Hypercalcemia Diagnosis and management

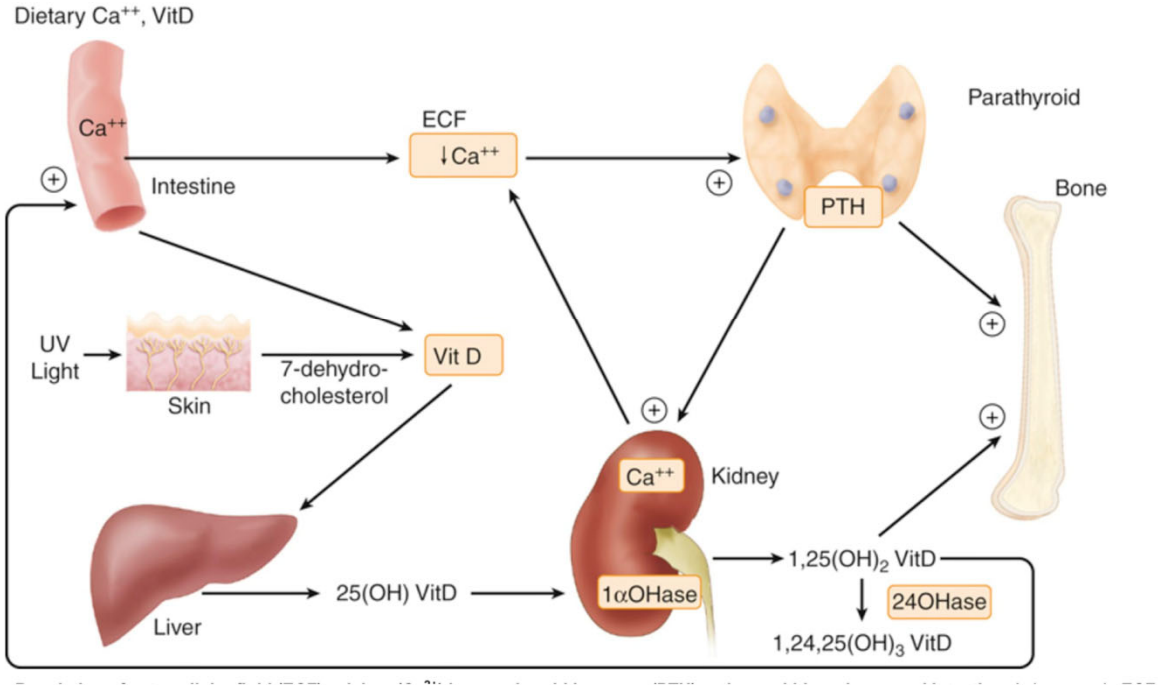
José C de Souza MD

Endocrinologist at Logan Health

Introduction to calcium metabolism

- A healthy adult has a total of 1 kg of calcium:
  - 99% in crystal structure of bone mineral.
  - 1% in soluble form in the extracellular and intracellular fluid compartment.
    - Half of the extracellular calcium is in the ionized form
    - Muscle contraction
    - Secretion of neurotransmitters and hormones
    - Coagulation pathway.

A brief view of calcium metabolism



Prevalence of Hypercalcemia

- **General Population**
  - Estimated prevalence: **~0.1–0.5%** in unselected adults.
  - Most cases are **mild and incidental**, often picked up on routine labs.

Most common causes

- **Primary hyperparathyroidism (PHPT)**
- Accounts for **~80–90%** of outpatient cases.
- Prevalence of PHPT: **1–4 per 1,000 adults**, higher in postmenopausal women.
- Incidental hypercalcemia is often how it's discovered.
- **Malignancy-associated hypercalcemia (MAH)**
- Leading cause in **hospitalized** or acutely ill patients.
- Occurs in **10–20%** of patients with advanced cancer, especially:
  - Lung (especially squamous cell)
  - Breast
  - Renal
  - Multiple myeloma

Other Less Common Causes

- Granulomatous disease (sarcoidosis, TB)
- Vitamin D or A intoxication
- Thiazide diuretics, lithium
- Adrenal insufficiency or thyrotoxicosis (rarely significant)
- Familial hypocalciuric hypercalcemia (rare, benign, lifelong)
- Immobilization

Symptoms of Hypercalcemia

Gastrointestinal Symptoms

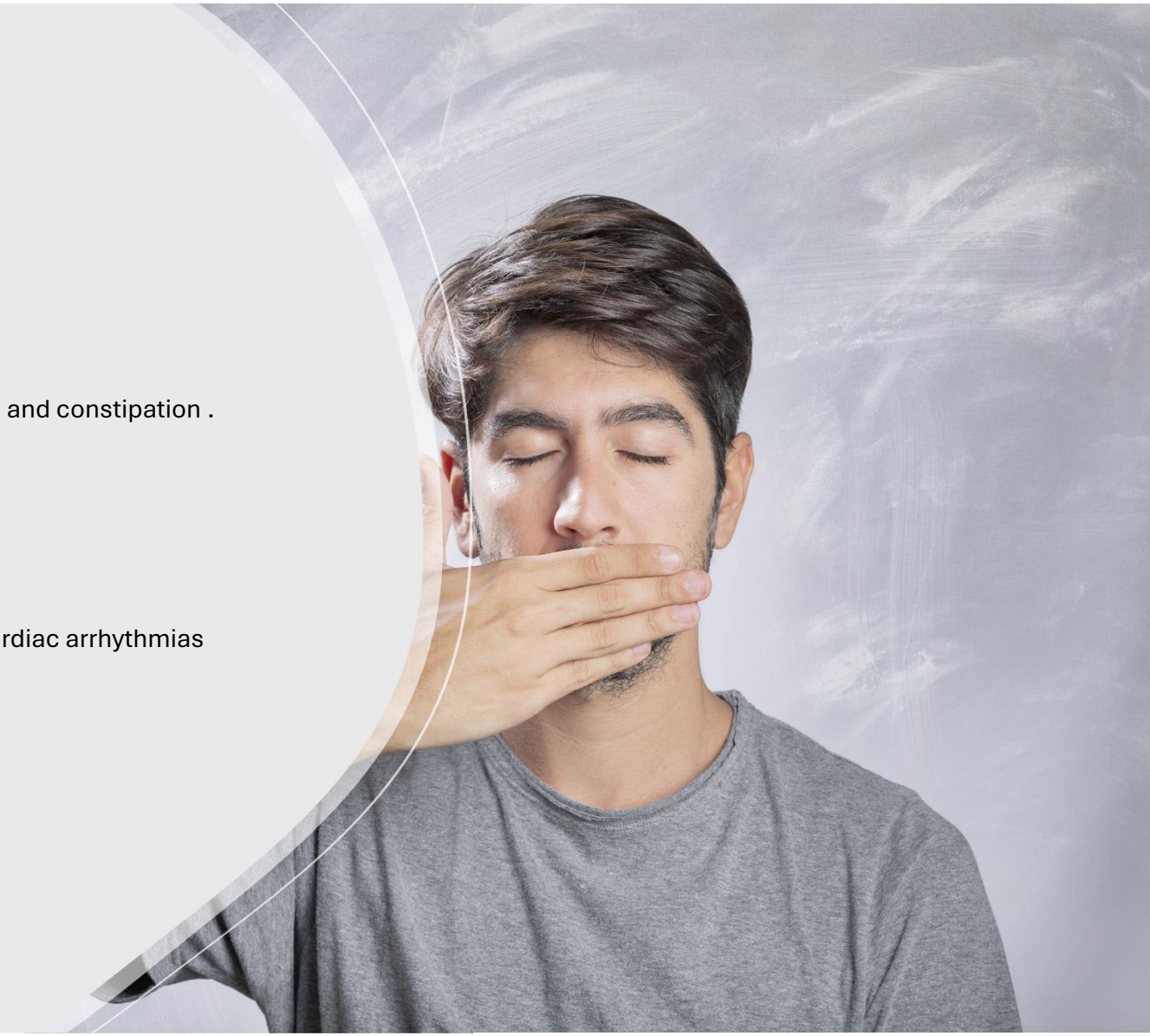
Patients may experience nausea, vomiting, and constipation .

Neurological Manifestations

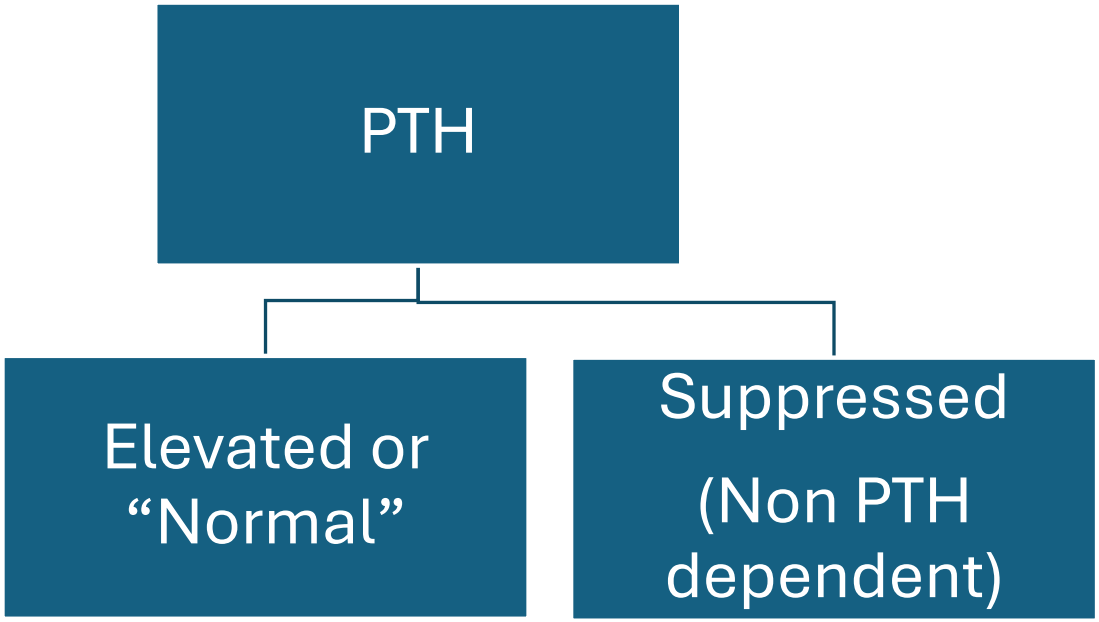
Confusion, fatigue, and muscle weakness.

Renal and Cardiac Effects

Increased thirst, frequent urination, and cardiac arrhythmias may develop,



Mechanism of hypercalcemia



Diagnostic work up for patients with hypercalcemia:

- PTH
- CMP
  - Calcium (can be normal in ”normocalcemic hyperparathyroidism”)
  - Phosphorus
  - Protein
  - BUN /Cr
- 25 OH Vitamin D
- 24 hrs.. urine Calcium and cr.
  - FECA= Uca x ser cr./ Ca vs Ur. Cr.
  - FECA < 0.001 = Familial Hypocalciuric Hypercalcemia (Urine calcium < 100 mg/24 hrs.)
  - FECA > 0.01= HPT (Urine Ca > 200 mg/24 hrs..

Clinical manifestations of HPT

- Symptoms severity correlates w/ calcium levels
- Most frequently asymptomatic
- Asymptomatic with end organ damage
  - Kidney stones in 10-25% of cases
  - Osteoporosis
    - Cortical bones more severely affected

Work up for patients w/ low PTH

- 1,25 dihydroxy vitamin D
- SPEP
- PTHRP
- Chest CT

Hyperparathyroidism definition:

- **Primary Hyperparathyroidism**

Cause	Frequency	Description / Notes
Solitary parathyroid adenoma	**~80–85%**	Single benign tumor of one gland; most common cause. Usually sporadic.
Parathyroid hyperplasia	**~10–15%**	Diffuse or asymmetric enlargement of all four glands. Seen in familial syndromes or sporadically.
Parathyroid carcinoma	**<1%**	Very rare; causes markedly high Ca and PTH. Often with palpable neck mass, severe hypercalcemia.

Secondary Hyperparathyroidism

- Normal Calcium and elevated PTH level.
- Causes:
  - CKD
  - Vitamin D deficiency
  - Low calcium diet
  - Malabsorption (post bariatric surgery)

Tertiary hyperparathyroidism

- Long term ESKD
- Elevated Calcium and PTH level.

Treatment of hyperparathyroidism

- Who needs treatment?
- **NIH Consensus Criteria** (updated by the **Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism**, 2014)

Category	Surgical Indication
Serum Ca	>1 mg/dL above upper limit
Bone	T-score ≤ –2.5 at spine/hip/radius or vertebral fracture
Renal	CrCl <60 mL/min, urine Ca >400 mg/d, or stones/nephrocalcinosis
Age	<50 years
Patient preference / poor follow-up	Consider surgery

Imaging in Hyperparathyroidism

Importance of Imaging

Imaging studies are crucial for **localizing abnormal parathyroid glands prior to surgical intervention.**

Ultrasound as First-Line Tool

Neck ultrasound is a non-invasive, first-line modality for detecting enlarged parathyroid glands, making diagnosis easier and safer.

Sestamibi and Advanced Imaging

Sestamibi scans with SPECT enhance localization accuracy, while CT or MRI is used when initial studies are inconclusive.

Identifies

4D CT

Which to choose?

For most patients: Sestamibi SPECT/CT is often the initial test due to its accuracy and functional information.

For challenging cases: If Sestamibi is negative/inconclusive, or if you have multi gland disease or previous neck surgery, 4D CT is recommended.

For optimal results: A combined approach (using both modalities) or a tailored strategy involving a nuclear medicine physician and radiologist provides the best chance for successful localization.

Surgical Solutions for Hyperparathyroidism

Exploratory Parathyroidectomy

Parathyroidectomy involves surgical removal of overactive parathyroid gland(s) to treat hyperparathyroidism effectively.

Minimally Invasive Techniques

Minimally invasive surgical approaches are often preferred for faster recovery and reduced scarring for patients.

Postoperative Monitoring

Monitoring calcium levels after surgery is crucial for managing patient recovery and ensuring symptom resolution.

Postoperative complications

Bleeding, vocal cord paralysis, laryngospasm

Hungry bone syndrome: Hypocalcemia, hypophosphatemia, hypocalciuria.

Medical treatment

- Maintain hydration
- Avoid Thiazide diuretics
- No need to abstain from calcium intake
- Cinacalcet for nonsurgical patients
- Bisphosphonates

Case 1

- 43 yo woman referred for hypercalcemia , previous hx. of kidney stone. Not feeling well for 2 years w/: fatigue, stress at work, decreased appetite w/wt. loss. No polys, no constipation , no resp sx.
- PMhx: Gest.DM, Anemia, kidney stone, Thyroid nodule, Pos. thyroid Abs.
- Surgeries: Bilateral tubal ligation, c-section, endometrial ablation, T&A.
- Meds: ergocalciferol , omeprazole, ondansetron.
- Fam & social Hx : unrmk

Case 1

- **Ca 11.5**
- Po4 4.0, Mg 1.0,
- **25 OH D 14 ng/dl**
- TP 7.4
- BUN 15/ cr 1.0
- CBC normal
- PTH 0.4 pmol /L (1.6-7.7)
- PTRP 0.5 pmol /L (<4.2)
- **1,25 OH 85 pg/ml (18-78)**
- **ACE 127 U/L (16-85)**
- Chest CT : **“mediastinal adenopathy” w/nodular and linear opacifications at the bases.**
- FNA of Right hilar LN: **“Benign LN w/ granulomas.”**

Case 2

- 50 yo woman referred for “recently “ noted hypercalcemia . No Hx of kidney stones or fractures . She does report excessive urination on HCTZ and occasional “bone pains”.
- PMH:
  - Palpitations, nicotine addiction, hyperlipidemia, vit d deficiency, OSA, Anxiety, PCOS
- Meds: Losartan/HCTZ 100/25; D3, Mirena IUD
- Surgeries:
  - Tonsillectomy, appy, Left salpingo-oophorectomy, tubal ligation.
- FamHx: unrmk.
- PE : BP 152/98; P 99 BMI 44.1.

Case 2

- Labs:
  - **Ca 11.2**, Po4 3.6
  - Bun/cr 10/0.6
  - **25 OH D 42 ng/ml**
  - **PTH 6.5 (1.5-8.0 pmol/l)**
  - Urine calcium 241 mg/24hrs
- Imaging:
  - Office US: ‘large PTH gland posterior to the right upper lobe of the thyroid gland”
  - Sestamibi/ spect: “negative”
- What to do???

Case 2

- Surgery findings:
  - 3 normal glands in the R superior, R inferior and L Inferior positions. **“markedly enlarged intrathyroidal left superior gland excised (1000 mg!).**
  - Intraoperative PTH:
    - Baseline: 7.2 pmol/l
    - 5 minutes :5.8 pmol/l
    - 10 minutes: 3.8 pmol/l
  - Frozen section: “hypercellular parathyroid gland consistent with an Adenoma.”

Thank you!