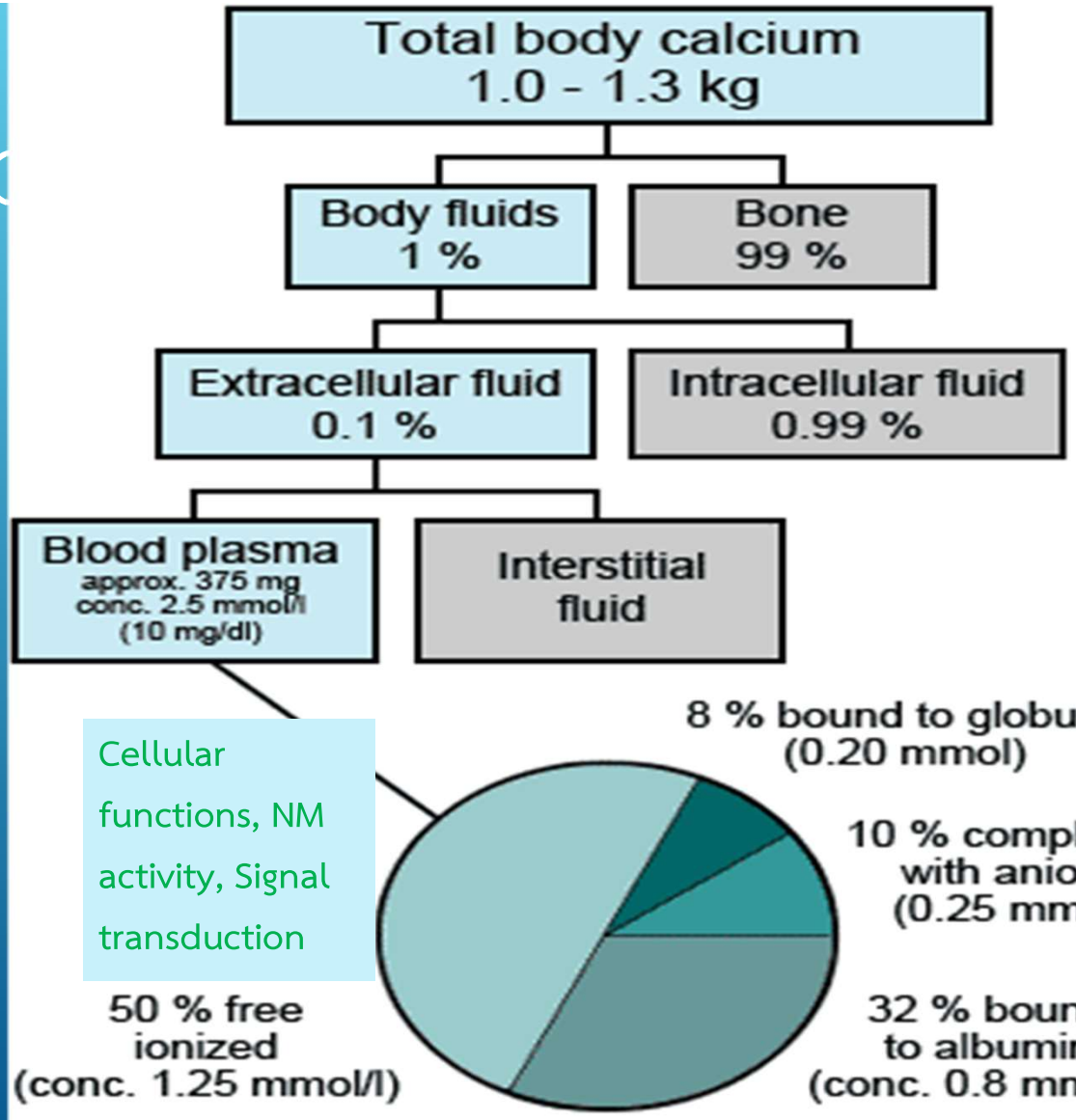
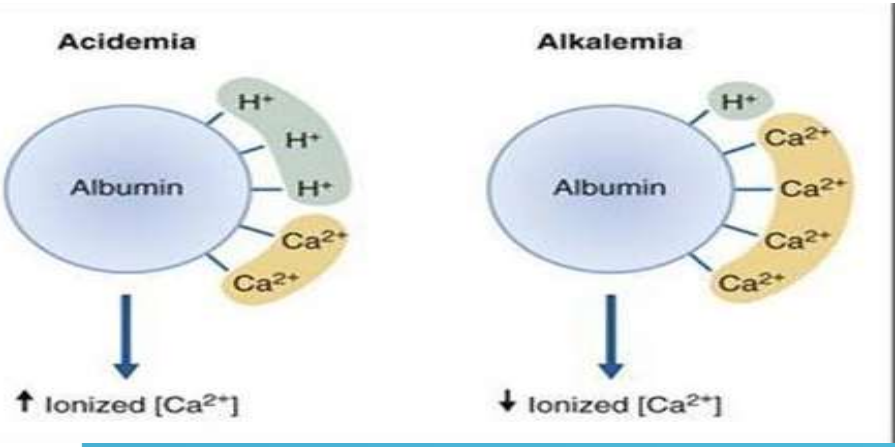
Dr. Lionman

CALCIUM METABOLISM AND PARATHYROID DISEASE



Cellular functions, NM activity, Signal transduction



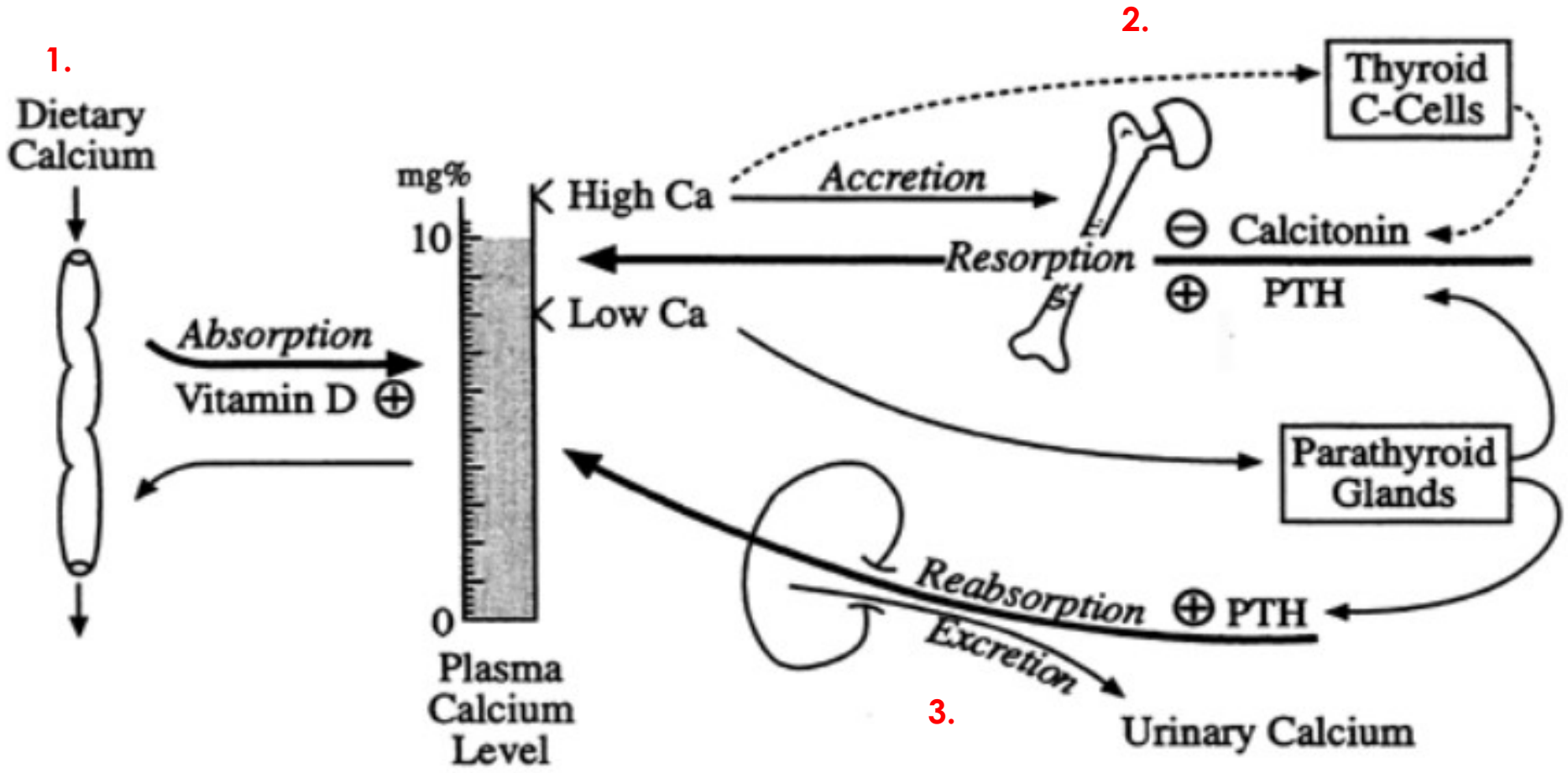
Ratio 0.5 mg/dl of calcium / 1 gm/dl of immunoglobulin

Phosphate, Citrate, Sulfate, Lactate

Ratio 0.8 mg/dl of calcium / 1 gm/L of albumin

Corrected Ca = calcium + 0.8 (4-serum albumin)

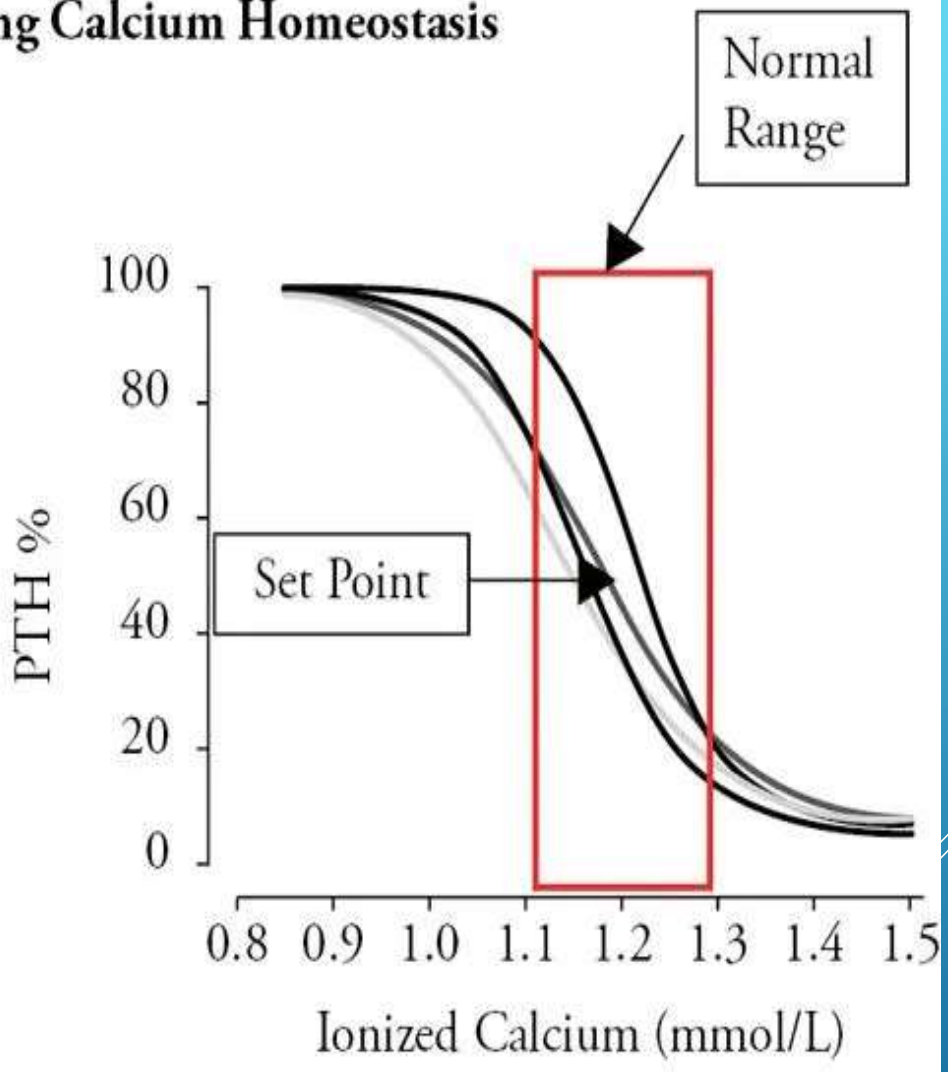
Higgins, C. (2007). Ionized calcium.



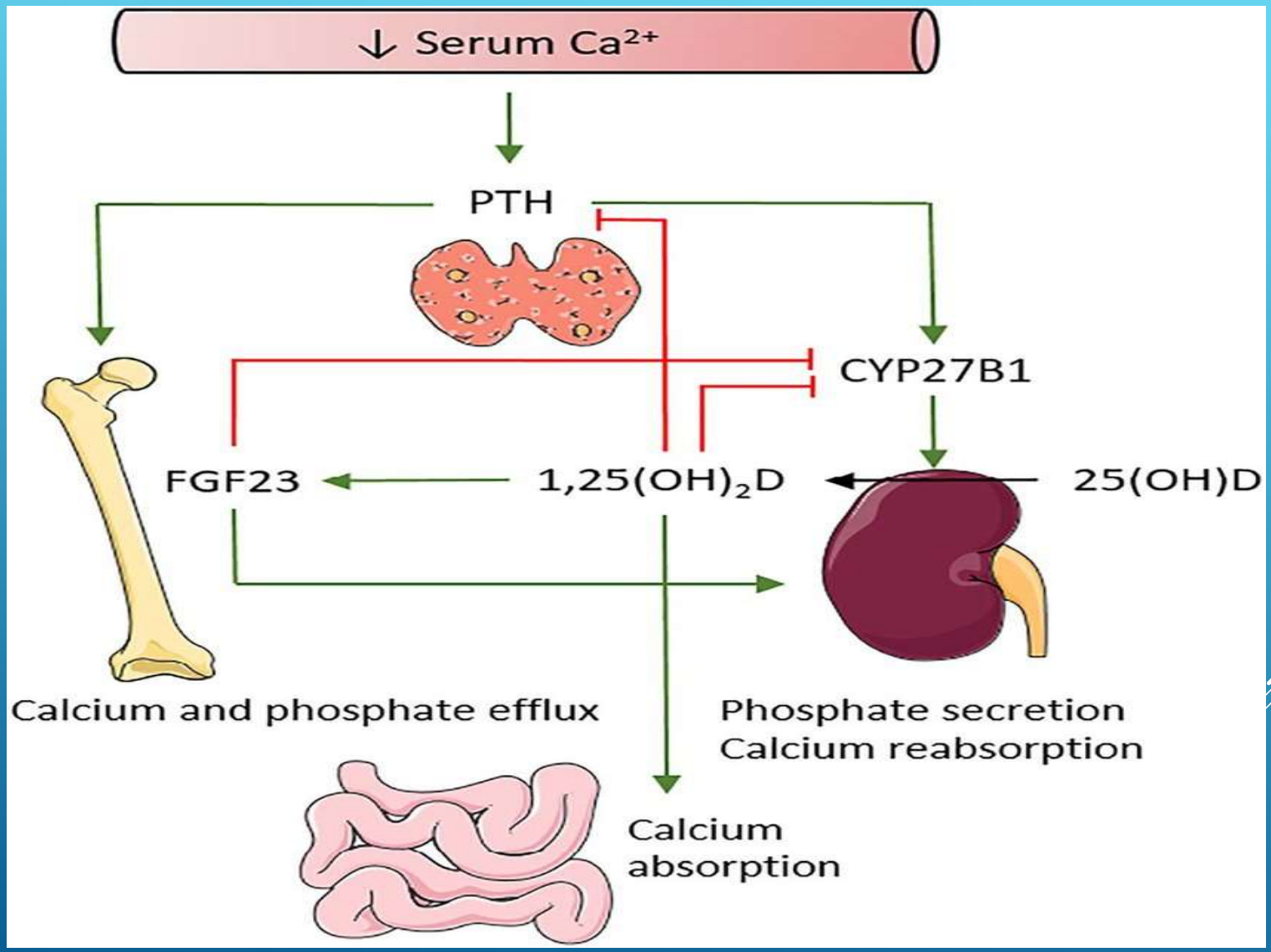
http://www2.csudh.edu/nsturm/CHE452/20_Calcium%20Homeostasis16.htm

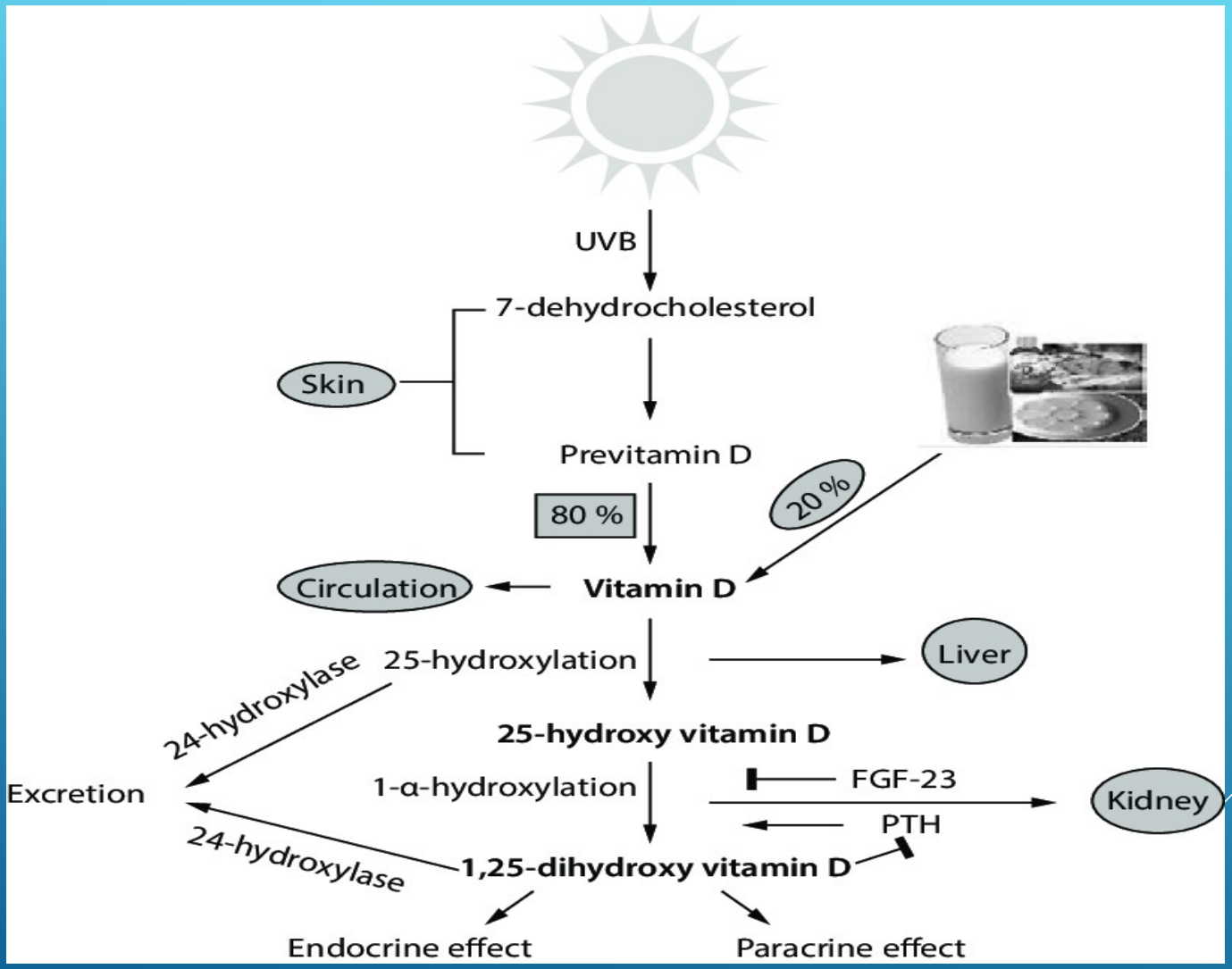
Maintaining Calcium Homeostasis

- Ca++/PTH relationship:
  – Sigmoid curve
- "Set point"= calcium at which PTH secretion is 50% of maximal



https://basicmedicalkey.com/disorders-of-calcium-metabolism/


↓ Serum Ca2+
PTH
CYP27B1
FGF23
1,25(OH)2D
25(OH)D
Calcium and phosphate efflux
Phosphate secretion
Calcium reabsorption
Calcium
absorption



DOI:10.11613/BM.2020.020501

HYPERCALCEMIA

HYPERCALCEMIA

- Albumin corrected calcium levels > UNL (≥ 10.6 mg/dl) or Ionized Ca > UNL
- Symptoms depend on calcium levels or rapid rate of increase

Table 2. Symptoms and Signs of Hypercalcemia[a]

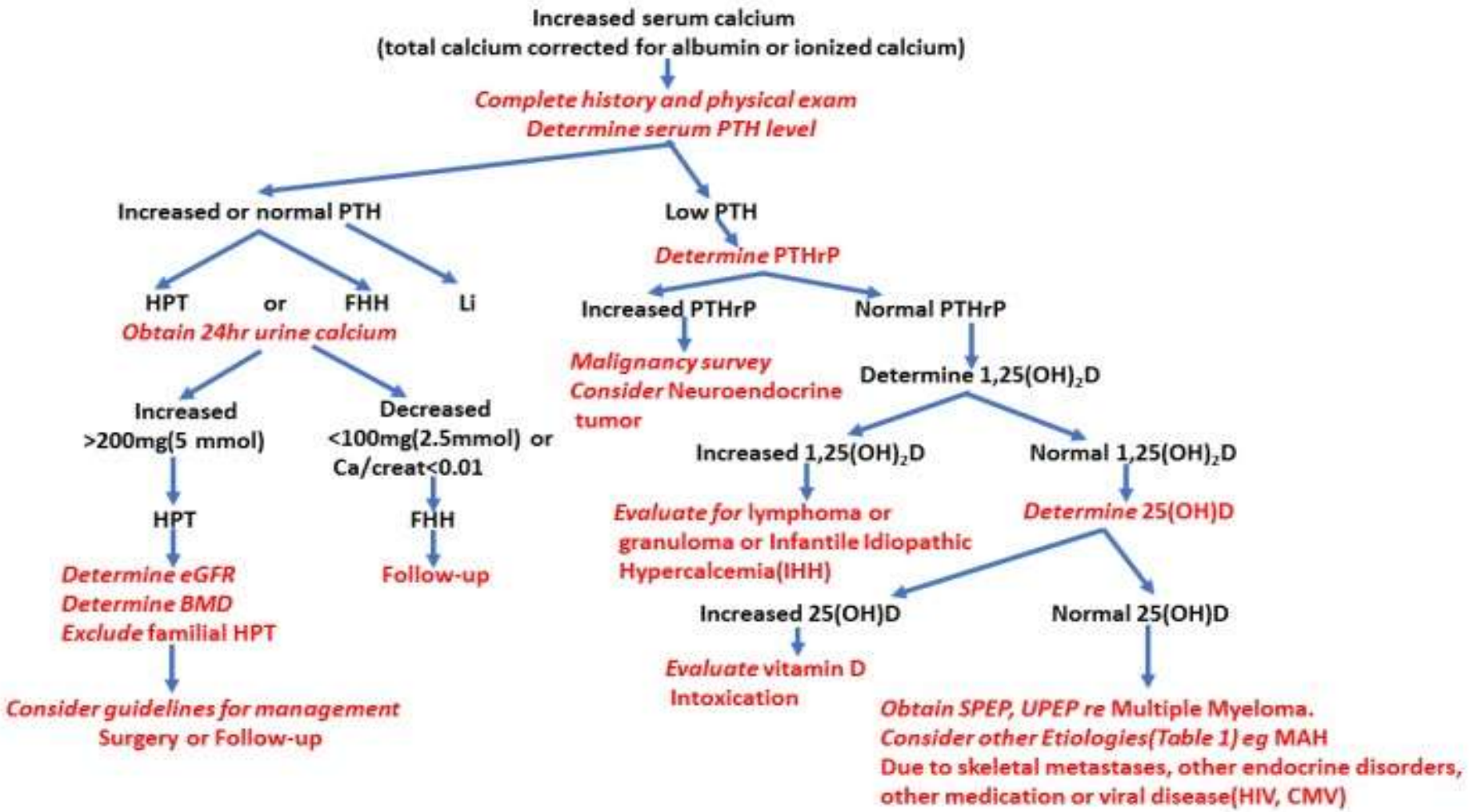
Gastrointestinal
Anorexia
Nausea
Vomiting
Abdominal pain
Constipation
Failure to thrive
Urinary
Polyuria
Hematuria
Nephrolithiasis
Neurologic
Hyperreflexia
Headache
Dizziness
Thirst
Irritability
Insomnia
Lethargy
Stupor
Coma
Psychiatric
Anxiety
Depression
Cognitive disturbances
Cardiac
Arrhythmias
Shortened QT interval
Musculoskeletal
Muscle weakness
Bone pain
Fractures

[a]Adapted based on Lietman et al[1] and Stanley and Shaw.[2]

April 2012Clinical Pediatrics 51(8):804-7

HYPERCALCEMIA

- Mild Ca: UNL -12 mg/dl
- Moderate: >12 – 14 mg/dl
- Severe: >14 mg/dl or symptomatic hypercalcemia (CNS or Cardiac symptoms)
- แนวทางการ Approach to hypercalcemia
  - Underlying disease and Drugs
  - Repeat serum calcium or IonizedCa, and PTH levels พร้อมกัน*********
  - ดูการตอบสนองของ PTH hormone ในภาวะ Hypercalcemia
    - PTH dependent Hypercalcemia (PTH >20 pg/ml)
    - PTH independent Hypercalcemia (PTH <20 pg/ml)



Available from: https://www.ncbi.nlm.nih.gov/books/NBK279129/

PTH DEPENDENT HYPERCALCEMIA

- Primary hyperparathyroidism
- Familial hypocalciuric hypercalcemia (UCCR <0.01 or 24 hr. Uca <100 mg)
  - AD, also appropriately called familial benign hypercalcemia,
  - Caused most often by mutations of the CASR gene found in parathyroid glands, kidney, and other organs.
  - เป็นตั้งแต่เกิด มักไม่มีอาการ ระดับมักจะไม่เกิน 12 mg/dl.
- Tertiary Hyperparathyroidism
  - Hyperplasia of parathyroid gland in ESRD patients

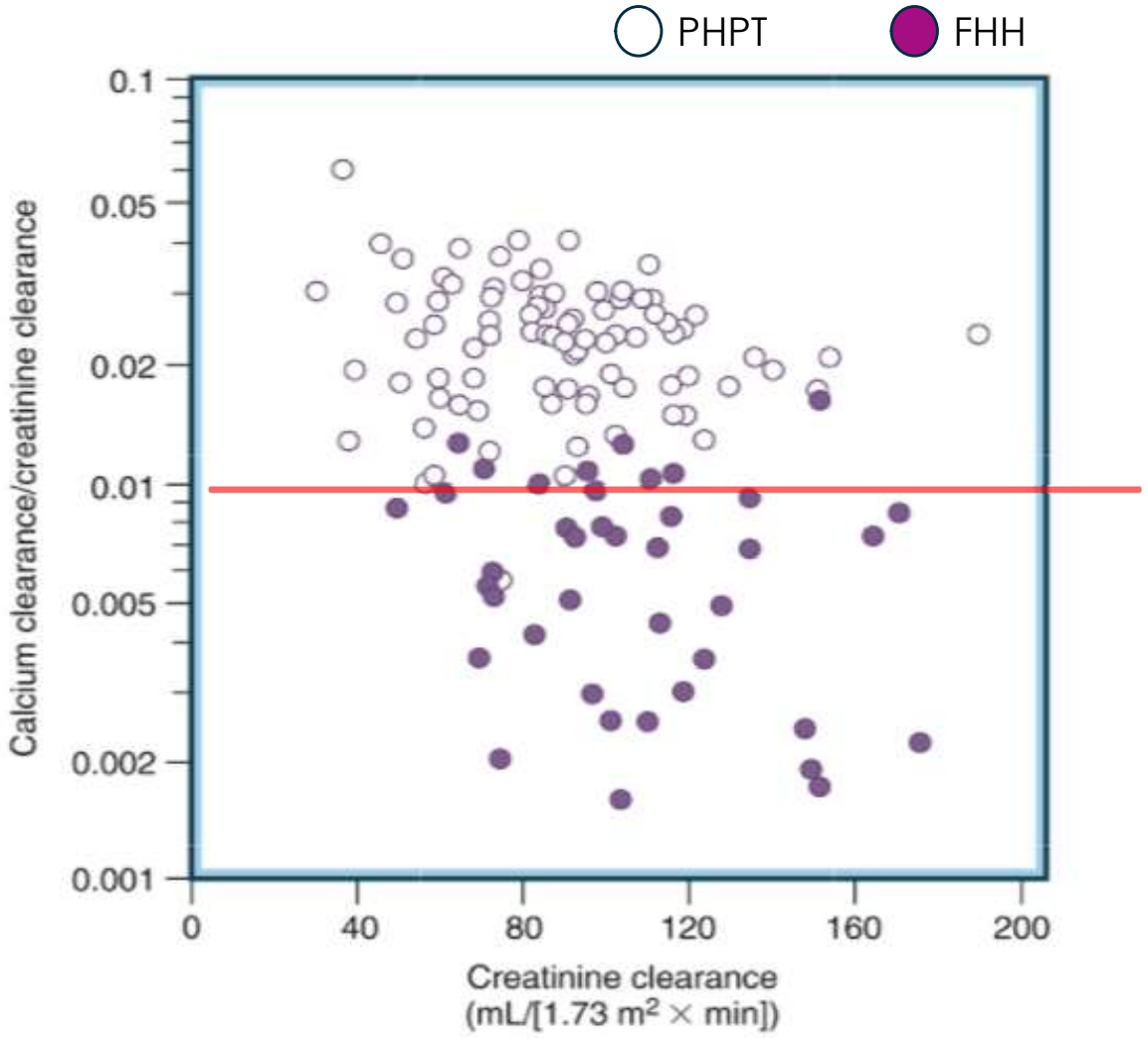


Figure 29.26

Index of urinary excretion rate for calcium as a function of creatinine clearance. Each point represents the mean of multiple determinations for a hypercalcemic patient with familial hypocalciuric hypercalcemia (filled circles) or with typical primary hyperparathyroidism (open circles). The data are based on average 24-hour urinary excretion values and average fasting serum samples.

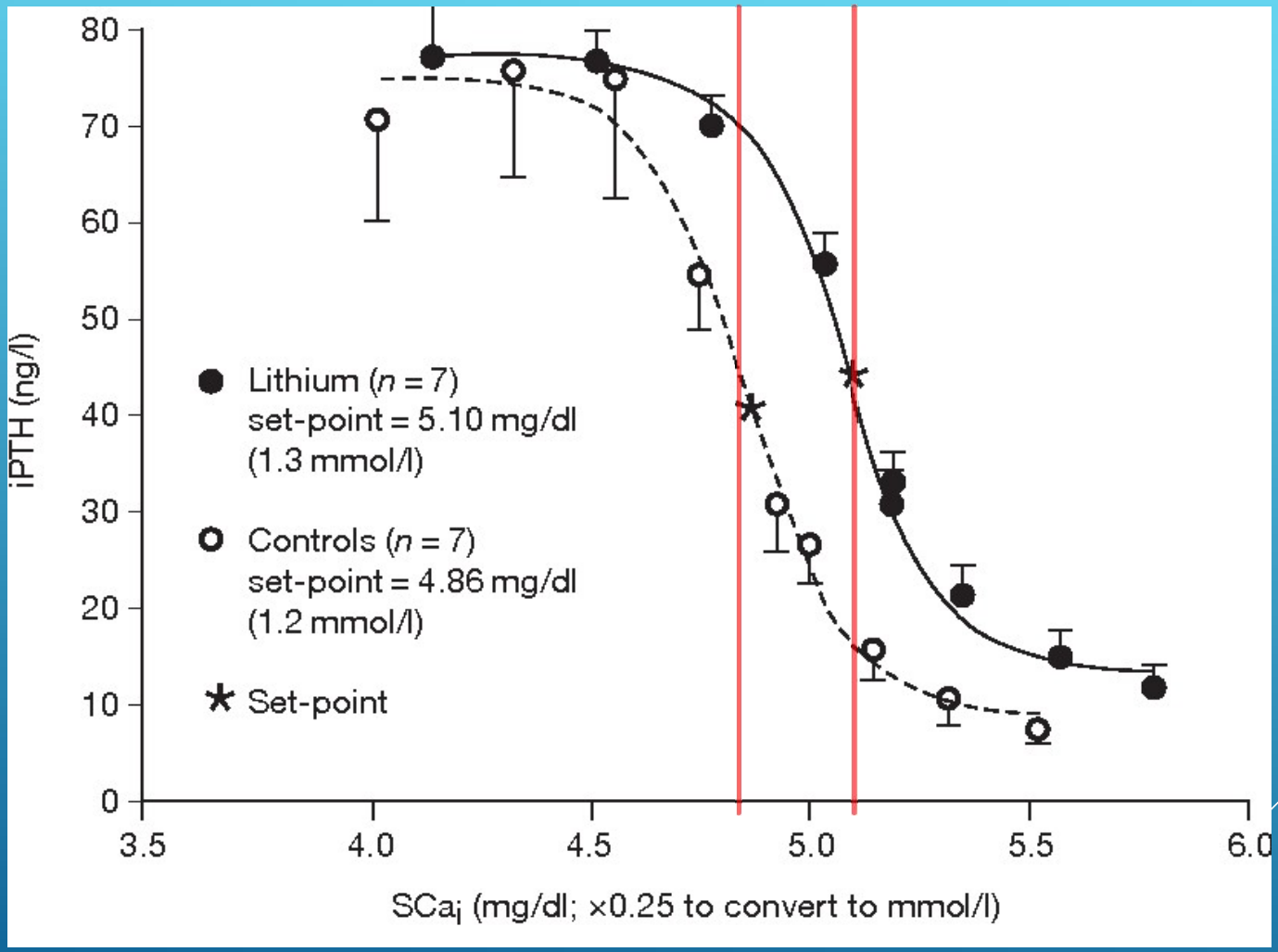
From Marx SJ, Attie MF, Levine M, et al. The hypocalciuric or benign variant of familial hypercalcemia: clinical and biochemical features in fifteen kindreds. *Medicine*. 1981;60:397–412.

0 Notes

ADD NOTE +

PTH DEPENDENT HYPERCALCEMIA

- Lithium ingestion
  - Treatment of bipolar affective disorders with lithium commonly leads to mild, persistent increases in blood calcium.
  - Patients taking lithium usually tolerate mild hypercalcemia without obvious symptoms, Except : Nephrogenic DI -> worsening of hypercalcemia
  - Lithium increases the set-point for PTH secretion when it is added to isolated parathyroid cells in vitro.



Khairallah, Walid et al. "Hypercalcemia and diabetes insipidus in a patient previously treated with lithium." *Nature Clinical Practice Nephrology* 3 (2007): 397-404.

PTH INDEPENDENT HYPERCALCEMIA

- Hypercalcemia of malignancy: Severe Hypercalcemia (die 1-2 months after hypercalcemia)
  - PTHrP dependent: Squamous cell cancers of the lung, head and neck, esophagus, cervix, vulva, and skin; breast cancer; renal cell cancer; and bladder cancer; pheochromocytoma; neuroendocrine tumor; T-cell lymphoma
  - Extra renal active vitamin D production (extra-renal 1α-hydroxylase): hematologic malignancy
  - Local osteolytic disease (including metastases): multiple myeloma increase RANKL -> increase osteoclast activity
  - Ectopic PTH secretion from tumors: Neuroendocrine tumor

PTH INDEPENDENT HYPERCALCEMIA

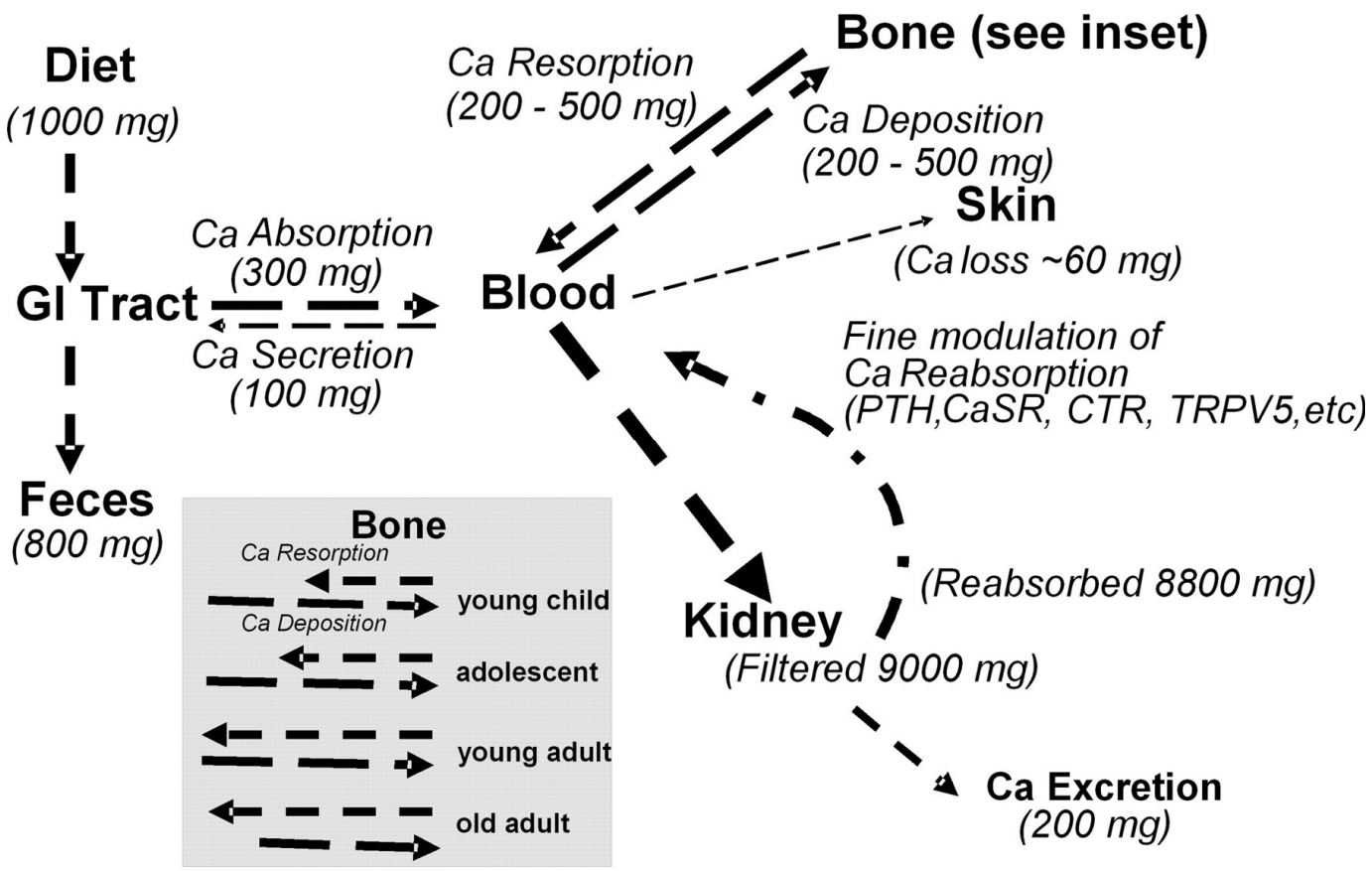
- Excess vitamin D
  - Ingestion of excess vitamin D or vitamin D analogues or Topical vitamin D analogues
  - Granulomatous disease: Tuberculosis and sarcoidosis

1,25(OH)2D level (ng/mL)	1,25(OH)2D level (nmol/L)	Laboratory diagnosis
<10	<25	Severe deficiency
<20	<50	Deficiency
20–30	50–75	Insufficiency
30–100	75–250	Normal in sunny countries
>100	>250	Excess
>150	>325	Intoxication

DOI:10.1177/0300060520943421

PTH INDEPENDENT HYPERCALCEMIA

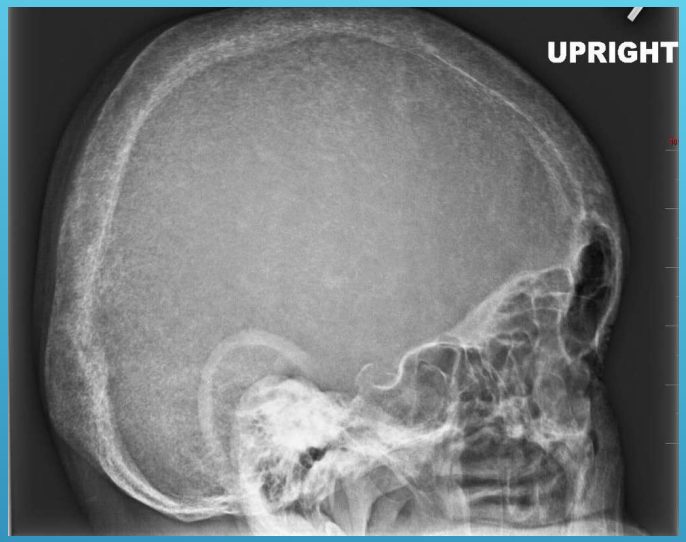
- Endocrine disease
  - Adrenal insufficiency (hemoconcentration and increased albumin levels,), thyrotoxicosis (direct action of thyroid hormone to stimulate bone resorption), Acromegaly (Stimulate bone resorption), Pheochromocytoma (PTHrP or PTH secretion)
- Drugs
  - Vitamin A intoxication: (action of retinoids to stimulate bone resorption)
  - Milk-alkali syndrome: (triad of hypercalcemia, metabolic alkalosis, and renal failure, excessive absorption of calcium and absorbable alkali
  - Thiazide diuretics: (increase proximal tubular calcium reabsorption)
  - Theophylline (unknown mech.)
  - PTH analogue

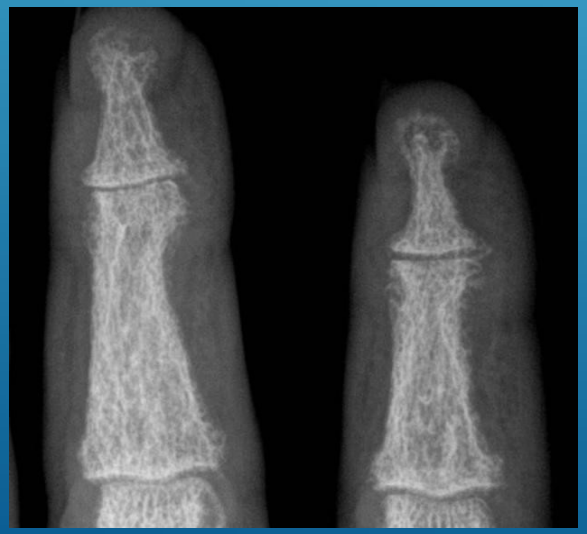


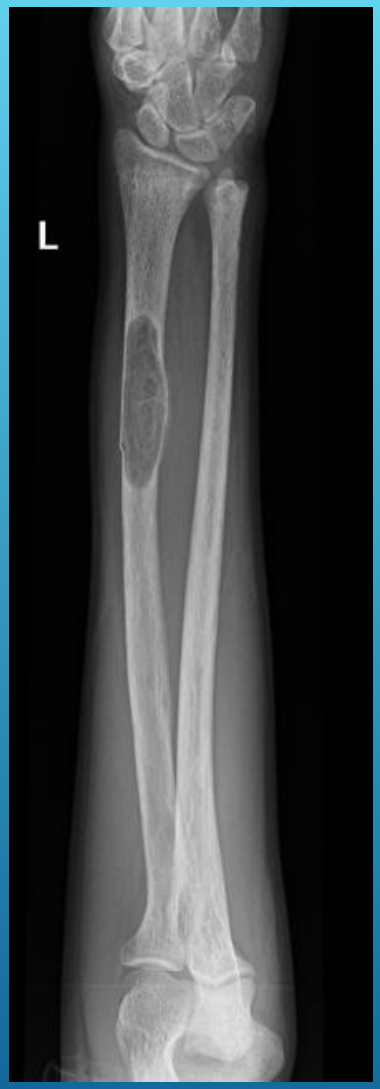
CJASN July 2006, 1 (4) 641-654; DOI: https://doi.org/10.2215/CJN.01451005

PRIMARY HYPERPARATHYROIDISM

- Primary abnormality of parathyroid tissue leads to inappropriate secretion of PTH.
- Biochemical phenotype of hypercalcemia and hypophosphatemia, loss of cortical bone, hypercalciuria, and the various clinical sequelae of chronic hypercalcemia.
- 70-80% parathyroid adenoma (one and more), 20% hyperplasia, <1% carcinoma
- Classic: Stone (kidney stone), Bone (painful, secondary osteoporosis, osteitis fibrosa cystica). Moans (depression, memory loss, psychosis), Groans (Constipation, N/V)
- Other features that have been reported in association with classic severe primary hyperparathyroidism are conjunctival calcifications, band keratopathy, hypertension (50%)


UPRIGHT

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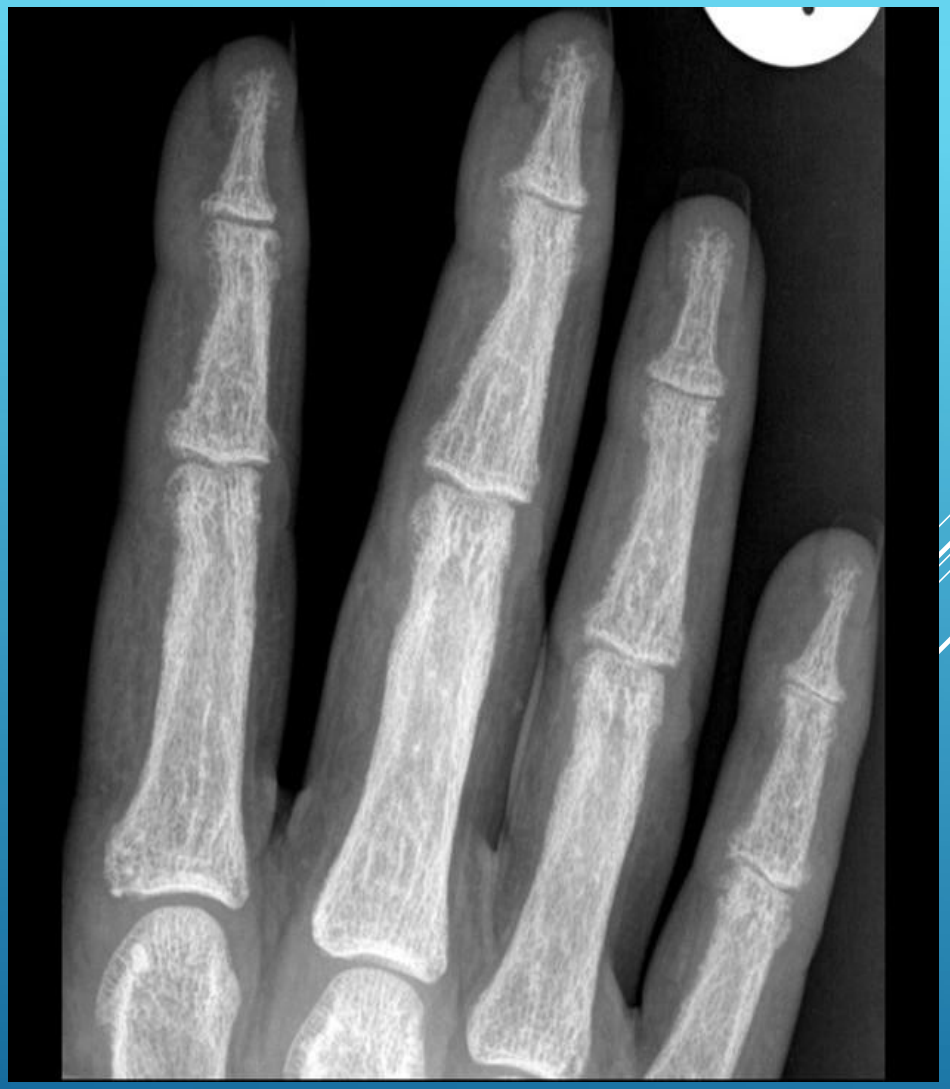


PRIMARY HYPERPARATHYROIDISM

- Incidence: 0.12-0.15 per 1000 patients, more common in female (2-3X), mean age 50-60 years old.
- Mostly patients with PHPT are asymptomatic
- Inherited Primary Hyperparathyroidism
  - Primary Hyperparathyroidism <35 (40) year-old, recurrent disease, multiple gland or hyperplasia disease.
  - MEN1 (pan-pa-pit)
  - MEN2A (Med-pa-pheo)

PRIMARY HYPERPARATHYROIDISM

- Management: parathyroidectomy (focus parathyroidectomy)

TABLE 29.1 Indications for Surgery in Primary Hyperparathyroidism

Modified from Bilezikian JP, Khan AA, Potts Jr JT, Third International Workshop on the Management of Asymptomatic Primary Hyperthyroidism. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Third International Workshop. *J Clin Endocrinol Metab.* 2009;94:335–339. Based upon recommendations of the 2014 NIH-sponsored Workshop on the Management of Asymptomatic Primary Hyperparathyroidism.

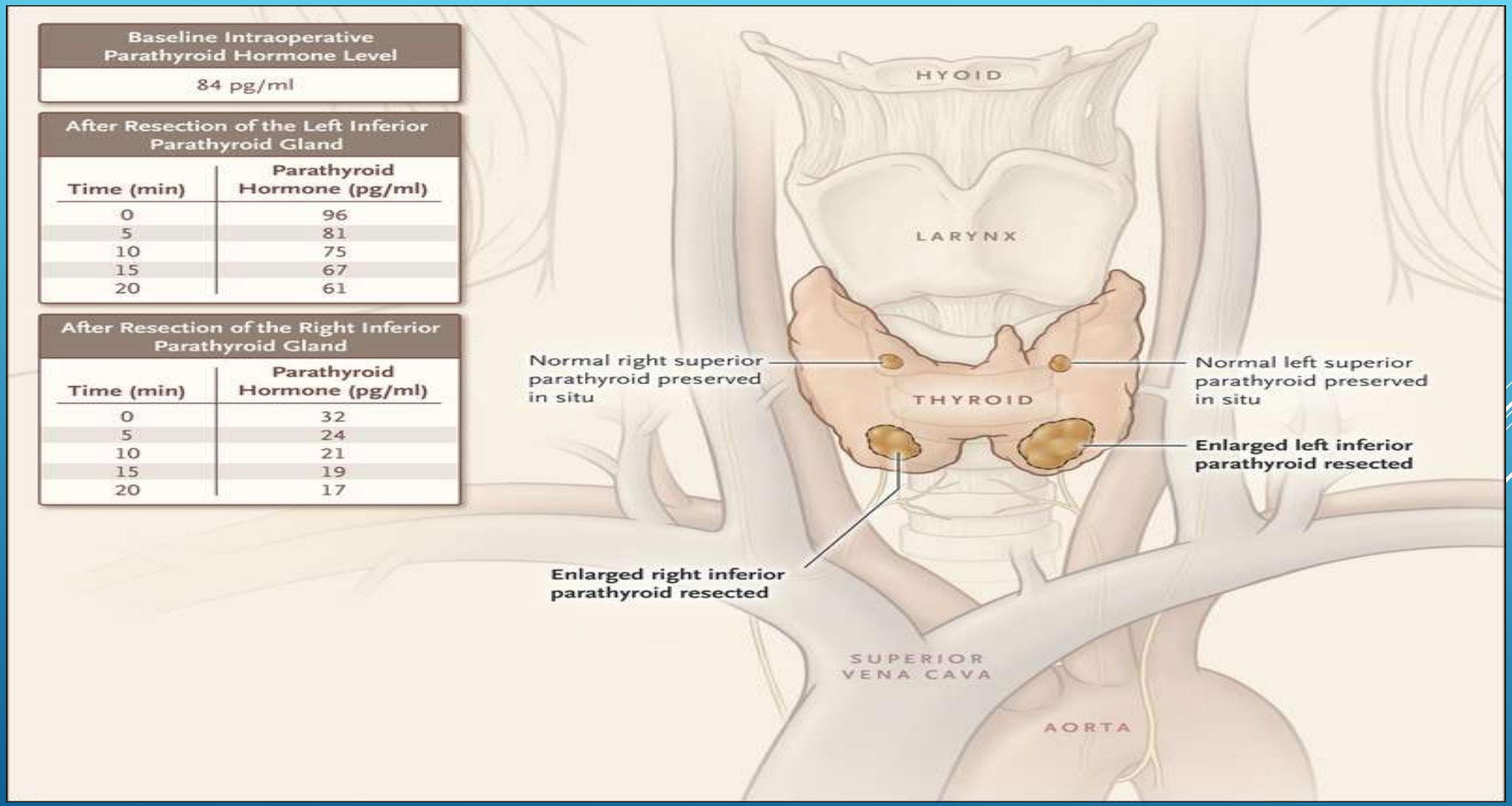
Overt clinical manifestations of disease
Kidney stones or nephrocalcinosis
Fractures or classic radiographic findings of osteitis fibrosa
Classic neuromuscular disease
Symptomatic or life-threatening **hypercalcemia**
Serum calcium >1 mg/dL above upper limit of normal
Creatinine clearance <60 mL/min, presence of stone(s) by radiograph, CT, or ultrasound
Urinary calcium >400 mg/day plus other urinary biochemical indices of stone risk
Bone mineral density low (T score ≤−2.5) at any site[a]
Presence of vertebral fracture by radiograph or by vertebral fracture analysis on DXA
History of fragility fracture
Young age (<50 years)
Uncertain prospects for adequate medical monitoring

CT, Computed tomography; *DXA*, dual-energy x-ray absorptiometry.

Baseline Intraoperative Parathyroid Hormone Level
84 pg/ml

After Resection of the Left Inferior Parathyroid Gland	
Time (min)	Parathyroid Hormone (pg/ml)
0	96
5	81
10	75
15	67
20	61

After Resection of the Right Inferior Parathyroid Gland	
Time (min)	Parathyroid Hormone (pg/ml)
0	32
5	24
10	21
15	19
20	17



N Engl J Med 2018; 379:1050-1059

PRIMARY HYPERPARATHYROIDISM

- Medical treatment
  - No rationale for dietary calcium restriction in patients with asymptomatic PHPT.
    - Low calcium intake -> increase PTH levels
  - Keep 25-OHD level 20-30 ng/ml, Closely monitor calcium levels and urine calcium excretions.
  - Estrogen and SERM: limit evidence
  - Alendronate: Oral Bisphosphonate
    - RCTs shown a positive effect of alendronate on BMD at the lumbar spine and hip in PHPT. There are currently no fracture data with bisphosphonate therapy in PHPT.
    - No significant change in calcium and PTH levels
  - Cinacalcet
    - effective in lowering, and often normalizing, serum calcium and increasing serum phosphate in patients with PHPT.
    - No consistent effects on BMD

Treatment of hypercalcemia

Intervention	Mode of action	Onset of action	Duration of action
Isotonic saline hydration	Restoration of intravascular volume Increases urinary calcium excretion	Hours	During infusion
Calcitonin	Inhibits bone resorption via interference with osteoclast function Promotes urinary calcium excretion	4 to 6 hours	48 hours
Bisphosphonates	Inhibit bone resorption via interference with osteoclast recruitment and function	24 to 72 hours	2 to 4 weeks
Loop diuretics*	Increase urinary calcium excretion via inhibition of calcium reabsorption in the loop of Henle	Hours	During therapy
Glucocorticoids	Decrease intestinal calcium absorption Decrease 1,25-dihydroxyvitamin D production by activated mononuclear cells in patients with granulomatous diseases or lymphoma	2 to 5 days	Days to weeks
Denosumab	Inhibits bone resorption via inhibition of RANKL	4 to 10 days	4 to 15 weeks
Calcimimetics	Calcium-sensing receptor agonist, reduces PTH (parathyroid carcinoma, secondary hyperparathyroidism in CKD)	2 to 3 days	During therapy
Dialysis	Low or no calcium dialysate	Hours	During treatment

RANKL: receptor activator of nuclear factor kappa-B ligand; PTH: parathyroid hormone; CKD: chronic kidney disease.

* Loop diuretics should not be used routinely. However, in patients with renal insufficiency or heart failure, judicious use of loop diuretics may be required to prevent fluid overload during saline hydration.

Data from: Shane E, Dinaz I. Hypercalcemia: Pathogenesis, clinical manifestations, differential diagnosis, and management. In: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism (Sixth Edition). American Society of Bone and Mineral Research 2006; 179.

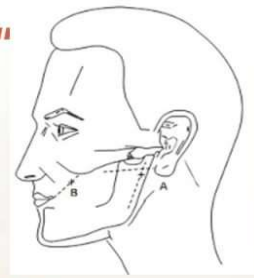
HYPOCALCEMIA

HYPOCALCEMIA

- Alb corrected serum calcium < 8.8 mg/dL (LNL) or as a serum ionized calcium concentration < 4.7 mg/dL (LNL)
- Sign and Symptoms: Neuromuscular irritability, including perioral paresthesias, tingling of the fingers and toes, and spontaneous or latent tetany.
- Profound hypocalcemia or during acute falls in serum calcium, grand mal seizures or laryngospasm also may be observed.
- Electrocardiographic abnormalities: prolonged QT intervals and marked QRS complex and ST-segment changes that may mimic acute myocardial infarction.

Chvostek's sign

- Facial muscle twitching upon tapping the preauricular region over the facial nerve
- Present at baseline in up to 25% of people
- Tap area 0.5 to 1 cm below the zygomatic process of the temporal bone, 2 cm anterior to the ear lobe, and on a line with the angle of the mandible
- Other conditions include rickets, diphtheria, measles, scarlet fever and myxedema.

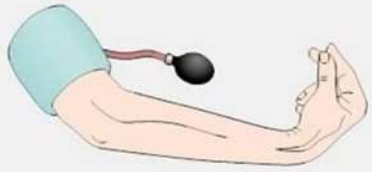


Grading:

1. Twitching of lip at angle of mouth
2. Twitching of alar nasi
3. Twitching of lateral angle of eye
4. Twitching of all facial muscles

Trousseau's sign

- Flexion of the wrist, thumb, and metacarpophalangeal joints and hyperextension of the fingers
- Brachial artery occlusion by inflation of a blood pressure cuff above systolic blood pressure
- More sensitive (94%) than the Chvostek's sign (29%) for hypocalcemia
- Other positive sign is hypomagnesemia



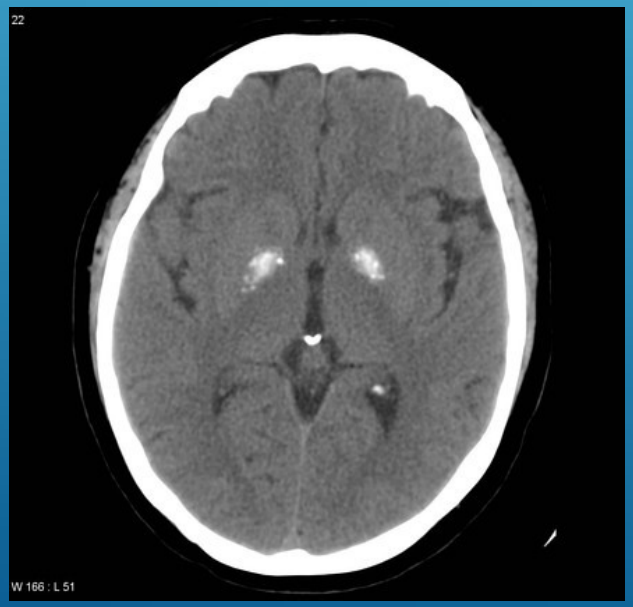
Methods:

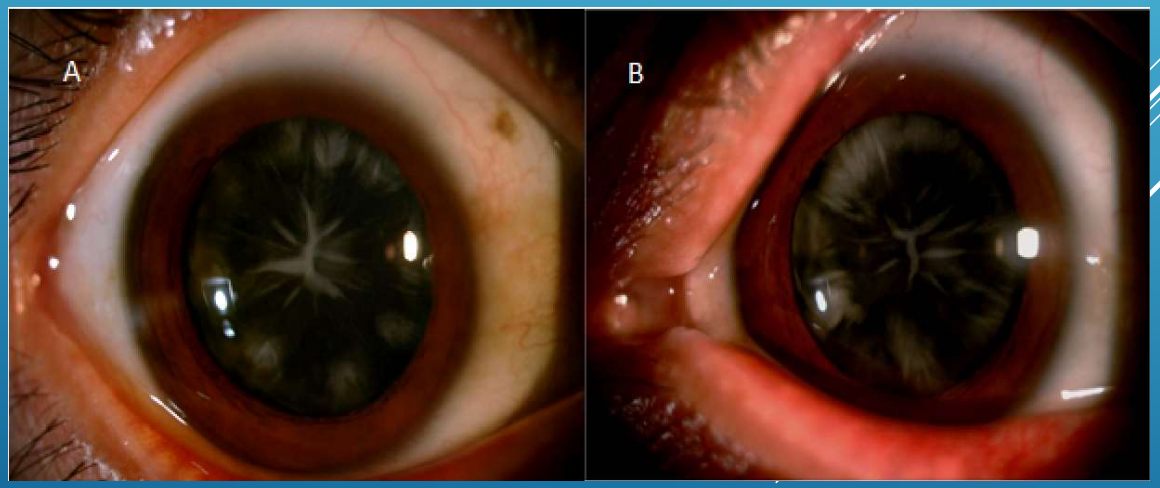
- Inflated pressure cuff to a pressure greater than SBP 20 mmHg for 3 minutes to occluded the brachial artery
- Subsequent neuromuscular irritability will induce spasm

http://www.thaiendocrine.org/th/2018/07/15/american-thyroid-association-statement-on-postoperative-hypoparathyroidism-diagnosis-prevention-and-management-in-adults/

HYPOCALCEMIA

- Longstanding hypocalcemia associated with hyperphosphatemia (observed with PTH deficiency or resistance) may lead to calcification of the basal ganglia → occasionally, extrapyramidal disorders.
- Calcium deposits in the lens may lead to cataract formation.





•DOI:10.4172/2155-9570.1000588

HYPOCALCEMIA

- แนวทางการ Approach to hypocalcemia
- Ix: Serum calcium, PO4, Mg, and PTH levels, 25-OHD levels พร้อมกัน
- Corrected HypoMg ก่อนเสมอ (impair PTH secretion and PTH resistance)
- ดูการดูการตอบสนองของ PTH hormone ในภาวะ Hypocalcemia
  - ภาวะเหล่านี้แนะนำวัด IonizedCa: Alkalosis, massive blood transfusion-citrate

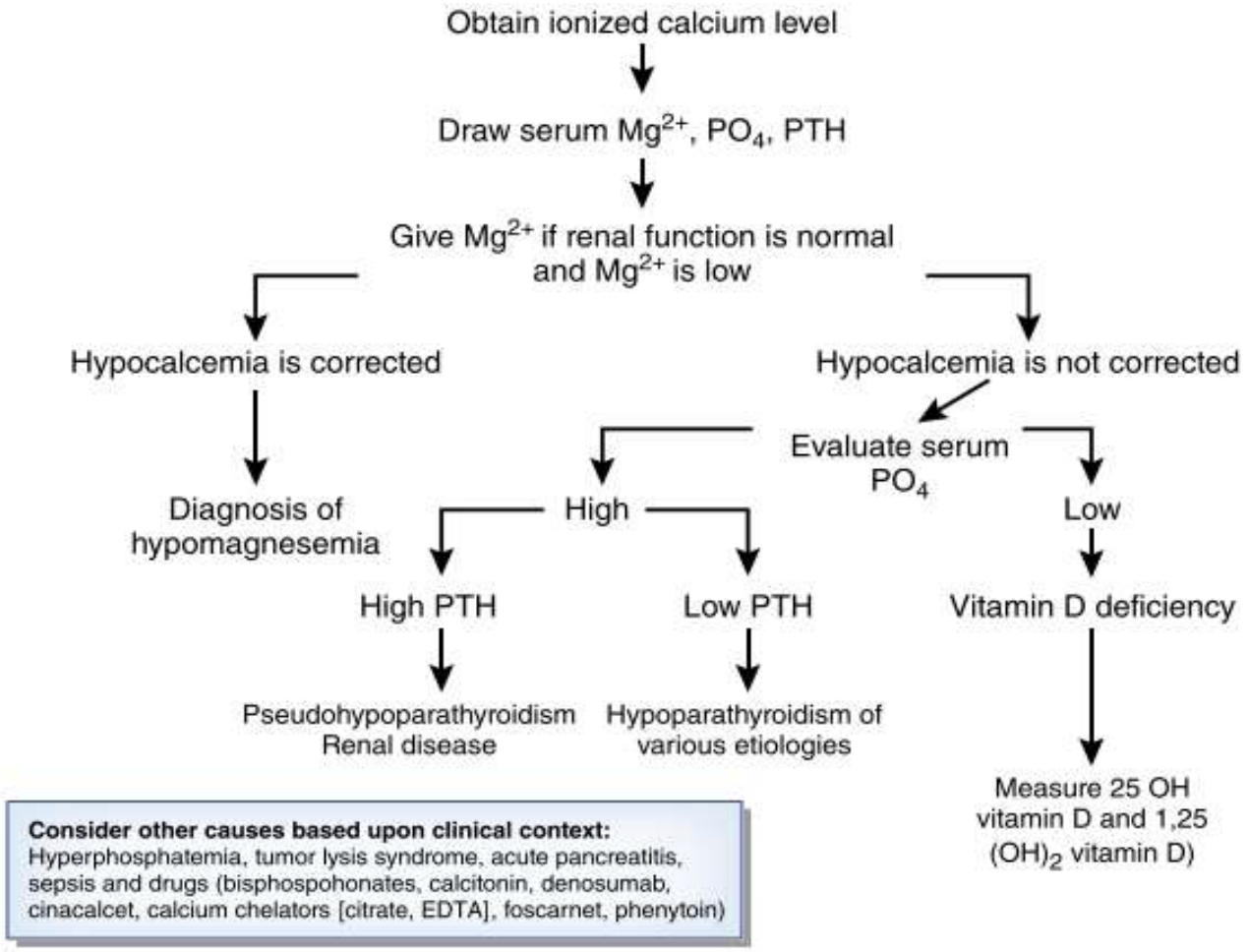


Figure 1. | Diagnostic algorithm for patients presenting with hypocalcemia. Mg^{2+}, magnesium; PO_4, phosphorus; PTH, parathyroid hormone.

PTH RELATED DISORDER (HIGH PO4)

- PTH low to normal
  - Hypoparathyroidism
    - Congenital disease: DiGeorge syndrome, X-linked or autosomal inherited hypoparathyroidism, Autoimmune polyglandular syndrome type I
    - Postsurgical hypoparathyroidism
    - Post radioactive iodine thyroid ablation
    - Infiltrative disease: TB, hemochromatosis, Wilson disease, tumor metastasis
  - Impair PTH secretion
    - hypomagnesemia, hypermagnesemia, respiratory alkalosis

PTH RELATED DISORDER (HIGH PO4)

- PTH high
  - PTH resistance
    - Hypomagnesemia
    - Pseudohypoparathyroidism: AHO

VITAMIN D RELATED DISORDER (PO4 LOW)

- PTH high
  - Vitamin D deficiency (25-OHD levels <20 ng/ml)
    - Dietary absence
    - Malabsorption
    - Anti-convulsant (Phenytoin, Phenobarbital, carbamazepine) and anti tuberculosis (rifampicin) accelerated loss of vitamin D)
  - Impaired 25 hydroxylation: liver disease, INH
  - Impaired 1α hydroxylation: renal disease
  - Ricket type I : lack of 1α hydroxylase Enz.
  - Ricket type 2: lack of Calcitriol receptor
  - Phenytoin: Target organ resistance to the biologic effects of $1,25(OH)_2D_3$, acceleration of the hepatic catabolism of vitamin D metabolites.

OTHER CAUSES

- Excessive deposition into skeleton
  - Osteoblastic malignancies: Breast and prostate cancer
  - Hungry bone syndrome
- Loss of IonizedCa: binding with anion e.g. citrate, lactate, sulfate, respiratory alkalosis
- Hyperphosphatemia: tumor lysis syndrome, rhabdomyolysis, and phosphate ingestion or infusion
- Critical illness: septic shock, pancreatitis
  - Inflammatory cytokine -> PTH resistance and impaired PTH secretion and reduced calcitriol production
- HIV patients: chronic inflammation.
  - Poor intake, malabsorption, liver disease, renal disease
  - PIs may also inhibit 1α-hydroxylase.

DRUG-INDUCED HYPOCALCEMIA

- Anti-resorptive agents -> inhibit bone resorption
  - Zoledronic acid and denosumab
- Cinacalcet (calcimimetic drugs)
  - Increase sensitivity of CaSR -> Suppress PTH secretion and PTH gene transcription
- Drug induced hypomagnesemia
  - Cisplatin, aminoglycosides, amphotericin B, Alcohol consumption
- Loop diuretic drugs
  - Decrease calcium reabsorption
- Laxatives or enema agents: Sodium phosphate preparations

TREATMENT OF HYPOCALCEMIA

- Acute severe symptomatic
  - Neuromuscular irritability, carpopedal spasm, or electrocardiogram (EKG) changes.
  - 100 mg of elemental calcium should be infused over a period of 10 to 20 minutes
  - Order 10% Calcium gluconate 10 ml IV slowly push in 10 minutes**** and then maintenance with 0.5-1.5 mg/kg/hr.
  - Correct hypomagnesemia
  - Start oral active vitamin D (alfacalcidol duration of action 3-7 d, calcitriol duration of action 2-3 d) and calcium supplement
  - Monitor calcium levels q 6-8 hr. and adjustable dosage.

Compound	MW[a]	Mineral Ion Content		Available Formulations					
				Oral Preparations			Parenteral Preparations		
				Compound	Mineral Ion Content		Compound	Mineral Ion Content	
		mg/g	mmol/g		mg/g	mmol/g		mg/g	mmol/g
Calcium									
Ca carbonate	100	400	10.0	1250 mg[b]	500 mg	12.5 mmol			
Ca phosphate	310	383	9.6	1565 mg	600 mg	15.0 mmol			
Ca acetate	158	253	6.3	668 mg[b]	167 mg	4.2 mmol			
Ca citrate	498	210	6.0	950 mg[b]	200 mg	5.0 mmol			
Ca lactate	218	130	4.6	650 mg[b]	84 mg	2.1 mmol			
Ca glubionate		64	1.7	5 mL	115 mg	2 mmol			
Ca gluconate	430	93	2.3	1000 mg[b]	93 mg	2.3 mmol	10% soln	93 mg/10 mL	2.3 mmol/10 mL

TREATMENT OF HYPOCALCEMIA

- Chronic treatment
  - Calcium carbonate 1-3 gm of elemental calcium per day.
    - Divided dose of 1 gm or less
  - Vitamin D supplement
    - If impaired renal 1α-hydroxylation
      - such as in renal failure, hypoparathyroidism (or PTH resistance), or the vitamin D–dependent rickets syndromes.
      - Calcitriol or alfacalcidol 0.25-1 mcg per day max dose 2-3 mcg per day
    - Vitamin deficiency or accelerated loss:
      - Ergocalciferol: 40000-60000 IU per week in 3-4 week. and then 20000 U per week
      - Cholecalciferol

MONITOR OF HYPOCALCEMIA TREATMENT

- Especially in hypoparathyroidism patients.
  - Keep low to normal calcium levels (8-8.5 mg/dl)
  - 24 hr. urine calcium < 250 mg/day. If present -> start HCTZ 12.5-50 mg/day
  - Normal PO4 and Normal Mg levels
  - Ca x P product < 55

Product	Vitamin D content (40 IU = 1 µg)
Fresh eel	1,200 IU/100 g
Fresh wild salmon	600–1,000 IU/100 g
Herring in oil	808 IU/100 g
Marinated herring	480 IU/100 g
Salmon (cooked/baked)	540 IU/100 g
Fresh farmed salmon	100–250 IU/100 g
Canned fish (tuna, sardines)	200 IU/100 g
Mackerel (cooked/baked)	152 IU/100 g
Fresh codfish	40 IU/100 g
Shiitake mushrooms	100 IU/100 g
Egg yolk	54 IU/egg yolk
Cheese	7.6–28 IU/100 g
Human milk	1.5–8 IU/100 ml
Human milk during vitamin D supplementation	~20 IU/100 ml
Cow's milk	0.4–1.2 IU/100 ml

- General population: vitamin D supplement 600-800 IU/day
- Higher risk: 1500-2000 IU/day
- Keep 25-OHD level >30 ng/ml