Calcium and Parathyroid Disorders

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Objectives

- Review calcium physiology and homeostasis
- Hormones involved in calcium homeostasis
- Clinical manifestations of hypercalcemia
- Review the causes of hypercalcemia
- Approach to the evaluation and workup of hypercalcemia
- Treatment of hypercalcemia
- Clinical presentation and workup of primary hyperparathyroidism
- Treatment of primary hyperparathyroidism
- Pathophysiology of hypoparathyroidism and newer treatment paradigms

Introduction

- Calcium is one of the most abundant minerals in the body. It has may important biologic functions
- Normally 1000-2000 g of calcium is present in human body (99% located in the skeleton)
- The remainder is distributed throughout the ECF and soft tissues
- The efflux and influx of calcium across the skeleton occurs constantly, mediated by osteoclastic and osteoblastic activity

How is calcium outside the skeletal system distributed?

- In blood, total calcium concentration is normally 8.5-10.2 mg/dL. Approximately 50% is ionized
- The remainder is bound to negatively charged proteins—predominantly albumin and immunoglobulins; may also be loosely complexed with phosphate, sulfate, citrate, and other anions

Protein binding of calcium

- Influenced by pH
- Metabolic alkalosis: increases protein binding→decreased ionized calcium level
- Metabolic acidosis: decreases protein binding→ increased ionized calcium level
- Remember that serum calcium levels should always be adjusted for serum albumin levels

Corrected calcium

- For every 1 g decrease in serum albumin <4 g/dL, the measured serum calcium decreases by 0.8 mg/dL

- **Corrected calcium=**

  [Ca in mg/dL] + [0.8 x (4-albumin in g/dL)]

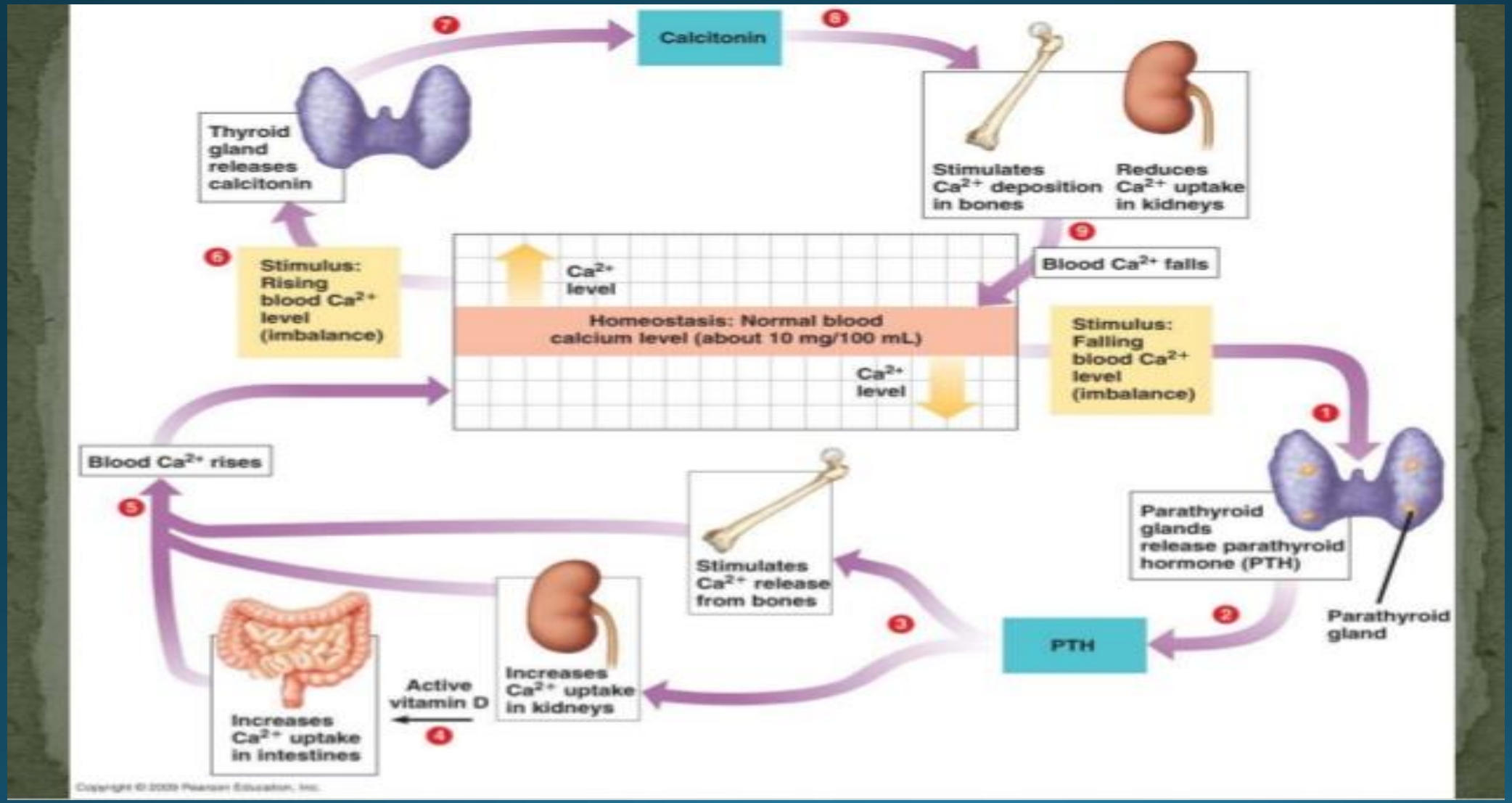
Calcium Functions

- Muscle contraction
- Nerve conduction
- Bone formation
- Intracellular signaling
- Enzyme regulation
- Coagulation
- Maintenance of plasma membranes

Calcium Metabolism

- Average dietary intake 400-1500 mg/day
- Daily intestinal absorption 200-400 mg/day
- Renal calcium excretion regulated by blood ionized calcium level
- Approx 8-10 gr/day filtered by glomeruli; 2-3% (200 mg) excreted in urine
- Approx 65% reabsorbed in the PCT
- Approx 20% in the loop of Henle (requires a protein paracellin-1)

Calcium Homeostasis



Clinical Manifestations of Hypercalcemia

Renal "stones"
Nephrolithiasis
Nephrogenic diabetes insipidus
Dehydration
Nephrocalcinosis

Skeleton "bones"
Bone pain
Arthritis
Osteoporosis
Osteitis fibrosa cystica in hyperparathyroidism (subperiosteal resorption, bone cysts)

Gastrointestinal "abdominal moans"
Nausea, vomiting
Anorexia, weight loss
Constipation
Abdominal pain
Pancreatitis
Peptic ulcer disease

Neuromuscular "psychic groans"
Impaired concentration and memory
Confusion, stupor, coma
Lethargy and fatigue
Muscle weakness
Corneal calcification (band keratopathy)

Cardiovascular
Hypertension
Shortened QT interval on ECG
Cardiac arrhythmias
Vascular calcification

Other
Itching
Keratitis, conjunctivitis

Causes of Hypercalcemia

Parathyroid hormone-related
- Primary hyperparathyroidism*
  Sporadic, familial, associated with multiple endocrine neoplasia I or II
- Tertiary hyperparathyroidism
  Associated with chronic renal failure or vitamin D deficiency

Malignancy
- Humoral hypercalcemia of malignancy* (mediated by PTHrP)
  Solid tumors, especially lung, head, and neck squamous cancers, renal cell tumors
- Local osteolysis* (mediated by cytokines)
  multiple myeloma, breast cancer

Vitamin D-related
- Vitamin D intoxication
- Granulomatous disease sarcoidosis, berylliosis, tuberculosis
- Hodgkin's lymphoma

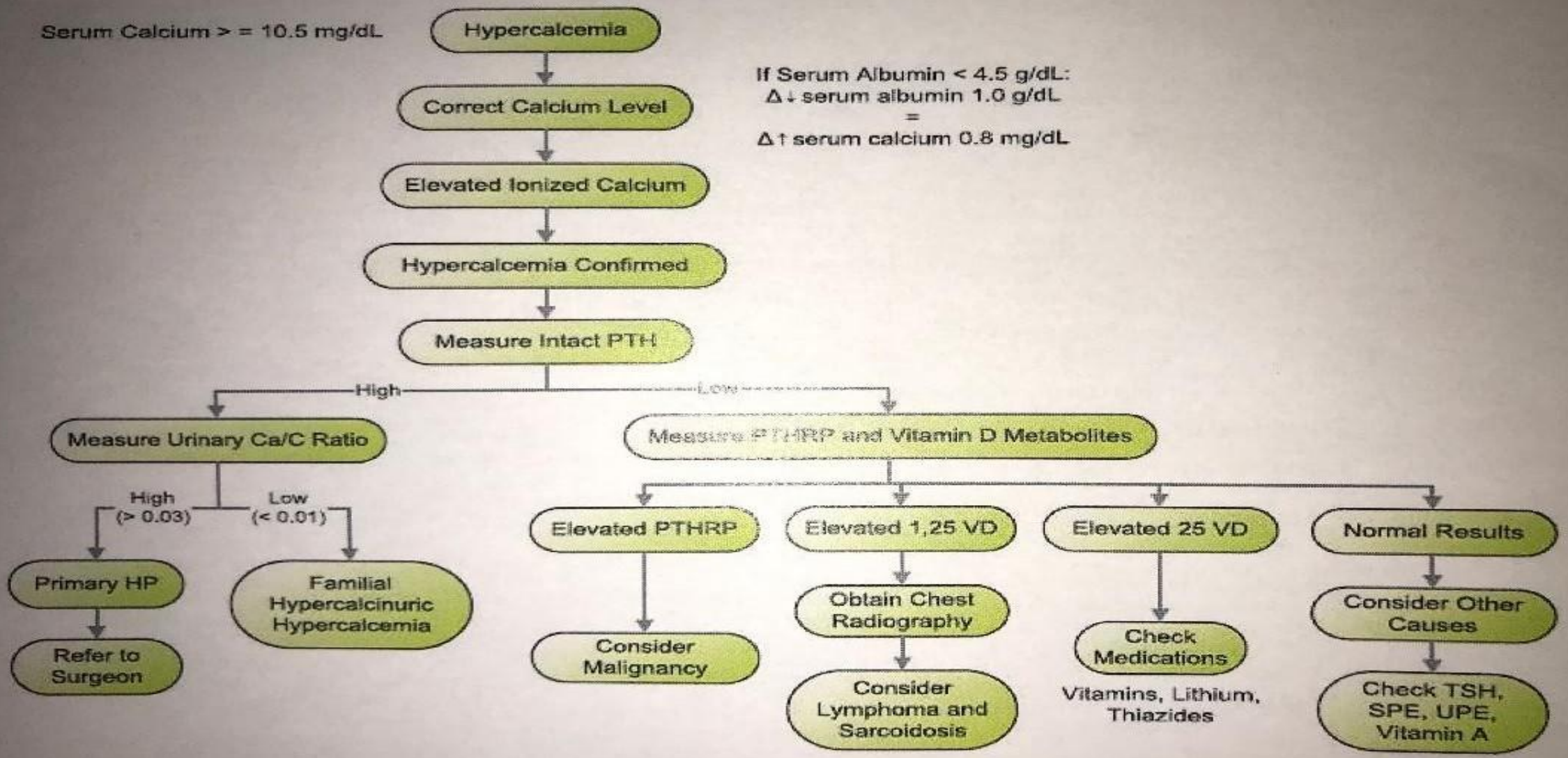
Medications
- Thiazide diuretics (usually mild)*
- Lithium
- Milk-alkali syndrome (from calcium antacids)
- Vitamin A intoxication (including analogs used to treat acne)

Other endocrine disorders
- Hyperthyroidism
- Adrenal insufficiency
- Acromegaly
- Pheochromocytoma

Genetic disorders
- Familial hypocalciuric hypercalcemia: mutated calcium-sensing receptor

Other
- Immobilization, with high bone turnover (e.g., Paget's disease, bedridden child)
- Recovery phase of rhabdomyolysis

Diagnostic Approach to Hypercalcaemia - Summary



Diagnostic approach to hypercalcemia which is a modified algorithm published in UptoDate online.[5] PTH indicates parathyroid hormone; PTHRP, parathyroid hormone-related peptide; 1,25 VD; 1,25-dihydroxyvitamin D; 25 VD, 25-hydroxyvitamin D; Ca/C, calcium/creatinine;

Causes of Hypercalcemia

- **Elevated or Non-suppressed PTH**

Primary hyperparathyroidism

Solitary adenoma, multiple adenoma, hyperplasia, carcinoma

Tertiary hyperparathyroidism

Advanced CKD, severe Vit D deficiency, calcium malabsorption

Miscellaneous

FHH

Suppressed PTH

Malignancy

Humoral mediated (PTHrP), Vit D mediated, myeloma, lytic bone metastases

Drug induced

Milk-alkali, Vit D intoxication, Vit A intoxication, lithium, thiazides

Other Endocrinopathies

Thyrotoxicosis, adrenal insufficiency, pheochromocytoma

Immobilization

Paget's disease

- Among all causes of hypercalcemia, pHPT and malignancy are the most common (>90% of cases)
- Therefore, the diagnostic approach usually involves distinguishing between the two
- Patients with hypercalcemia of malignancy generally have higher [Ca] levels and are more symptomatic compared to pHPT
- Always first confirm true hypercalcemia (albumin-corrected and ionized calcium levels)

Primary Hyperparathyroidism

- 80% due to solitary adenoma
- Much less common due to multiple adenomas or hyperplasia
- Parathyroid carcinoma very rare
- Majority of cases diagnosed on routine lab finding of elevated [Ca]
- Elevated or “normal” iPTH levels

Vitamin D mediated hypercalcemia

- Elevated levels of 1,25 OHD3 seen with:
  - --excessive intake of this metabolite
  - --extra renal production (granulomatous disease and lymphoma)
  - --increased renal production (induced by pHPT but not PTHrp)
- CXR/CT imaging may be helpful (look for malignancy or sarcoidosis)
- Steroid-responsive (decreases calcitriol production by the activated mononuclear cells)

Hypercalcemia of Malignancy

- Most common cause of inpatient hypercalcemic crisis
- Complicates 10-30% of malignancies
- Usually presents in the context of advanced, clinically obvious disease

Humoral hypercalcemia of Malignancy

- Majority induced by PTHrp
- Induces bone resorption by binding to PTH receptor type 1
- Many solid tumors (squamous cell H/N, lung, esophagus, breast, kidney)
- Low levels of PTH and 1,25 OHD_3

Hypercalcemia of Malignancy

- Direct destruction of bone (myeloma or lytic metastatic disease)
- Multiple myeloma—hypercalcemia via locally produced osteolytic peptides (OAF also known as IL-1B). Can show very high [Ca] but normal ionized calcium levels
- Elevated alkaline phosphatase levels
- Myeloma: anemia, renal insufficiency, hypercalcemia (abnormal SPEP, light chains, immunofixation studies)

Hypercalcemia of Malignancy—Vit D mediated

- Increased calcitriol production due to increased 1-alpha-hydroxylase expression by lymphoproliferative tissues
- Lab findings include low PTH and PTHrp, elevated 1,25 OHD3

Medication-Induced hypercalcemia

- **Thiazide diuretics**: increase [Ca] reabsorption in the distal tubule→decrease urinary calcium excretion

- **Lithium**: increases the PTH "set point," so higher [Ca] levels are needed to turn off PTH secretion; results in low urine calcium so biochemistry mimics that of FHH

Other Causes of Hypercalcemia

- Milk-alkali syndrome
- Hyperthyroidism
- Adrenal insufficiency
- Pheochromocytoma
- Pagets disease with immobilization

Treatment of Hypercalcemia--Goals

- Lowering the serum calcium levels

--inhibiting bone resorption
--increasing urinary calcium excretion
--decreasing intestinal calcium absorption

- Treatment of the underlying disease

Hypercalcemia Treatment

- Patients with mild hypercalcemia (<12 m/dL) do not require immediate treatment. Maintain adequate hydration, avoid volume depletion and inactivity, and stop causative medications
- Moderate hypercalcemia (12-14 mg/dL), especially if acute and symptomatic, requires more aggressive treatment
- Patients with severe hypercalcemia (>14 mg/dL) should be treated intensively

- The initial and most important step in the treatment of severe hypercalcemia is correction of ECF volume with **IV saline hydration**
- A reasonable regimen is isotonic saline at 200-300 mL/hr, then adjust to maintain urine output at 100-150 mL/hr
- Adverse effects: edema, CHF

- Following adequate hydration, **IV furosemide** 20-40 mg to promote calciuresis
- Adverse effects: dehydration, hypokalemia, hypomagnesemia

Calcitonin

- Beneficial in patient with severe hypercalcemia, along with saline hydration and bisphosphonates
- Works rapidly by increasing renal calcium excretion and by decreasing bone resorption (via interference with osteoclast function)
- Salmon calcitonin 4-8 IU/kg every 6-12 hours
- Efficacy limited to the first 48 hours

Bisphosphonates

- Inhibit osteoclast-mediated bone resorption
- Maximum effect occurs in 2-4 days, so usually given with saline and/or calcitonin
- Pamidronate or zoledronic acid IV
- Adverse effects: hypocalcemia, hypophosphatemia, renal insufficiency, ONJ

Denosumab

- Human monoclonal antibody against RANKL—inhibits the binding of RANK to RANKL→inhibits osteoclast function
- FDA approved for treatment of hypercalcemia of malignancy
- Adverse effects: fatigue, nausea, hypocalcemia, hypophosphatemia, dermatitis/rash, ONJ

Other Treatment Options

- **Glucocorticoids:** patients with Vit D-mediated hypercalcemia; corticosteroids reduce [Ca] via decreasing calcitriol production by the activated mononuclear cells
- **Hemodialysis:** patients with severe hypercalcemia who cannot tolerate bisphosphonates or aggressive hydration (renal or cardiac failure)
- **Cinacalcet:** calcimimetic agent; parathyroid carcinoma or CKD
- **Parathyroidectomy:** only cure for hypercalcemia due to PHPT

Parathyroid disease

Parathyroid Hormone

- PTH is the major circulating regulator of calcium homeostasis
- Acts directly on bone and kidney cells
- Acts indirectly on the GI tract via production of 1,25D3
- Over a very narrow concentration range, ionized calcium is reciprocally related to the circulating PTH concentration; mediated by the CaSR

Primary Hyperparathyroidism

- Enlargement of 1 or more parathyroid glands, resulting in over-production of PTH
- ↑ release of calcium from bones
- ↑ excretion of calcium in urine
- ↑ calcium absorption in duodenum

- Most common cause is solitary adenoma (80%)
  --hyperplasia in most other cases
  --parathyroid carcinoma is rare

pHPT Epidemiology

- The most common cause of hypercalcemia in ambulatory care in the US
- ~100K people annually
- Most often in people age 50-60 (women 2-3x more common than men)

“Classic pHPT symptoms”

- Nephrolithiasis
- Anorexia, N/V
- Constipation
- Fatigue/weakness
- Insomnia
- Depression
- “brain fog”
- Hair loss
- Polydipsia/polyuria
- arthralgias

pHPT Diagnosis

- Hypercalcemia in conjunction with elevated or non-suppressed PTH level
- Some patients have normocalcemic pHPT
- Levels can fluctuate, so repeated lab measurements may be required
- [Ca] should be adjusted for albumin. PHPT can present with an elevated ionized Ca despite a normal albumin-adjusted [Ca]

Normocalcemic pHPT

- Elevated PTH but normal levels of serum and ionized calcium
- Rule out secondary causes of PTH elevation (renal insufficiency, malabsorption, Vit D deficiency, use of bisphosphonates or denosumab)

Remember to rule out FHH

- Autosomal dominant disorder of the CaSR
- Consider in patients **with family history**, longstanding hypercalcemia, urine calcium <100 mg/24h AND a calcium/creatinine clearance <0.01
- This is rare. The majority of patients with elevated calcium and PTH and low/normal 24h urine calcium are going to have……primary HPT

PHPT Treatment: Surgery

- Parathyroidectomy is an option for all patients with diagnosed pHPT as it is the only curative measure

- Surgery is recommended in all of those patients in whom one or more of the following is present:

- Serum calcium >1 mg/dL above lab upper limit normal
- Skeletal involvement: evidence of fracture by VFA, vertebral XR, or BMD T score ≤ 2.5 at any site
- Renal involvement: eGFR or CrCl < 60 mL/min; nephrocalcinosis or nephrolithiasis (by XR, US, or other imaging modality); hypercalciuria (>250 mg/d women or >300 mg/d men)
- Age < 50

Surgery cannot be recommended to improve neurocognitive function, cardiovascular indices, or quality of life (inconclusive evidence)

- Pre-operative imaging is not recommended for diagnostic purposes (biochemical diagnosis)
- Imaging recommended for those going for surgery to localize the abnormal gland(s)
- Imaging modalities include neck US, technetium-99-m-sestamibi scintigraphy, and contrast 4D CT

Monitoring Non-Surgical Patients

- For patients whom surgery is contraindicated or who refuse surgery, monitoring can be an option. BMD tests should be performed every 1-2 years and labs should be evaluated at least yearly

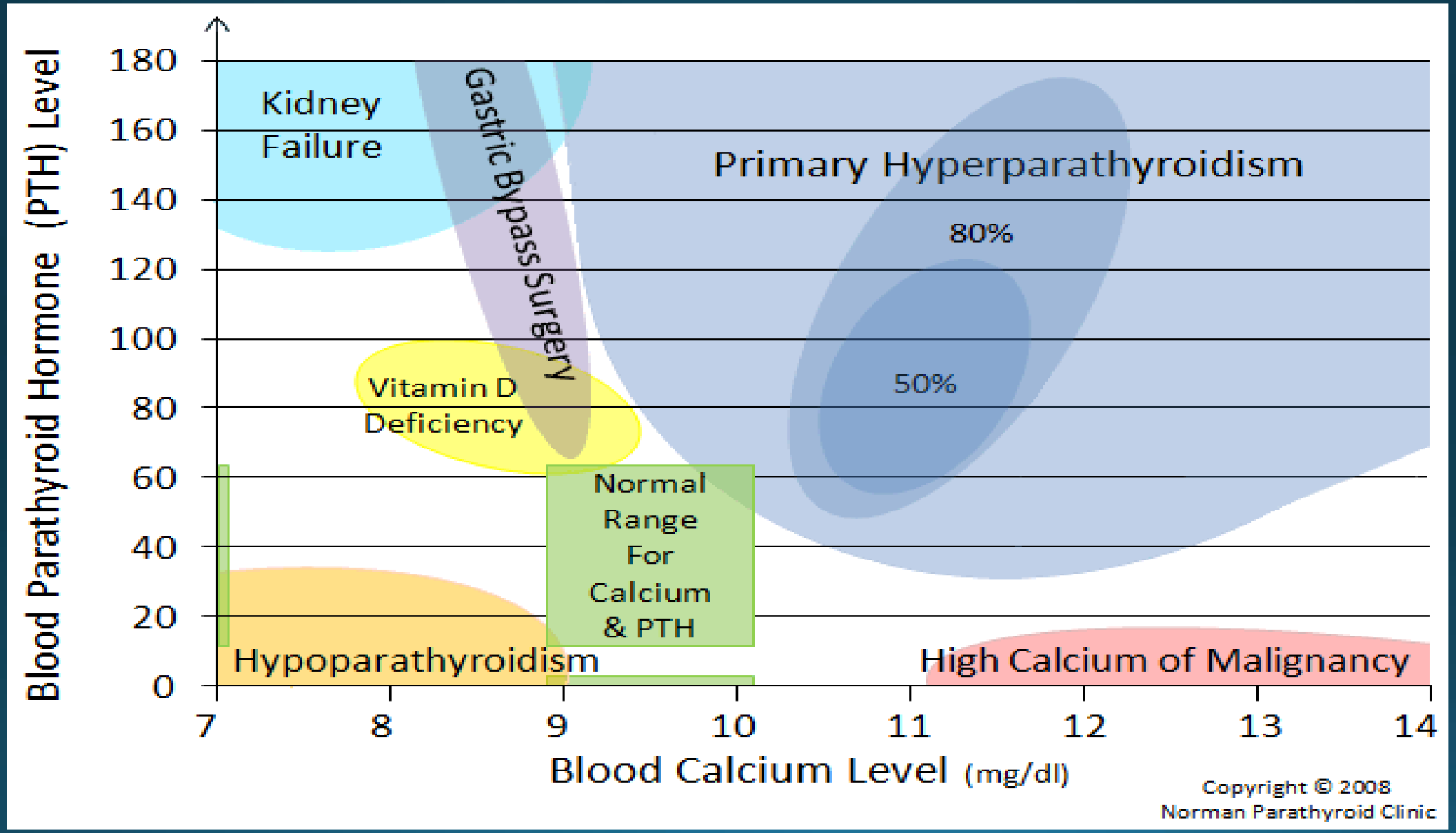
- According to IOM guidelines, dietary calcium intake should not be restricted and Vit D levels should be maintained in normal range

Medical Management--Cinacalcet

- Currently, the only medication shown to lower [Ca] in patients with PHPT
- Normalizes [Ca] in 70%-80% of patients with PHPT
- However it does not affect PTH, and has not been shown to improve BMD, kidney stones, HPT symptoms, or qol
- Close monitoring necessary due to risk of QT prolongation, arrhythmias, CHF, and hypotension

Medical Management—Antiresorptive therapy

- May be used in patients with T-scores ≤2.5 (at LS, hip, or radius) or who have fragility fractures
- Have been shown to be effective in preventing decreases in BMD and reducing bone remodeling
- May be used in combination with cinacalcet in non-operative patients


Blood Parathyroid Hormone (PTH) Level
180
160
140
120
100
80
60
40
20
0
Kidney Failure
Gastric Bypass Surgery
Primary Hyperparathyroidism
80%
50%
Vitamin D Deficiency
Normal Range For Calcium & PTH
Hypoparathyroidism
High Calcium of Malignancy
7
8
9
10
11
12
13
14
Blood Calcium Level (mg/dl)
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Hypoparathyroidism

- Rare disorder of mineral metabolism
- Characterized by hypocalcemia, absent or deficient production of PTH, and hyperphosphatemia
- Neuromuscular irritability—due to hypocalcemia
- Soft tissue deposition of insoluble calcium phosphate—primarily due to hyperphosphatemia

Hypoparathyroidism--Etiologies

- Most commonly results from anterior neck surgery (75%)

--occurs in between 0.12 and 4.6% of surgeries

--chronic hypoparathyroidism established only after 12 (guideline change—previously defined as >6 months

- Autoimmune disease (PTH alone or polyglandular syndrome)

- Hypermagnesemia and severe hypomagnesemia—suppresses PTH and can cause functional hypoparathyroidism

Genetic Forms of Hypoparathyroidism

- Polyglandular deficiency (APS, APECED), DiGeorge's syndrome, Bartter's syndrome
- ADH-1 (activating mutation in CaSR)
- ADH-2 (activating mutation in G protein α11 subunit

- Hypoparathyroidism is distinguished from pseudohypoparathyroidism (elevated PTH)—genetic disorder of PTH resistance

- Also distinguished from secondary hypocalcemia (Vit D deficiency, malabsorption) which has elevated PTH

Clinical Manifestations

- Acute hypocalcemia can be medical emergency (seizures and laryngospasm)
- Typical: mild and nonspecific neuromuscular symptoms, paresthesias, “brain fog”
- Soft tissue calcifications (basal ganglia, kidney)
- Hypercalciuria: due to large amounts of calcium and active Vitamin D required to maintain normal [Ca] levels

Hypoparathyroidism

Update of guidelines from 2022 international task force

- Chronic post-surgical hypoparathyroidism is now defined as lasting ≥ 12 months
- May be predicted by PTH <10 pg/mL in first 12-24 h after surgery
- Hypocalcemia defined as low ionized or total corrected calcium in presence of inappropriately low iPTH on 2 occasions at least 2 weeks apart
- In patients with nonsurgical hypoPT who have a (+) FH, who have syndromic features, or who are age <40 genetic testing is recommended

Common Symptoms and Complications

- Cataracts
- Infections
- Nephrocalcinosis/Nephrolithiasis
- Renal insufficiency
- Seizure/laryngospasm
- Depression/neurocognitive changes
- ICVD/arrhythmia

Goals of Chronic Management

1. Prevent signs/symptoms of hypocalcemia
2. Maintain [Ca] slightly below normal
3. Maintain calcium-phosphate product to below 55 mg^2/dL^2
4. Avoid hypocalcemia
5. Avoid hypercalcemia
6. Avoid renal and other extraskeletal calcifications

Conventional Treatment

- **Calcium:** carbonate, citrate--amount required varies significantly; some patients require up to 9 gm/daily
- **Active Vitamin D:** calcitriol—typically between 0.25-2 mcg daily
- **Thiazides:** promote RT calcium retention; used when hypercalciuria present
- **Phosphate binders:** rarely used (only when phosphorus levels >6.5 mg/dL)

Newer Paradigm

- Conventional use of higher doses of calcium and Vitamin D increase risk for hypercalciuria, renal calcinosis/stones, CKD, and ectopic soft tissue calcifications

- In addition, patients are often symptomatic with reduced QOL complaints despite normalized calcium levels