

Hyperparathyroidism (Hypercalcemia)

副甲狀腺高能症（高血鈣）

盧子文醫師

(簡碼:7376; GSM: 46-05211)

高醫附設中和紀念醫院

highker@gap.kmu.edu.tw

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學習目標

1. 瞭解鈣離子在體內的正常代謝並能進一步解釋高血鈣的致病機轉。
2. 高血鈣疾病的鑑別診斷以及鑑別診斷的方法
3. 高血鈣的緊急處理以及治療方法

學習資源

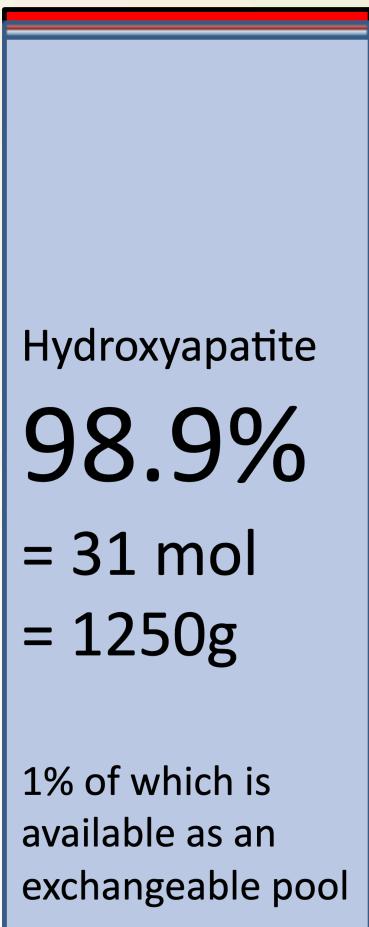
1. Harrison's Principle of Internal Medicine, 21th ed
2. 台灣內分泌學會-副甲狀腺新知專刊
3. Williams Textbook of Endocrinology - 14th Edition
4. UpToDate- Primary hyperparathyroidism
5. UpToDate- hypercalcemia
6. Guyton and Hall textbook of medical physiology
11e

Calcium Metabolism

Calcium Distribution

- Total 1 to 2 Kg of Ca in adult human body:
 1. ~ 99% in the skeleton → hydroxyapatite
 2. 0.1~0.15% in ECF (extracellular fluid)
 3. 0.6% in ICF (intracellular fluid)
- In blood, total Ca is 8.5 to 10.5 mg/dl:
 1. 50% is ionized (iCa).
 2. 41% bind to proteins (predominantly albumin)
 3. ~9% bind to Phosphate, citrate, sulfate, etc.

Distribution of calcium in the human body



1% of total body calcium is present in the cells
0.1% of total body calcium is in the extracellular fluid:

Ionised Calcium: Ca^{++}

50%

1.2 mmol/L

Protein-bound Calcium:

41%

1.2 mmol/L

Anion-bound calcium:

9 %, 0.2 mmol/L

- Present as free, active cation
- Diffuses easily across capillary membranes

- Bound mainly to albumin
- Cannot diffuse across capillary membranes

- Bound to small anionic molecules, eg. phosphate and citrate
- diffuses easily across capillary membranes

Calcium Homeostasis

- Serum protein concentrations affect measured TCa concentrations:
 - Adjust TCa (mg/dL) upward by 0.8 times the deficit in serum albumin (g/dL):
Corrected Ca = (Ca) + {0.8 × (4.0 - albumin)}
- The concentration of ionized calcium in the ECF must be maintained within a narrow range because of the critical role calcium plays in a wide array of cellular functions.

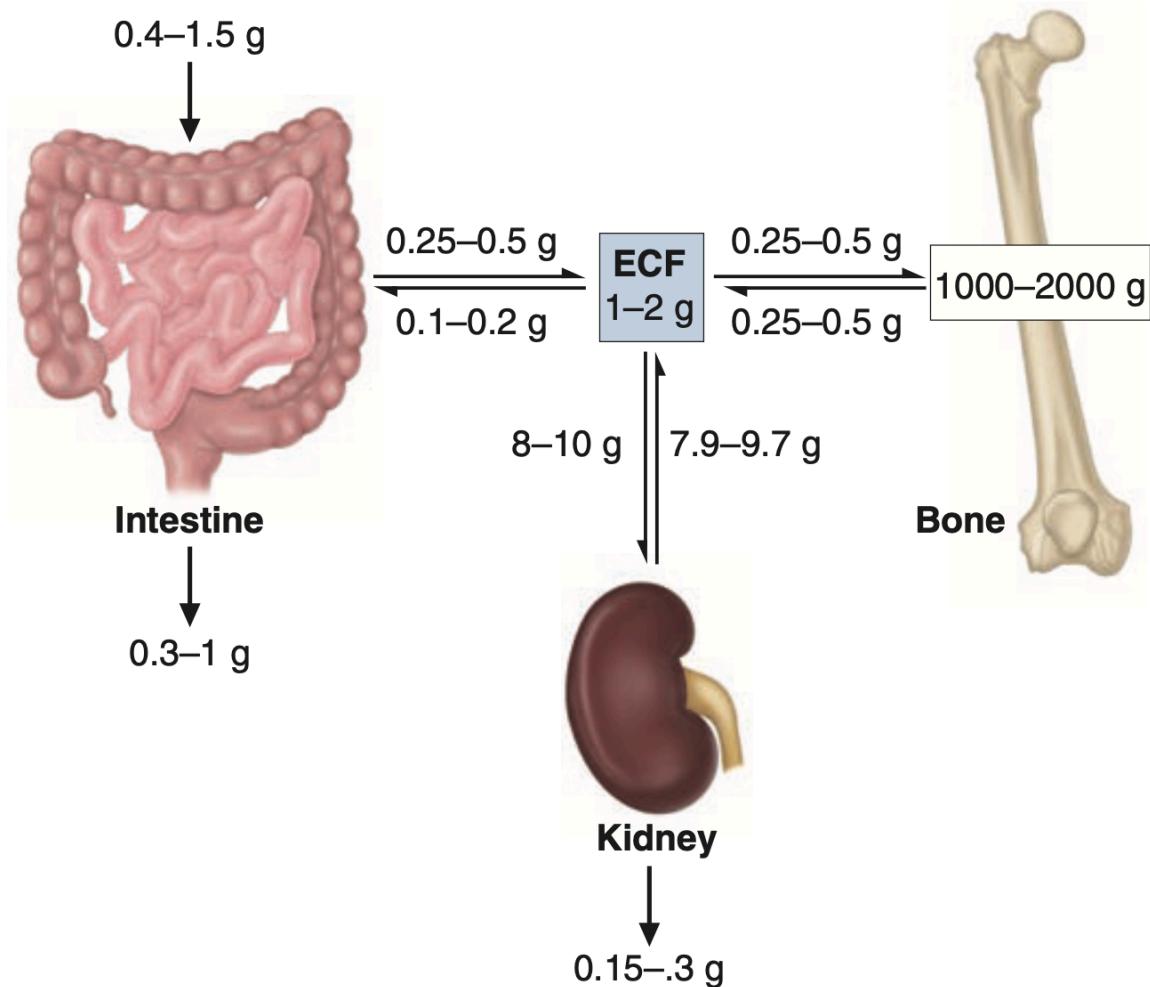


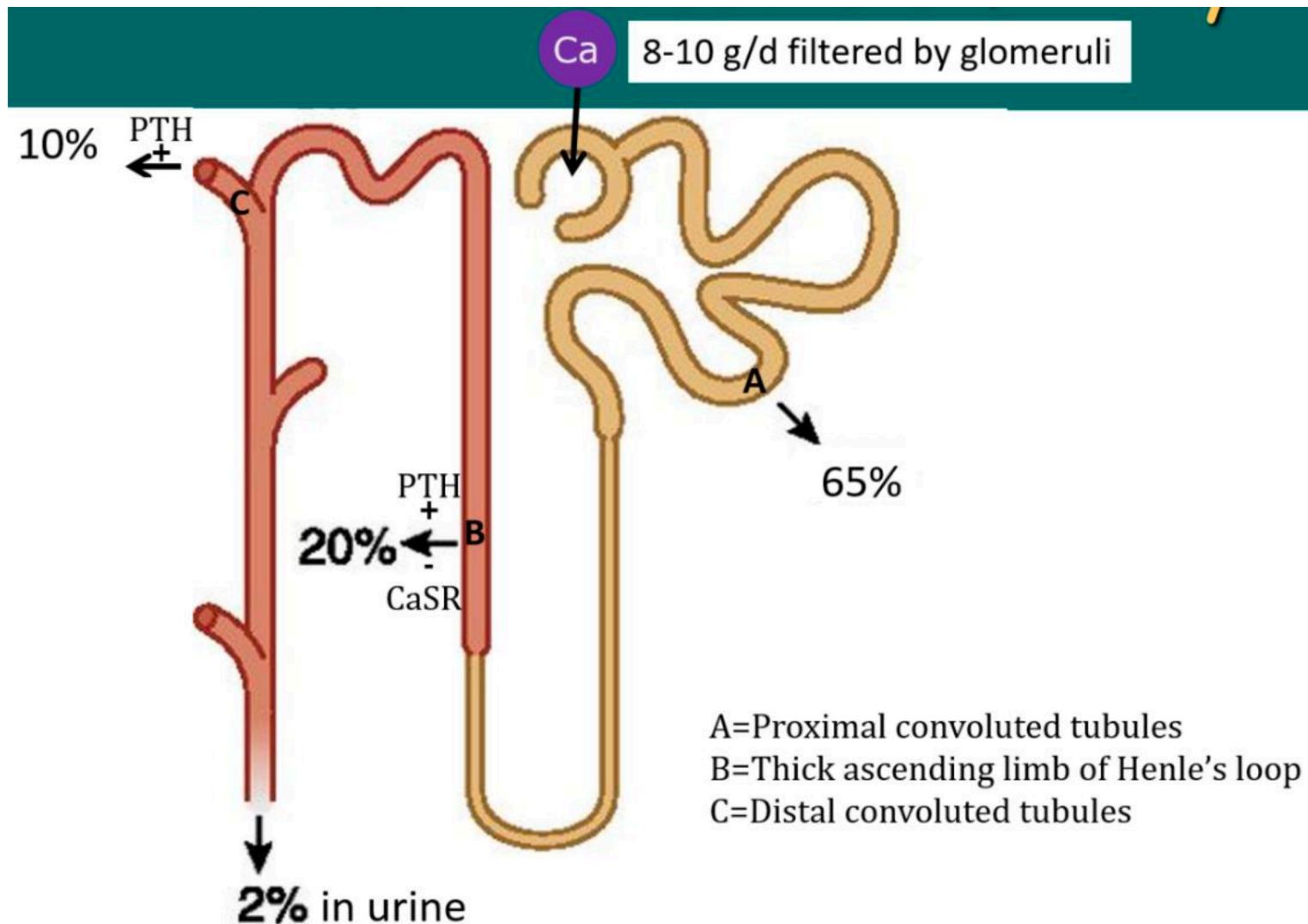
FIGURE 409-3 Calcium homeostasis. Schematic illustration of calcium content of extracellular fluid (ECF) and bone as well as of diet and feces; magnitude of calcium flux per day as calculated by various methods is shown at sites of transport in intestine, kidney, and bone. Ranges of values shown are approximate and were chosen to illustrate certain points discussed in the text. In conditions of calcium balance, rates of calcium release from and uptake into bone are equal.

Calcium Homeostasis-Intestine

- Intestinal absorption of ingested Ca:
 1. Passive (paracellular) mechanism:
→ 5% of daily Ca intake
 2. Active (transcellular) mechanism:
→ 20% ~ 70%, controlled by $1,25(OH)_2D$
- Locations of active Ca transport:
→ Mainly in duodenum and proximal jejunum
- Gastric acid required for good Ca absorption

Calcium Homeostasis-Kidney

- Renal excretion of absorbed Ca:
 1. 8-10 g/d filtered by glomeruli, 2-3% in urine
 2. 65% reabsorbed in proximal convoluted tubules(PCT), coupled to NaCl reabsorption
 3. 20% in thick ascending limb of Henle's loop 1)
Need paracellin-1 (a tight junctional protein) 2)
Inhibited by ↑ [Ca] or [Mg], via CaSR
 4. ~10% in DCT: with calbindin-D28k, Ca^{2+} - ATPases and Na^+/Ca^{2+} exchangers by PTH



Calcium Homeostasis-Bone

- Total skeletal Ca contents change slowly, contrast with relatively high daily rate of Ca fluxes into and out of bone (250~500mg), a process mediated by osteoblast & osteoclast
- Sustained Ca intake <200 mg/d → ↑ PTH and $1,25(OH)_2D$ → activate osteoclastic bone resorption → bone loss ↑ → negative Ca balance
- Very high Ca intake >4g/d → downregulate intestine active transport, renal reabsorption

Calcium related hormone

Parathyroid Hormone (PTH)

Parathyroid Hormone-Related Protein
(PTHrp)

Calcitonin

Vitamin D

Parathyroid Hormone (PTH)

- Secreted by parathyroid Chief cell
- PreProPTH (115 Amino acids) → ProPTH (90 A.a.)
→ PTH (84-amino-acid single-chain peptide)
- Biologically active: amino-terminal portion PTH (1–34)
- Extensively metabolized by liver (70%) and kidney (20%)
- Half-life in blood: 2 minutes
- The primary function of PTH is to maintain the extracellular fluid (ECF) calcium concentration within a narrow normal range.

Parathyroid Hormone (PTH)

Site of action:

1. directly on kidney and bone
 - Kidney: (1) inhibit P transport **in PCT**.
(2) ↑ Ca reabsorption in DCT.
(3) stimulate 25(OH)D-1α-hydroxylase to enhance the synthesis of 1,25-dihydroxyvitamin *D*(1,25[OH]₂D) **in PCT**.
 - Bone: (1)continued exposure → **bone resorption**
(2)intermittent(1~2h/d) → **bone formation**
2. indirectly on intestine (via 1,25(OH)2D)

Bone Remodeling

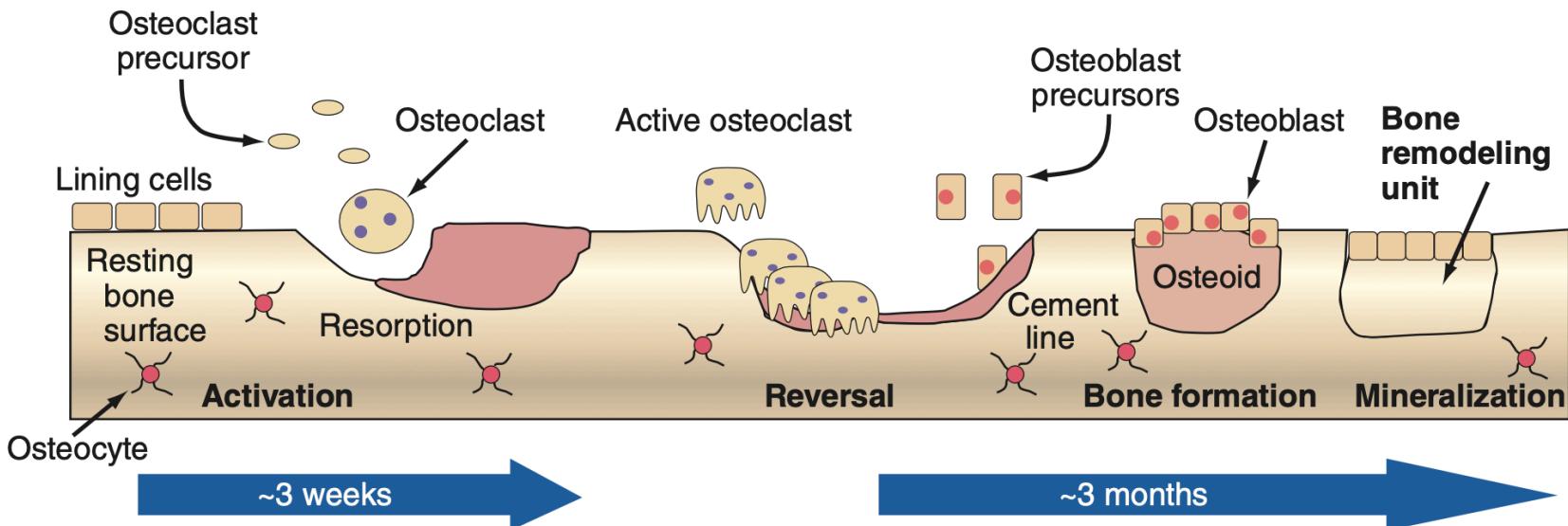


FIGURE 409-2 Schematic representation of bone remodeling. The cycle of bone remodeling is carried out by the basic multicellular unit (BMU), which consists of a group of osteoclasts and osteoblasts. In cortical bone, the BMUs tunnel through the tissue, whereas in cancellous bone, they move across the trabecular surface. The process of bone remodeling is initiated by the recruitment of osteoclast precursors, perhaps to sites of microdamage. These precursors fuse to form multinucleated, active osteoclasts that mediate bone resorption. Osteoclasts adhere to bone and subsequently remove it by acidification and proteolytic digestion. As the BMU advances, osteoclasts leave the resorption site and osteoblasts, derived from marrow precursors and previously inactive bone lining cells, move in to cover the excavated area and begin the process of new bone formation by secreting osteoid, which eventually is mineralized into new bone. After osteoid mineralization, osteoblasts flatten and form a layer of lining cells over new bone, become osteocytes, or die.

Parathyroid Hormone (PTH)

- Bone remodeling:
 - **Osteoblast**: PTH receptors (+), crucial to bone-forming effect of PTH
 - **Osteoclast**: PTH receptors (-), PTH-mediated stimulation of osteoclast act via cytokines from osteoblast

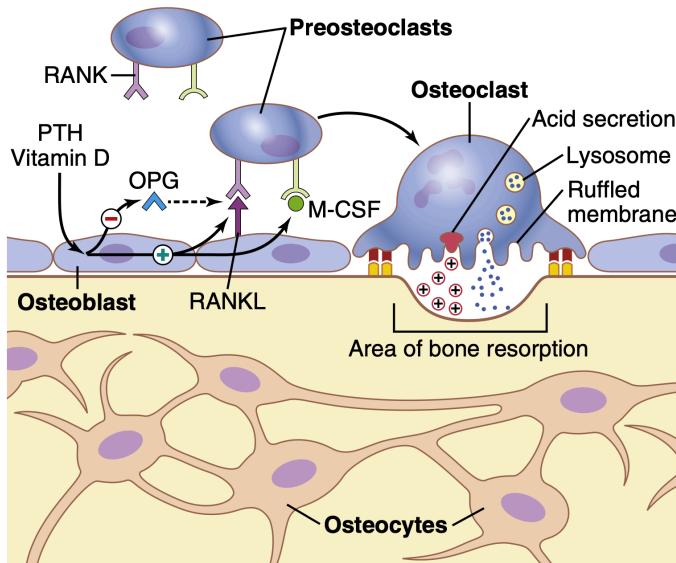


Figure 80-6. Bone resorption by osteoclasts. Parathyroid hormone (PTH) binds to receptors on osteoblasts, causing them to form receptor activator for nuclear factor κ B ligand (RANKL) and to release macrophage-colony stimulating factor (M-CSF). RANKL binds to RANK and M-CSF binds to its receptors on preosteoclast cells, causing them to differentiate into mature osteoclasts. PTH also decreases production of osteoprotegerin (OPG), which inhibits differentiation of preosteoclasts into mature osteoclasts by binding to RANKL and preventing it from interacting with its receptor on preosteoclasts. The mature osteoclasts develop a ruffled border and release enzymes from lysosomes, as well as acids that promote bone resorption. Osteocytes are osteoblasts that have become encased in bone matrix during bone tissue production; the osteocytes form a system of interconnected cells that spreads throughout the bone.

Parathyroid Hormone-Related Protein (PTHrp)

- Many different cell types produce PTHrp:
①brain ②pancreas ③heart ④lung ⑤mammary tissue
⑥placenta ⑦endothelial cell ⑧smooth m.
- PTH and PTHrp, distinctive products of different genes, exhibit considerable homology
- PTH/PTHrp receptor (500 A.a., also known as PTH-1 receptor, PTH1R) respond equally to PTH and PTHrp, while PTH2R respond only to PTH.

Similarities and Differences in Structures of PTH and PTHrp

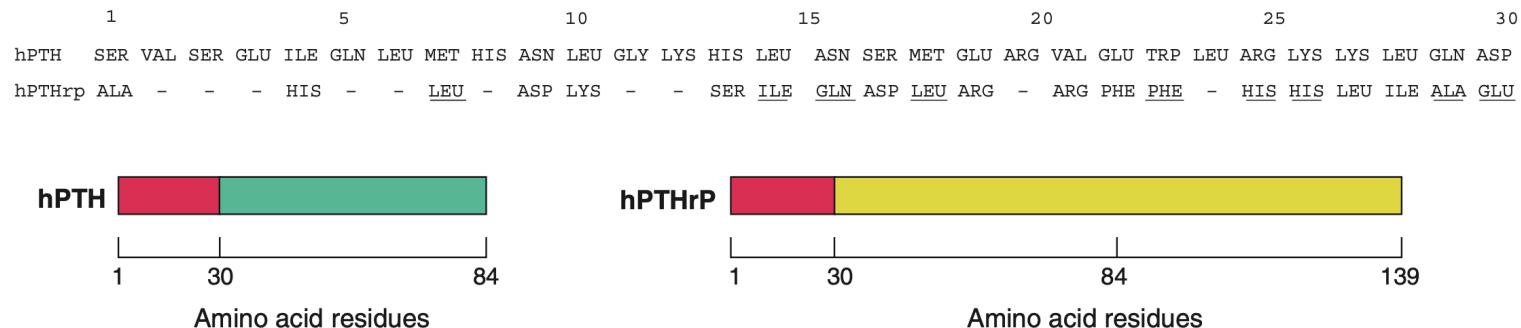


FIGURE 410-1 Schematic diagram to illustrate similarities and differences in structure of human parathyroid hormone (hPTH) and human PTH-related peptide (hPTHrp).
Close structural (and functional) homology exists between the first 30 amino acids of hPTH and hPTHrp. The PTHrp sequence may be ≥139 amino acid residues in length. PTH is only 84 residues long; after residue 30, there is little structural homology between the two. Dashed lines in the PTHrp sequence indicate identity; underlined residues, although different from those of PTH, still represent conservative changes (charge or polarity preserved). Ten amino acids are identical, and a total of 20 of 30 are homologues.

Calcitonin

- Hypocalcemic hormone, antagonist to PTH
- Medical significance: as tumor marker in MTC and as an adjunctive Tx in severe hyperCa
- Inhibit osteoclast-mediated bone resorption (mainly) and stimulate renal Ca clearance
- Induce analgesic effects on hypothalamic cell by receptors for calcitonin gene-related peptide (CGRP) or amylin
- Major source of calcitonin: the thyroid (parafollicular cells or C cells)

Vitamin D

- Vitamin D must first be converted through a succession of reactions in the liver and the kidneys to the final active product, 1,25-dihydroxycholecalciferol, also called $1,25(OH)_2D_3$.
- Cholecalciferol (Vitamin D₃) Is Formed in the Skin.
- Cholecalciferol Is Converted to 25-Hydroxycholecalciferol in the Liver.
- Formation of 1,25-Dihydroxycholecalciferol in the Kidneys and Its Control by Parathyroid Hormone.
- Calcium Ion Concentration Controls the Formation of 1,25-Dihydroxycholecalciferol.

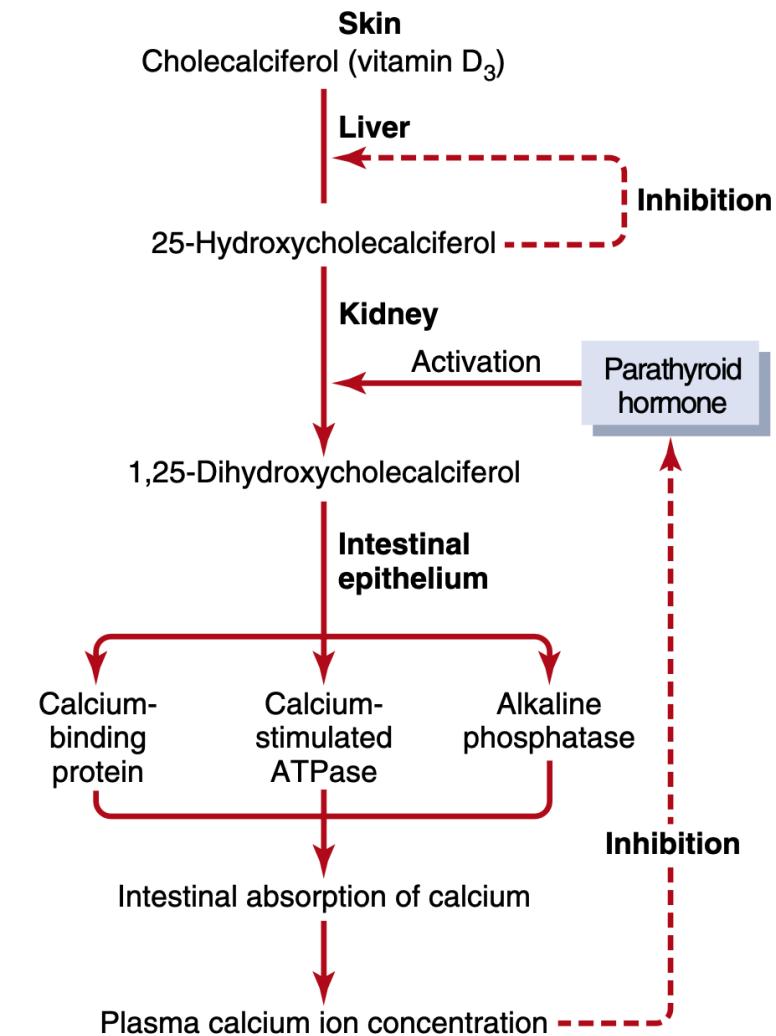
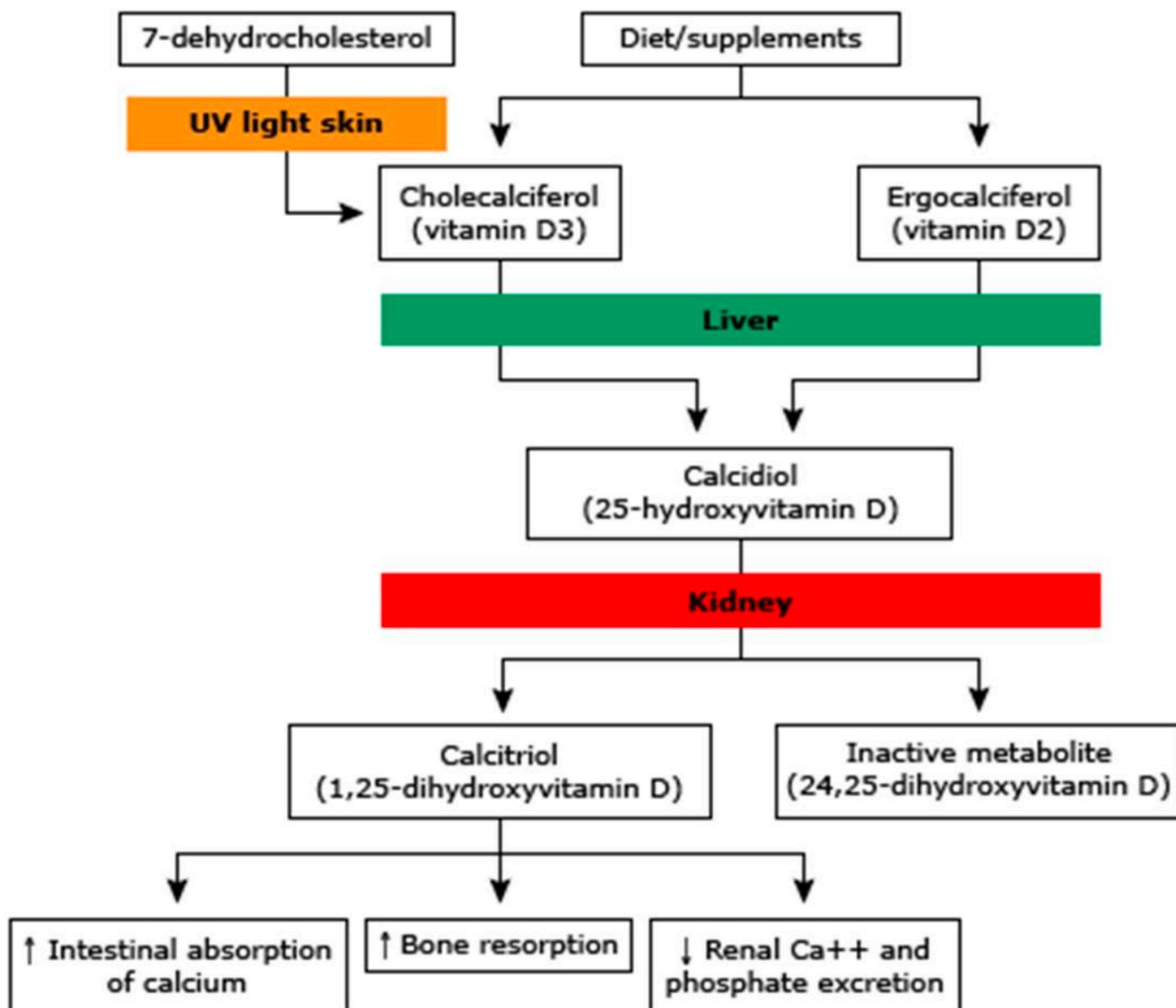


Figure 80-8. Activation of vitamin D₃ to form 1,25-dihydroxycholecalciferol and the role of vitamin D in controlling the plasma calcium concentration.



Summary of Effects of Parathyroid Hormone and Vitamin D

- (1) PTH stimulates bone resorption, causing release of calcium into the extracellular fluid;
- (2) PTH increases calcium reabsorption and decreases phosphate reabsorption by the renal tubules, leading to decreased excretion of calcium and increased excretion of phosphate;
- (3) PTH is necessary for conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol, which, in turn, increases calcium absorption by the intestines.

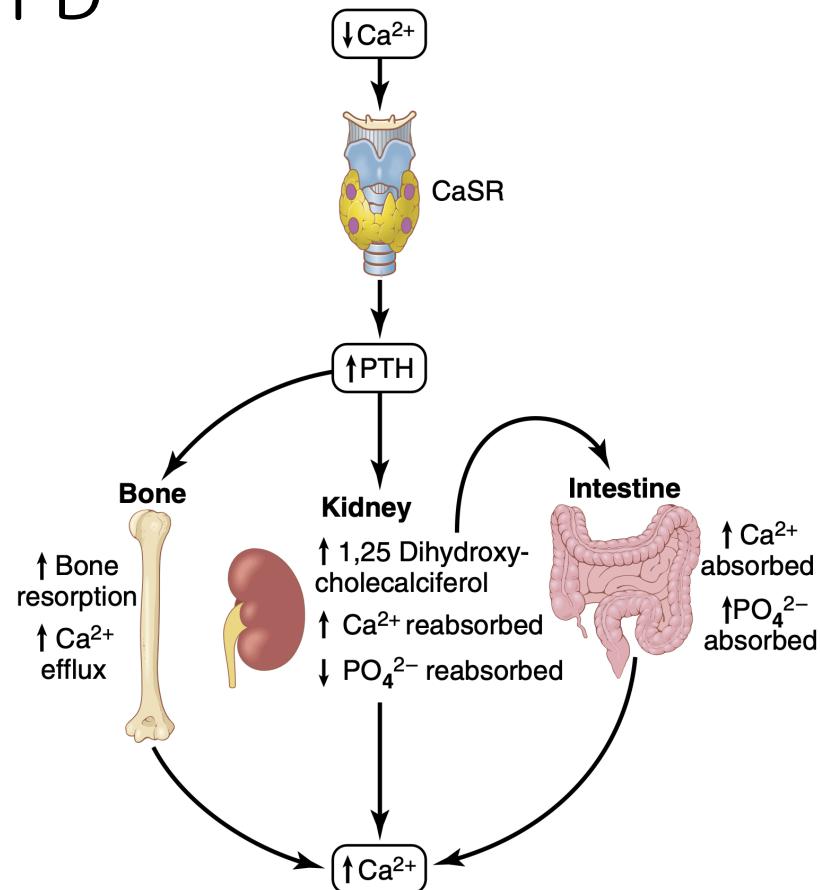


Figure 80-14. Summary of effects of parathyroid hormone (PTH) on bone, the kidneys, and the intestine in response to decreased extracellular fluid calcium ion concentration. CaSR, Calcium-sensing receptor.

Hypercalcemia

Hypercalcemia

- Primary hyperparathyroidism and malignancy-associated hypercalcemia are the most common causes (>90%).
- Asymptomatic, mild hypercalcemia (11 mg/dL) is usually due to primary hyperparathyroidism
- Hypercalcemia of malignancy is usually acute, symptomatic and severe (14 mg/dL)
- Hypophosphatemia suggests elevated PTH or PTHrp

Hypercalcemia

- Symptoms and signs (S/S):
 1. Usually occur if TCa >12mg/dL and more severe in acute hypercalcemia
 2. fatigue, depression, mental confusion, anorexia, nausea, vomiting, constipation, reversible renal tubular defects, polyuria, short QT interval, arrhythmia
 3. Stupor, coma, azotemia, and cardiac arrest may develop in severe hypercalcemia (TCa=15~18mg/dL)
- “painful bones, renal stones, abdominal groans, and psychic moans”

TABLE 410-1 Classification of Causes of Hypercalcemia**I. Parathyroid-Related**

- A. Primary hyperparathyroidism
 - 1. Adenoma(s)
 - 2. Multiple endocrine neoplasia
 - 3. Carcinoma
- B. Lithium therapy
- C. Familial hypocalciuric hypercalcemia

II. Malignancy-Related

- A. Solid tumor with metastases (breast)
- B. Solid tumor with humoral mediation of hypercalcemia (lung, kidney)
- C. Hematologic malignancies (multiple myeloma, lymphoma, leukemia)

III. Vitamin D-Related

- A. Vitamin D intoxication
- B. ↑ 1,25(OH)₂D; sarcoidosis and other granulomatous diseases, lymphoma
- C. ↑ 1,25(OH)₂D; impaired 1,25(OH)₂D metabolism due to 24-hydroxylase deficiency or increased 1,25(OH)₂D synthesis due to inactivating mutations involving the sodium-dependent phosphate co-transporters

IV. Associated with High Bone Turnover

- A. Hyperthyroidism
- B. Immobilization
- C. Thiazides
- D. Vitamin A intoxication
- E. Fat necrosis

V. Associated with Renal Failure

- A. Severe secondary hyperparathyroidism
- B. Aluminum intoxication and adynamic bone disease
- C. Milk-alkali syndrome

Parathyroid-Dependent Hypercalcemia

- primary hyperparathyroidism
- Tertiary hyperparathyroidism
- familial hypocalciuric hypercalcemia(FHH)
- lithium-induced hypercalcemia.

Parathyroid-Independent Hypercalcemia

- In parathyroid-independent hypercalcemia, PTH secretion is appropriately suppressed.
- PTH levels are invariably lower than 25 pg/mL(usually lower than normal or undetectable.)
- Most affected patients have malignant hypercalcemia

Diagnostic studies

- Hyperparathyroidism (HPT) and malignancy account for 90% of cases of ↑ Ca;
- HPT more likely if asymptomatic or chronic; malignancy (usually overt) more likely if acute or symptomatic.
- Check iCa, PTH, PO₄:
 - ↑ or high normal PTH: Ca/Cr clearance ratio <0.01 → FHH
 - ↓ PTH: check PTHrP, ALP, & search for malignancy and vit D: ↑ 25-(OH)D

Primary Hyperparathyroidism

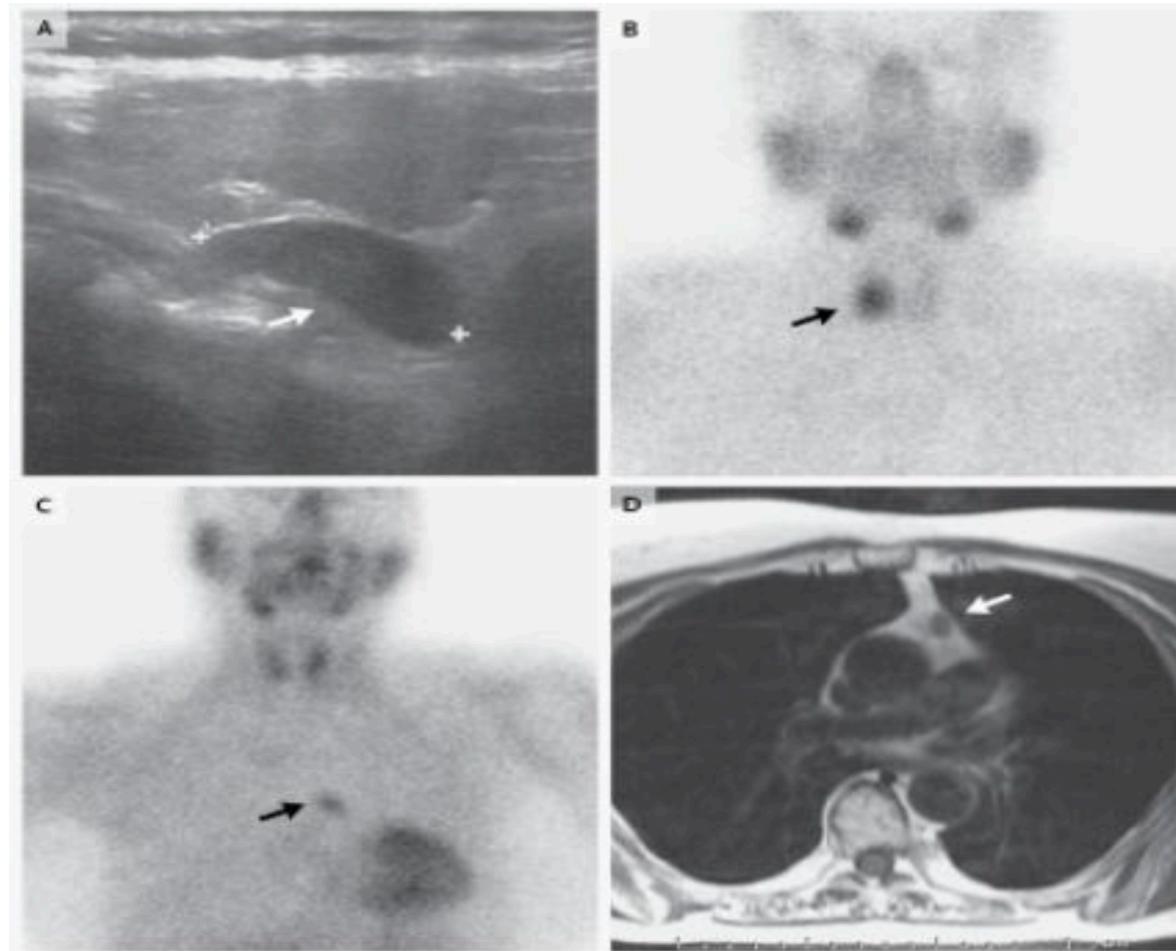
- PTH ↑ → Ca ↑ , P ↓ . Great variation in S/S.
- Asymptomatic hyperparathyroidism (80%) is the milder form. Hypercalcemic parathyroid crisis (with dehydration and coma) is rare.
- Involve mainly the kidney & skeletal system:
 1. Nephrolithiasis → urinary tract obstruction and infection → loss of renal function
 2. Osteitis fibrosa cystica (subperiosteal resorption): very rare due to early detection

Primary Hyperparathyroidism

- Neuromuscular S/S: proximal muscle weakness, easy fatigability, muscle atrophy
- Gastrointestinal S/S: vague abdominal complaints, duodenal ulcer (In MEN1, may due to pancreatic tumors secreting excessive gastrin → Zollinger-Ellison syndrome)
- Etiology: 85% solitary adenoma (mostly inferior glands), 15% hyperplasia, 1% carcinoma
- MEN 1 & MEN 2A

Diagnosis: PTH ↑ , serum Ca ↑ , serum P ↓

Localization: Ultrasound, ^{99m}Tc MIBI scan, MRI



Treatment of asymptomatic Primary Hyperparathyroidism

- Surgery (下表任一條件)
- If surgery declined/deferred, can treat with **cinacalcet(擬鈣劑)** (\downarrow Ca & PTH but may not \uparrow BMD)

TABLE 410-2 Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism^a

PARAMETER	GUIDELINE
Serum calcium (above normal)	>1 mg/dL
Renal	Creatinine clearance <60 mL/min 24-h urine for calcium >400 mg/d and increased stone risk by biochemical stone risk analysis Presence of nephrolithiasis or nephrocalcinosis by x-ray, ultrasound, or CT
Skeletal	BMD by DXA: T score <-2.5 at lumbar spine, total hip, femoral neck, or distal one-third radius Vertebral fracture by x-ray, CT, MRI, or VFA
Age	<50

Guidelines for Monitoring Asymptomatic Primary Hyperparathyroidism

TABLE 410-3 Guidelines for Monitoring in Asymptomatic Primary Hyperparathyroidism

PARAMETER	GUIDELINE
Serum calcium	Annually
Renal	eGFR, annually; serum creatinine, annually. If renal stones suspected, 24-h biochemical stone profile, renal imaging by x-ray, ultrasound, or CT
Serum creatinine	Annually
Skeletal	Every 1–2 years (3 sites), x-ray or VFA of spine if clinically indicated (e.g., height loss, back pain)

Abbreviations: CT, computed tomography; eGFR, estimated glomerular filtration rate; VFA, vertebral fracture assessment.

Other Parathyroid-Related Cause of Hypercalcemia

- Lithium therapy:
 1. 10% patients treated for bipolar
 2. Remitting when lithium is stopped
 3. Higher [Ca] required to lower PTH
- Familial hypocalciuric hypercalcemia (FHH):
CaSR mutation => Secretion of PTH ↑ , renal Ca reabsorption ↑
- Jansen's disease: Excessive biologic activity of the PTH receptor in target tissues due to PTH1R mutation

Malignancy-Related Hypercalcemia

- Mechanisms of hypercalcemia in malignancy: (as many as 20% of cancer patients) (The etiologic mechanisms may be multiple)
 1. PTHrp responsible for **humoral hypercalcemia of malignancy (HHM)**: squamous cell carcinoma of lung and renal tumors
 2. **Osteoclast activation factor (interleukin 1 and lymphotoxin or tumor necrosis factor)**: local bone destruction in leukemia, lymphoma, multiple myeloma
 3. Increased $1,25(OH)_2D$ in blood produced by lymphocytes in B cell lymphomas

Vitamin D-Related Hypercalcemia

- Vitamin D Intoxication:
 1. $1,25(OH)_2D \uparrow$
 2. Responsive to glucocorticoids Sarcoidosis and Other Granulomatous Diseases (ex: tuberculosis, fungal infection):
- Macrophage from granulomatous tissue convert $25(OH)D$ to $1,25(OH)_2D$
- Idiopathic Hypercalcemia of Infancy:
 1. Usually referred to as William's syndrome
 2. Aortic stenosis, mental retard, elfin facies

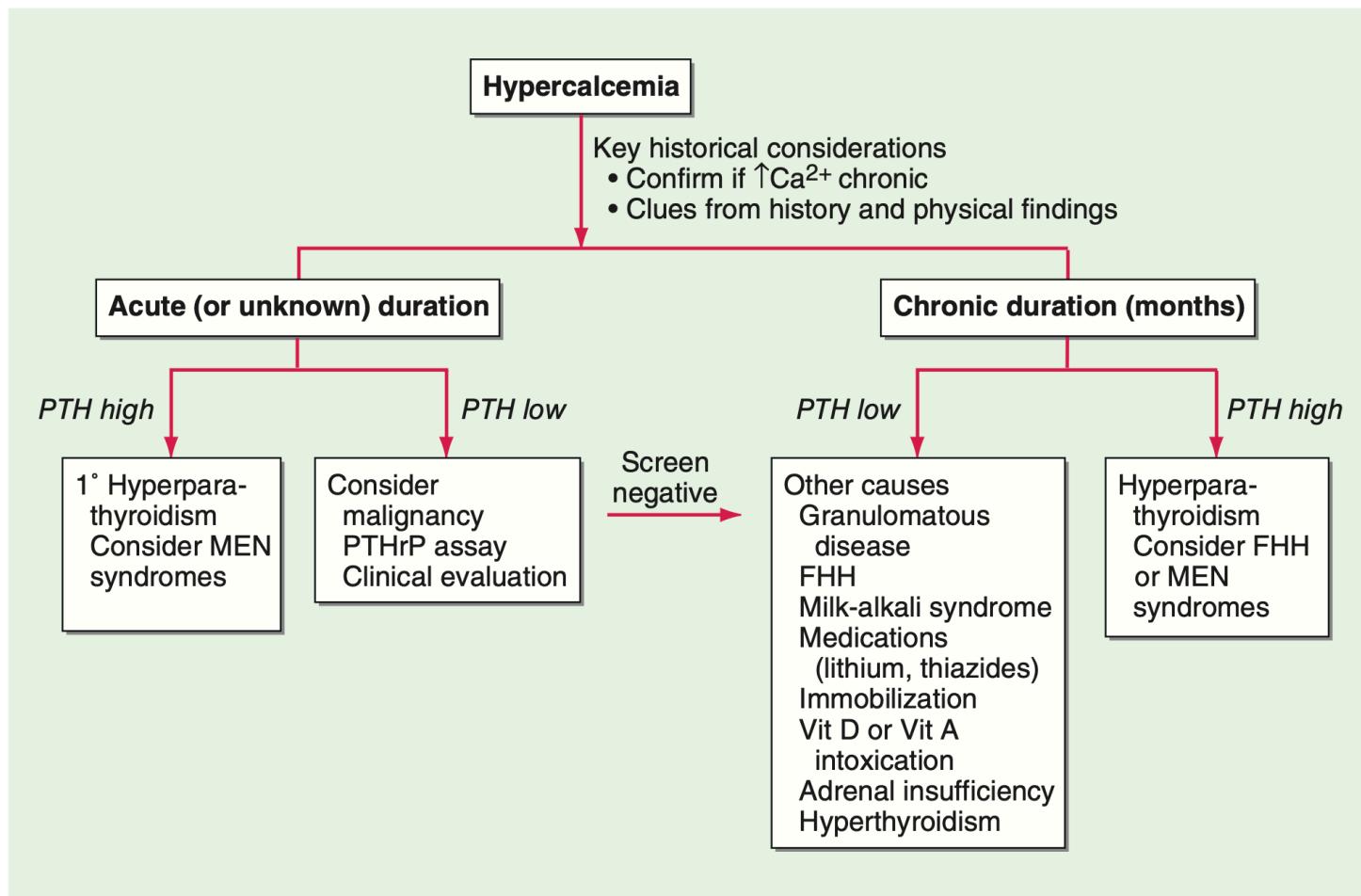
Hypercalcemia Associated with High Bone Turnover

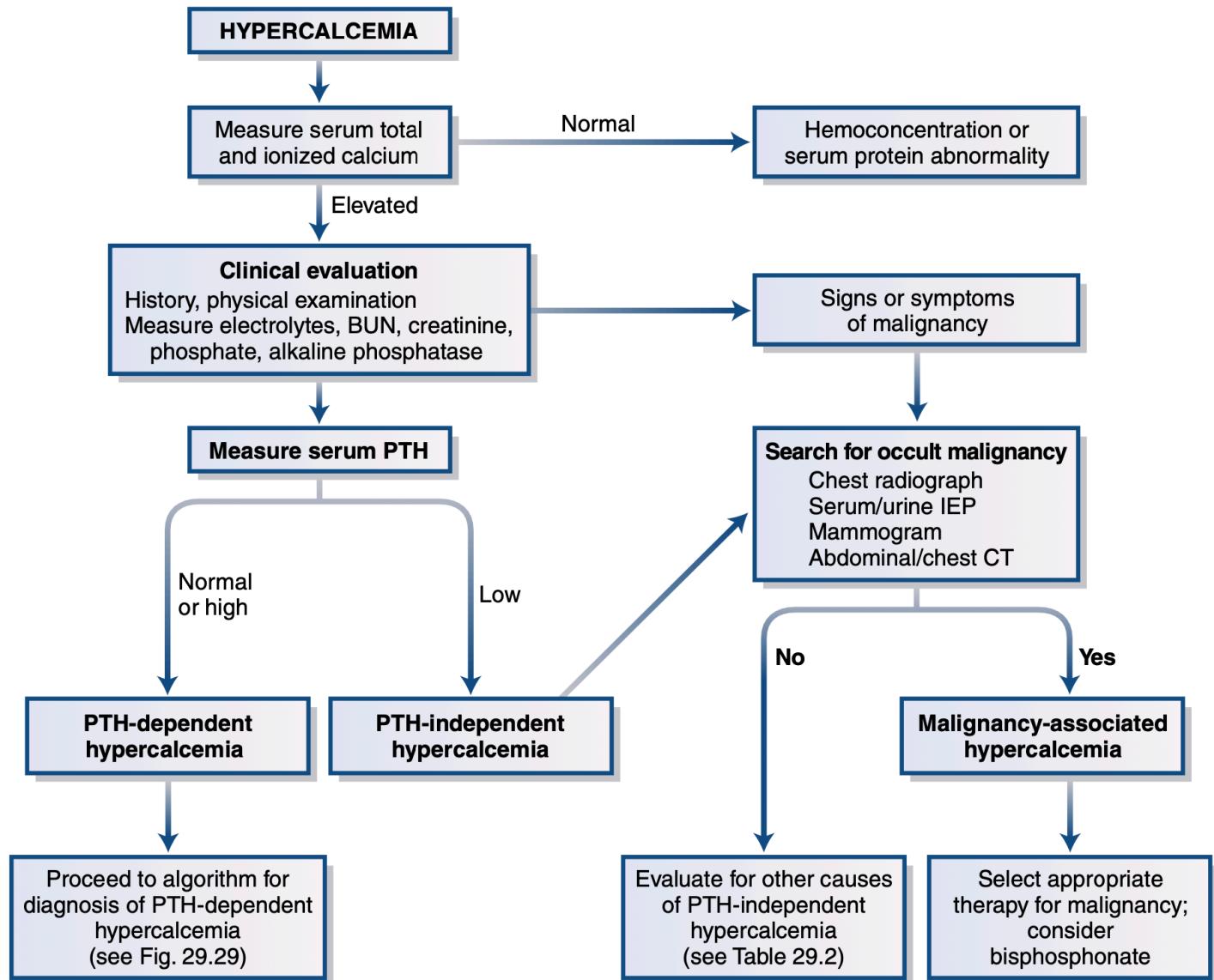
- Hyperthyroidism (20%):
→ Bone resorption > bone formation
- Immobilization:
→ Rare cause of hypercalcemia
- Thiazides:
→ enhanced **proximal** tubular reabsorption of Ca in response to Na depletion of **distal** tubule
- Vitamin A Intoxication:
→ ingestion of 50,000~100,000 Unit/D of VitA

Hypercalcemia Associated with Renal Failure

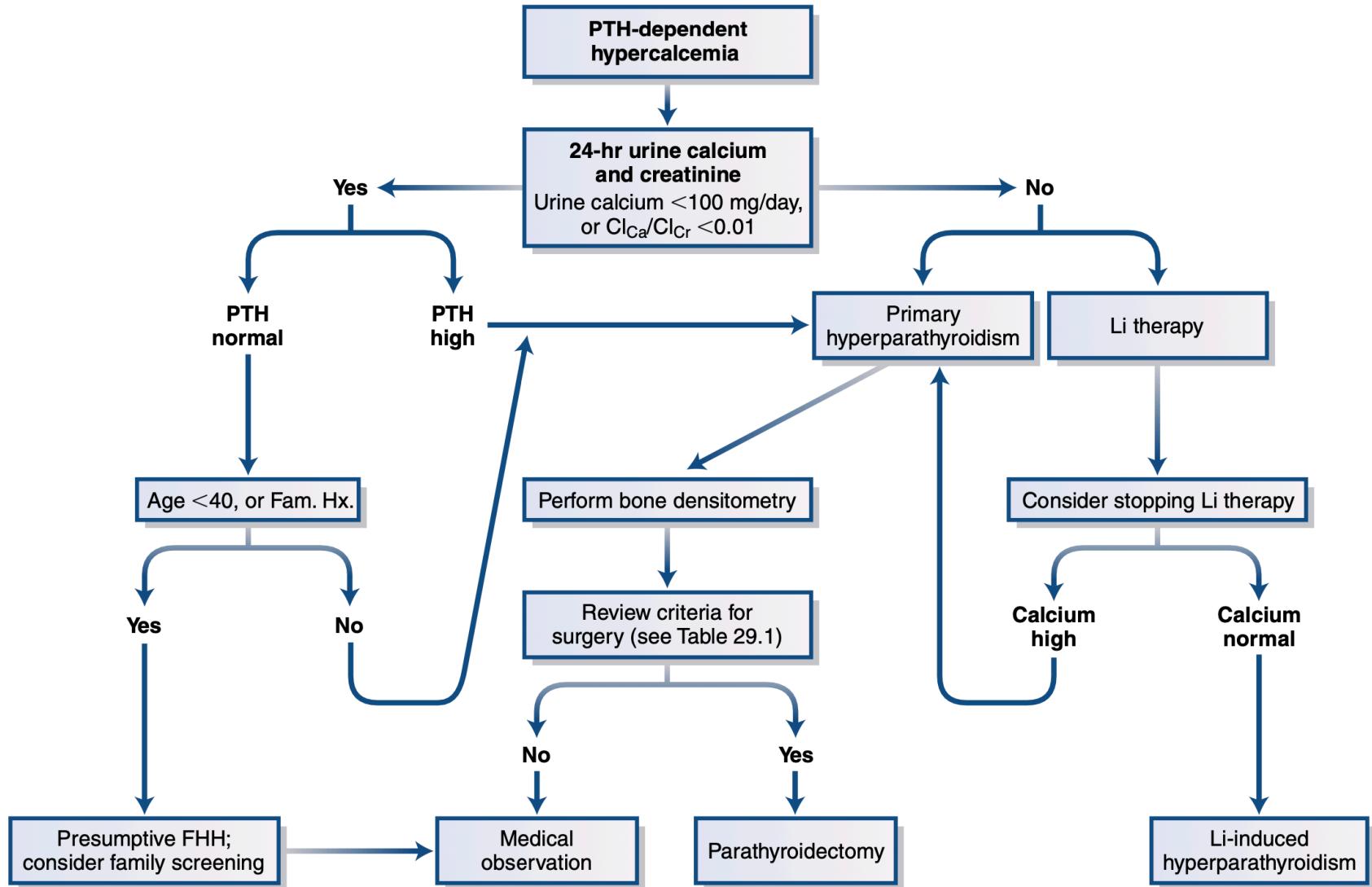
- Severe Secondary Hyperparathyroidism:
 - Bone pain, ectopic calcification, pruritus
 - Renal osteodystrophy (osteitis fibrosa cystica) due to excessive PTH action on bone, and **osteomalacia related to the circulating levels of FGF23** (inhibiting renal 1-alpha hydroxylase, causing reduction in $1,25(OH)_2$ vitamin D)
- Aluminum Intoxication
 - “Aplastic” or “adynamic” bone disease
- Milk-Alkali Syndrome:
 - excessive ingestion of Ca

Algorithm for the evaluation of patients with hypercalcemia





• **Fig. 29.28** Approach to the management of the hypercalcemic patient. *BUN*, blood urea nitrogen; *CT*, computed tomography; *IEP*, immunoelectrophoresis; *PTH*, parathyroid hormone.



• **Fig. 29.29** Approach to the management of the hypercalcemic patient with parathyroid hormone-dependent hypercalcemia. Cl , clearance; *Fam. Hx.*, family history; *FHH*, familial hypocalciuric hypercalcemia; *Li*, lithium; *PTH*, parathyroid hormone.

Therapies for Hypercalcemia: Acute management

Acute Treatment of Hypercalcemia (BMJ 2015;350:h2723)			
Treatment	Onset	Duration	Comments
Normal saline (4–6 L/d)	h	during Rx	Natriuresis → ↑ renal Ca excretion
Furosemide	h	during Rx	Use cautiously, only if volume overloaded
Bisphosphonates	1–2 d	var.	Inhibit osteoclasts, useful in malignancy; caution in renal failure; risk of jaw osteonecrosis; monitor for hypocalcemia
Calcitonin	h	~48 hrs	Bridging Rx, quickly develops tachyphylaxis
Glucocorticoids	days	days	Useful in some malig, granulomatous disorders & vitamin D intox.
Denosumab (JCEM 2014;99:3144)	days	months	Monoclonal Ab against RANKL; typically used in hyperCa of malignancy; not renally cleared
Hemodialysis	min	during Rx	If other measures ineffective or contraindicated

Therapies for Hypercalcemia: Chronic management

- For primary hyperparathyroidism:
 - Avoid thiazide diuretics and extremes of Ca intake (neither too high nor too restrictive)
 - Estrogen replacement therapy or raloxifene: postmenopausal women
 - Oral bisphosphonates
- For malignant hypercalcemia:
 - IV bisphosphonates, prednisone, oral phosphate use until anti-cancer Tx takes effect
 - Denosumab: monoclonal Ab that binds to receptor activator of nuclear factor- κ B (RANKL) and prevents it from binding to the receptor RANK on osteoclast precursors and mature osteoclasts

TABLE 410-4 Therapies for Severe Hypercalcemia

TREATMENT	ONSET OF ACTION	DURATION OF ACTION	ADVANTAGES	DISADVANTAGES
Most Useful Therapies				
Hydration with normal saline	Hours	During infusion	Rehydration invariably needed	Volume overload
Forced diuresis; normal saline plus loop diuretic	Hours	During treatment	Rapid action	Volume overload, cardiac decompensation, intensive monitoring, electrolyte disturbance, inconvenience
Pamidronate	1–2 days	10–14 days to weeks	High potency; intermediate onset of action	Fever in 20%, hypophosphatemia, hypocalcemia, hypomagnesemia, rarely jaw necrosis
Zoledronate	1–2 days	>3 weeks	Same as for pamidronate (lasts longer)	Same as pamidronate above
Denosumab	1–2 days	>3 weeks	Strongest antiresorptive	Occasional severe hypocalcemia, rarely jaw necrosis, skin infections
Special Use Therapies				
Calcitonin	Hours	1–2 days	Rapid onset of action; useful as adjunct in severe hypercalcemia	Rapid tachyphylaxis
Phosphate oral	24 h	During use	Chronic management (with hypophosphatemia); low toxicity if P <4 mg/dL	Limited use except as adjuvant or chronic therapy
Glucocorticoids	Days	Days, weeks	Oral therapy, antitumor agent	Active only in certain malignancies, vitamin D excess, and sarcoidosis; glucocorticoid side effects
Dialysis	Hours	During use and 24–48 h afterward	Useful in renal failure; onset of effect in hours; can immediately reverse life-threatening hypercalcemia	Complex procedure, reserved for extreme or special circumstances

Summary

- Calcium homeostasis: the role of kidney, bone, intestine, and parathyroid
- The most common cause of hypercalcemia and other related differential diagnosis
- Treatment guideline of asymptomatic hyperparathyroidism
- Mechanisms of malignancy-related hypercalcemia
- Therapy for hypercalcemia

國考題

52.下列有關原發性副甲狀腺高能症(primary hyperparathyroidism)的敘述，何者錯誤？

- A.副甲狀腺瘤造成之副甲狀腺高能症，此時副甲狀腺之腫瘤多半是單一腺瘤(isolated adenoma)
- B.副甲狀腺瘤可能是多發性內分泌腫瘤(multiple endocrine neoplasia)的一種臨床表現
- C.常表現高血鈣、高血磷及低血氯
- D.血鈣濃度高於14 mg/dL(3.5 mmol/L)時，病理學報告經常是副甲狀腺癌

ANS : C

- C: patients with hyperparathyroidism frequently had phosphate levels in the low normal range (less than 3 mg/100 ml) and chloride levels in the high normal range (greater than 102 mEq/L) 高血鈣、低血磷、高血氯
- D: A potential clue to the diagnosis is offered by the degree of calcium elevation. Calcium values of 3.5 – 3.7 mmol/L (14 – 15 mg/dL) are frequent with carcinoma and may alert the surgeon to remove the abnormal gland with care to avoid capsular rupture.

10.高血鈣急症的治療原則下列那一項最不適當?

- A.立即補充生理食鹽水
- B.使用thiazide類利尿劑
- C.惡性腫瘤引發高血鈣可以考慮給予雙磷酸鹽(bisphosphonates)
- D.維生素D造成的高血鈣症可以考慮使用類固醇治療

ANS : B

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Hemodialysis	min	during Rx	If other measures ineffective or contraindicated

53. 實體腫瘤(solid tumor)引起之高血鈣症，最常因腫瘤分泌下列何者而引起？

- A. 副甲狀腺素(parathyroid hormone)
- B. 罂骨細胞活化因子(osteoclast activating factor, OAF)
- C. 副甲狀腺素相關肽(parathyroid hormone-related peptide, PTHrP)
- D. $1,25(\text{OH})_2 \text{D}$

ANS : C

Thanks for your attention!

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