Interpretation of Calcium and Parathyroid Disorders

What are the pitfalls?

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Learning Objective

At the end of this module, you will learn the following:

- **Hypercalcemia**
  - Describe the physiology of Calcium –Intact PTH
  - Differentiate between the causes of hypercalcemia based on the mechanism by which calcium is increased.

- **Hyperparathyroidism**
  - Distinguish the causes of hyperparathyroidism and how to differentiate.
  - Differentiate between primary hyperparathyroidism and hypocalciuric hypercalcemia.

- **Hypocalcemia**
  - Given a case of hypocalcemia, select the most likely etiology based upon labs.
Case 1

- 30 years old female establishes her care with you.
- She has h/o HTN and needs refill on HCTZ as she ran out of it 4 weeks ago. She c/o mild dry cough.
- She denies any other PMH.
- She takes multivitamins once a day.
- O/E She is thin built. Vitals are stable.
- Rest of the exam was normal.
- Her Calcium is found to be 10.9 mg/dl (8.5-10.6)
- You decided to repeat Calcium with PTH.

Labs

- Calcium 10.9 mg/dl (8.6-10.6) with albumin 3.8
- Intact PTH 70 pg/ml (14-72)
- 25 OH Vit D 38 ng/ml (30-100)
- 1,25 OH Vit D 90 pg/ml (18-78)
- PO 4 2.7 mg/dl (2.7-4.5)
- Creatinine 1.1 mg/dl
Case 1
What is the most likely diagnosis?

A. Primary hyperparathyroidism
B. Familial Hypocalciuric Hypercalcemia
C. Secondary Hyperparathyroidism
D. Malignancy
E. None of the above

PTH Regulation

- ↓Ca → ↑PTH secretion (WHILE ↑Ca → ↓PTH secretion)
- **Seconds to minutes** — exocytosis of PTH from secretory vesicles into the extracellular fluid.
- **Minutes to one hour** — reduction in the intracellular degradation of PTH.
- **Hours to days** — increase in PTH gene expression
- **Days to weeks** — proliferation of parathyroid cells (also stimulated by low serum calcitriol concentrations)
- ↑PO4 and ↓1,25 Vit D → ↑PTH transcription and proliferation
Calcium Regulation

- PTH
  - ↑ Bone resorption
  - 1. ↑ Ca reabsorption
  - 2. ↓ PO4 reabsorption
  - 3. ↑ 1,25(OH)2 D

- 25 OH Vit D
  - ↑ Ca absorption
  - ↑ PO4 absorption

- 1,25(OH)2 D (Gut and Bone)
  - ↑ Ca absorption
  - ↑ PO4 absorption

Review: Basic Metabolic Control of Calcium Metabolism

- Key Players:
  - Calcium, Intact PTH, PO4
  - 1,25 OH Vit D, 25 OH Vit D
  - Creatinine, urine calcium

- Low calcium: + PTH
- High calcium: - PTH

- PTH:
  - + renal calcium resorption
  - + renal phosphate excretion
  - + renal 1,25 Vit D3 synthesis from 25 OH Vit D (by stimulating 1 alpha-hydroxylase)
    - + calcium resorption from bone

- 1,25 Vit. D:
  - + gut absorption of calcium
  - + gut absorption of phosphate
Labs

- Calcium 10.9 mg/dl (8.6-10.6) with albumin 3.8
- Intact PTH 70 pg/ml (14-72)
- 25 OH Vit D 38 ng/ml (30-100)
- 1,25 OH Vit D 90 pg/ml (18-78)
- PO4 2.7 mg/dl (2.7-4.5)
- Creatinine 1.1 mg/dl
- 24 hr urine calcium 320 mg/24 hrs

Case 1
What is the most likely diagnosis?

A. Primary hyperparathyroidism
B. Familial Hypocalciuric Hypercalcemia
C. Secondary Hyperparathyroidism
D. Malignancy
E. None of the above
Primary Hyperparathyroidism

Definition:
High Calcium, High PTH or Inappropriately elevated PTH with high or high normal calcium.

Causes:
- Parathyroid gland Adenoma (80-90%)
- MEN1 (3 P, Hyperplasia of parathyroid glands)
- MEN 2 a (MTC, Pheochromocytoma, Primary Hyperparathyroid)
- Parathyroid Neoplasia
- (mutations in HRPT2)
A 42-year-old male is being evaluated for Primary hyperparathyroidism.

He was found to have hypercalcemia on screening laboratory.

He has no history of nephrolithiasis. He has always had normal blood pressure and has no history of peptic ulcer disease.

He has no family history of similar calcium disturbances.

On physical examination, blood pressure is 134/84 mm Hg, and heart rate is 80 beats/min.

Examination is normal.

Laboratory test results:

- Calcium = 10.9 mg/dL (8.5-10.6)
- Phosphorus = 2.7 mg/dL
- Creatinine = 1.0
- 1,25 OH Vit D = 99 pg/ml (18-78)
- 25-Hydroxyvitamin D = 36 ng/mL
- Urinary calcium = 400 mg/24 h
- PTH = 110 pg/mL (14-72)

Case 2

Which one of the following is the indication for surgery?

A. Age
B. Calcium
C. PTH level
D. Male
E. No indication
Guidelines for Parathyroid surgery in Primary Hyperparathyroidism

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<td>1.0 mg/dl</td>
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<tr>
<td>24 hr urine ca</td>
<td>&gt;400mg/d</td>
<td>&gt;400mg/d</td>
<td>Not indicated</td>
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<td>Cr Clearance</td>
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<td>Reduced by 30%</td>
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<td>Z score &lt;-2.0 forearm</td>
<td>T-score &lt;-2.5 at any site</td>
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<td>Age</td>
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Familial Hypocalciuric Hypercalcemia

- Autosomal dominant syndrome of asymptomatic hypercalcemia
- Must be ruled out before sending patient to surgery for primary HPTH
- **Inactivating mutation of CaSR** (PTH less sensitive to Ca)
- PTH and Calcium will be high or high normal
- Low Urine Calcium
- Diagnose by measuring Ca/Cr clearance ratio = [24-hour Urine Ca x serum Cr] ÷ [Serum Ca x 24-hour Urine Cr]
  - HPTH > 0.02
  - FHH < 0.01
Case 3

- 66 year old woman is seen in ER for malaise and confusion. She has smoked 1 pack of cigarettes a day for the past 40 years.
- Physical examination reveals distant breath sounds.
- Chest radiograph shows a 1.2-cm mass in the upper lobe of the right lung.
- A bone scan indicates no evidence of focal or metastatic disease.
- Laboratory studies:
  - CBC = Normal
  - Calcium = 15.8 mg/dL
  - Phosphorus = 4.0 mg/dL
  - Cr= 1.1mg/dl
  - Intact parathyroid hormone = < 1.0 pg/ml (14-72)
  - 25 OH Vit D = 30 ng/dl (30-100)
  - 1,25 OH vit D = 35 pg/ml (18-78)

Case 3
Which of the following is the most likely cause of the patient’s hypercalcemia?

A. Parathyroid adenoma
B. Parathyroid hyperplasia
C. Humoral hypercalcemia of malignancy
D. Multiple myloma
E. Granulomatous disease
Causes of Hypercalcemia - (with PTH interpretation)

**PTH Dependent (PTH high)**
- Primary hyper-PTH (Asymptomatic)
- Familial hypocalciuric hypercalcemia
- Tertiary hyper-PTH
- Lithium toxicity

**PTH Independent (PTH appropriately suppressed)**
- Malignancy (Hospitalized pts)
- Sarcoidosis, Granulomatous disease
- Thyrotoxicosis
- Immobilization
- Adrenal Insufficiency
- Drugs (HCTZ)
- Milk Alkali Syndrome
- Vitamin D excess
Lab Differential Diagnosis of Hypercalcemia

<table>
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<tr>
<th></th>
<th>Ca</th>
<th>PO₄</th>
<th>U₉₉</th>
<th>25(OH)D</th>
<th>1,25(OH)D</th>
<th>PTH</th>
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<tr>
<td>PHPT</td>
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<td>Sarcoid</td>
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<td>↑ Vit D</td>
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Case 4

- A 60-year-old woman comes to your office after getting repeat Dexa 4 weeks.
- Her initial Dexa was done 6 years ago which was normal.
- She has never taken estrogen, but does take calcium supplements, 600 mg daily.
- Current Dexa shows T score of –2.7 at the spine and –2.6 at the hip.
- She has no family history of osteoporosis or fracture. She does not smoke cigarettes. She is working, has no personal history of fracture, and has never taken steroids.
- She is very much concerned about her bone loss.
- On physical examination, blood pressure is 128/84 mm Hg, and heart rate is 88 beats/min. You detect a small, diffuse goiter that is not tender.
- Laboratory test results:
  - Calcium = 9.0 mg/dL (8.6-10.6), Albumin = 3.8 g/dL
  - Phosphorus = 3.3 mg/dL
  - PTH = 114 pg/mL (14-72)
  - Albumin = 3.8 g/dL
  - 25-Hydroxyvitamin D = 9 ng/mL (30-100)
  - Creatinine 1.0 mg/dl
  - Serum and urine protein electrophoresis, normal

What should you do next?

A. Start 50,000 iu Vit D weekly
B. Start Fosamax 70 mg weekly
C. Start Fosamax 35 mg weekly
D. Start 50,000 iu Vit D weekly with Boniva monthly
E. Start 50,000 Iu Vit D with 35 mg Fosamax weekly
Secondary Hyperparathyroidism

- **Secondary hyperparathyroidism** refers to the excessive secretion of (PTH) by parathyroid gland in response to hypocalcemia and associated hypertrophy of the glands.
- This disorder is especially seen in patients with Vit D deficiency OR
- chronic renal failure

![Diagram of PTH and Calcium]

**Case 5**

60-year-old woman with long-standing hypertension and hemodialysis-dependent renal failure due to interstitial nephritis

On physical examination, blood pressure is 150/70 mm Hg, height is 69 inches, and weight is 155 pounds (BMI = 22.9 kg/m²)

Laboratory test results:
- Calcium = 11.5 mg/dL (8.6-10.6),
- Albumin = 2.4 g/dL
- PTH = 800 pg/mL (14-72)
- Po4 = 5.0 (2.7-4.5)
- 1,25 OH vit D = 16 pg/ml (18-78)
- 25 OH vit D = 28 ng/dl
- Creatinine = 5.5 mg/dl
Case 5
What is the most likely diagnosis?

A. Primary hyperparathyroidism
B. Parathyroid carcinoma
C. Secondary Hyperparathyroidism
D. Tertiary Hyperparathyroidism

Mineral Metabolism in Secondary Hyperparathyroidism

- ↑ PTH
- ↓ Ca++
- ↑ PTH
- Systemic Toxicity
  - nervous system
  - cardiac
  - endocrine
  - immunologic
  - cutaneous

- osteitis fibrosa
- demineralization
- fractures
- bone pain

- ↑ Pi
- ↓ 1,25 D₃
- FGF-23
- 25 D₃

Early Treatment Needed to Avoid Parathyroid Hyperplasia and Calcitriol Resistance

- Increased Parathyroid Gland Mass
- Decreased VDR # and Sensitivity
- Calcitriol Resistance
- Decreased Calcium Receptors

CKD Stage 3 & 4  Stage 5


Cinacalcet: a 2nd Generation Calcimimetic

- Sensipar is indicated for the treatment of
- secondary hyperparathyroidism in patients with chronic kidney disease; In three large randomized controlled clinical trials, cinacalcet given in doses of 30-180mg orally each day was associated with effective decrease in PTH levels over 26 weeks compared with placebo decrease in Ca, P and Ca X P
- parathyroid carcinoma;
- Primary hyperparathyroidism for whom parathyroidectomy is not clinically appropriate or is contraindicated.


Khawaja
Normocalcemic Primay hyperparathyroidism

- “forme fruste of PHTP – High PTH with normal calcium
- All causes of secondary hyperparathyroidism must be ruled out.
- The differential diagnosis also includes primary hyperparathyroidism with concomitant vitamin D deficiency.
- In 37 patients with normocalcemic hyperparathyroidism, 41 percent developed evidence for progressive hyperparathyroid disease.

Duration median three years (range 1 to 8) of observation.

Four individuals with normal serum calcium levels had successful parathyroid surgery.

Silverber J Clin Endo Meta 2003 88:5348
Ann of Med 2004 117:365
J Clin Endo Meta 2007 92:3001

Normocalcemic Primary Hyperparathyroidism

<table>
<thead>
<tr>
<th>Table 1. Demonstration of biochemical differences between conditions associated with elevated parathyroid hormone levels</th>
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<tr>
<td>Corrected total serum calcium Normal High Normal Normal</td>
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<tr>
<td>Ionized calcium Normal or high High Normal Normal</td>
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<tr>
<td>Parathormone level High High High High</td>
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<tr>
<td>25 hydroxy vitamin D Normal low or normal High Normal</td>
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<tr>
<td>24 urinary calcium Normal Normal or high Normal High</td>
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HPT, hyperparathyroidism; NHPT, normocalcemic HPT.
Etiology of hyperparathyroidism

- **Primary** (or inappropriately high PTH with High or High normal Ca²⁺)
  - Adenoma 90%
  - Hyperplasia 10%
  - Carcinoma < 0.1%

- **Secondary** (PTH as a response to low Ca²⁺, calcium is normal or low normal)
  - Chronic Renal Failure
  - Vitamin D Deficiency

- **Tertiary**
  - Continued excess PTH secretion following prolonged secondary hyperparathyroidism in kidney disease.

Case 6

- A 50-year-old man has been having myalgias and some sporadic twitching of various muscles.
- His medical history is remarkable for idiopathic cardiomyopathy for which he underwent heart transplant 2 years ago. He also reports h/o total thyroidectomy 4 yrs ago due to retrosternal goiter causing obstructive symptoms.
- His medications include Calcium carbonate 1250 bid, Calcitriol 2 pills a day, Hctz 25 mg once a day and Cyclosporin.
- Physical examination - remarkable for a positive Chvostek sign and trace bilateral pedal edema.
- Laboratory test results:
  - Calcium = 6.9 mg/dL with alb 3.0 g/dl
  - Magnesium 1.6
  - Creatinine = 1.2 mg/dL
  - 25 OH Vit D = 30 ng/dl
  - Phosphorus = 4.8 mg/dL (2.7-4.5)
  - Intact PTH = 10 pg/mL
What do you think he has?

A. Hypoparathyroidism  
B. Pseudohypoparathyroidism  
C. Secondary hyperparathyroidism  
D. Magnesium deficiency  
E. Malignancy

Causes of Hypocalcemia

Hypoalbuminemia 
Acis Base disturbance

- With Low PTH
- Destruction of gland (Autoimmune, surgery)
- Abnormal development
- Genetic defects
- Altered PTH regulation

Mg disorders

- With High PTH
- Vit D deficiency or Resistance
- Renal insufficiency
- Psudohypoparathyroidism
- Low Mg
- Extravascular deposition
- Hyperphosphatemia
- Severe sepsis
- Drugs
Pseudohypoparathyroidism

- “Chemical hypoparathyroidism” with
  - ↓ Ca; ↑ PO₄
- But: ↑ serum PTH
- Resistance to PTH action by target organs
- Defect in second messenger (e.g., Gₐ activity) → ↓ action of PTH
- Characteristic physical appearance in some subtypes: short stature, mental retardation, obesity, short 4th metacarpal bone, hypothyroidism, hypogonadism
- Kidney does not respond to PTH infusion with increased cAMP excretion
- Subtypes

Laboratory Differential Diagnosis of Hypocalcemia

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<tr>
<th>1,25(OH)₂D</th>
<th>PTH</th>
<th>Ca</th>
<th>Po₄</th>
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<td>PTH-resistance</td>
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Take Home message to interpret Calcium-Parathyroid disorders

History/Physical

1. Look at Calcium and PTH together.
   Remember PTH actions (calcium reabsorption, phosphaturia (low serum P), 1,25 OH Vit D production) and counterregulation.

2. High calcium with High/inappropriately high PTH
   Cr normal – check FE ca (PTHP VS FHH)
   Cr high – Tertiary Hyperparathyroid

3. High calcium with suppressed PTH – Look for secondary causes of hypercalcemia

4. If calcium is low/LN/ Normal with High PTH (Secondary Hyperparathyroid)
   – Check 25 Oh Vit d & Creatinine

5. If Calcium is low with low PTH – (Post op, Autoimmune)
   If seems too complicated ------ call me!!