium metabolism

- Calcium, phosphorus
- Dynamic markers of bone metabolism
- Calcitropic hormones
  - Parathyroid hormone
  - Vitamin D
    - 25-hydroxyvitamin D
    - 1,25-dihydroxyvitamin D

Storage form: index of vitamin D sufficiency or insufficiency
Useful Indices of calcium metabolism

- Calcium, phosphorus
- Dynamic markers of bone metabolism
- Calcitropic hormones
- Measurement of bone mass
REDUCED BONE MASS IS A KEY RISK FACTOR FOR FRACTURE

Relationship Between BMD and Fracture Risk in Untreated Patients

Reduced bone mass is a key risk factor for the fragility fracture
Dual Energy X-Ray Absorptiometry (DXA): Central Devices

Features of bone densitometry by DXA (dual energy X-ray absorptiometry)

- Safe
- Accurate
- Precise
- Normative population databases
- Correlates with fracture risk
- A diagnostic standard for osteoporosis
Bone loss as a function of age

Referents for comparisons of bone mass measurements

- **Z-score**: a measure of bone density in standard deviations from normal age- and sex-matched cohorts

- **T-score**: a measure of bone density in standard deviations from cohorts at peak bone mass (25-30 years old)
Interpreting T-scores (World Health Organization)

Correlates with lifetime fracture risk for Caucasian Women

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• Normal calcium homeostasis
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• Hypercalcemia
• Hypocalcemia
• Osteoporosis
## Causes of Hypercalcemia

- **Primary Hyperparathyroidism**
- **Malignancy**
- **Other endocrinopathy**
  - Hyperthyroidism
  - Pheochromocytoma
  - VIPoma
  - Adrenal insufficiency
- **Medications**
  - Lithium
  - Thiazide diuretics
  - Thyroid hormone
  - Vitamin A
  - Vitamin D

- **Vitamin D**
  - Toxicity
  - Granulomatous disease
    - Tuberculosis
    - Sarcoidosis
    - Any other
- **Lymphoma**
- **FHH**
- **Immobilization**
- **Acute or chronic renal disease**

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### Major Causes of Hypercalcemia

*(From Mundy and Martin)*

<table>
<thead>
<tr>
<th>Cause</th>
<th># of Patients</th>
<th>% of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Hyperparathyroidism</td>
<td>111</td>
<td>54</td>
</tr>
<tr>
<td>Malignancy</td>
<td>72</td>
<td>35</td>
</tr>
<tr>
<td>Others (sarcoid, thyroid, vit D, etc)</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Unknown</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>
PRIMARY HYPERPARATHYROIDISM

- A common endocrine disorder characterized by incompletely regulated, excessive secretion of parathyroid hormone from one or more parathyroid glands.

- Primary Hyperparathyroidism is associated with hypercalcemia and elevated levels of parathyroid hormone.

Human Parathyroid Hormone
PRIMARY HYPERPARATHYROIDISM

Before 1970: A disease of bone, stones, and groans
CHANGING CLINICAL PROFILE OF PRIMARY HYPERPARATHYROIDISM

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrolithiasis</td>
<td>57%</td>
<td>51%</td>
<td>37%</td>
<td>17%</td>
</tr>
<tr>
<td>Hypercalciuria</td>
<td>Not reported</td>
<td>36%</td>
<td>40%</td>
<td>39%</td>
</tr>
<tr>
<td>Overt Skeletal Disease</td>
<td>23%</td>
<td>10%</td>
<td>14%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0.6%</td>
<td>18%</td>
<td>22%</td>
<td>80%</td>
</tr>
</tbody>
</table>
Biochemical and hormonal profile in Primary Hyperparathyroidism

<table>
<thead>
<tr>
<th>Index</th>
<th>Patients</th>
<th>nl range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dl)</td>
<td>10.7±0.1</td>
<td>8.4-10.2</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>2.9±0.1</td>
<td>2.5-4.5</td>
</tr>
<tr>
<td>Alk Phos (IU/l)</td>
<td>114±4</td>
<td>&lt;100</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>121±7</td>
<td>10-65</td>
</tr>
<tr>
<td>25-OH Vit D (ng/ml)</td>
<td>21±1</td>
<td>9-52</td>
</tr>
<tr>
<td>1,25-OH₂ Vit D (pg/ml)</td>
<td>59±2</td>
<td>15-60</td>
</tr>
<tr>
<td>Urinary calcium (mg)</td>
<td>248 ± 12</td>
<td>250-300</td>
</tr>
<tr>
<td>DPD (nmol/mmol Cr)</td>
<td>17 ± 6</td>
<td>4-21</td>
</tr>
</tbody>
</table>
PRIMARY HYPERPARATHYROIDISM

Before 1970: A disease of bone, stones, and groans
Since 1970: A disease of asymptomatic hypercalcemia

BONE MASS MEASUREMENTS IN PRIMARY HYPERPARATHYROIDISM
**Bone and stone disease in primary hyperparathyroidism: 1965-2007**

Mallette, Bilezikian, Heath & Aurbach
1965-1972  
n=57

Silverberg, Bilezikian et al.
1984-2007  
n=121

<table>
<thead>
<tr>
<th>Condition</th>
<th>1965-1972</th>
<th>1984-2007</th>
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</thead>
<tbody>
<tr>
<td>Nephrolithiasis</td>
<td>37%</td>
<td>17%</td>
</tr>
<tr>
<td>Bone disease</td>
<td>14%</td>
<td>1.4%</td>
</tr>
<tr>
<td>(Radiological)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BMD in Postmenopausal Women With Primary Hyperparathyroidism**

Silverberg, Bilezikian et al.
JBMR, 1989
Normal Bone

<table>
<thead>
<tr>
<th>Skeletal Site</th>
<th>Cancellous</th>
<th>Cortical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>***</td>
<td>*</td>
</tr>
<tr>
<td>Total Hip</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>*</td>
<td>***</td>
</tr>
<tr>
<td>Radius (1/3 site)</td>
<td>*</td>
<td>***</td>
</tr>
</tbody>
</table>

Cortical

Cancellous

Densitometric and Histomorphometric Characteristics of Bone in Primary Hyperparathyroidism

• Cancellous bone (lumbar spine): relatively well preserved

• Cortical bone (distal radius): preferentially affected
TO CUT IT OUT OR TO LEAVE IT IN...

A KEY CLINICAL DILEMMA IN PRIMARY HYPERPARATHYROIDISM

Guidelines for Parathyroid Surgery
(NIH Workshop, 2002)

- Hypercalcemia (> 1 mg/dl above normal)
- Stone or overt bone disease
- Marked hypercalciuria (> 400 mg/day)
- Reduced bone density (T<-2.5)
- Age (<50 years old)

Bilezikian and Silverberg
New Eng J Med 350:1746-1751, 2004
Humoral Hypercalcemia of Malignancy

Malignant tumors synthesize and secrete humors that stimulate osteoclast-mediated bone resorption
Parathyroid Hormone-Related Protein as an Etiology of HHM

Criteria

- Produced by the tumor
- Blood level correlates with hypercalcemia
- Mimics the clinical syndrome
- Reducing the PTHRP “burden” reverses hypercalcemia

Circulating PTHRP Levels in Hypercalcemia of Malignancy

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>% Elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTLV-1 T-cell lymphoma</td>
<td>99%</td>
</tr>
<tr>
<td>Classical squamous cell carcinoma</td>
<td>85%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>58%</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>50%</td>
</tr>
<tr>
<td>Myeloma and other hematological malignancies</td>
<td>21%</td>
</tr>
</tbody>
</table>

CAUSES OF HYPERCALCEMIA

- Primary Hyperparathyroidism
- Malignancy
- Other endocrinopathy
  - Hyperthyroidism
  - Pheochromocytoma
  - VIPoma
  - Adrenal insufficiency
- Medications
  - lithium
  - thiazide diuretics
  - thyroid hormone
  - Vitamin A
  - Vitamin D
- Vitamin D
  - Toxicity
  - Granulomatous disease
    - Tuberculosis
    - Sarcoidosis
    - Any other
- Lymphoma
- FHH
- Immobilization
- Acute or chronic renal disease

Symptoms, signs, and treatment of hypercalcemia

To be discussed tomorrow!
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- Normal calcium homeostasis
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- Hypocalcemia
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Hypocalcemia

- Hypoparathyroidism
  - Deficient secretion of parathyroid hormone
- Secondary hyperparathyroidism
  - Appropriate response to hypocalcemic stimulus
- Other causes
**Hypocalcemia**

_Hypoparathyroidism - Deficient secretion of parathyroid hormone_

- **Autoimmune hypoparathyroidism**
  - Multiple end-organ endocrine gland insufficiency
  - Isolated parathyroid gland deficiency
- **Familial hypoparathyroidism**
  - Defective processing of PTH gene product
  - Defective cellular trafficking of PTH gene product
  - Developmental agenesis (X-linked)
- **Activating mutations of the calcium receptor**
- **Congenital (DeGeorge Syndrome)**
- **Post-surgical hypoparathyroidism**

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**Hypocalcemia**

_Secondary Hyperparathyroidism - Appropriate response to hypocalcemic stimulus_

- **Vitamin D deficiency**
  - Nutritional
  - Malabsorption
  - Liver disease
  - Renal disease
- **Vitamin D resistant states**
  - Vitamin D resistant rickets
  - Vitamin D dependent rickets
- **Drugs**
  - Foscarnet
  - Pentamidine
  - Ketoconazole
- **Pseudohypoparathyroidism**
Symptoms, signs, and treatment of hypocalcemia

To be discussed tomorrow!

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• Normal calcium homeostasis
• Useful indices of calcium metabolism
• Hypercalcemia
• Hypocalcemia
• Osteoporosis
Postmenopausal Osteoporosis

- Osteoporosis
  6 to 8 million US women age ≥ 50
- Low bone mass
  20 to 24 million
- Fractures
  40% will suffer an osteoporotic fracture in their lifetime
  - Vertebral: 15.6%
  - Hip: 17.5%
  - Forearm: 16.0%
- 1.5 million fractures annually

Human Costs of Osteoporosis

- Impaired function, decreased mobility
- More bone loss due to decreased activity
- Compressed abdomen, reduced appetite
- Reduced pulmonary function
- Sleep disorders
- Shortened survival
- Poor self esteem


Photo courtesy of the National Osteoporosis Foundation
Incidence of Osteoporosis and Osteopenia


Osteoporosis: defining the Problem

“A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.”

Independent Risks for Hip Fracture in Older Women

Major Risk Factors
- Age
- Any fracture after age 50
- The menopause
- Maternal history of hip fracture
- Glucocorticoids
- Smoking
- Alcohol abuse
- High bone turnover
- Low body weight (<127 lbs)

Therapeutic Goals

Bone Remodeling

- Stabilize or increase BMD
- Maintain trabecular architecture
- Increase mineralization density of bone matrix

Therapeutic Goals
THERAPEUTIC CONSIDERATIONS

• HOW TO PREVENT?
• HOW TO TREAT?

Diagnosis, evaluation and treatment of osteoporosis

To be discussed tomorrow!