Calcium and Parathyroid

MAHMOUD ALSAYED MD

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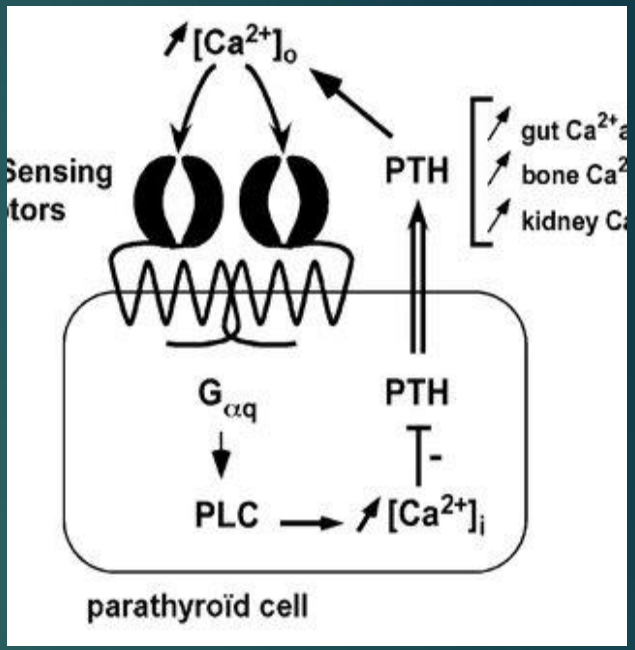
PTH regulation

- The parathyroid gland senses the concentration of **extracellular ionized calcium** through a **cell-surface calcium-sensing receptor (CaSR**) for which calcium is an agonist
- CaSR:
  - **thyroid C** cells, which secrete CT in direct relationship to extracellular calcium
  - the **distal nephron** of the kidney, where calcium excretion is regulated
  - the **placenta**, where fetal-maternal calcium fluxes occur
  - the **brain** ?
  - **gastrointestinal** (GI) tract
  - **bone** cells

- Genetic and functional disorders of the CaSR have been described:
  - Activating defects cause hypocalcemia
  - Inactivating defects cause hypercalcemia

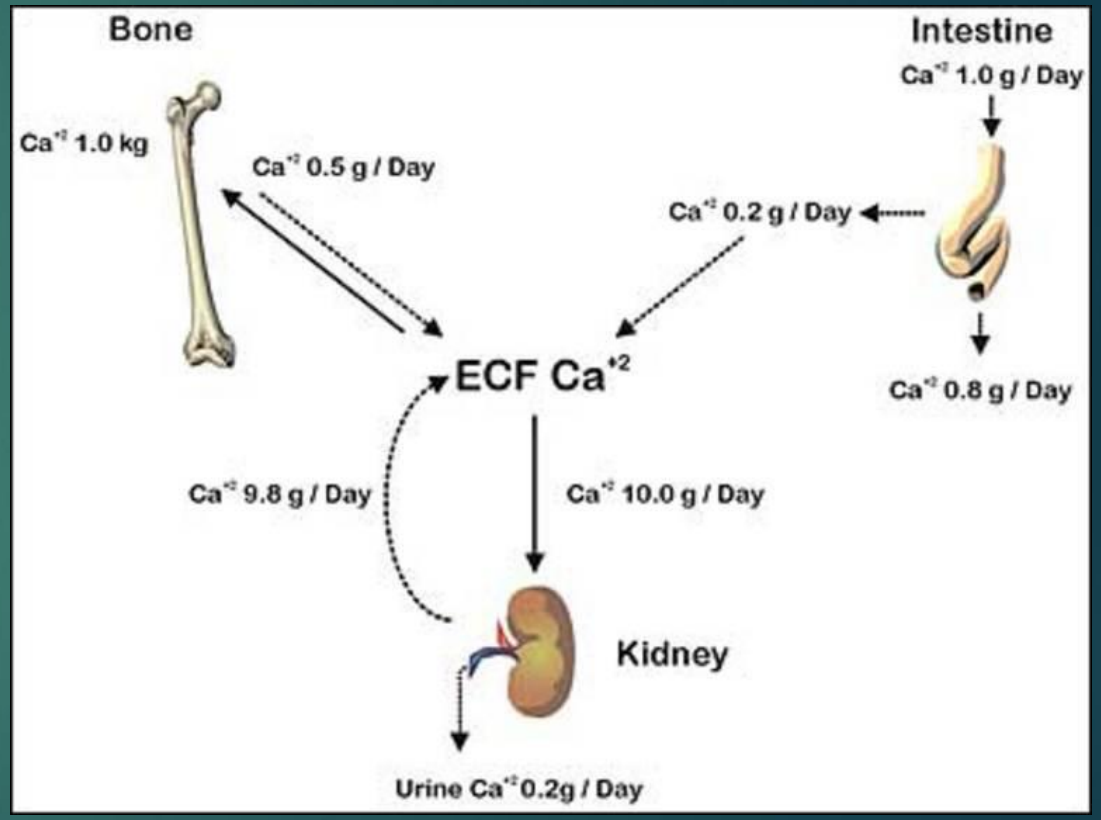
Secretory Regulation Of Parathyroid Hormone And The Calcium Sensor

- The major regulatory signal for PTH secretion is **ionized serum calcium**
- **Serum calcium inversely affects PTH secretion**
  - An increase in ionized calcium inhibits PTH secretion by increasing intracellular calcium through the release of calcium from intracellular stores and the influx of extracellular calcium through cell membranes and channels
- Serum calcium also inversely regulates transcription of the **PTH gene**
- Increased levels of 1,25-dihydroxyvitamin D inhibit **PTH gene transcription**



Biologic Effects Of Parathyroid Hormone

- PTH regulates serum **calcium and phosphorus** concentrations through receptors on **bone, intestine, and kidney**
- **Direct GI** effect of PTH on intestinal calcium or phosphate absorption **is weak**
- PTH stimulates **renal production of 1,25-D → absorption of Ca and phos**



Biologic Effects Of Parathyroid Hormone

- The **skeletal effects** of PTH are mediated through the **osteoblast**
  - Osteoblast cells express **PTH receptors**
  - Osteoblasts communicate with osteoclasts through the **RANK-OPG pathway**

- "**continuous**" High levels of PTH increase osteoclastic bone **resorption**
- Low levels, especially if delivered **episodically**, seem to increase osteoblastic **bone formation**

Biologic Effects Of Parathyroid Hormone

- PTH causes hypercalcemia and hypophosphatemia

- In the kidney, PTH:
  - increases the reabsorption of calcium, in the distal convoluted tubule
  - inhibits the reabsorption of phosphate in the renal proximal tubule

Magnesium

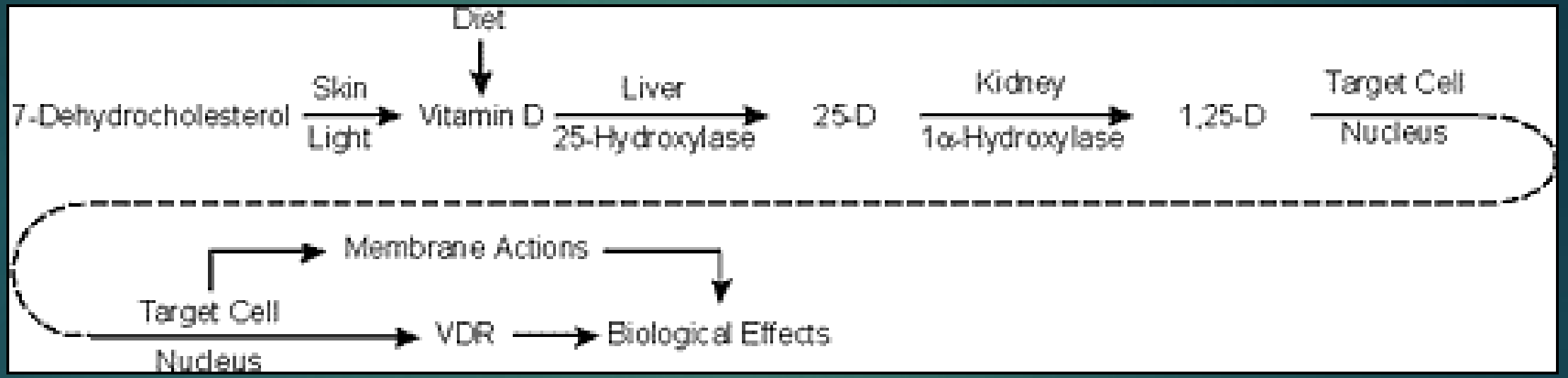
- **Hypermagnesemia can inhibit PTH secretion**
- **Hypomagnesemia can stimulate PTH secretion**
- Prolonged depletion of magnesium will inhibit PTH biosynthesis and secretion
- Hypomagnesemia also attenuates the biological effect of PTH by interfering with its signal transduction

VITAMIN D

- Endogenous (vitamin D3)
  - Cholecalciferol (vitamin D3), is synthesized in the skin from the cholesterol under the influence of UV radiation
  - D3 is also available in oral supplements
- Exogenous (vitamin D2)
  - Ergocalciferol is produced by UV irradiation of the plant sterol ergosterol
  - Available through the diet

VITAMIN D

- **Metabolism and Activation**



Effects of 1,25-dihydroxy Vitamin D on Mineral Metabolism

- **Bone**
  - Promotes **mineralization of osteoid**
  - **Increases resorption at high doses**
- **Kidney**
  - Decreases calcium excretion
  - Decreases phosphorus excretion
- **GI Tract**
  - Increases calcium absorption
  - Increases phosphorus absorption
- **Blood**
  - **Increases calcium**
  - **Increases phosphorus**

Total vs. Ionized Calcium

- Calcium in the blood is
  - bound to plasma proteins (~45%), notably albumin
  - bound to small anions such as phosphate and citrate (~10%)
  - free or ionized state (~45%) (metabolically active)

- Normal serum concentrations of total calcium range 8.5 and 10.6 mg/dL
- Ionized calcium between 4.65-5.30 mg/dL

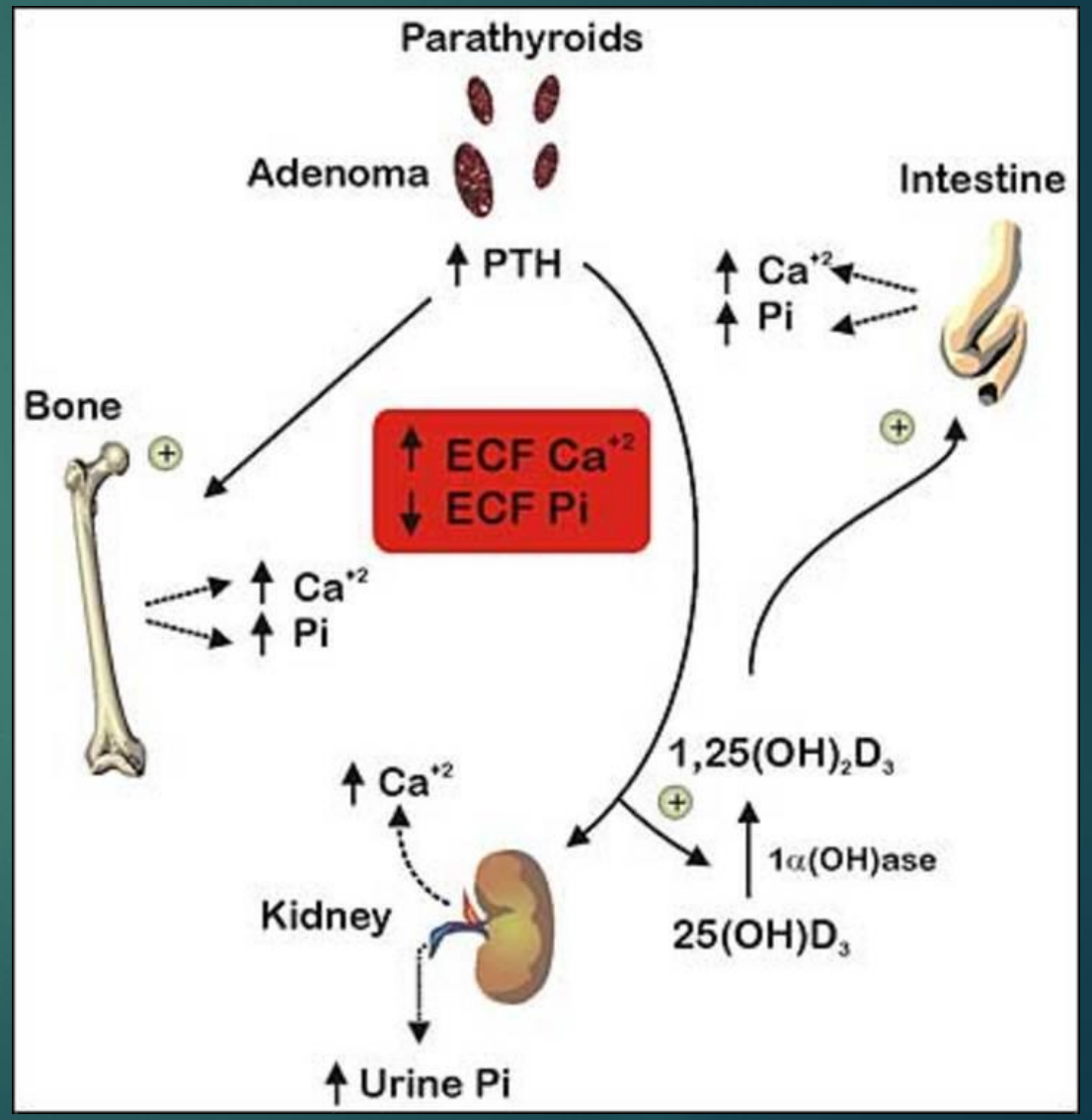
- Corrected calcium (mg/dL) = measured total serum calcium (mg/dL) + [4.0- serum albumin (g/dL) X 0.8]

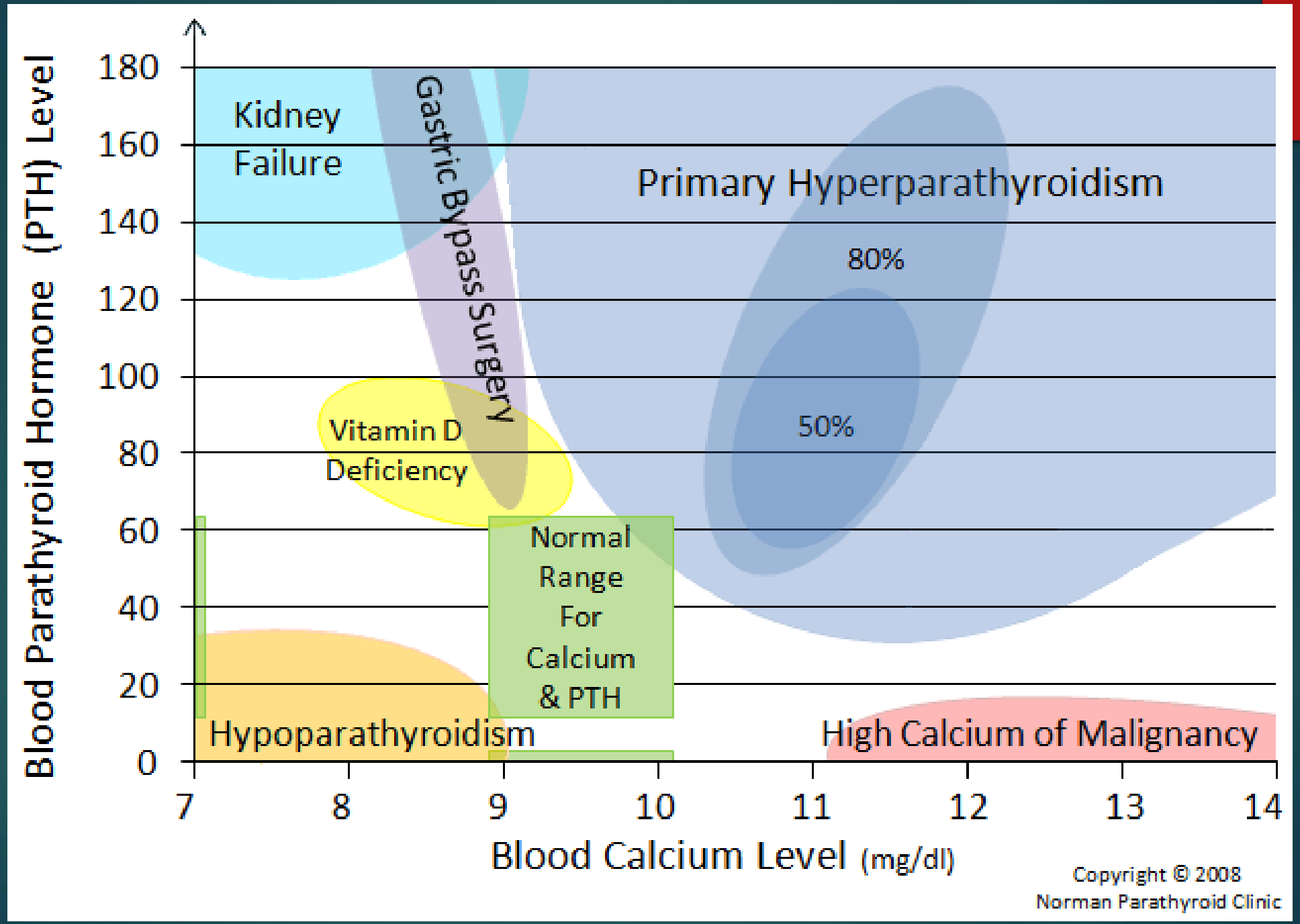
Approach to Hypo-/Hypercalcemia

- Reduction in serum calcium → Stimulate PTH release →
  - increase bone resorption
  - Increase renal calcium reabsorption
  - stimulate renal conversion of 25-oh D3 to 1,25(OH)2D3 → intestinal calcium absorption

Approach to Hypo-/Hypercalcemia

- Decreased PTH and decreased 1,25(OH)2D3 should accompany hypercalcemia unless PTH or 1,25(OH)2D is causal




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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Hypercalcemic Disorders

- Medication-Induced
  - **Thiazides**
  - **Lithium**
  - **Vitamin D**
  - **Vitamin A**
  - **Milk-Alkali Syndrome**
  - **Estrogens “and Antiestrogens”**
  - **Theophylline**
  - **Aluminium Intoxication**

Hypercalcemic Disorders

- **Endocrine Disorders with Excess PTH Production**
  - **Primary sporadic hyperparathyroidism**
  - **Familial hyperparathyroidism**
  - **Secondary hyperparathyroidism**
  - **Tertiary hyperparathyroidism**
  - **FHH**

- **Endocrine Disorders without Excess PTH Production**
  - Hyperthyroidism, hypoadrenalism, pheochromocytoma, VIPoma,

Hypercalcemic Disorders

- **Malignancy-Associated Hypercalcemia**
  - with elevated PTHrP
  - with elevation of other systemic factors - increased 1,25(OH)2D3 in lymphomas, IL-6, hemolytic lesions

Hypercalcemic Disorders

- Inflammatory Disorders Causing Hypercalcemia
  - **Granulomatous Disorders**
  - **AIDS**
- Pediatric Syndromes
  - **Williams Syndrome**
  - **Idiopathic Infantile Hypercalcemia**
- **Immobilization**

History and Physical Examination

- Signs and symptoms are relevant to hypercalcemia
- Signs and symptoms are relevant to the causal disorder
- Hypercalcemic manifestations
  - Acute onset and severe vs. chronic and relatively mild

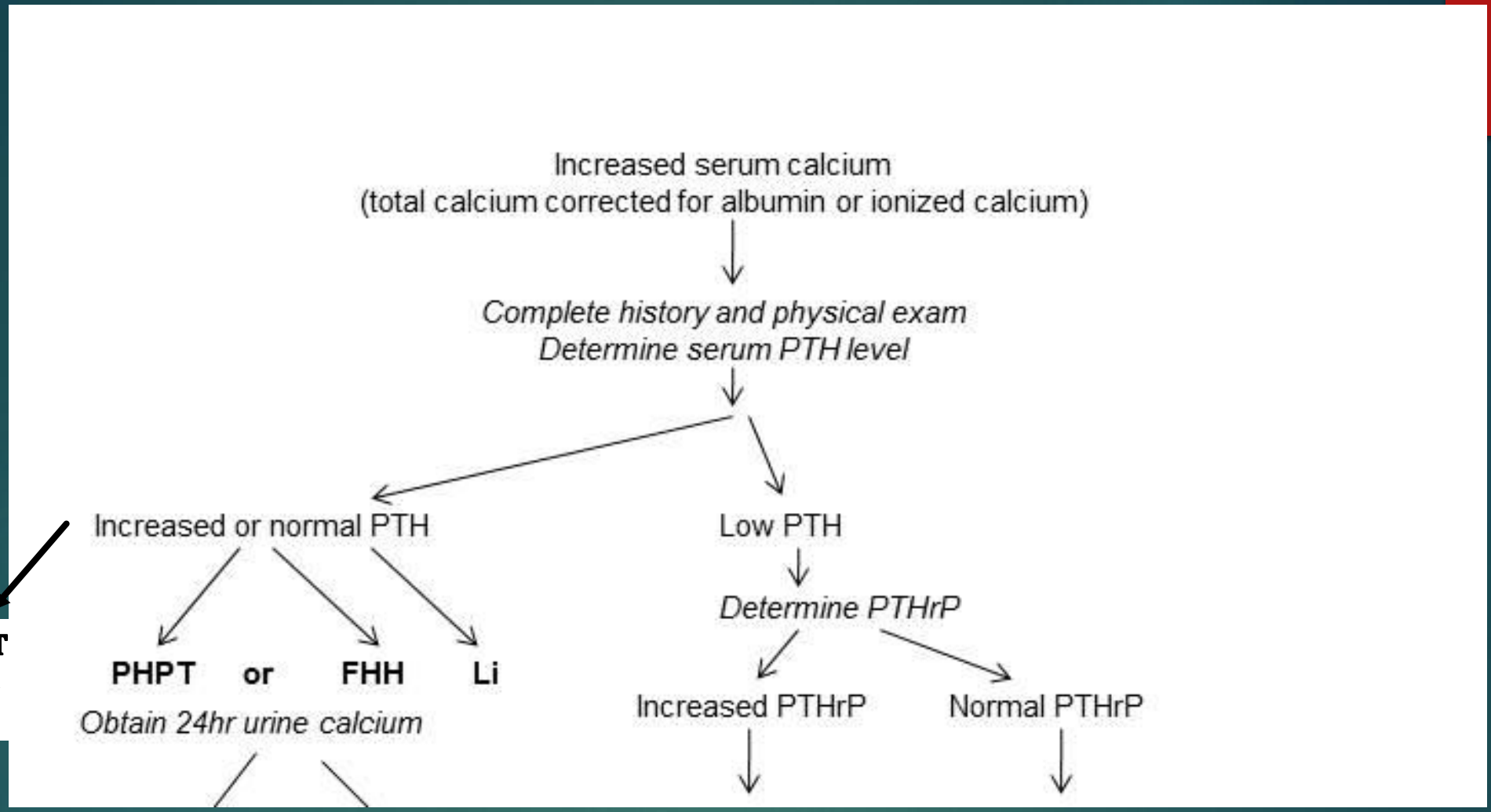
- Most patients are symptomatic when Ca >14 mg/dL
- In both acute and chronic cases the major manifestations affect **gastrointestinal, renal and neuromuscular function**

Manifestations of Hypercalcemia

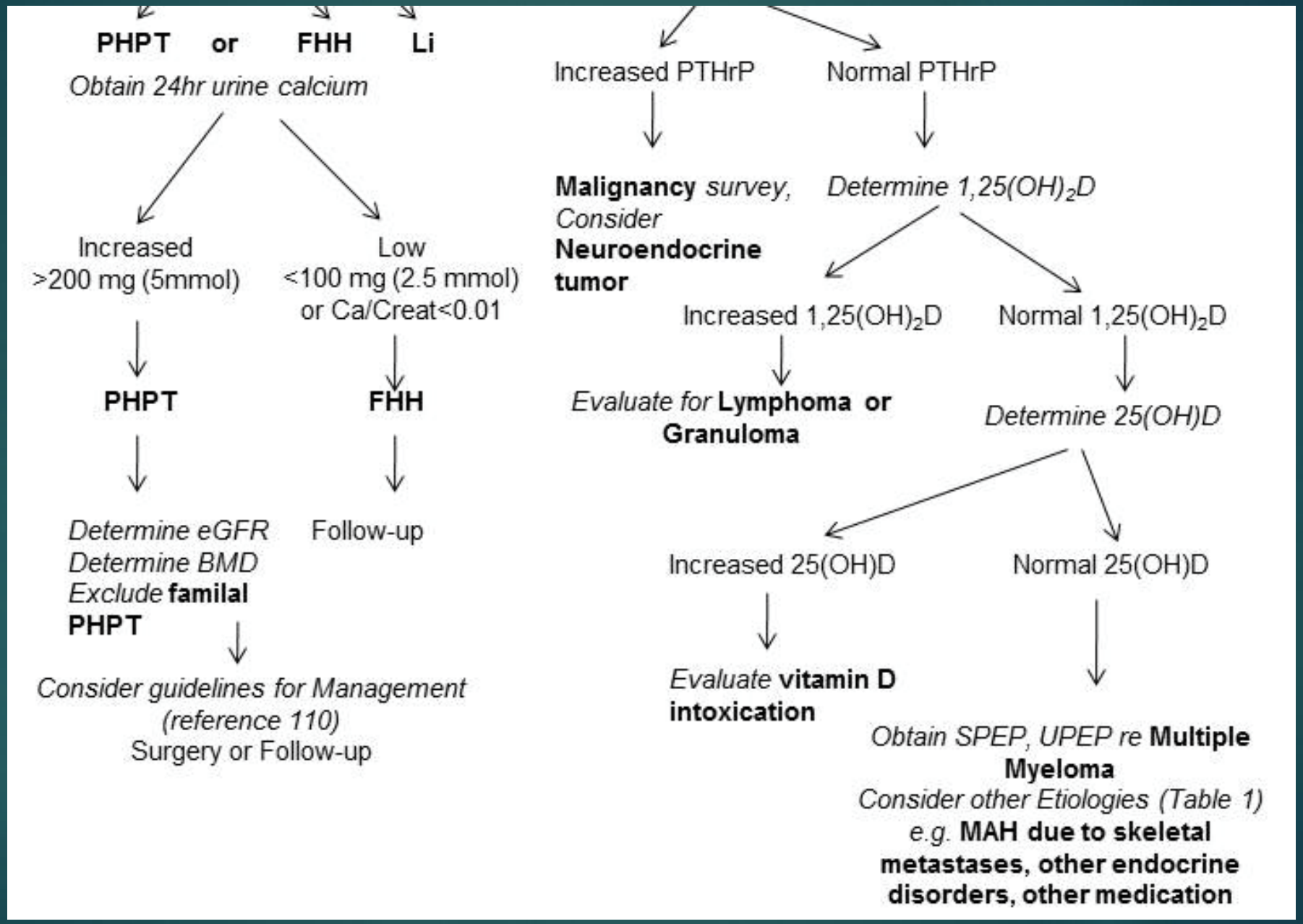
	Acute	Chronic
Gastrointestinal	Anorexia, nausea, vomiting	Dyspepsia, constipation, pancreatitis
Renal	Polyuria, polydipsia → dehydration	Nephrolithiasis, nephrocalcinosis
Neuromuscular	Depression, confusion, stupor, coma	Weakness
Cardiac	Bradycardia, first degree atrioventricular shortened QT interval Can be life-threatening	Hypertension, block, digitals sensitivity

Laboratory Examination

- Laboratory testing should be guided by the results of a **careful history and a detailed physical examination**
- Laboratory screening may include
  - Serum total Ca… ionized calcium
  - CMP (Serum creatinine and eGFR, Albumin, LFT, Lytes)
  - iPTH
  - Phosphorus
  - Mg
  - 25(OH)D … 1,25(OH)2DCBC
  - UA and 24 hour urine collection for calcium and creatinine



Secondary HPT Due to low Vit D or low eGFR


PHPT or FHH Li
Obtain 24hr urine calcium
Increased >200 mg (5mmol)
Low <100 mg (2.5 mmol) or Ca/Creat<0.01
PHPT
FHH
Determine eGFR
Determine BMD
Exclude familal PHPT
Follow-up
Consider guidelines for Management (reference 110)
Surgery or Follow-up
Increased PTHrP
Normal PTHrP
Malignancy survey, Consider Neuroendocrine tumor
Determine 1,25(OH)2D
Increased 1,25(OH)2D
Normal 1,25(OH)2D
Evaluate for Lymphoma or Granuloma
Determine 25(OH)D
Increased 25(OH)D
Normal 25(OH)D
Evaluate vitamin D intoxication
Obtain SPEP, UPEP re Multiple Myeloma
Consider other Etiologies (Table 1)
e.g. MAH due to skeletal metastases, other endocrine disorders, other medication

Case 1 hypercalcemia

31 MTF patient was seen for follow up.

PCP labs showed Ca 10.2-10.7 in 2023

Next step?

HYPOCALCEMIA

- Hypocalcemia can present as an asymptomatic laboratory finding or as a severe, life-threatening condition

- Distinguishing *acute from chronic* hypocalcemia and *asymptomatic from severely symptomatic* hypocalcemia is critical for determining appropriate therapy

CLINICAL PRESENTATION OF HYPOCALCEMIA

- The hallmark of acute hypocalcemia is **neuromuscular irritability**
- **Neuromuscular irritability**
  - Chvostek's sign
  - Trousseau's sign:
  - **Paresthesias:** numbness and tingling in their fingertips, toes, and the perioral region
  - Tetany
  - **Seizures (focal, petit mal, grand mal)**
  - Muscle cramps
  - Muscle weakness
  - **Laryngospasm**
  - Bronchospasm

CLINICAL PRESENTATION OF HYPOCALCEMIA

- **Neurological signs and symptoms**
  - Extrapyramidal signs due **to calcification of basal ganglia** – chronic hypoCa
  - Calcification of cerebral cortex or cerebellum – chronic hypoCa
  - Personality disturbances
  - **Irritability**
  - **Impaired intellectual ability**
  - **Nonspecific EEG changes**
  - **Increased intracranial pressure**
  - Parkinsonism
  - Choreoathetosis
  - **Dystonic spasms**

CLINICAL PRESENTATION OF HYPOCALCEMIA

- **Cardiac**
  - **Prolonged QT** interval on EKG
  - Congestive heart failure
  - Cardiomyopathy

CLINICAL PRESENTATION OF HYPOCALCEMIA

- **Smooth muscle involvement**
  - Dysphagia
  - **Abdominal pain**
  - Biliary colic
  - Dyspnea
  - **Wheezing**

CLINICAL PRESENTATION OF HYPOCALCEMIA

- **Mental status**
  - **Confusion**
  - Disorientation
  - Psychosis
  - Fatigue
  - Anxiety
  - **Poor memory**
  - **Reduced concentration**

ETIOLOGY OF HYPOCALCEMIA

- Hypocalcemia can result from
  - Disorders of **vitamin D metabolism and action**
  - **Hypoparathyroidism**
  - **Resistance to PTH**

ETIOLOGY OF HYPOCALCEMIA

- **Inadequate vitamin D production and action**
  - Nutritional deficiency
  - Lack of sunlight exposure
  - Malabsorption
  - Post-gastric bypass surgery
  - End-stage liver disease and cirrhosis
  - Chronic kidney disease
  - Vitamin D-dependent rickets type 1 and type 2

ETIOLOGY OF HYPOCALCEMIA

- **Inadequate PTH production/Hypoparathyroidism**
  - **Functional hypoparathyroidism**
  - Magnesium depletion
  - Magnesium excess
  - **PTH resistance -** Pseudohypoparathyroidism
  - Post-thyroidectomy (cancer, Grave's disease, MNG.
  - Post-parathyroidectomy

ETIOLOGY OF HYPOCALCEMIA

- **Drugs**
  - Intravenous bisphosphonate therapy or Denosumab therapy – especially in patients with vitamin D insufficiency or deficiency
- Rapid transfusion of large volumes of citrate-containing blood
- Acute critical illness
- "Hungry bone syndrome"
- Osteoblastic metastases
- Acute pancreatitis
- Rhabdomyolysis

Acute Symptomatic Hypocalcemia

- Acute hypocalcemia can be life-threatening,
  - tetany, seizures, cardiac arrhythmias, laryngeal spasm, or AMS
- **Calcium gluconate is the preferred intravenous calcium** salt as calcium chloride often causes local irritation
- Calcium gluconate contains 90 mg of elemental calcium per 10 mL ampule, and usually 1 to 2 ampules (180 mg of elemental calcium) diluted in 50 to 100 mL of 5% dextrose is infused over 10 minutes
- This can be repeated until the patient's symptoms have cleared

Acute Symptomatic Hypocalcemia

- With persistent hypocalcemia → **calcium gluconate drip** over longer periods of time may be necessary.
- The goal should be to raise the serum ionized calcium concentration into the low normal range (~1.0 mM) and control the patient's symptoms.
- Drip rates **of 0.5-2.0 mg/kg/hour** are recommended
- As soon as possible, oral calcium supplementation should be initiated and, if warranted, therapy with vitamin D or its analogues.

Case 2 hypocalcemia

25 yo woman was seen in the hospital for hypocalcemia.

She c/o tingling and numbness for ~ 6 mo

Ca 5 -4.5

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