Endocrine Physiology of Bone and Calcium Disorders

John P. Bilezikian, M.D.
Professor of Medicine and Pharmacology
Chief, Division of Endocrinology
Tuesday, February 17, 2009

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

The Calcium-Sensing Receptor

- Type I ligands: Direct receptor binding
- Type II ligands: Allosteric modulation
Regulation of Parathyroid Hormone

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

- Regulation of serum calcium and phosphate
- Bone remodeling
- Regulation of 1,25-dihydroxyvitamin D levels

PTH: Effect on Serum Calcium

Blood → Calcium

↑Calcium → Kidney
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 remodeling
- Regulation of parathyroid hormone

Relationship between 25-hydroxyvitamin D and PTH

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 (estrogens and androgens)
- 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

Outline of Lecture

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

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

FROM: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism; 2nd Ed.
Useful indices of calcium metabolism: biochemical markers of bone turnover

**Bone resorption**
- N-telopeptide (NTx)
- C-telopeptide (CTx)
- Deoxypyridinoline (free, total)

**Bone formation**
- Bone-specific alkaline phosphatase
- Osteocalcin
- Propeptides type I collagen (P1NP)

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

\(^1\) Sornay-Rendu E. J Bone Miner Res. 2005;20:1813-19.
Storage form: index of vitamin D sufficiency or insufficiency

VITAMIN D DEFICIENCY IN MEDICAL INPATIENTS

Normal laboratory reference range

Normal physiologic range

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.

Relative Risk ofFracture

Bone density (SD units)

Dual Energy X-Ray Absorptiometry (DXA)

- Hologic Delphi
- GE Lunar Prodigy
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)

![Graph showing BMD and T-Score](image-url)
Diagnostic Standard

T-SCORE

Interpreting T-scores (World Health Organization)

Correlates with lifetime fracture risk for Caucasian Women

- Osteoporosis
- Low Bone Mass (Osteopenia)
- Normal Bone Mass

T-score

2/17/2009
Outline of Lecture

- Normal calcium homeostasis
- Useful indices of calcium metabolism
- 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
MAJOR CAUSES OF HYPERCALCEMIA
(From Mundy and Martin)

<table>
<thead>
<tr>
<th></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

Hypoparathyroidism
PRIMARY HYPERPARATHYROIDISM

Before 1970: A disease of bone, stones, and groans
## Emergence of the Modern 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>

### Figure 2
Changing proportion of asymptomatic patients with clinical manifestations of HPT at 6 year intervals.
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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrolithiasis</td>
<td>37%</td>
<td>17%</td>
</tr>
<tr>
<td>Bone disease (Radiological)</td>
<td>14%</td>
<td>1.4%</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>

*Differs from radius, p<.05

Cortical

Cancellous
Densitometric and Histomorphometric Characteristics of Bone in Primary Hyperparathyroidism

• Cancellous bone (lumbar spine): relatively well preserved

• Cortical bone (distal radius): preferentially affected (i.e. reduced)

TO CUT IT OUT OR TO LEAVE IT IN…

A KEY CLINICAL DILEMMA IN PRIMARY HYPERPARATHYROIDISM
Guidelines for Parathyroid Surgery
(Bilezikian et al., 3rd International Workshop, J Clin Endocrinol Metab, 2009)

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


Potential Physiological Functions of PTHRP

- Lactation
- Placental Calcium Transport
- Neonatal Calcium Metabolism
- Proliferation and Differentiation of the Skin
- Bone Growth
- Chondrocyte Development
- Smooth Muscle Function
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!
Outline of Lecture

- Normal calcium homeostasis
- Useful indices of calcium metabolism
- Hypercalcemia
- Hypocalcemia
- Osteoporosis

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

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
  - Ketaconazole
- Pseudohypoparathyroidism
Symptoms, signs, and treatment of hypocalcemia

To be discussed tomorrow!

Outline of Lecture

- 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%
- 2.0 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

Incidence of Osteoporosis and Osteopenia

Men

Women


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
- Bone Density
- Age
- Fragility fracture
- Family history
- The menopause (i.e. estrogen deficiency)

#### Other Important Risk Factors
- Glucocorticoids
- Smoking
- Alcohol abuse
- Low body weight (<127 lbs)
- Fall Risk
- Bone Turnover

---

#### Minor Risk Factors (cont)
- Tallness at age 26
- Fair to poor self-rated health
- Previous hyperthyroidism
- Long-acting benzodiazepines
- Excessive caffeine intake
- Not walking for exercise
- Weight loss since age 25
- <4 hours/day on feet
- Inability to rise from a chair without using arms
- Poor depth perception
- Poor contrast sensitivity
- Tachycardia at rest

---


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!