Approach to a patient with hypercalcemia

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Background

• Hypercalcemia is a problem frequently encountered in clinical practice

• Most common causes:
  • primary hyperparathyroidism
  • malignancy
Mechanisms of calcium homeostasis

1. Parathyroid gland releases PTH
2. PTH stimulates Ca²⁺ release from bones
3. Parathyroid glands release parathyroid hormone (PTH)
4. Increases Ca²⁺ uptake in intestines
5. Blood Ca²⁺ rises
6. Stimulus: Rising blood Ca²⁺ level (imbalance)
7. Calcitonin
8. Stimulates Ca²⁺ deposition in bones
9. Blood Ca²⁺ falls
10. Homeostasis: Normal blood calcium level (about 10 mg/100 mL)
11. Parathyroid gland

Stimulus: Falling blood Ca²⁺ level (imbalance)

Thyroid gland releases calcitonin

Active vitamin D

Increases Ca²⁺ uptake in intestines

Stimulates Ca²⁺ release from bones

Stimulates Ca²⁺ deposition in bones

Reduces Ca²⁺ uptake in kidneys
Clinical case #1

• 69 yo female, no significant PMHx
• Recently diagnosed hypercalcemia
• ROS: mild fatigue
• No FHx of calcium abnormalities
• No calcium supplements, normal diet
• PE- unremarkable
Clinical case - cont

- Hb/Hct = nl
- Na = 138 mEq/L (136 – 142)
- K = 3.7 mEq/L (3.5 – 5.0)
- Bicarbonate = 24 mEq/L (21 – 28)
- **Serum Ca = 11.6 mg/dL (8.2 – 10.2)**
- Serum phosphorus = 2.4 mg/dL (2.3 – 4.7)
- **Serum creatinine = 1.3 mg/dL (0.6 – 1.2)**
- 25 (OH) D = 59.2 ng/mL (25 – 80)
- Albumin = 4.1 g/dL (3.5 – 5.0)
Evaluation

• Is it true hypercalcemia?
  • Confirm in multiple measurements
  • Assess albumin level
    • abnormal albumin will alter serum Ca level

  • Corrected serum Ca
    
    \[0.8 \times (4.0 - \text{pt Alb}) + \text{serum Ca}\]

• Severe acidosis or alkalosis (measure ionized Ca)
• Dehydration – will cause a false increase in serum Ca
Evaluation

Hypercalcemia - confirmed, then measure intact parathyroid hormone level (PTH)

- PTH high or inappropriately normal for the serum Ca level
  - Primary hyperparathyroidism
  - Tertiary hyperparathyroidism
  - Familial hypocalciuric hypercalcemia (FHH)
  - Lithium associated hypercalcemia (increases the set point of CAsR for calcium)
  - Ectopic PTH secretion – rare
Evaluation

• PTH suppressed

• History of malignancy – malignancy associated hypercalcemia
  
  • Humoral hypercalcemia of malignancy (PTH-related peptide)
  • 1,25 (OH)2 D (hematologic malignancies)
  • Osteolytic metastases
  • Multiple myeloma
Evaluation

- PTH suppressed
  - No history/suspicion of malignancy
    - measure
      - 25 (OH) D
      - 1,25 (OH)2D
Evaluation

• Increased 25 OHD
  • vitamin D intoxication

• Increased 1,25 OH2D
  • granulomatous disease

• Normal vitamin D
  • Milk- alkali (Ca supplementation)
  • Hypervitaminosis A
  • Hyperthyroidism
  • Adrenal insufficiency
  • other
Primary hyperparathyroidism (PHPT)

• Most common etiology of outpatient hypercalcemia
• Third most common endocrine disorder
• Prevalence 2-3:1000 women and 1:1000 men
• Diagnosis in the 60th decade
• Can coexist with malignancy in 15% of cancer patients
Incidence

Yeh, JCEM 2013
Diagnosis

- Most often discovered incidentally
- Nephrolithiasis – most common 15 - 20%
- Typical symptoms of hypercalcemia
- Nonspecific symptoms such as weakness, fatigue, neuromuscular dysfunction, neuropsychiatric disturbances
- Bone mineral density may show osteopenia or osteoporosis with predilection for the radius
Symptomatology

• **Mild** (serum Ca <12 mg/dL)
  - asymptomatic or nonspecific symptoms (fatigue, depression, constipation, mild polyuria, mild increase in thirst, mild impairment in cognition)

• **Moderate** (Ca 12-14 mg/dL)
  - anorexia, nausea, abdominal pain, muscle weakness, depressed mental status, dehydration

• **Severe** (Ca>14 mg/dL)
  - lethargy, disorientation, coma
Laboratory findings

- High normal or elevated serum calcium
- Low normal to decreased serum phosphate
- Increased or inappropriately normal serum PTH
- Increased total alkaline phosphatase
- Increased markers of bone turnover – (CTx-telopeptide)
- Increased 1,25 (OH)2 D
- 24-hour urine for calcium above the upper limit of normal
Differential diagnosis

- Familial Hypocalciuric Hypercalcemia
  - $\text{FeCa} = \left[\frac{\text{UCa}}{\text{PCa}}\right] / \left[\frac{\text{UCr}}{\text{PCr}}\right]$ ( <1% )
    - Mutations in Ca sensing receptor gene
- Tertiary hyperparathyroidism
- Parathyroid carcinoma
- Parathyroid cyst
- Ectopic PTH production
Recommendations for evaluation of patients with asymptomatic PHPT

Table 3. Recommendations for the Evaluation of Patients With Asymptomatic PHPT

<table>
<thead>
<tr>
<th>Recommended</th>
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<tbody>
<tr>
<td>Biochemistry panel (calcium, phosphate, alkaline phosphatase activity, BUN, creatinine, 25(OH)D</td>
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<tr>
<td>PTH by second- or third-generation immunoassay</td>
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<tr>
<td>BMD by DXA</td>
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<tr>
<td>Lumbar spine, hip, and distal 1/3 radius</td>
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<tr>
<td>Vertebral spine assessment</td>
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<tr>
<td>X-ray or VFA by DXA</td>
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<tr>
<td>24-h urine for:</td>
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<tr>
<td>Calcium, creatinine, creatinine clearance</td>
</tr>
<tr>
<td>Stone risk profile</td>
</tr>
<tr>
<td>Abdominal imaging by x-ray, ultrasound, or CT scan</td>
</tr>
<tr>
<td>Optional</td>
</tr>
<tr>
<td>HRpQCT</td>
</tr>
<tr>
<td>TBS by DXA</td>
</tr>
<tr>
<td>Bone turnover markers (bone-specific alkaline phosphatase activity, osteocalcin, P1NP [select one]; serum CTX, urinary NTX [select one])</td>
</tr>
<tr>
<td>Fractional excretion of calcium on timed urine sample</td>
</tr>
<tr>
<td>DNA testing if genetic basis for PHPT is suspected</td>
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Abbreviations: BUN, blood urea nitrogen; P1NP, procollagen type I N-propeptide; CTX, C-telopeptide cross-linked collagen type I; NTX, N-telopeptide of type I collagen. This evaluation is for PHPT, not to distinguish between PHPT and other causes of hypercalcemia.
Changes in criteria for surgical intervention

Table 1. Guidelines for Surgery in Asymptomatic PHPT: A Comparison of Current Recommendations With Previous Ones

<table>
<thead>
<tr>
<th></th>
<th>1990</th>
<th>2002</th>
<th>2008</th>
<th>2013</th>
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<tbody>
<tr>
<td>Measurement</td>
<td></td>
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<tr>
<td>Serum calcium</td>
<td>1–1.6 mg/dL (0.25–0.4 mmol/L)</td>
<td>1.0 mg/dL (0.25 mmol/L)</td>
<td>1.0 mg/dL (0.25 mmol/L)</td>
<td>1.0 mg/dL (0.25 mmol/L)</td>
</tr>
<tr>
<td>Skeletal</td>
<td>BMD by DXA: Z-score ≤ −2.0 (site unspecified)</td>
<td>BMD by DXA: T-score ≤ −2.5 at any site</td>
<td>BMD by DXA: T-score ≤ −2.5 at any site</td>
<td>A. BMD by DXA: T-score ≤ −2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. eGFR reduced by &gt;30% from expected</td>
<td>A. eGFR reduced by &gt;30% from expected</td>
<td>A. eGFR &lt; 60 cc/min</td>
<td>A. Creatinine clearance &lt; 60 cc/min</td>
<td></td>
</tr>
<tr>
<td>B. 24-h urine for calcium &gt;400 mg/d (&gt;10 mmol/d)</td>
<td>B. 24-h urine for calcium &gt;400 mg/d (&gt;10 mmol/d)</td>
<td>B. 24-h urine for calcium not recommended</td>
<td>B. 24-h urine for calcium &gt;400 mg/d (&gt;10 mmol/d) and increased stone risk by biochemical stone risk analysis</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>&lt;50</td>
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Bilezikian, JCEM, 2014,99(10):3561-3569
Monitoring of the normocalcemic patient with PHPT

- Calcium and PTH annually
- DXA every 1-2 years

Progression to hypercalcemic PHPT
- Follow guidelines

Progression of disease
- Worsening BMD or fracture
- Kidney stone or nephrocalcinosis

Surgery

Figure 1. Algorithm for monitoring patients with normocalcemic PHPT.

Bilezikian, JCEM, 2014,99(10):3561-3569
Monitoring patients with PHPT who do not undergo surgery

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<tbody>
<tr>
<td>Serum calcium Skeletal</td>
<td>Biannually DXA, annually (forearm)</td>
<td>Biannually DXA, annually (3 sites)</td>
<td>Annually DXA, every 1–2 y (3 sites)</td>
<td>Annually Every 1–2 y (3 sites), x-ray or VFA of spine if clinically indicated (eg, height loss, back pain)</td>
</tr>
<tr>
<td>Renal</td>
<td>eGFR, annually; serum creatinine, annually</td>
<td>eGFR, not recommended; serum creatinine, annually</td>
<td>eGFR, not recommended; serum creatinine, annually</td>
<td>eGFR, annually; serum creatinine, annually. If renal stones suspected, 24-h biochemical stone profile, renal imaging by x-ray, ultrasound, or CT</td>
</tr>
</tbody>
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Bilezikian, JCEM, 2014,99(10):3561-3569
Localization studies

• If a decision to treat surgically has been made, localizing studies may be helpful for the surgical procedure

  • Sestamibi scan + SPECT detects about 90% of primary tumors

• US: sensitivity 70% in detecting solitary adenomas
  • Poor sensitivity for multiple gland disease
Medical management

• Vit D repletion: 800-1000 IU/day (goal >20 ng/dL)
• Ca intake: per general guidelines (food sources preferred)
• Maintaining good oral hydration
• Hormone replacement therapy or raloxifene in postmenopausal women
• Anti-resorptive therapy (bisphosphonates)
• Calcimimetics (cinacalcet)
Cinacalcet treatment of PHPT

Peacock, JCEM, 2009,94(12):4860-4867
Alendronate treatment in PHPT

Khan, JCEM 2004, 89(7):3319-3325

LS
TH
FN
DR

Khan, JCEM 2004, 89(7):3319-3325
Back to our case...

- PTH = 87.6 pg/mL (10 – 50)
- 24 hr urine Ca = 318 mg/24 hr (100 - 250)
- 24 hr urine Cr = 2.2 g/24 hr (0.63 – 2.3)
  - FeCa= 1.6%

Primary hyperparathyroidism
Neck US

RT INF TO THY LONG

Parathyroid adenoma
Doppler imaging of the parathyroid adenoma

RT INF TO THY LONG

Polar artery
Sestamibi scan
Treatment

- Resection of a 280 mg right inferior parathyroid adenoma
- Post surgery calcium levels normalized
- Symptomatology improved

- ! Non specific symptoms may not improve with surgery.
- In patients with vit. D deficiency, weeks after surgery the PTH can be elevated –secondary HPTH
Case #2

- 57 year old Caucasian female
- Past medical history of hepatitis C

- Endocrinology service was consulted for acute symptomatic hypercalcemia with serum Ca level as high as 18 mg/dl, requiring multiple hospitalizations, and refractory to treatment with hydration, bisphosphonates and cinacalcet.
Laboratory

- **Serum Ca = 12.5 mg/dl (8.2 – 10.2)**
- **PTH = 8.4 pg/ml (10 – 50)**
- **PTHrp = 0.3 pmol/L (<2.0)**
- **Phos = 2.6 mg/dL (2.3 – 4.7)**
- **Cr = 1.8 mg/dl (0.6-1.2)**
- **1,25 (OH)2 vit D = 100 pg/ml (16-65)**
- **25 OHD = 54.8 ng/ml (25-80)**
- **ACE = 78 u/l (8-53)**
Case #2

- Evaluated by multiple subspecialties (ID, pulmonary medicine and oncology) for concerns regarding either a malignancy or granulomatous disease.
- Further history taking revealed that she had a buttocks augmentation procedure using silicone injections.
- PET-CT imaging revealed multiple granulomas in the gluteal region.
- Biopsy confirmed silicone induced granulomas.
Chest abdomen and pelvis CT at the initial evaluation
Case #2 - course

• Initial treatment: oral prednisone 20 mg /day
  • Reduction of serum Ca to 11.1 mg/dl

• Dose was increased to 40 mg/day
  • Normalization of serum Ca and 1,25 (OH)2 vit D
PET – silicone granulomas in the gluteal region

Pre-treatment
6 months after initiation of treatment
Management – general considerations

• Correct underlying cause when possible
  • Treatment of primary hyperparathyroidism
  • Diet modifications, adjusting Ca supplements
  • Discontinuing vitamin D supplement
  • Cinacalcet or 3 1/2 gland parathyroidectomy (tertiary hyperparathyroidism)
• Adjusting medications (HCTZ, Lithium)
• Treatment of granulomatous diseases
• Treatment of malignancy
Key points

• First step in evaluating a new diagnosis of hypercalcemia is confirming it

• Over 90% of cases are due to PHPT and hypercalcemia of malignancy

• Therapy for hypercalcemia needs to be directed at the underlying etiology
Key points

- Criteria for surgery in PHPT
  - Age <50
  - Serum Ca 1 point > upper NL
  - BMD T score <= -2.5
  - Vertebral fracture
  - Cr Cl <60 cc/min
  - Urinary Ca > 400 mg/24 hr and increased stone risk
  - Nephrolithiasis or nephrocalcinosis by Xray, US or CT
Hypercalcemia

True?

yes

no

Measure intact PTH

High/inappropriately normal

FeCa

CKD

<1%

>1%

PHPT

FHH

THPT

Suppressed

Malignancy

No malignancy

25OHD & 1,25OH2D

High 1,25OH2D

Granulomatous disease

Lymphoma

High 25 OHD

Toxicity

normal

Dietary Ca
Vit A
Hyperthyroidism
Adrenal insufficiency
Pheochromocytoma

Treat underlying cause
Thank you!