IRIM 2012: Calcium Cases

Carolyn Becker MD
Brigham and Women’s Hospital
Harvard Medical School

Case

- A 65 yo man with multiple myeloma is admitted with pneumonia and sepsis.
- Exam: febrile, BP 80/60, P 120, alert and 0x3. Decreased BS at left base. No bony tenderness.
- Labs:
  - Calcium 18.5 mg/dl
  - K 3.5
  - HCO3 22
  - Phos 4.0 mg/dl
  - Albumin 5.5 g/dl

Question: What Test Would You Order Next?

A. PTHrP
B. 24 hour urine for calcium excretion
C. Bone scan
D. Ionized calcium
E. 1,25-dihydroxy-vitamin

Case

- With vigorous hydration and antibiotics, patient feels greatly improved and wants to go home.
- Repeat labs after hydration show:
  - Calcium 15.7 mg/dl
  - Intact PTH 30 pg/ml
  - 25OHD 32 ng/ml
  - Albumin 3.5 g/dl

Case

- Ionized calcium came back completely normal
- Case of “pseudohypercalcemia” from excess myeloma proteins (immunoglobulins) binding calcium and affecting total Ca measurement

Distribution of Calcium

- Total body calcium is 1000 g (99% in skeleton)
- Less than 1% is soluble in intracellular and extracellular fluid compartments
- Approx. 50% of soluble Ca++ is ionized and 50% is bound
- Only ionized Ca++ is biologically active

Case

- 55 year old F with HTN x 5 years
- PMH: menopause age 53
  - 1000 mg calcium in diet daily
  - HCTZ 12.5 mg/d
- FH: she is adopted
- ROS: hot flashes

Labs:
- Calcium 10.8 mg/dl (normal 8.6 – 10.4)
- Albumin 4.0 g/L
- Last year: Ca 9.9 mg/dl
- Repeat labs:
  - Calcium 10.2, PTH 72
  - Calcium 10.9, PTH 56 (normal PTH 10 – 65)

What is the Most Likely Cause of Her Hypercalcemia?
A. Normocalcemic hyperparathyroidism
B. Primary hyperparathyroidism
C. Secondary hyperparathyroidism
D. Thiazide-induced hypercalcemia
E. Familial benign hypercalcemia

Key Regulator of Calcium Homeostasis

PTH

Calcium Sensing Receptor on Parathyroid Cell

PTH Secretion is Regulated by the Ionized Calcium Concentration at the Calcium Sensing Receptor

1. High [Ca²⁺]ECF
   - Ca²⁺ binds to receptor
   - Receptor activation leads to inhibition of PTH secretion

2. Low [Ca²⁺]ECF
   - Ca²⁺ not bound to receptor
   - No inhibition
   - PTH is secreted
   - PTH secretion in body leads to increased [Ca²⁺]ECF

Bone
- Parathyroid
  - PTH
  - Ca²⁺
  - Pi
  - 1,25(OH)₂D₃
  - 1α(OH)ase
  - 25(OH)D₃
  - Urine Pi
  - Kidney

Intestine
- Vitamin D
  - 1α(OH)ase
  - 25(OH)D₃
  - 1,25(OH)₂D₃
Symptoms and Signs of PHPT

- “Stones”
- “Bones”
- “Abdominal groans”
- “Psychic moans”
- Polyuria/nocturia
- Cardiovascular?
- Neurologic?

Primary Hyperparathyroidism (PHPT)

- Accounts for 80-90% of hypercalcemia in asymptomatic outpatients
- 75-85% are asymptomatic
- 75% are women; incidence 2% in PMW
- Average age at diagnosis: 55 years
- 10-20% have kidney stones or bone disease (osteoporosis)
- Calcium elevation mild (10.5 – 11.5 mg/dl)
- PTH elevated in 85%; “normal” in 15%

What Other Tests Are Recommended?

A. None, the diagnosis is clear
B. 24 hour urine calcium
C. 25-hydroxy-vitamin D
D. DXA of spine, hip, and 1/3 distal radius
E. C and D

Vitamin D and Hyperparathyroidism

- Patients with PHPT often have vitamin D deficiency
- Results in secondary HPT, higher PTH levels, and increased adenoma size
- Consensus conference recommends checking and correcting vitamin D deficiency in every patient with PHPT prior to surgical intervention

Does Correcting Vit D Deficiency Worsen Hypercalcemia in PHPT?

- Vitamin D replacement had no significant effect on serum calcium
- Reduced PTH by 25%
- Reduced bone turnover

What Would You Do Now?

A. Monitor her over time
B. Increase her calcium intake to 1800 mg daily
C. Send her to a parathyroid surgeon
D. Begin alendronate 70 mg weekly
E. Begin cinacalcet 30 mg daily
**2008 Consensus Guidelines:**

**Who should have parathyroid surgery?**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms/stones</td>
<td>Present</td>
</tr>
<tr>
<td>Serum Ca</td>
<td>1.0 mg/dl above normal</td>
</tr>
<tr>
<td>BMD</td>
<td>T-score -2.5 or below</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 50 yr</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>Reduced to &lt;60 ml/min</td>
</tr>
</tbody>
</table>

Bilezikian JP et al. J Clin Endocrinol Metab 2009; 94:335

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**Monitoring Patients With PHPT Who Do Not Undergo Surgery**

<table>
<thead>
<tr>
<th>MEASUREMENT</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium</td>
<td>Annually</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Annually</td>
</tr>
<tr>
<td>Urinary calcium</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Bone density</td>
<td>1-2 years (3-sites)*</td>
</tr>
<tr>
<td>Abdominal U/S, KUB</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

Bilezikian JP et al. J Clin Endocrinol Metab 2009; 94:335

*Not universally accepted; Sankaran S et al. J Clin Endocrinol Metab 2010 95:1653

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**Biochemical Stability of Untreated PHPT**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>BASELINE (N=62)</th>
<th>YEAR 5 OF FOLLOW-UP (N=35)</th>
<th>YEAR 10 OF FOLLOW-UP (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>10.3±0.1</td>
<td>10.6±0.1</td>
<td>10.3±0.1</td>
</tr>
<tr>
<td>Serum parathyroid hormone (pg/ml)</td>
<td>118±9</td>
<td>115±6.7</td>
<td>106±26</td>
</tr>
<tr>
<td>Urinary calcium (mg/day)</td>
<td>232±18</td>
<td>195±20</td>
<td>152±34</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/liter)</td>
<td>98±26</td>
<td>101±29</td>
<td>110±13</td>
</tr>
<tr>
<td>Serum 1,25-dihydroxyvitamin D (pg/ml)</td>
<td>36±2</td>
<td>38±3</td>
<td>32±6</td>
</tr>
</tbody>
</table>

Nearly 1/3 had progression of disease


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**Follow Up**

- Patient elected to be monitored without surgery or treatment
- She maintained 800 – 1000 mg elemental calcium in diet and 800 IU vitamin D3 daily
- Labs remained stable over the next 2 years but BMD declined significantly at spine and hip to T-score -2.6 and -2.3, respectively

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**What Would You Do Now?**

A. Monitor her over time
B. Increase her calcium intake to 1800 mg daily
C. Send her to a parathyroid surgeon
D. Begin raloxifene 60 mg daily
E. Begin cinacalcet 30 mg daily

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**Microarchitecture of Bone in Primary Hyperparathyroidism**

Primary Hyperparathyroidism: Bone Density Profile

Do Patients with PHPT Have a Higher Fracture Risk?

Approach to Patients with PHPT Followed Without Surgery

Non-Pharmacologic Antiresorptives
- Dietary Calcium
- Vitamin D
- Hydration
- Mobilization
- Avoid thiazides & lithium if possible

- Estrogen
-Raloxifene
- Bisphosphonates
- Cinacalcet
- Denosumab?

Alendronate Increases BMD in Primary Hyperparathyroidism

Lumbar Spine BMD

Structure of the Calcimimetic Cinacalcet

Cinacalcet Mimics a High Ca State at the Calcium Sensing Receptor
Effect of Cinacalcet on Serum Calcium in PHPT

Effect of Cinacalcet on Bone Density in PHPT
- Patients with PHPT on cinacalcet showed no improvement in BMD after 5.5 years of use.
- Though cinacalcet is FDA-approved for PHPT in patients unable to have surgery, the high cost and failure to improve BMD make it less appealing for most patients.

Our Patient, Continued
- She tried alendronate and ibandronate but had significant GI upset.
- She asked to see a surgeon who could perform “minimally invasive parathyroidectomy” (MIP).

Surgical and Pathologic Findings in PHPT
- 80% solitary adenoma
- 15% 4-gland hyperplasia
- 2-4% multiple adenomas
- <0.5% parathyroid carcinoma

Surgery for PHPT
- Standard bilateral neck exploration
- Minimally invasive parathyroidectomy
  - Local anesthesia
  - Single gland resection
  - Intraoperative PTH monitoring

One Year Post-Op
- BMD stabilized at all sites
- She is doing well
**Case**

- A 40 year old woman is admitted with altered mental status after 72 hours of N/V, and epigastric pain.
- She was recently on vacation and drank a lot of alcohol
- She has a history of PUD in the past
- She is on no prescription medications
- While on vacation, she developed abdominal pain over several days that became severe
- In the ER, her total serum calcium is 16.2 mg/dl

**Physical exam**

- She was disoriented, writhing in pain: BP 110/90, P 100, T 102 F
- Skin turgor was poor; oral mucosa dry
- No thyromegaly or lymphadenopathy
- Heart/lung exam unremarkable
- Breast exam negative for masses
- Abdomen: + epigastric tenderness without rebound;
- Neuro: lethargic; not tremulous; nonfocal

**Labs**

- K+ 3.1, HCO3 37
- BUN 28, Creat 2.0
- Calcium 16.2
- Ionized Ca 1.75
- Phosphate 3.0
- Intact PTH < 10
- 25OHD 45 ng/ml
- 1,25OHD < 15
- Amylase 1300
- Lipase 1800

**Treatment**

- Vigorous IV saline hydration (200-300 cc/hr or more) plus K+, antibiotics, and analgesics given
- Follow up labs are shown:

<table>
<thead>
<tr>
<th>LABS</th>
<th>Ca</th>
<th>Cr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>11.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Day 2</td>
<td>8.5</td>
<td>0.6</td>
</tr>
</tbody>
</table>

**What is the Underlying Cause of the Hypercalcemia?**

A. Malignancy  
B. Addison’s disease  
C. Acute renal failure  
D. Milk-alkali syndrome  
E. Pancreatitis

**Further history**

- During several days PTA, she consumed multiple bottles of Tums (calcium carbonate) and Alka Seltzer (sodium bicarbonate) due to abdominal pain
Milk Alkali Syndrome

- Triad of hypercalcemia, renal insufficiency, and metabolic alkalosis associated with ingestion of large amounts of calcium and absorbable alkali
- 1915: Bertram Sippy introduced hourly ingestion of milk/cream + alkaline powders for PUD ----> renal failure, alkalosis, hypercalcemia

Milk-Alkali Syndrome

- By 1985 with advent of PPIs, MAS was rarely seen
- More recently, PMP women taking excess calcium for osteoporosis have led to increase in MAS
- Occasional patients still take lots of calcium carbonate for GI upset

Typical Response of Ca and PTH in Milk Alkali Syndrome

![Graph showing response of calcium and PTH](http://emedicine.medscape.com/article/123324-overview)

Pathogenesis

- Ingestion of excess calcium and alkali can be handled by most (↑ calcitriol and ↑ PTH)
- Intake of 10 – 15 gm calcium carbonate per day is often needed for the syndrome
- Hypercalcemia induces renal vasoconstriction, decreased GFR and bicarbonate reabsorption at renal tubule
- Metabolic alkalosis increases tubular reabsorption of calcium
- Hypovolemia (N/V) further decreases GFR

Pathogenesis

- Hyperphosphatemia is common when excess MILK (containing 250 mg phosphorus per 8 oz) and alkali are ingested but NOT when only calcium (eg. TUMS) and alkali are ingested
- Hypophosphatemia is seen in 40% of those with excess CaCO3 ingestion
- History is KEY to making the diagnosis

Differential Diagnosis of Non-PTH Mediated Hypercalcemia

**ABSORPTIVE**
- Excess exogenous vitamin D*
  - Vitamin D intoxication
- Excess endogenous vitamin D*
  - Granulomatous lymphomas
- Excess calcium
  - Milk-alkali syndrome

**RESORPTIVE**
- Multiple myeloma
- Immobilization (Paget's)
- Hyperparathyroidism
- Malignant osteolytic bone disease
- Addison's disease
-PTHrP-mediated
  - Squamous cell CA
  - Renal cell CA
- Local metastases
- Breast CA
- Excess vitamin A

Note that all may involve some degree of renal insufficiency and inability to excrete calcium

* Involves excess resorption also
In-Patient Hypercalcemia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>% of total cases (n=1628)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>45%</td>
</tr>
<tr>
<td>PHPT</td>
<td>25%</td>
</tr>
<tr>
<td>Renal failure</td>
<td>10%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>20%</td>
</tr>
</tbody>
</table>


Work-up for Non-PTH Mediated Hypercalcemia

HISTORY AND PHYSICAL EXAM ARE KEY!

- SPEP, UPEP
- 25(OH) vitamin D
- 1,25(OH)2 vitamin D
- Serum ACE
- Cortisol
- Vitamin A (if indicated)
- PTHrP (rarely necessary)
- CXR
- Bone scan
- Mammography
- CT scan of chest, abdomen, pelvis
- Lymph node or tissue biopsy

Management of Hypercalcemia

- Vigorous IV hydration; no furosemide unless CHF/volume overloaded*
- IV bisphosphonate should be used early on (pamidronate or zoledronic acid) EXCEPT in suspected MAS; takes 48 hrs or longer to work
- Calcitonin 4 U/kg SQ q 12 hrs is quick
- Cinacalcet 30 mg PO 1-2 x per day for PHPT as bridge to surgery
- Treat underlying disease

*LeGrand 2008; Ann Intern Med 149:259

LifeThreatening Hypercalcemia in a Woman With Addisonian Crisis: Reversal with Hydrocortisone

Case

- An 80-year-old F comes in with back pain after lifting a heavy glass table.
- PE notable for tenderness in lumbar region
- X-ray shows a partial compression fracture at L1

Painful vertebral fracture

Case

- CBC, TSH, lytes, BUN, creatinine, glucose: normal
- Calcium 12.6 mg/dl
- Intact PTH 11 pg/ml (normal 10-65)
- Alk phos 240 U/L
- GGTP, LFTs normal

What is the Most Likely Etiology of the Hypercalcemia?

A. Malignancy  
B. Primary hyperparathyroidism  
C. Vitamin D intoxication  
D. Paget’s disease  
E. Sarcoidosis

Additional Testing

- SPEP, UPEP nl  
- 25(OH)D 15 ng/ml  
- 1,25(OH)2D 12 ng/ml  
- CXR no infiltrates  
- Bone scan → multiple metastases to bone

Multiple Bony Metastases

Day After Admission

- On further questioning, patient admits that she has refused mammograms and breast exams for 30 years  
- Left breast is totally replaced by tumor with peau d’orange appearance and skin necrosis

Peau d’orange appearance of infiltrative breast cancer

Bisphosphonate Therapy for Severe Hypercalcemia

- Doses  
  - Pamidronate 30-90 mg over 2-4 hrs  
  - Zoledronic acid 4 mg over 20 mins  
- Acute Side effects  
  - Acute phase rxns  
  - Renal insufficiency  
  - Hypocalcemia

Vertebral Metastasis

Follow Up

- She was started on hormonal therapy for breast cancer, vitamin D3 800 IU daily and monthly intravenous zoledronic acid  
- Bone pain resolved and fractures healed.  
- She lived for another 3 years

Baron R, Ferrari S, Russell RGG. Bone 2010 [epub]
Case

• A 30 yo woman with SLE develops ESRD and requires hemodialysis. Over a period of years, her serum calcium and PTH levels rise dramatically.
• Labs:
  - Total calcium cor = 12.5 mg/dl (8.8-10.4)
  - Intact PTH = 6300 pg/ml (10 – 65)
  - Alk phos = 978 U/L (30 – 118)
• She goes for 3.5 gland parathyroidectomy after failing medical management with cinacalcet.

Labs Post-op

• Postoperatively, she develops profound, symptomatic hypocalcemia requiring massive doses of intravenous calcium gluconate for over 3 weeks in the hospital.
• Labs after 3 weeks in hospital:
  - Total Calcium 6.8 mg/dl (nl 8.8-10.4)
  - Phos 1.7 (nl 2.5-5).
  - Intact PTH 30 (nl 10-65)
  - Mg 2.1
  - Albumin 3.5

“Factitious” Hypocalcemia

• Decreases in protein concentrations or hemodilution can lead to misleadingly low total serum calcium
• To avoid this, measure ionized serum calcium directly or, correct for serum albumin:
  - Add 0.8 mg/dl to total Ca for every 1 g/dL of albumin below 4.0 g/dL (not always accurate in hospitalized patients)

What is the Single Most Important Cause of Her Persistent Hypocalcemia?

A. Borderline hypomagnesemia
B. Surgical hypoparathyroidism
C. Hungry bone syndrome
D. Undiagnosed vitamin D deficiency
E. Adynamic bone disease

Hungry Bone Syndrome

• First described in 1948 by Albright and Reifenstein
• Hypocalcemia with varying degrees of hypophosphatemia after parathyroidectomy
• Due to avid retention of calcium in demineralized bones as result of previous primary or secondary hyperparathyroidism

Hungry Bone Syndrome

• Depends on preoperative level of PTH and duration of hyperparathyroidism;
• High alkaline phosphatase and/or osteitis fibrosa cystica preoperatively are major predictors
• Occurs in up to 30% of patients with PHPT and virtually all with secondary HPT
• Usually resolves within in 2-3 weeks but rarely, can persist for months or years

“Brown tumor” of osteitis fibrosa cystica
Follow Up

- She required prolonged infusions of intravenous calcium and multiple admissions for recurrent, symptomatic hypocalcemia for 2 years following the parathyroid surgery
- Now is doing well on regimen of calcium and calcitriol (1,25(OH)₂D)

Causes of Hypocalcemia (↑ PTH)

**Calcium Deficiency**
- Chronic renal failure
- Ca²⁺ malabsorption
- Hyperphosphatemia
- Drugs
- Pancreateatitis
- "Hungry bone syndrome" post-PTX
- Miscellaneous

**Vitamin D Deficiency**
- Inadequate sun exposure
- Inadequate dietary intake
- Fat malabsorption
- Anticonvulsants
- Nephrotic syndrome
- Chronic renal failure
- Inherited disorders*

*includes vitamin D and PTH resistant states

Causes of Hypocalcemia and Low PTH (Hypoparathyroidism)

- Genetic syndromes
  - DiGeorge syndrome
  - PTH gene mutations
  - Activating mutations of CaSR
- Infiltrative
  - Wilson’s syndrome
  - Hemochromatosis I
  - Iron overload in thalassemia
  - Granulomatous, malignancy
- Autoimmune
  - Polyglandular failure Type 1 (HAM)
  - Sporadic isolated
  - Activating antibodies vs CaSR
- Hypomagnesemia

Neuromuscular Signs and Symptoms of Hypocalcemia

- Paresthesias of fingers, toes, circumoral
- Tetany, carpopedal spasm, muscle cramps
- Chvostek sign
- Trousseau’s sign
- Seizure
- Prolonged QT
- Laryngospasm
- Bronchospasm
- Basal ganglia calcifications

Case

- A 48 yo male with muscle weakness, paresthesias, and cramping in his hands and feet
- PMH: morbid obesity rx’d with Roux-en-Y gastric bypass surgery 12 mos ago; takes MVI
- ROS: Chronic diarrhea; 120 lbs weight loss
- PE: + Chvostek and Trousseau’s sign

- Labs
  - Hct 30%, MCV 72
  - Calcium 6.5 mg/dl
  - Albumin 3.0 g/L
  - Ca_correct 7.3 mg/dl
  - Phos 2.0 mg/dl
  - PTH 225 pg/ml (10-65)
What is the Most Likely Cause of the Hypocalcemia?

A. Magnesium deficiency
B. Calcium deficiency
C. Vitamin D deficiency
D. B and C
E. All of the above

Other Tests

- Magnesium 1.5
- 25-hydroxy-vitamin D < 7 ng/ml
- Alkaline phosphatase 180 U/L (<110)

SECONDARY HYPERPARATHYROIDISM

Roux-en-Y and Metabolic Bone Disease

- Roux-en-Y is leading bariatric surgery in US
- Up to 25% develop Ca deficiency by 2 years; 48% by 4 years
- Up to 52% develop Vit D deficiency by 2 years

Symptoms of Metabolic Bone Disease in Patients s/p MBS

- Myalgias and arthralgias
- Muscle weakness
- Fatigue
- Paresthesias
- Muscle cramping
- Bone pain
- Trouble walking
- Fractures/pseudofractures

Malabsorptive Bariatric Surgery (MBS) and Metabolic Bone Disease

- Roux-en-Y
- O/M or Excluded Stomach
- Jejunum
- Transverse Intestine
- Peach
### Management of Metabolic Bone Disease After Bariatric Surgery

- Ergocalciferol 50,000 IU 2-3 times per week; may need 1-3 doses PER DAY
- Calcitriol (1,25-dihydroxy-vitamin D) 0.25 - 1.0 mcg 1-2 times per day
- Advise dietary Ca and calcium citrate; may need large doses

### Acute Treatment of Symptomatic Hypocalcemia

- Intravenous calcium gluconate
  - 90 mg elemental calcium per 10 ml ampule
  - 1-2 ampules in 50-100 cc D₅W IV infusion over 10 minutes
- 10 ampules in 1000 cc D₅W IV over 24 hrs for persistent hypocalcemia
- Treat hypomagnesemia if present

### Summary

- Disorders of calcium metabolism are common in primary care medicine
- Calcium disorders may be acute and life-threatening, or mild and chronic
- Proper diagnosis requires an understanding of calcium homeostasis
- Optimal treatment depends on severity of disorder as well as etiology

### Summary

- PHPT is the most common cause of hypercalcemia among healthy outpatients
- Malignancy and PHPT are the most common etiologies among inpatients
- PTH is the key regulator of calcium homeostasis and is the key test to check in any patient with abnormal Ca

### References