Calcium, Vitamin D, PTH Disorders

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Disclosure
I have nothing to disclose related to this topic

Topic Outline
- Calcium/Vitamin D/PTH physiology
  - Normal compensatory responses when calcium homeostasis is perturbed
- Work up for hypercalcemia
  - What surgeons need to know
- Diagnosing primary hyperparathyroidism
  - Normocalcemic primary hyperparathyroidism
  - Differential diagnoses:
    - Familial hypocalciuric hypocalcemia (FHH)
    - Medications
- Treatment of postoperative hypoparathyroidism
- Cases

Primary Hyperparathyroidism 4th IW
- The surgical management of asymptomatic primary hyperparathyroidism: proceedings of the fourth international workshop.
  - Udelsman R, Akerström G, Biagini C, Duh QY, Miccoli P, Niederle B, Tozelli P.
- Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the fourth international workshop.
- Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the fourth international workshop.
- Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the fourth international workshop.
**PTH & Calcium**

**Normal Physiology**

- **PTH secretion**
  - Regulated by ica** in the blood (major regulator)
  - Response within seconds to minutes
- **Others:**
  - Mg**
  - PO₄²⁻
  - 1, 25(OH)D

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**Role of Vitamin D & Calcium**

- **25 OHD – vitamin D store**
  - ½ life 2 weeks
  - Correlates with secondary hyperparathyroidism
  - 1, 25 D – Most active form
- **Not typically measured when assessing for D def**
  - 1 α hydroxylase enzyme – tightly regulated

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**Defining Vitamin D Sufficiency**

**Endocrine Society Guidelines**

- Sufficiency: > 30 ng/ml
- Insufficiency: 20 - 30 ng/ml
- Deficiency: < 20 ng/ml

**Institute of Medicine**

- Sufficiency: ≥ 20ng/mL
- Insufficiency: 10-20 ng/ml
- Deficiency: < 10 ng/mL

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**PTH, Vitamin D, Calcium**

- **PTH: direct renal effects**
  - ↑Ca reabsorption
  - ↑Phos excretion
  - ↑ 1 α hydroxylase
- **PTH: direct bone effect**
- **PTH: indirect bone effect**
  - ↑Ca/Phos absorption via 1,25 D
Secondary Hyperparathyroidism

- **Vitamin D related**
  - Sun/Diet deprivation
  - Malabsorption (fat)
    - Small bowel, pancreatic, hepatic biliary diseases
    - Celiac disease
  - Medications ↑ metabolism
    - Anticonvulsants, HAART, steroids
- **Impaired Absorption**
  - GI disorders
    - calcium and/or vitamin D malabsorption
    - Aging, corticosteroid treatment
- **Chronic Kidney Disease**
  - ↓ 1,25 (OH) D, hyperphosphatemia
- **Renal Leak Hypercalciuria**
  - ↑↑ 24 hr urine calcium
- **Medications**
  - Anticonvulsants, HAART, steroids
  - Bisphosphonates, denosumab
  - Lithium
- **Other causes**
  - Hungry bone syndrome
  - Pseudo-hypoparathyroidism
    - Resistance to PTH (bone and/or kidney)
  - High PTH, low Ca++/high PO\(_4\)^2-

Hyperparathyroidism

- **Primary**
  - Parathyroid adenoma or hyperplasia
  - Rarely carcinoma
- **Secondary**
  - Compensatory mechanism to restore normal ionized calcium level
  - Normal or low normal or low calcium, with elevated PTH
- **Tertiary**
  - Usually due to longstanding chronic kidney disease, on dialysis
  - Parathyroid hyperplasia → autonomous production → ↑ calcium and PTH

Summary of PTH Effects

- **Major effects**
  - Directly: bone and kidney
  - Indirectly: small intestine
- **Bone**
  - Mobilizes calcium from bone
  - Diseased forms of hyper-secretion: bone resorption → osteopenia/osteoporosis (cortical bone more affected than trabecular bone)
- **Kidney**
  - ↑ 1, 25 vit D production (up-regulates 1 alpha hydroxylase)
  - ↑ calcium reabsorption
  - ↑ phosphate excretion
- **Small Intestine**
  - ↑ calcium/phosphate absorption (via Kidney : ↑ 1, 25 vit D production)

Secondary Hyperparathyroidism

- **Calcium sensing receptor**
  - ↓ Serum Ca\(^{2+}\)
  - ↑ Parathyroid Glands
  - ↑ Bone Ca\(^{2+}\) efflux
  - ↓ PO\(_4\)^2- efflux
  - ↑↑ 1,25(OH)\(_2\)D\(_3\)
  - ↓ Serum Calcium

Hypercalcemia

**PTH measurable**
- Primary hyperparathyroidism
- Familial hypocalciuric hypercalcemia
- Medications
  - Lithium and Thiazide
- Rare malignancy making PTH
- Tertiary hyperparathyroidism

**PTH unmeasurable**
- PTHrp malignancy
- ↑ 1,25(OH)D from granulomatous disease or leukemia
- ↑ 25(OH)D from vitamin D toxicity
- Milk alkali syndrome (excessive calcium intake with renal insufficiency)
- Immobilization
- Vitamin A toxicity
- Theophylline toxicity
- Endocrine causes
  - Hyperthyroidism
  - Acute adrenal insufficiency
  - Pheochromocytoma
  - Acromegaly

Primary Hyperparathyroidism (PHPT)

**Evaluation**
- PTH, Calcium, albumin, phosphate, Cr/GFR (alkaline phosphatase)
  - Albumin corrected calcium: calcium (in mg/dL) + (0.8x (4-albumin in g/dL)
- Ionized calcium  Reliable lab
  - Helpful if ↑ albumin, paraproteinemia, perturbed acid/base patients, making serum calcium less reliable
  - 4-10% patients may have normal serum calcium but elevated ionized calcium in PHPT

**Simultaneously measured**

<table>
<thead>
<tr>
<th></th>
<th>Calcium</th>
<th>PTH</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic/usual</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Normocalcemic PHPT</td>
<td>Normal</td>
<td>↑</td>
<td>(inappropriately ↑)</td>
</tr>
<tr>
<td>Also PHPT</td>
<td>↑ (intermittently ↑)</td>
<td>Normal (inappropriately ↑)</td>
<td>(inappropriate PTH when hypercalcemic)</td>
</tr>
</tbody>
</table>
Familial Hypocalciuric Hypercalcemia (FHH)

- Autosomal dominant
  - Inactivating mutations in the CaSR gene
  - Relative hyposensitivity to calcium level
- Lifelong hypercalcemia
- Surgery is NOT indicated
- Localization studies can be misleading
  - Asymmetry in the size of the glands in FHH

PTH inappropriately normal or mildly elevated
- 80%: PTH normal/↑calcium
- 20%: PTH mildly↑/↑calcium
- Relative low urine calcium excretion
  - Normal or low urine calcium (<100mg)
  - Low calcium to creatinine clearance ratio (<0.01)

Work with Your Endocrinologist

PHPT - Evaluation

- Measuring 25(OH) vitamin D in all patients with PHPT – recommended by 3rd & 4th IW
  - Vitamin D deficiency may worsen clinical picture
  - Normalizing vitamin D lowers PTH
- Correct vitamin D deficiency prior to definitive decision on management of PHPT
  (Also important for definitive diagnosis of PHPT)
- Maintain vitamin D > 20ng/mL (3rd & 4th IW)
  - Higher vitamin D threshold may lower PTH further

PHPT vs FHH

- 54 patients with FHH & 97 patients with PHPT
- Stopped calcium, diuretics (thiazide/loop) for 3-6 days. Excluded patients on lithium
- Significant overlap in urine calcium excretion
  - CCC ratio best diagnostic value
  - >0.02: 65% PHPT and 2% FHH. If < 0.02, genetic studies

PHPT - Evaluation

- Assess urine calcium excretion
  - To differentiate Familial Hypocalciuric Hypercalcemia
  - 24 hour urine calcium excretion or CCC ratio
- Calcium to creatinine clearance ratio (CCC ratio)
  - PHPT typically higher CCC > 0.02, > 90% likelihood of PHPT
  - FHH typically low CCC < 0.01, >95% likelihood of FHH
  - Vitamin D replete – important to interpret the result

U-Ca X S-creat

S-Ca X U-creat

Spot or timed urine collections
Simultaneous urine/serum measurements

Eastell et al. JCEM 2014

Eastell et al. JCEM 2014

3rd and 4th IW
< 0.01 → FHH
> 0.02 → PHPT
Genetic studies in-between

Look for prior Ca levels
NI → PHPT

1mmol = 40mg
0.01
Overlap

1000mg
500mg
250mg
100mg
Assessment of PHPT
Medication Interference

Thiazide
- ↓ urine ca excretion
- Can cause ↑ ca (with detectable PTH level)
  - May unmask PHPT in some patients
- Can worsen hypercalcemia in patients with PHPT

Stop and reassess

Lithium
- Shift the Ca-PTH curve to the right
  - Higher set point of calcium to suppress PTH secretion
- 10-20% hypercalcemia - hypocalciuria (↓ renal ca excretion)
- PTH inappropriately normal or elevated
- Long term use may lead to PHPT (hyperplasia or adenoma)

Stop and reassess

Normocalcemic PHPT

- RIGOROUSLY EXCLUDE SECONDARY HYPERPARATHYROIDISM
  - Vitamin D def, renal disease, renal calcium leak (24 hour urine calcium), malabsorption, medications (see secondary hyperparathyroidism slide)
  - Study off of all supplements & thiazide diuretics
  - Discontinue lithium if medically feasible to make the diagnosis
  - Confirm with at least 2 PTH levels over a period of 3-6 months
  - Obtain ionized calcium (reliable lab to measure ionized calcium)
    - 4-10% normal calcium but ↑ ionized calcium (not true normal Ca PHPT)
  - Consider close follow up before deciding surgery
    - Work with your endocrinologist
  - If the diagnosis is correct, it may represent the earliest form of symptomatic PHPT

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Normocalcemic PHPT

<table>
<thead>
<tr>
<th>Clinical f/u of 37 patients clinically defined NC PHPT</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ca++, corr</td>
<td>9.4 (0.1)</td>
<td>9.3 (8.5-10.2)</td>
</tr>
<tr>
<td>Serum PO4²⁻</td>
<td>3.3 (0.1)</td>
<td>3.2 (2.1-4.3)</td>
</tr>
<tr>
<td>Uca</td>
<td>193 (12)</td>
<td>192 (70-350)</td>
</tr>
<tr>
<td>25 OHDng/mL</td>
<td>33 (1)</td>
<td>32 (9-54)</td>
</tr>
<tr>
<td>PTH (10-65,IRMA)</td>
<td>93.5 (5)</td>
<td>79 (65-182)</td>
</tr>
</tbody>
</table>

Mean follow up 3.1 years, up to 8 years
- 14% kidney stones, 11% fragility fractures
- 57% osteoporosis (combined spine, hip and distal 1/3 radius)
- 40% developed progression during follow up
- Surgery in 7: pathology similar to typical PHPT
  - 4 normocalcemic patients
  - 3 normocalcemic → hypercalcemic patients

Summary
PHPT - Recommendations

- Hold diuretics (2 weeks)
  - D/C Lithium if possible (may be problematic to stop)
- Assess vitamin D status
- Address vitamin D insufficiency/deficiency
  - low U-Ca & elevated PTH
- Reassess all biochemical parameters once vitamin D is replete
- Rule out other secondary causes of hyperparathyroidism
- Hold calcium & vitamin D supplements (3 to 6 days before & during re-assessment) for urine calcium excretion
- Obtain good FH

Eastell et al JCEM 2014
Hypoparathyroidism

- Hypocalcemia
- Hyperphosphatemia
- Hypercalciuria
  - Loss of renal calcium retaining effect of PTH

**Hypoparathyroidism - Treatment**

**Acute treatment (for severe symptoms)**

- IV Calcium gluconate 10 ml 10% (1amp) providing about 90mg of elemental calcium. Lasts 2-3 hours.
- Continuous gtt (various regimens)
  - 10 amps in 1L D5W \(\rightarrow 1 \text{ cc} \approx 1 \text{ mg} \text{ of calcium (0.9mg)}\)
  - Can start with initial infusion 50cc/hour
  - Typical requirement 0.5mg-1.5mg/kg/hour
  - Maintain iCa\(^++\) > 1mmol/L
  - Taper as iCa\(^++\) in the low mid range and symptoms abate
    - If calcium is measured, correct for albumin
- Start oral therapy: calcium and calcitriol while on gtt
- Check Mg, treat if low with IV & initiate oral Mg
- Monitor closely: EKG, frequent iCa\(^++\) monitoring 1-2 h
- Cautions with renal failure patients

**Chronic Treatment**

- 1-3 g of elemental calcium in divided doses
- Add calcitriol (0.25 ug qd – 0.5ug bid)
- Hypercalciuria problematic
  - A thiazide diuretic may be needed
- Maintain calcium in the low normal range
- Add phosphate binders if high phosphate
- Treatment vitamin D deficiency if concomitant vitamin D deficiency
- Work with your friendly endocrinologist

**Calcium Supplementation**

- Calcium carbonate: 40% elemental calcium
  - 1250mg of calcium carbonate = 500mg of calcium
  - Require acid for absorption, take with food
- Calcium citrate: 21% elemental calcium
  - Better in patients on PPI or older patients at risks for achlorhydria
  - Can be taken anytime

- Smaller frequent dosing may be better than larger doses

*Harvey JA et al. J Bone Miner Res 1988*
### Case 1: Traps for the Surgeon – What to Avoid

- **69 yo ♂, osteopenia**
  - PMH
    - COPD, CAD
  - S/p chole
    - on Questran in the past for diarrhea
  - Meningioma
  - Seizure, on Dilantin

<table>
<thead>
<tr>
<th>LAB</th>
<th>7/3/08</th>
<th>9/23/08</th>
<th>10/31/08</th>
<th>11/26/08</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</td>
<td>9.3</td>
<td></td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td>ALB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH</td>
<td>94 (H)</td>
<td>97 (H)</td>
<td>92 (H)</td>
<td>50</td>
</tr>
<tr>
<td>25 D</td>
<td>20 (L)</td>
<td>62</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0.62</td>
<td>0.67</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>ALKP</td>
<td>134(H)</td>
<td>119 (H)</td>
<td>150 (H)</td>
<td></td>
</tr>
</tbody>
</table>

Ergo 50,000IU/wk Normal 1/2009

**PTH/ALKP Levels Can Take 3-6 Months to Normalize**

*Not Normocalcemic PHPT - Do Not Operate*

### Case 2: Traps for the Surgeon – What to Avoid

- **56 yo ♂ osteopenic**

<table>
<thead>
<tr>
<th>Lab</th>
<th>9/17/09</th>
<th>10/2/09</th>
<th>10/28/09</th>
<th>11/20/09</th>
<th>1/27/10</th>
<th>2/3/10</th>
</tr>
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<tbody>
<tr>
<td>Ca</td>
<td>8.9</td>
<td>9.8</td>
<td>9.6</td>
<td>10.1</td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td>Alb</td>
<td>4.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phos</td>
<td>3.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH (10-65)</td>
<td>80 (H)</td>
<td>62</td>
<td>51</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 D</td>
<td>53</td>
<td></td>
<td></td>
<td></td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Cr</td>
<td>0.6</td>
<td>0.71</td>
<td>0.61</td>
<td>0.65</td>
<td>0.62</td>
<td>386</td>
</tr>
<tr>
<td>Uca</td>
<td>502</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Started on HCTZ HCTZ 25mg BID

**Renal Leak Hypercalciuria**

### Case 3: Traps for the Surgeon – What to Avoid

- **31 yo man with a history of kidney stones**
  - Ca 10, PTH 93, Uca reported high (300mg)
  - Evaluated by 3 endocrinologists by report and was told to have PHPT and needed surgery

<table>
<thead>
<tr>
<th>Lab</th>
<th>12/13/13</th>
<th>3/26/14</th>
<th>6/20/14</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH</td>
<td>70</td>
<td>56</td>
<td>46</td>
</tr>
<tr>
<td>Ca</td>
<td>9.5</td>
<td>9.4</td>
<td>9.4</td>
</tr>
<tr>
<td>Phos</td>
<td>4.4</td>
<td></td>
<td>3.3</td>
</tr>
<tr>
<td>iCa</td>
<td>1.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alk phos</td>
<td>62</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>25 D</td>
<td>4</td>
<td>9</td>
<td>25</td>
</tr>
</tbody>
</table>

**Ergocalciferol**

**Vitamin D Deficiency**