Endocrine Physiology of Bone and Calcium Disorders

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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

Major Functions of Parathyroid Hormone

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

Regulation of Parathyroid Hormone

- Ionized calcium
- 1,25-dihydroxyvitamin D

PTH: Effect on Serum Calcium

Blood → Calcium → Kidney → 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

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

Blood  \[\uparrow\text{Calcium}\]
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
- Reverse
- Activation
- 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

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
VITAMIN D DEFICIENCY IN MEDICAL INPATIENTS

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

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)

**T-Score**

Diagnostic Standard

**BMD gm/cm²**

Spine: L1-L4

**Interpreting T-scores (World Health Organization)**

Correlates with life time fracture risk for Caucasian Women

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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
- FSH
- Immobilization
- Acute or chronic renal disease

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.

MAJOR CAUSES OF HYPERCALCEMIA

(From Mundy and Martin)

<table>
<thead>
<tr>
<th></th>
<th># OF PATIENTS</th>
<th>% OF TOTAL</th>
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<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>
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CHANGING CLINICAL PROFILE OF PRIMARY HYPERPARATHYROIDISM

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<tbody>
<tr>
<td>Nephrolithiasis</td>
<td>57%</td>
<td>51%</td>
<td>37%</td>
<td>17%</td>
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<tr>
<td>Hypercalcemia</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>
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</table>

Biochemical and hormonal profile in Primary Hyperparathyroidism

- Calcium (mg/dl) 10.7±0.1 8.4-10.2
- Phosphorus (mg/dl) 2.9±0.1 2.5-4.5
- Alk Phos (IU/l) 114±4 <100
- PTH (pg/ml) 121±7 10-65
- 25-OH Vit D (ng/ml) 21±1 9-52
- 1,25-OH2 Vit D (pg/ml) 59±2 15-60
- Urinary calcium (mg) 248 ± 12 250-300
- DPD (nmol/mmol Cr) 17 ± 6 4-21

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
1984-2007 n=121

Nephrolithiasis
37%
17%

Bone disease (Radiological)
14%
1.4%

BMD in Postmenopausal Women With Primary Hyperparathyroidism

Silverberg, Bilezikian et al. JBMR, 1989

Densitometric and Histomorphometric Characteristics of Bone in Primary Hyperparathyroidism

- Cancellous bone (lumbar spine): relatively well preserved
- Cortical bone (distal radius): preferentially affected

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>
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<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>
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CAUSES OF HYPERCALCEMIA

- Primary Hyperparathyroidism
- Malignancy
- Other endocrinopathy
  - Hypertension
  - Pheochromocytoma
  - VIPoma
- Adrenal insufficiency
- Medications
  - Lithium
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  - Vitamin D
- Vitamin D Toxicity
- Granulomatous disease
  - Tuberculosis
  - Sarcoidosis
- Any other
- Lymphoma
- FH
- Immobilization
- Acute or chronic renal disease

Symptoms, signs, and treatment of hypercalcemia
To be discussed tomorrow!

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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

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!

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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%
  Femoral: 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.”

Healthy bone

Osteoporotic bone


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)

Independent Risks for Hip Fracture in Older Women


Therapeutic Goals

↓ Bone Remodeling

Stabilize or increase BMD

Maintain trabecular architecture

Increase mineralization density of bone matrix

Therapeutic Goals

<table>
<thead>
<tr>
<th>THERAPEUTIC CONSIDERATIONS</th>
<th>Diagnosis, evaluation and treatment of osteoporosis</th>
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<tbody>
<tr>
<td>• HOW TO PREVENT?</td>
<td>To be discussed tomorrow!</td>
</tr>
<tr>
<td>• HOW TO TREAT?</td>
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