

Calcium disorders

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Case 1

- A 55-year-old man follows for hypertension
- No complaints
- Valsartan/Amlodipine, Atorvastatin
- BP is controlled. Normal examination
- Serum cr, K normal, ALT normal
- Serum calcium 11.3 mg (normal: 8.5-10.5)
- **How to approach serum calcium?**

Evaluation of high serum calcium

- Repeat serum calcium
- Check PTH
- Adjust for low albumin per formula (some labs do)
Or do ionized calcium
- Biotin can falsely ↓ PTH. So, stop for 2 days & retest
- Common causes:
 - Primary hyperparathyroidism (commonest)
 - Medications: vitamin D, calcium, HCTZ
 - Malignancy, multiple myeloma

Causes of hypercalcemia

Vitamin intoxication (D, A)

Immobilization

Thiazide, Teriparatide, Theophylline,
Tamoxifen, Lithium

Addison's disease, **A**cromegaly

Milk-alkali syndrome ($\uparrow\uparrow$ supplemental Ca^{++})

Inflammation/infection
(TB, sarcoidosis, fungal)

Neoplasia (kidney, lung, breast, MM,
bone mets, lymphoma, leukemia..)

Thyrotoxicosis

Rhabdomyolysis (recovery stage)

AIDS

Parathyroidism ($1^{\text{ry}}, 3^{\text{ry}}$)

Pheochromocytoma

Parenteral nutrition

FHH:
Familial hypocalciuric
hypercalcemia

Determining the cause of high serum calcium

- \uparrow (or high NL) PTH= 1^{ry} hyperparathyroidism
- No symptoms: usually 1^{ry} hyperparathyroidism
- Medications history
 - Thiazides (HCTZ, chlorthalidone) & Lithium can \uparrow Ca⁺⁺, \uparrow PTH
 - Stop for 3 months then repeat labs
- If PTH is low normal or low, evaluate for non-PTH causes
- Very high calcium with symptoms: think malignancy

Determining the cause of high serum calcium

- ↑↑↑ calcium, usually symptomatic: think malignancy
- PTHrp is high in hypercalcemia of malignancy (order if diagnosis is not clear)
- If no malignancy, look for other causes
- 1,25-(OH)₂ vitamin D is high in granulomas (TB, sarcoidosis), lymphoma
- 25-(OH) vitamin D is high with vitamin D intoxication
- If suspecting multiple myeloma, do SPEP & UPEP

Familial hypocalciuric hypercalcemia (FHH)

- High serum calcium with normal or mildly high PTH
- No symptoms, young (<30 y), family history of \uparrow Ca^{++}
- Low urine Calcium:

- Check 24-hr urine calcium & calcium-creatinine clearance (Ca/Cr Cl) ratio

(Ca/Cr Cl) ratio = $[\text{24-hour urine Ca} \times \text{serum Cr}] \div [\text{serum Ca} \times \text{24-hour urine Cr}]$

◆ < 0.01 with 24-hour urine <100 mg = highly likely FHH

- Genetic testing

Approach to hypercalcemia

• Repeat serum calcium (correct for albumin) or ionized calcium
 • PTH

High PTH

Primary hyperparathyroidism

Mildly high or high normal PTH

Primary hyperparathyroidism likely
Consider FHH

24-hour urine calcium
25-OH vitamin D
Ca/Cr Clearance ratio

25-OH vitamin D < 20 ng (50 nmol)

Replace, repeat 24-hr urine calcium & Ca/Cr
Cl ratio when 25-OH D > 20 ng

24-hr urine 100-300 mg
(2.5-5 mmol) & Ca/Cr Cl
ratio 0.01-0.02

Primary hyperparathyroidism
or FHH

Consider the following:

- Monitor calcium & PTH every 6 months
- Family screening for FHH
- CaSR sequence for FHH mutation

24-hr urine < 100 mg (2.5
mmol) & Ca/Cr Cl ratio < 0.01

FHH

24-hr urine > 300 mg (5 mmol)
& Ca/Cr Cl ratio > 0.02

Primary hyperparathyroidism

Low normal or low PTH

Non-PTH mediated
hypercalcemia

Diagnosed
malignancy

No clear
malignancy

PTHrp, 25-OH vitamin D
1,25-(OH)₂ vitamin D

↑ PTHrp

Malignancy

↑ 25-OH vitamin D

Vitamin D
intoxication

↑ 1,25-(OH)₂ vit. D

Granulomatous disease
(TB, sarcoidosis),
lymphoma

Normal

SPEP, UPEP

Normal

Consider other causes
(immobilization, hyperthyroidism,
adrenal insufficiency,...)

Abnormal

Multiple
myeloma

Primary hyperparathyroidism

- High serum calcium with high (or normal) PTH level
- Most often caused by a single parathyroid adenoma
- Evaluation:
 - Serum creatinine, eGFR, phosphorus
 - 25-hydroxyvitamin D
 - 24-hour urine calcium & creatinine excretion
 - DXA scan (lumbar spine, hip, distal 1/3 radius)
 - Renal imaging (X-ray, ultrasound or CT scan) to detect stones

Indication for surgery in primary hyperparathyroidism

- **Option for all patients** (symptomatic & asymptomatic)
- **Surgery is recommended if any of the following:**
 - Serum calcium **>1.0 mg (0.25 mmol)** above upper limit of normal
 - Osteoporosis (T score ≤ -2.5 on DXA) at any site
 - Vertebral fracture (by radiograph, CT, MRI, or vertebral fracture assessment)
 - eGFR <60 mL/min
 - 24-hour urinary calcium [>250 mg/day (6.25 mmol/d) in women; >300 mg/d (7.5 mmol/d) in men]
 - Nephrolithiasis or nephrocalcinosis (by radiograph, ultrasound, or CT)
 - Age < 50 years

Imaging in primary hyperparathyroidism

- Preoperative imaging is not recommended for diagnostic purposes
- Preoperative imaging is recommended for those who are going to have parathyroid surgery to locate the abnormal parathyroid gland(s)
- Preoperative imaging modalities include high resolution neck ultrasound, technetium-99 sestamibi scintigraphy, and contrast-enhanced four-dimensional (4D) computed tomography

Follow up if no surgery

- Monitor the following:
 - Serum calcium, 25-OH vitamin D every year
 - Serum creatinine, eGFR every year
 - DXA (3-site) every 1-2 years (as clinically indicated)
 - Spine imaging if indicated (height loss or symptoms of vertebral fracture)
 - Renal imaging (X-ray, U/S or CT), 24-hour urine calcium: if clinically indicated (suspected kidney stones)

When to recommend surgery in patients who are monitored?

- Serum calcium consistently **>1.0 mg (0.25 mmol)** above the upper limit of normal
- A low trauma fracture
- A kidney stone
- A significant reduction in BMD to a T-score ≤ -2.5 at any site
- A significant reduction in eGFR:
(>3 mL/min per year over 1-2 years)

Medical management of primary hyperparathyroidism: general measures

- This can be offered for patients who refuse surgery or when there is a contraindication for surgery
- Deficiencies in vitamin D and dietary calcium worsen hyperparathyroidism
- Adequate calcium diet:
 - 800 mg/ day for women <50 years and men <70 years
 - 1000 mg/ day for women >50 years and men >70 years
- Adequate vitamin D intake:
 - Serum 25-hydroxyvitamin D >30 ng (75 nmol)

Medical management of primary hyperparathyroidism: drug therapy

1) Cinacalcet:

- Used if serum calcium > 1 mg (0.25 mmol) above the upper limit of normal
- Decreases serum calcium
- Decreases PTH

2) Bisphosphonate (e.g. alendronate) or Denosumab:

- If low BMD

Normocalcemic primary hyperparathyroidism

- Normal total adjusted serum calcium, **normal ionized calcium** and high PTH on at least 2 tests over 3-6 months
- Rule out causes of secondary hyperparathyroidism (vitamin D deficiency, CKD, celiac disease, bariatric surgery, ↓ calcium intake, malabsorption by pancreatic insufficiency)
- No adequate studies to guide management
- Some physicians use the same indications for surgery in hypercalcemic primary hyperparathyroidism
- Many will obtain localization study before surgery

Case 2

- A 45-year-old woman presents with muscle pain & cramps, numbness over the hands for 3 months
- Thyroid surgery for “overactive thyroid” 6 months ago
- Thyroxine 100 mcg qd
- Normal BP, neck scar, thyroid is not palpable
- TSH 2.3, Serum cr, K normal, ALT normal
- Serum calcium 6.5 mg (normal: 8.5-10.5)
- **How to approach serum calcium?**

Causes of hypocalcemia

- Post-surgical (thyroid, parathyroid surgery)
- Autoimmune hypoparathyroidism
 - Can be isolated
 - Or with chronic mucocutaneous candidiasis + adrenal insufficiency (polyglandular syndrome type 1)
- Vitamin D deficiency
- Pseudohypoparathyroidism (PTH resistance)
- Acute or chronic kidney disease
- Acute pancreatitis
- Tumor lysis syndrome
- Hypomagnesemia, hyperphosphatemia
- Acute illness, sepsis

Manifestations of hypocalcemia

- Perioral numbness
- Paresthesia of hands and feet
- Muscle cramps & pains
- Carpopedal spasm
- Laryngospasm
- Seizures (focal or generalized)
- Fatigue, irritability, anxiety, depression
- Some have no symptoms

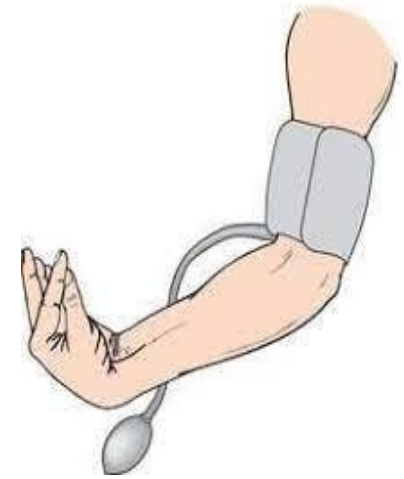
Approach to hypocalcemia

- 1) Repeat test
- 2) Check serum albumin
 - Correct calcium if albumin is low
 - Some labs will do the correction. There are calculators
- 3) Can check ionized calcium, but expensive
- 4) Check PTH
- 5) Check serum creatinine, phosphorus, magnesium, 25-OH vitamin D

Physical examination

- **Trousseau's sign:**

Induction of carpal spasm by inflation of a sphygmomanometer above systolic blood pressure for 3 minutes



- **Chvostek's sign:**

Contraction of the ipsilateral facial muscles elicited by tapping the facial nerve just anterior to the ear (may occur in normal persons)



Evaluation of hypocalcemia

| | PTH | Phosphorus | Magnesium | 25-OH vit D | creatinine |
|---------------------------------|----------------|-------------|-------------|-------------|------------|
| Hypoparathyroidism | ↓ | ↑ | Normal | Normal | Normal |
| Pseudohypoparathyroidism | ↑ | ↑ | Normal | Normal | Normal |
| Hypomagnesemia | Normal or ↓ | Normal | ↓ | Normal | Normal |
| Vitamin D deficiency | ↑ | ↓ or normal | Normal | ↓ | Normal |
| Chronic kidney disease | ↑ | ↑ | Normal or ↑ | Normal | ↑ |

Treatment of hypocalcemia

1) Acute symptoms or very low calcium [< 7 mg (1.75 mmol)]:

- IV calcium
- Check magnesium and potassium (replace if low)

2) Chronic treatment:

- Oral **elemental** calcium 1-2 grams/day
 - Ca carbonate = 40% elemental calcium (1250 mg = 500 mg)
 - Ca citrate = 21% elemental calcium
 - Ca lactate = 13%
- Vitamin D:
 - Calcitriol 0.25 to 2 mcg /day (higher doses can be used)
 - Or Alfacalcidol (one alpha) 0.25 to 2 mcg/day (may need \uparrow)

3) Target calcium is low normal [8 to 8.5 mg (2-2.15 mmol)]

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