Hypercalcemia

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Hypercalcemia
A Review

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Cancer-Associated Hypercalcemia

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Clinical Practice Guideline

ENDOCRINE SOCIETY
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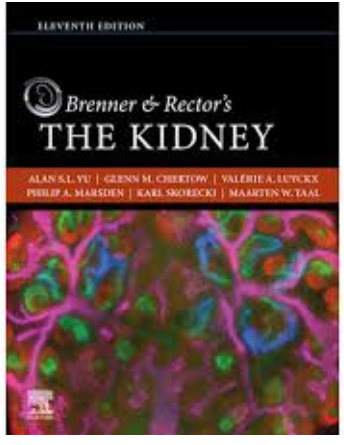

Treatment of Hypercalcemia of Malignancy in Adults: An Endocrine Society Clinical Practice Guideline

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Outline

1. Clinical manifestation
2. Calcium homeostasis and regulation
3. Approach to diagnosis of hypercalcemia
4. Treatment of hypercalcemia
5. Cancer-associated hypercalcemia
6. Workflow for management of cancer-associated hypercalcemia

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Clinical Presentation of Moderate to Severe Acute Hypercalcemia

Box 18.2 Clinical Features of Hypercalcemia

General

Malaise, tiredness, weakness

Neuropsychiatric

Impaired concentration, loss of memory, headache, drowsiness, lethargy, disorientation, confusion, irritability, depression, paranoia, hallucinations, ataxia, speech defects, visual disturbances, deafness (calcification of eardrum), pruritus, mental retardation (infants), stupor, coma

Neuromuscular

Muscle weakness, hyporeflexia or absent reflexes, hypotonia, myalgia, arthralgia, bone pain, joint effusion, chondrocalcinosis, dwarfism (infants)

Gastrointestinal

Loss of appetite, dry mouth, thirst, polydipsia, nausea, vomiting, constipation, abdominal pain, weight loss, acute pancreatitis (calcifying), peptic ulcer, acute gastric dilation

Kidney

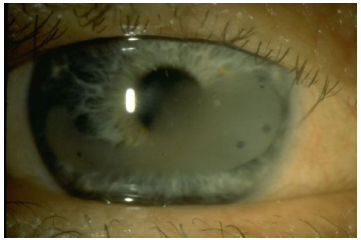
Polyuria, nocturia, nephrocalcinosis, nephrolithiasis, interstitial nephritis, acute kidney injury and chronic kidney disease

Cardiovascular

Arrhythmia, bradycardia, first-degree heart block, short Q-T interval, bundle branch block, arrest (rare), hypertension, vascular calcification

Metastatic Calcification

Band keratopathy, red eye syndrome, conjunctival calcification nephrocalcinosis, vascular calcification, pruritus



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Calcium homeostasis

Following the absorption in the intestine, calcium in the **extracellular fluid space** is **deposited in bone** (the major repository of calcium in the body) and is filtered in the kidney.

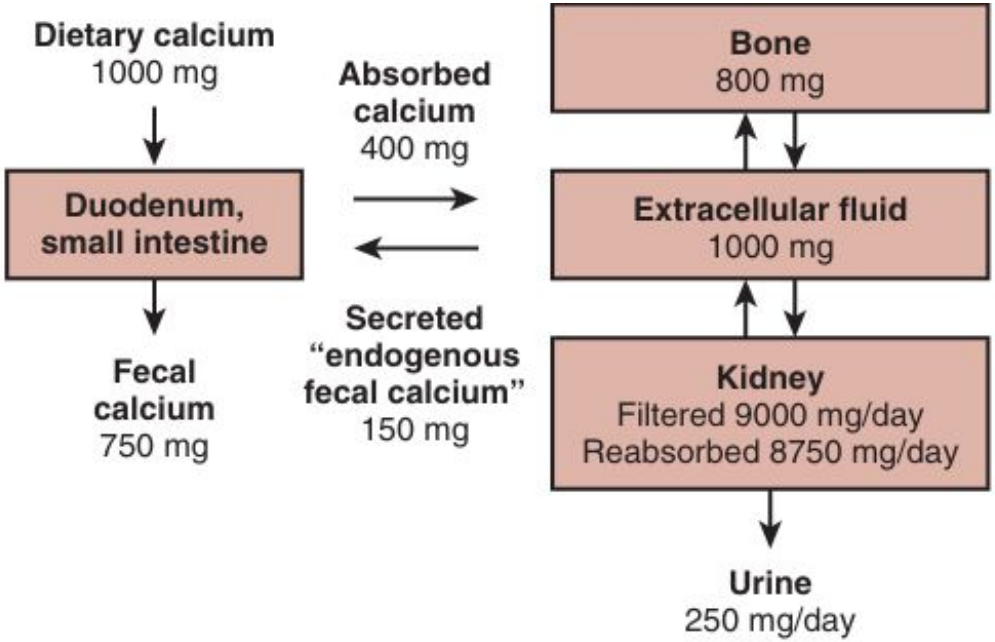


Fig. 7.1 Calcium homeostasis in normal humans showing the amounts of calcium absorbed in the intestine and reabsorbed by the kidney.

Bound and free form calcium in serum

- Calcium in plasma: **filterable** (**60%** of total calcium) and **bound** (**40%** of total calcium)
- Filterable calcium is composed of **calcium complexed to anions**, such as citrate, sulfate, and phosphate (**~10%** of total calcium) and **ionized calcium** (**~50%** of total calcium)
- Alkalemia is associated with a reduction in free calcium, whereas acidemia is associated with an increase in free calcium
- A **1-g/dL** change in **serum albumin** is associated with a **0.8-mg/dL** change in total serum calcium, and a **1-g/dL** change in **globulins** is associated with a **0.16-mg/dL** change in total serum calcium

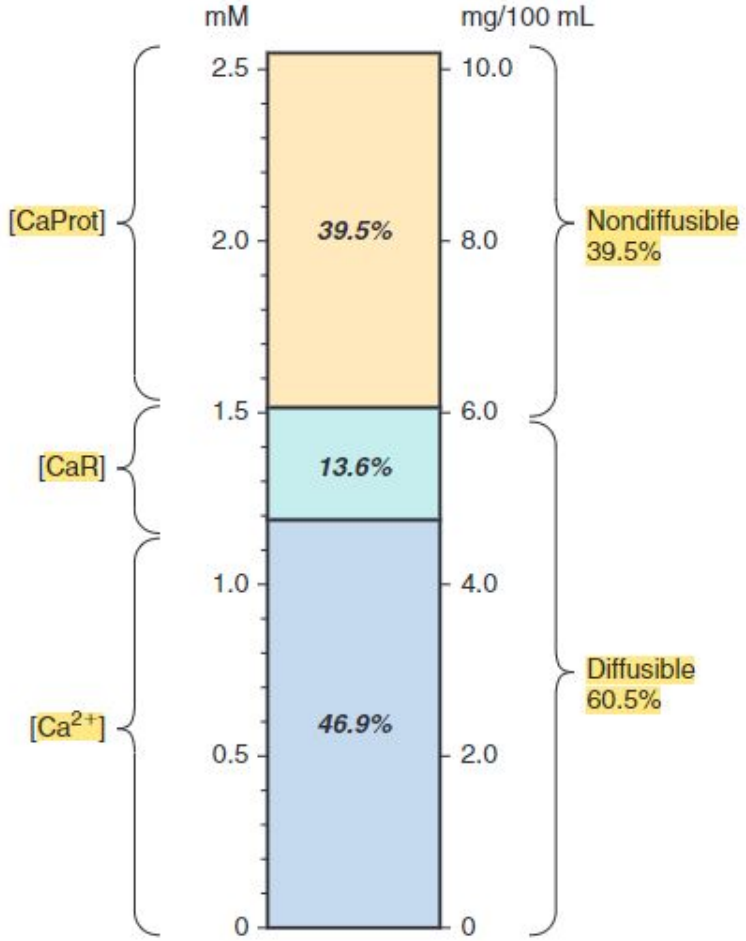
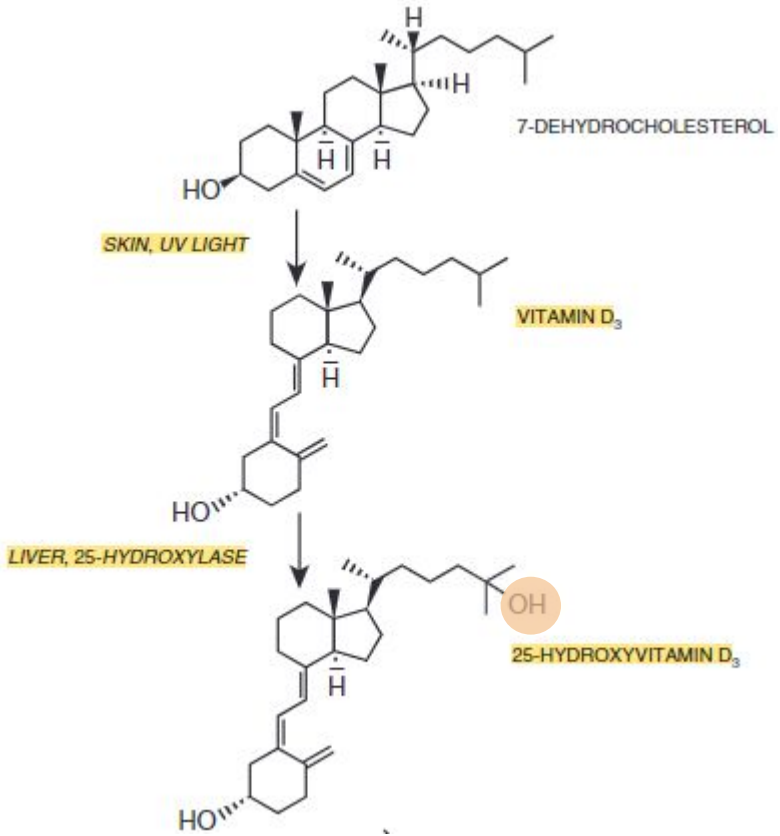


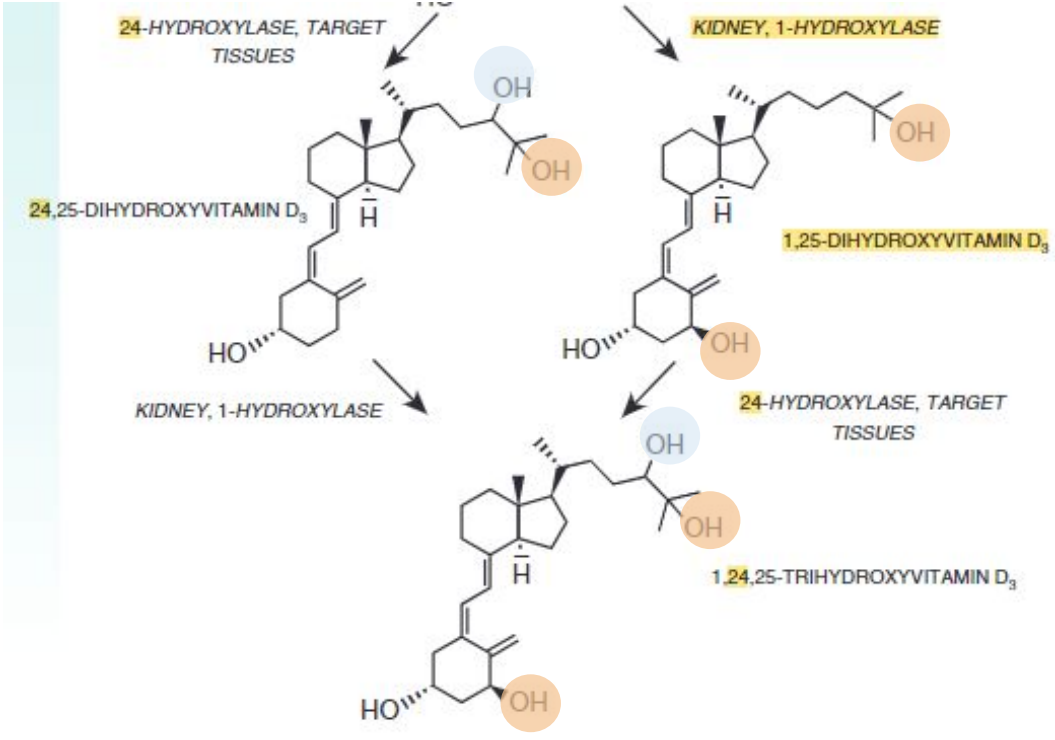
Fig. 7.2 Components of serum total calcium assessed by ultrafiltration data in normal human patients. *CaR*, Diffuse of both calcium

Metabolism of Vit D3.

Hyper Ca/P

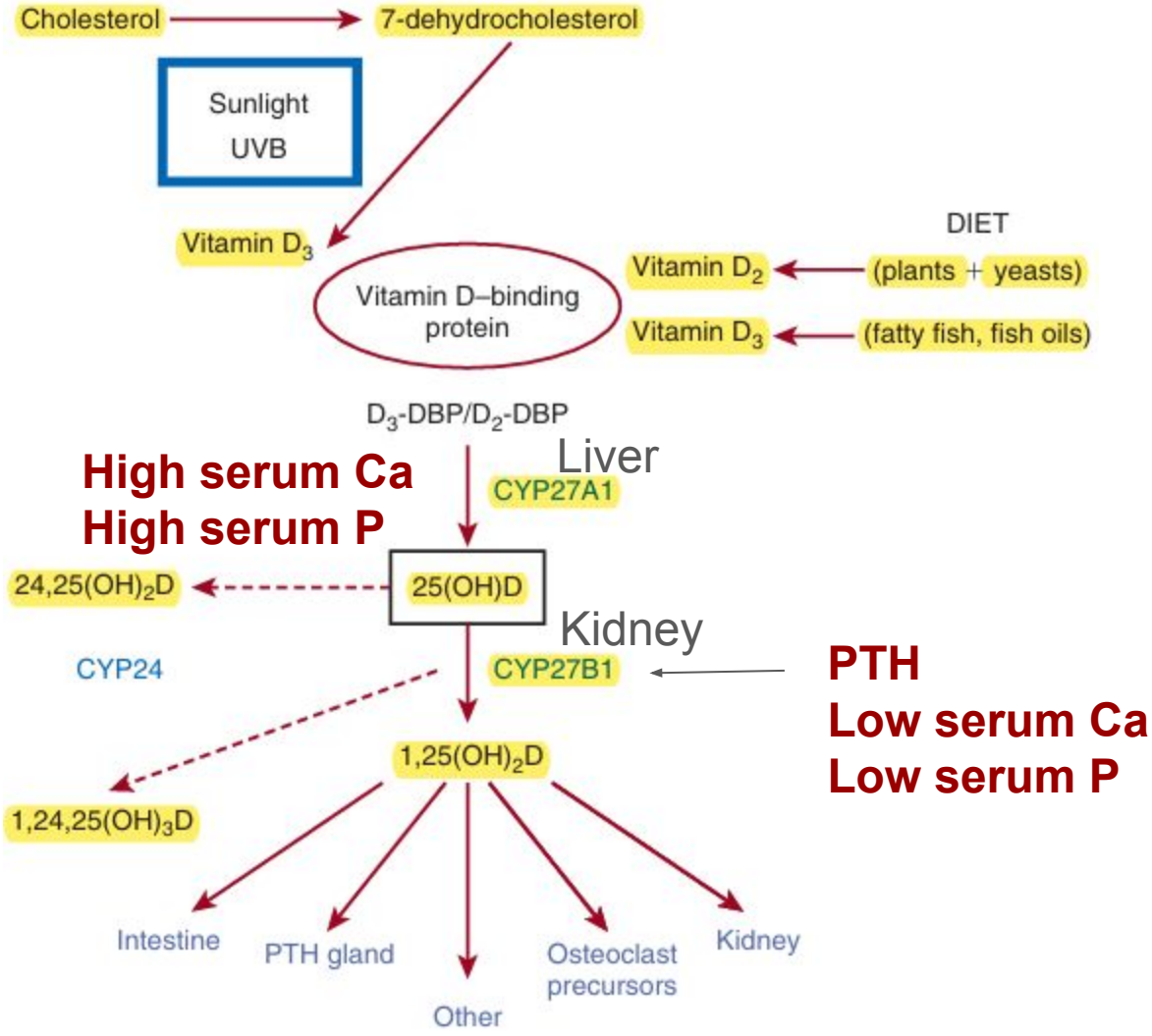
Ca, or P deficiency





A

Fig. 7.4 A. The formation and metabolism of vitamin D3. B. Physiologic change


Cholesterol
7-dehydrocholesterol
Sunlight
UVB
Vitamin D_3
DIET
Vitamin D_2
(plants + yeasts)
Vitamin D_3
(fatty fish, fish oils)
Vitamin D–binding protein
D_3-DBP/D_2-DBP
Liver
CYP27A1
High serum Ca
High serum P
24,25$(OH)_2$D
25(OH)D
Kidney
CYP24
CYP27B1
PTH
Low serum Ca
Low serum P
1,25$(OH)_2$D
1,24,25$(OH)_3$D
Intestine
PTH gland
Other
Osteoclast precursors
Kidney

CaSR and PTH

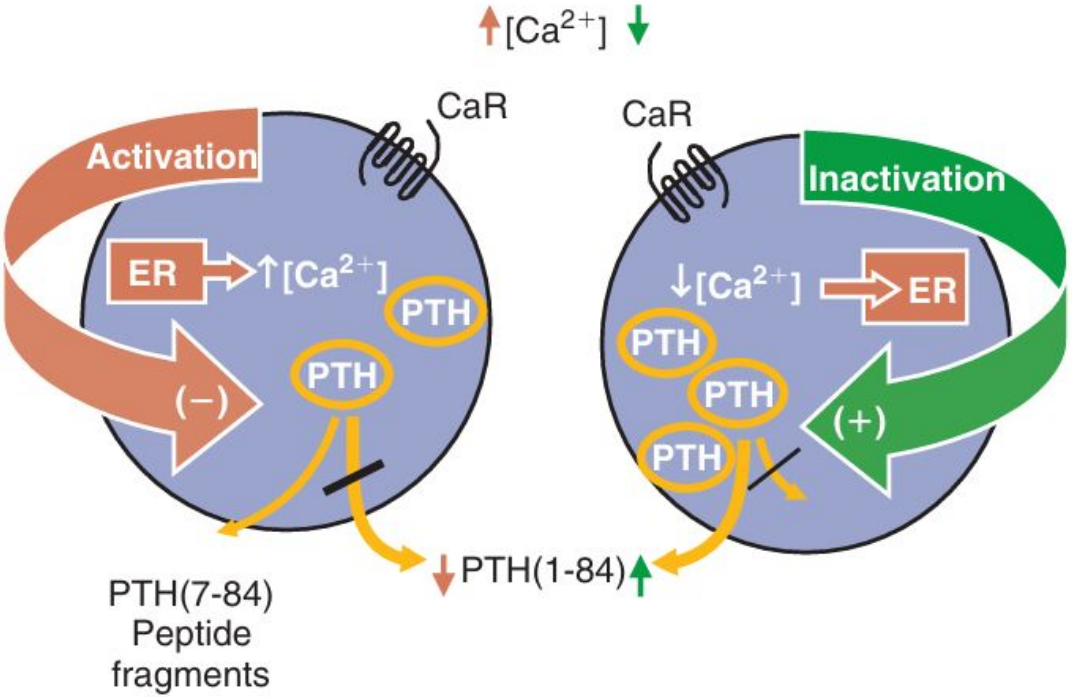
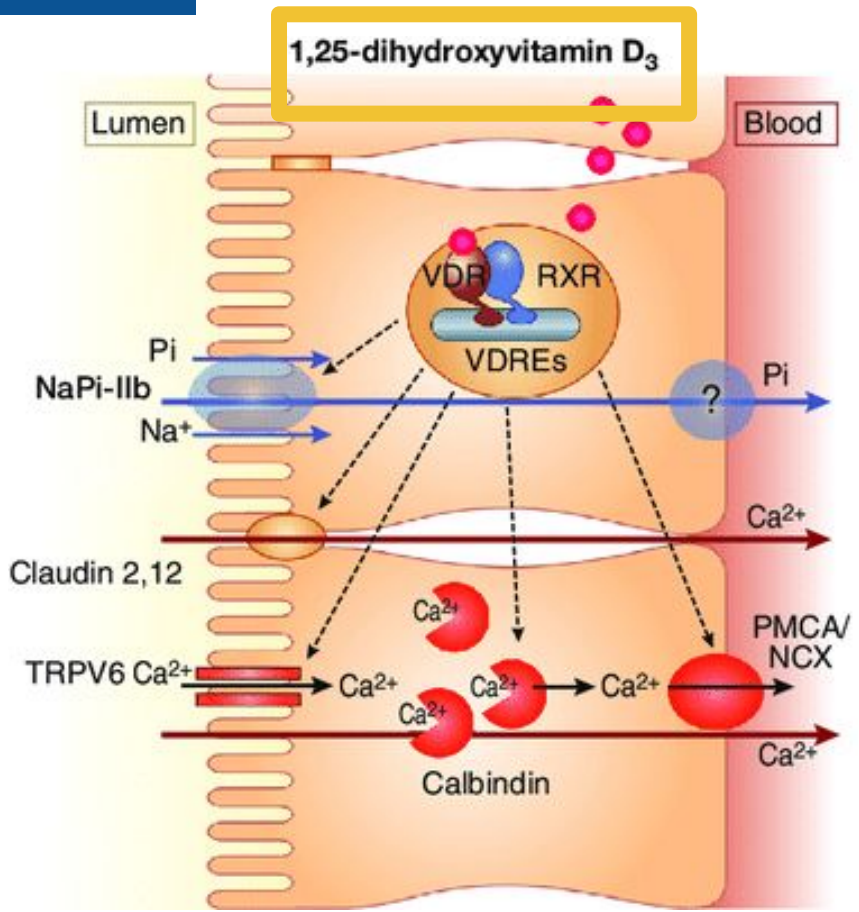


Fig. 53.3 Calcium-sensing receptor *(CaR).* Activation of the CaR by calcium stimulates phospholipase C, leading to increased inositol 1,4,5-triphosphate (IP_3), which mobilizes intracellular calcium and inhibits parathyroid hormone *(PTH)* synthesis. A decrease in serum calcium (Ca^{2+}) inhibits intracellular signaling, leading to increased PTH synthesis and secretion. *ER,* Endoplasmic reticulum. (From Friedman

Absorption calcium in intestine

The actions of 1α,25(OH)2D3 require the presence of the vitamin D receptor (VDR), a steroid hormone receptor, that binds 1α,25(OH)2D3 with high affinity

Intestinal transcellular Ca transport is regulated by 1α,25(OH)2D3, which increases the expression of **TRPV 6** channels, the intracellular concentrations of **calbindin D9K and D28K**, and the expression of the **plasma membrane pump.**



REABSORPTION OF CALCIUM ALONG THE TUBULE

60%–70% of total plasma calcium is **free (not protein bound)** and is filtered at the glomerulus

10,000 mg of complexed and ionized calcium are filtered by the glomerulus in a 24-hour period.

Only **1%–2%** of calcium filtered at the glomerulus appears in the urine

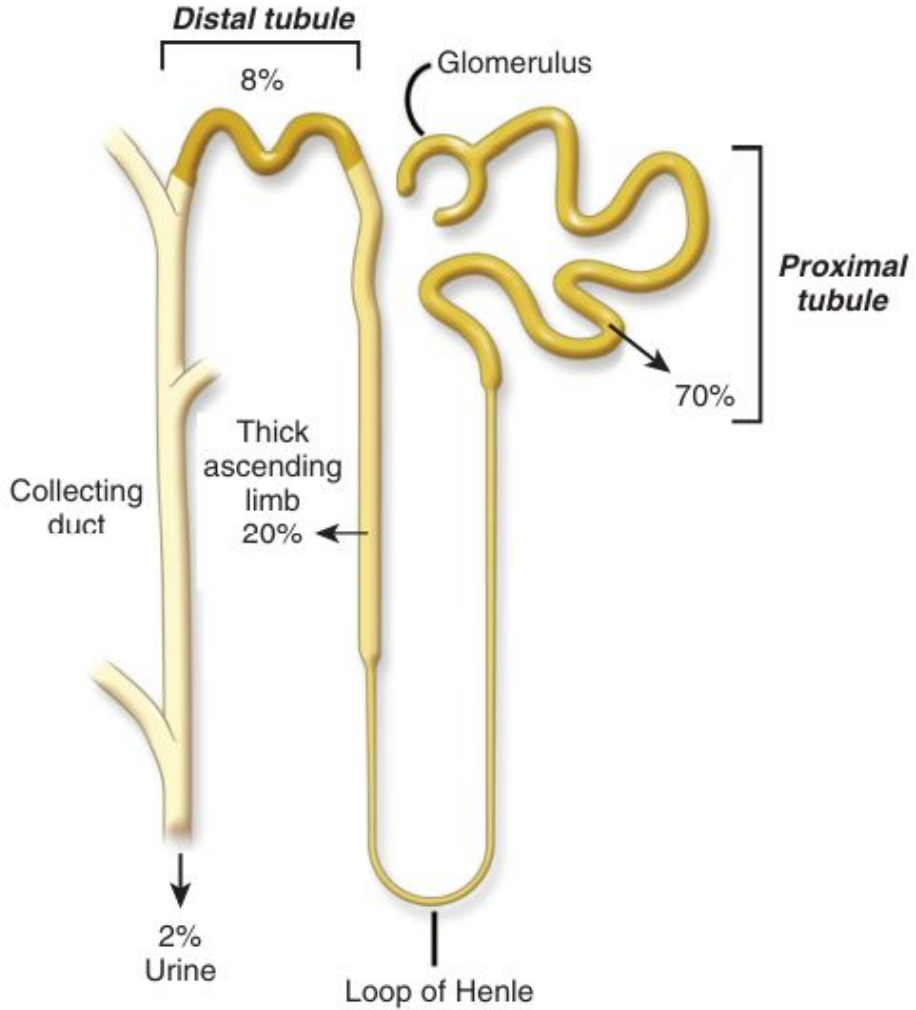


Fig. 7.5 Percentages of filtered calcium reabsorbed along the tubule.

Ca reabsorption in proximal tubule

- A large percentage (**~70%**) of filtered calcium (Ca2+) is **reabsorbed in the PT** mainly by **paracellular processes** that are linked with sodium (Na+) reabsorption
- Although the PT reabsorbs large amounts of Ca2+, primarily by paracellular processes, the rate of Ca2+ reabsorption is **not influenced** by factors or **hormones** that regulate calcium balance
- **Extracellular volume** status is the **major factor** that influences Ca2+ reabsorption in the PT, via its effects on Na+ reabsorption

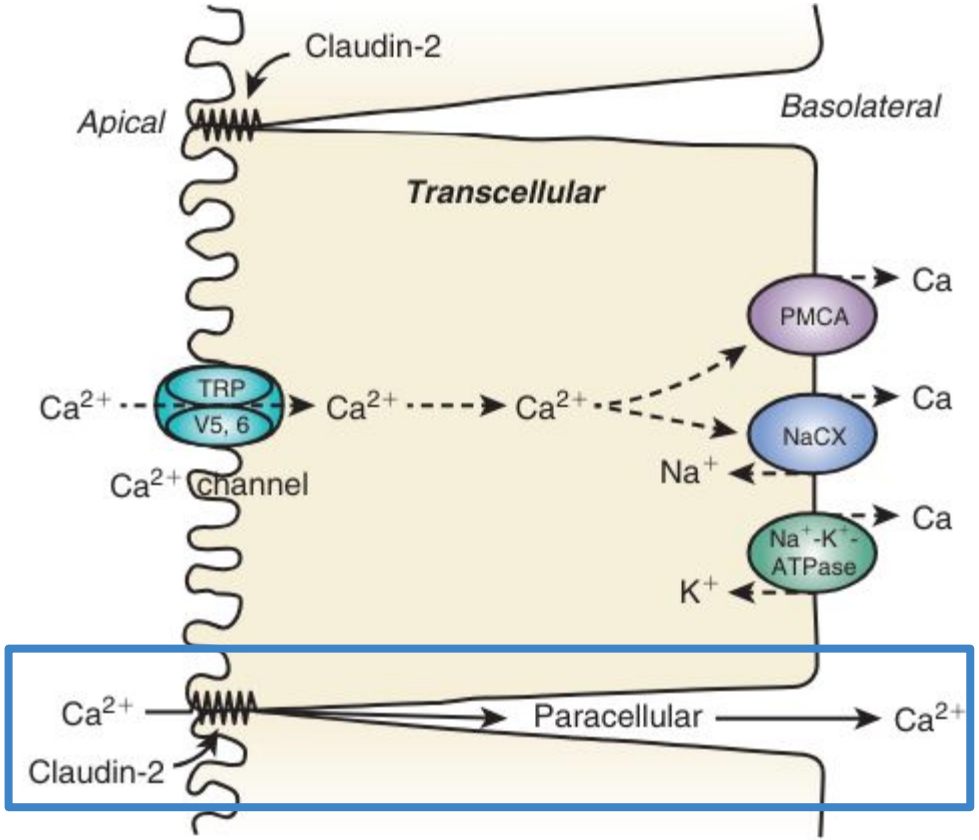


Fig. 7.6 Mechanisms by which calcium is transported in the proximal tubule. The majority of calcium is reabsorbed by paracellular mechanisms. A smaller percentage is reabsorbed by transcellular mechanisms.

Ca reabsorption in TALH

Between **20%–25%** of filtered Ca2+ is reabsorbed in the thick ascending loop of Henle, primarily by the **paracellular route**.

Claudin-16 (also known as paracellin), together with **claudin-19**, forms a paracellular pore.

- Loss-of-function mutations in the genes encoding claudin-16 and -19 result in familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC), which is characterized by renal Ca2+ and Mg2+ wasting due to defective thick ascending limb divalent cation reabsorption

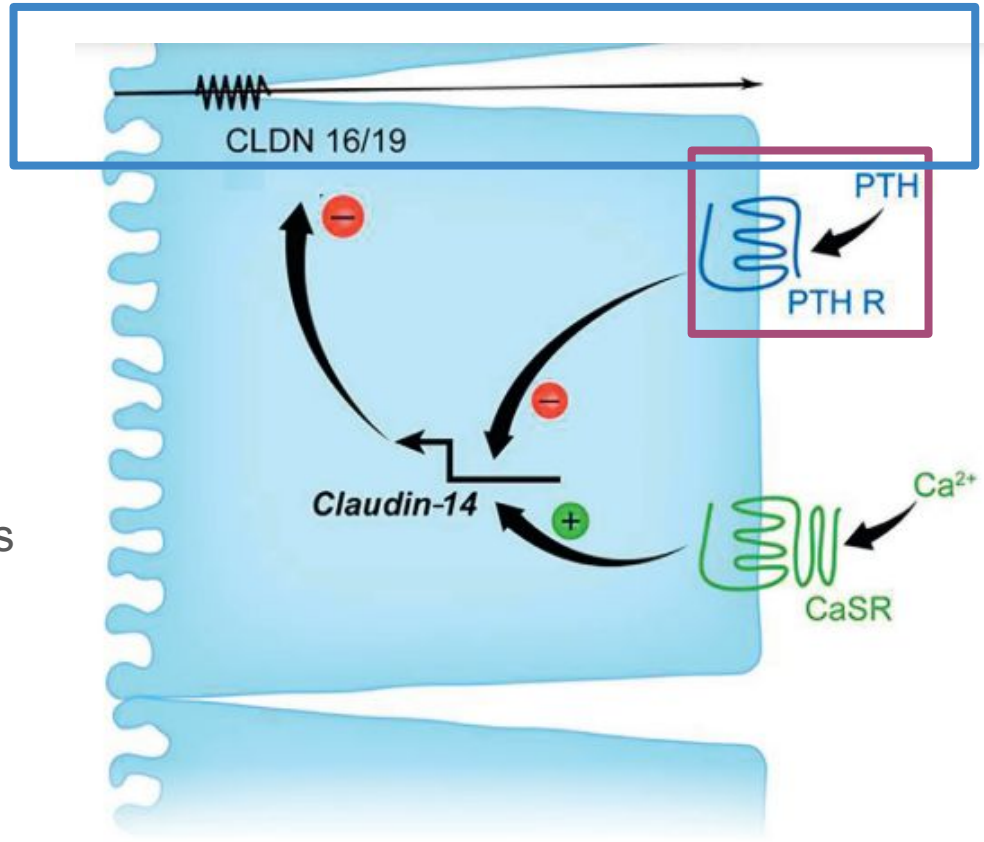
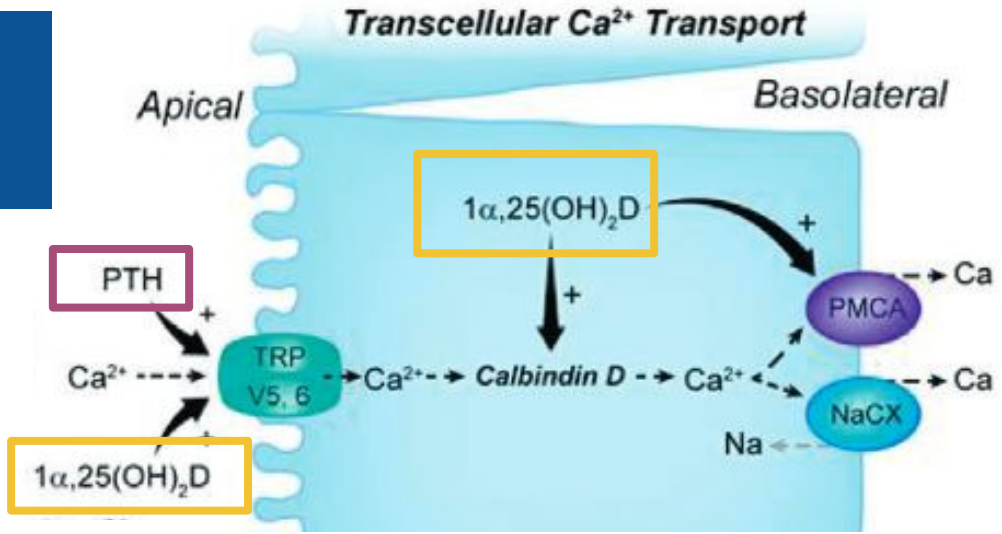
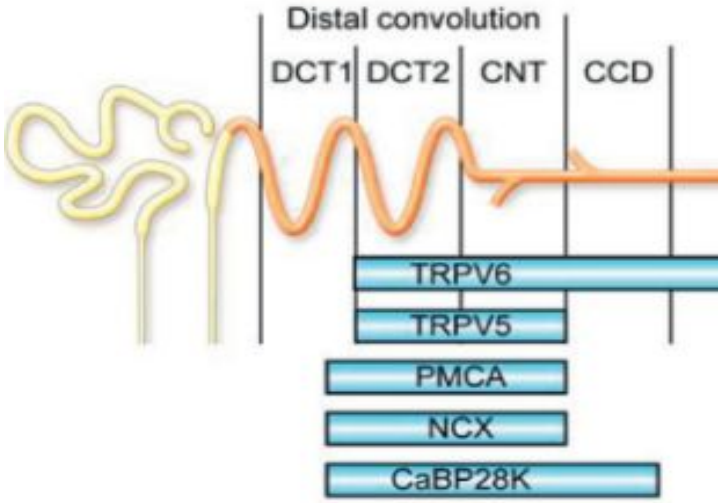


Fig. 7.7 Mechanisms and regulation of calcium transport in the thick ascending limb of Henle *(TALH)*. In the TALH, calcium is

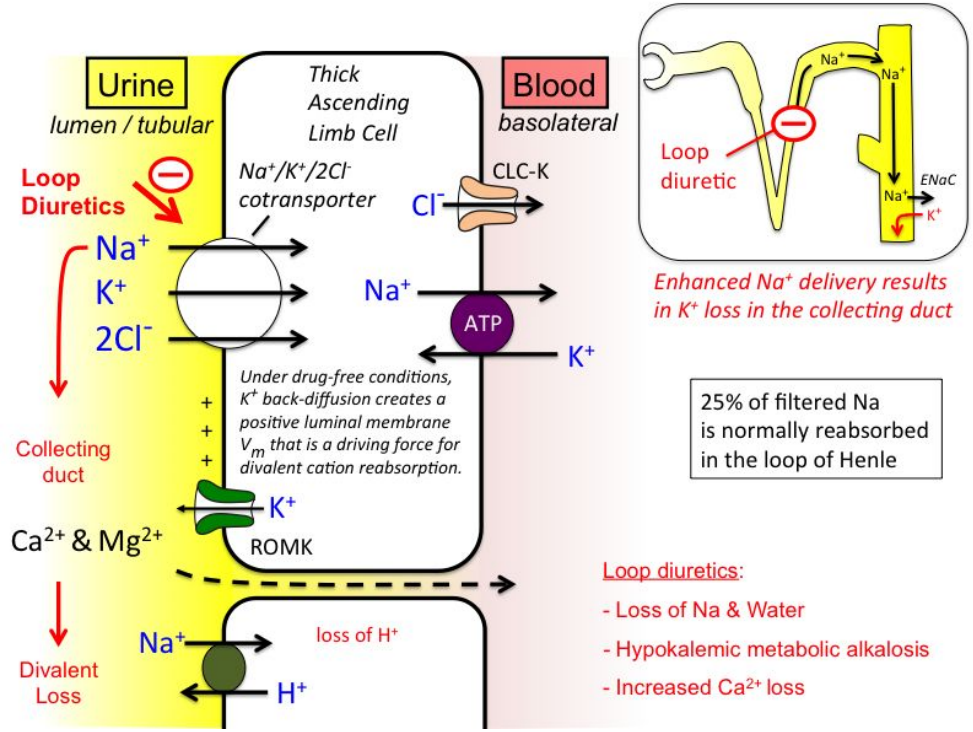
Ca reabsorption in DCT2 and Connecting tubule

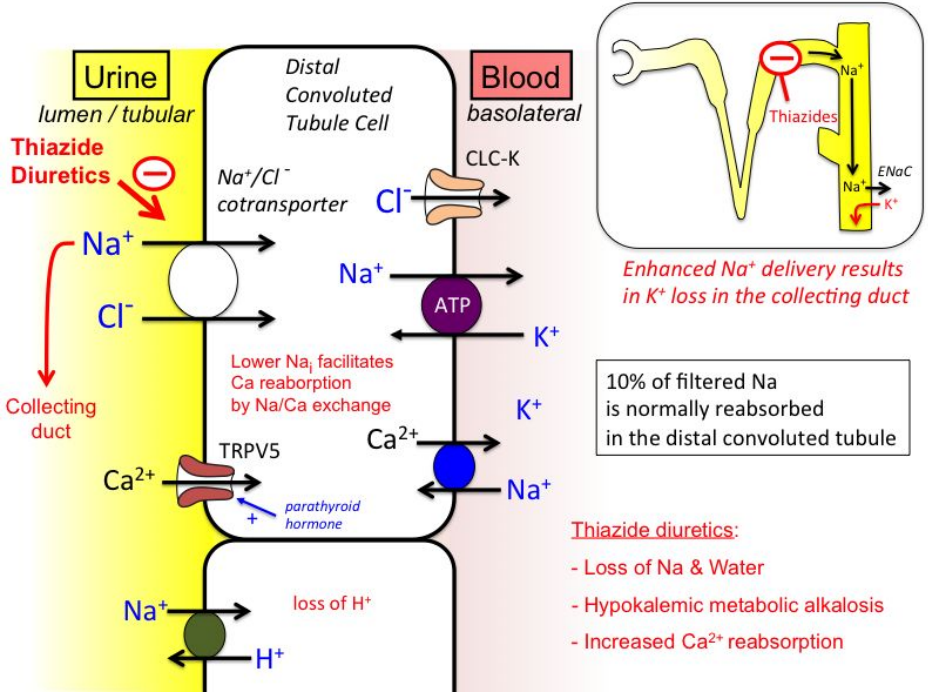
- In the distal convoluted tubule (primarily **DCT2**) and **connecting tubule** (together abbreviated as DT), **5%–10%** of filtered Ca2+ is reabsorbed by **active transport processes** against both an electrical and concentration gradient
- Ca2+ reabsorption in the DT occurs via a **transcellular pathway**, through **type 5 and 6 channels (TRPV5, TRPV6)**





Diuretics and Calciuria

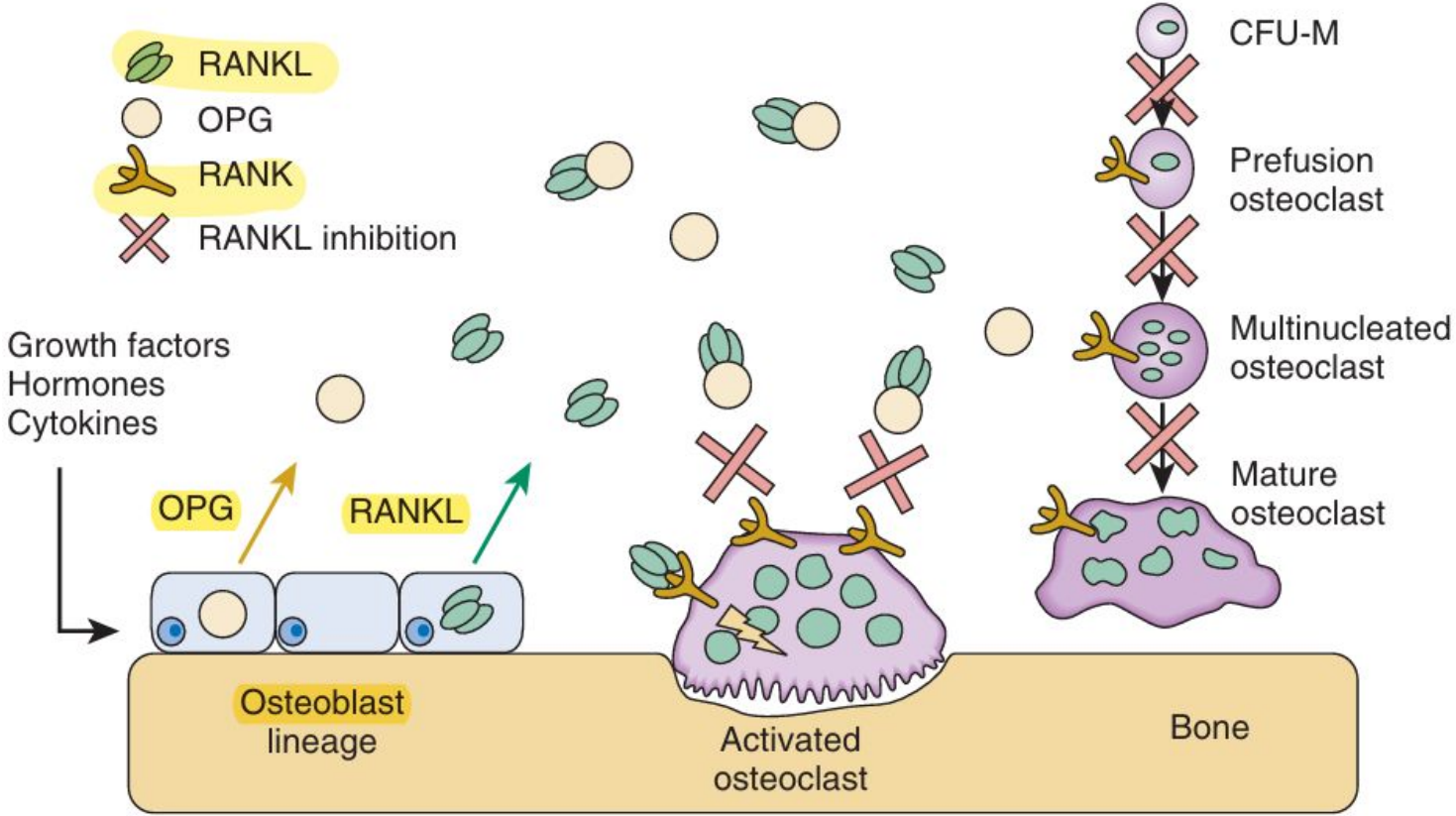


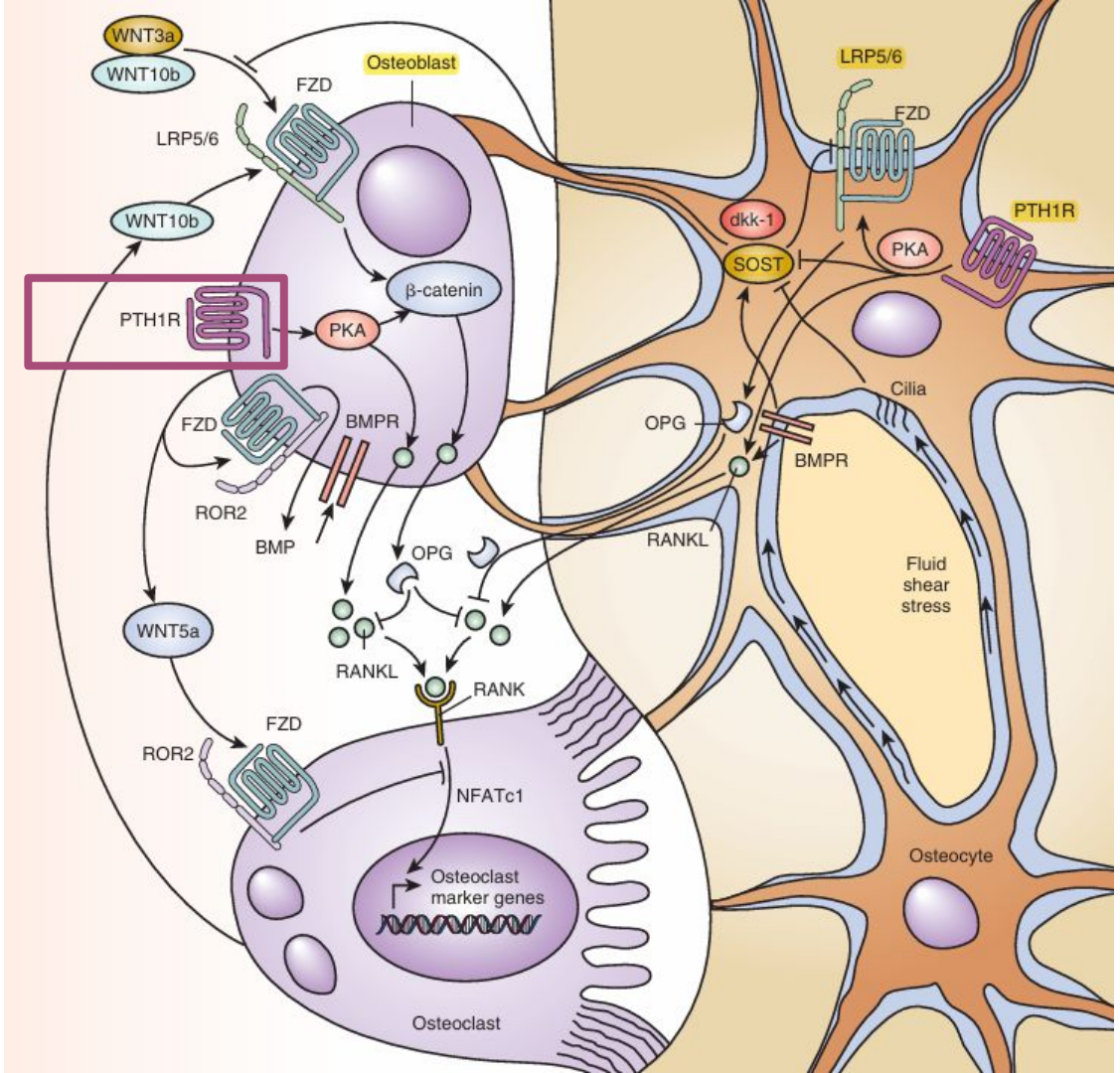


- **Mutations of NKCC2** are associated with the common form of **Bartter syndrome** and can be associated with **hypercalciuria**

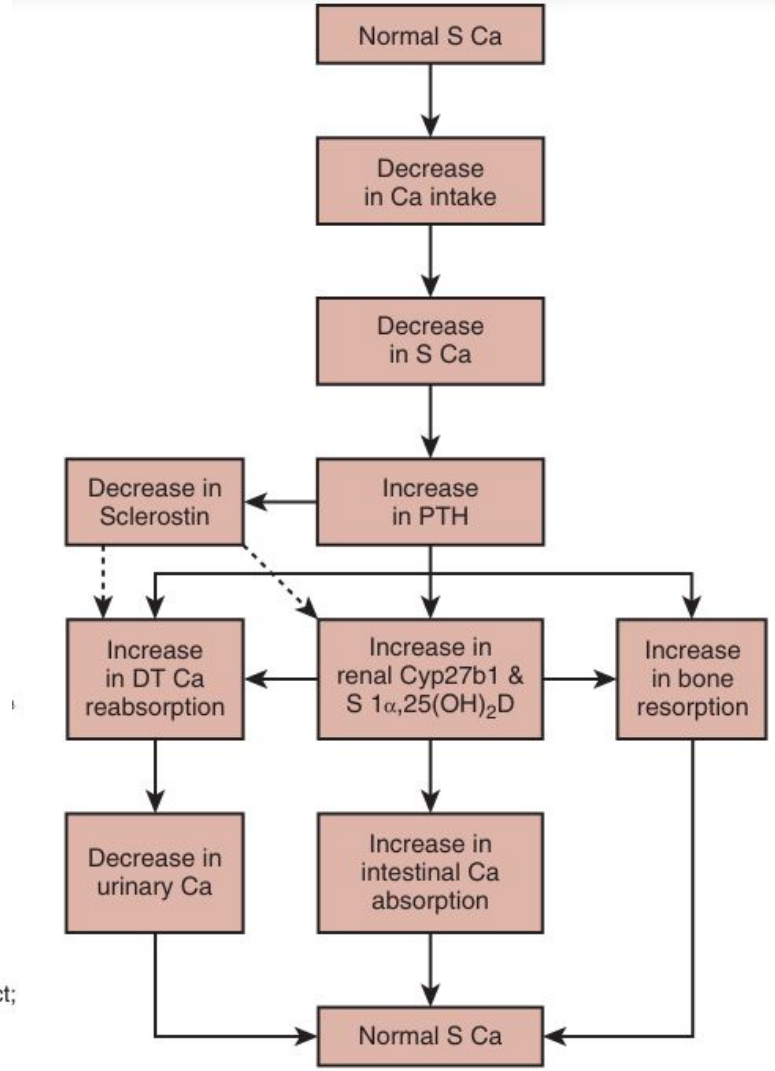
Humans with **Gitelman syndrome** and **inactivating mutations of the thiazide-sensitive Na-Cl** transporter have **hypocalciuria**, hypomagnesemia, and volume depletion

Ca and bone resorption




WNT3a
WNT10b
FZD
Osteoblast
LRP5/6
WNT10b
PTH1R
β-catenin
PKA
FZD
BMPR
ROR2
BMP
OPG
RANKL
WNT5a
RANKL
RANK
FZD
ROR2
NFATc1
Osteoclast marker genes
Osteoclast
LRP5/6
FZD
dkk-1
SOST
PKA
PTH1R
Cilia
OPG
BMPR
RANKL
Fluid shear stress
Osteocyte

Physiologic changes in response to decreases in serum calcium concentrations



S = serum; Ca = calcium; DT = distal tubule and connecting duct;
Cyp27b1 = 25(OH)D_3-1-hydroxylase cytochrome P450

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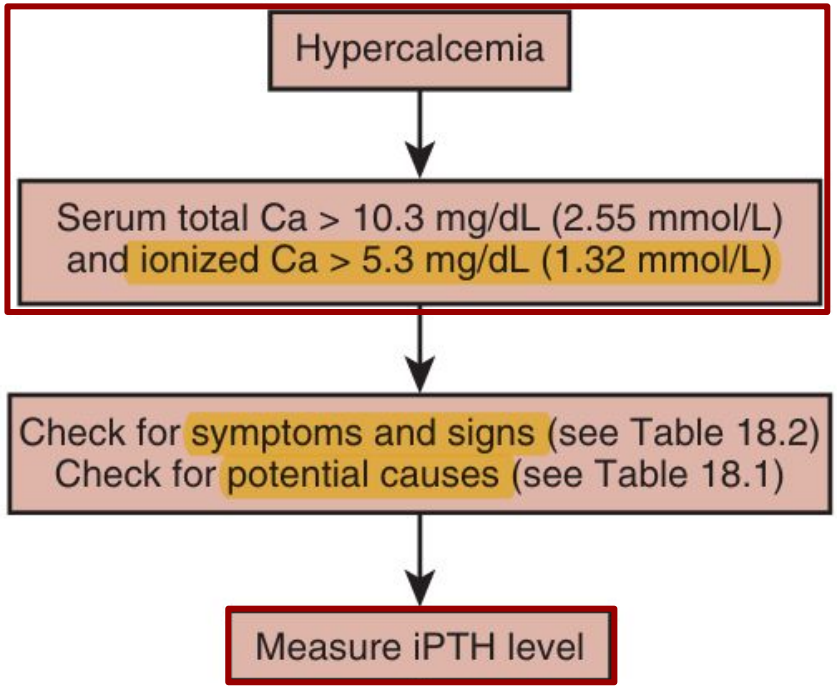
Approach to Diagnosis of Hypercalcemia



Patient presents with hypercalcemia

Patient history

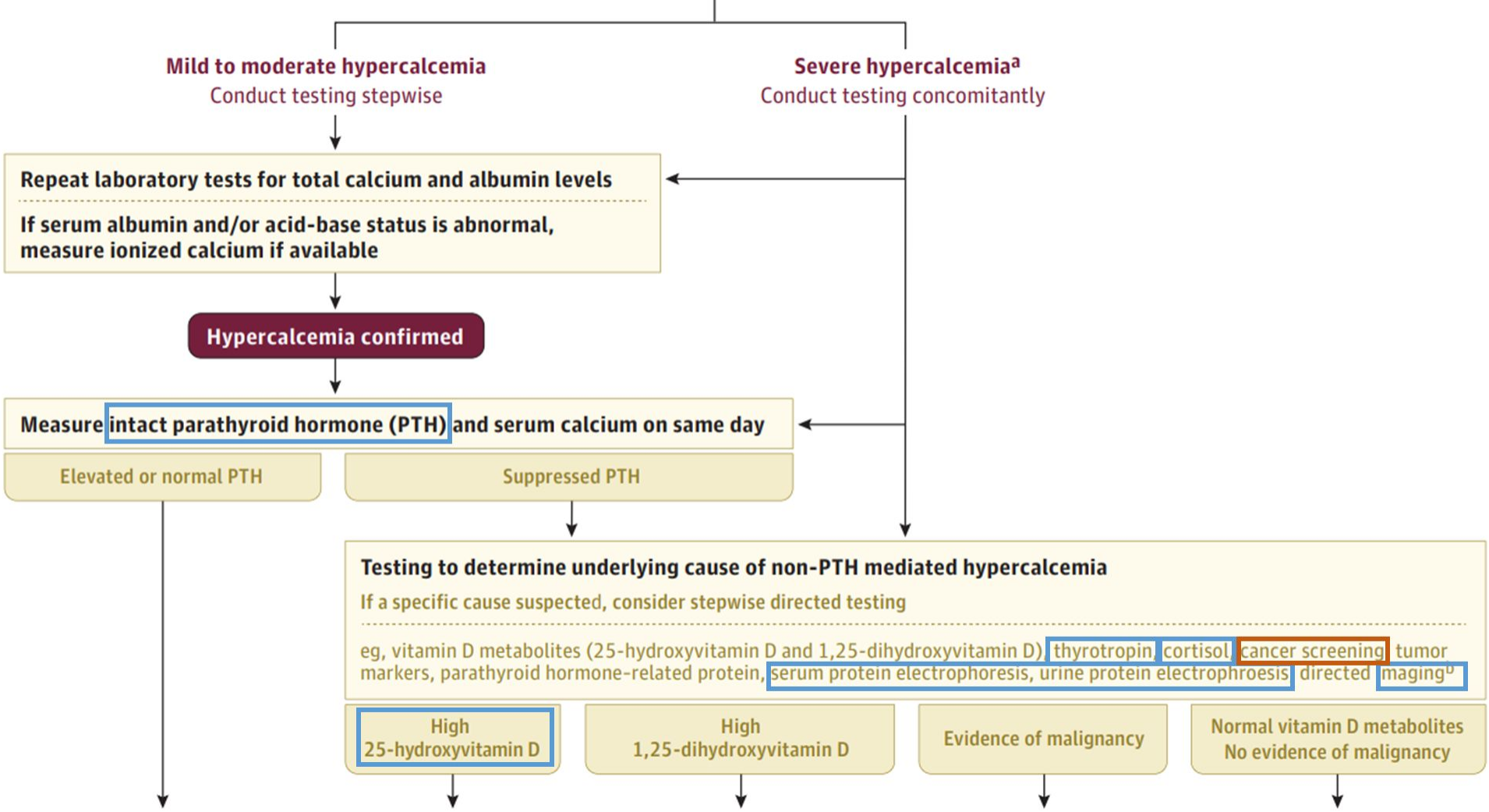
- Symptom presentation
  eg, asymptomatic, fatigue, constipation, nausea, vomiting, dehydration, confusion
- Severity
  - Mild, total calcium <12 mg/dL or ionized calcium 5.6-8.0 mg/dL
  - Moderate, total calcium 12-13.9 mg/dL or ionized calcium 8-10 mg/dL
  - Severe, total calcium ≥14 mg/dL or ionized calcium >10 mg/dL
- History of malignancy
- Medications and supplements used
  eg, thiazide diuretics, calcium, vitamin D, vitamin A
- Family history
  hypercalcemia or primary hyperparathyroidism

Physical examination

- Typically normal findings with mild or moderate hypercalcemia
- Presence of dehydration, somnolence, coma, lethargy, and/or change in cognition may occur with severe hypercalcemia
- Some findings may suggest a specific cause
  eg, lymphadenopathy may be a sign of malignancy, breast mass may indicate breast cancer, spinal tenderness and kyphosis may indicate fracture due to myeloma or metastatic disease

Review of prior laboratory data to determine duration of hypercalcemia

- Chronic (months to years) or acute (days to weeks)

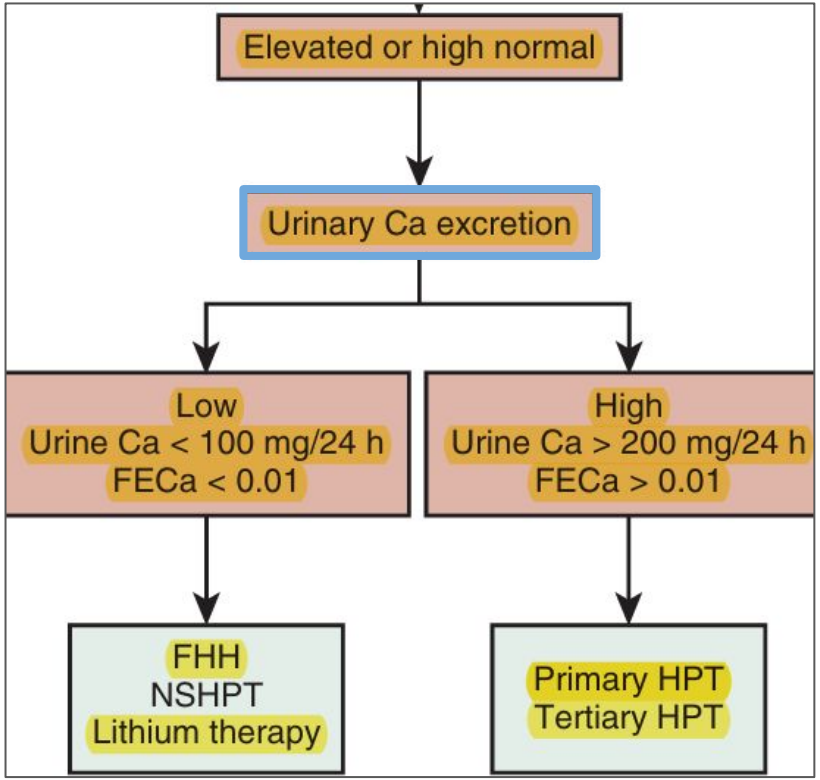

Mild to moderate hypercalcemia
Conduct testing stepwise
Severe hypercalcemia[a]
Conduct testing concomitantly
Repeat laboratory tests for total calcium and albumin levels
If serum albumin and/or acid-base status is abnormal, measure ionized calcium if available
Hypercalcemia confirmed
Measure intact parathyroid hormone (PTH) and serum calcium on same day
Elevated or normal PTH
Suppressed PTH
Testing to determine underlying cause of non-PTH mediated hypercalcemia
If a specific cause suspected, consider stepwise directed testing
eg, vitamin D metabolites (25-hydroxyvitamin D and 1,25-dihydroxyvitamin D) thyrotropin cortisol cancer screening tumor markers, parathyroid hormone-related protein, serum protein electrophoresis, urine protein electrophoresis directed maging[b]
High 25-hydroxyvitamin D
High 1,25-dihydroxyvitamin D
Evidence of malignancy
Normal vitamin D metabolites No evidence of malignancy

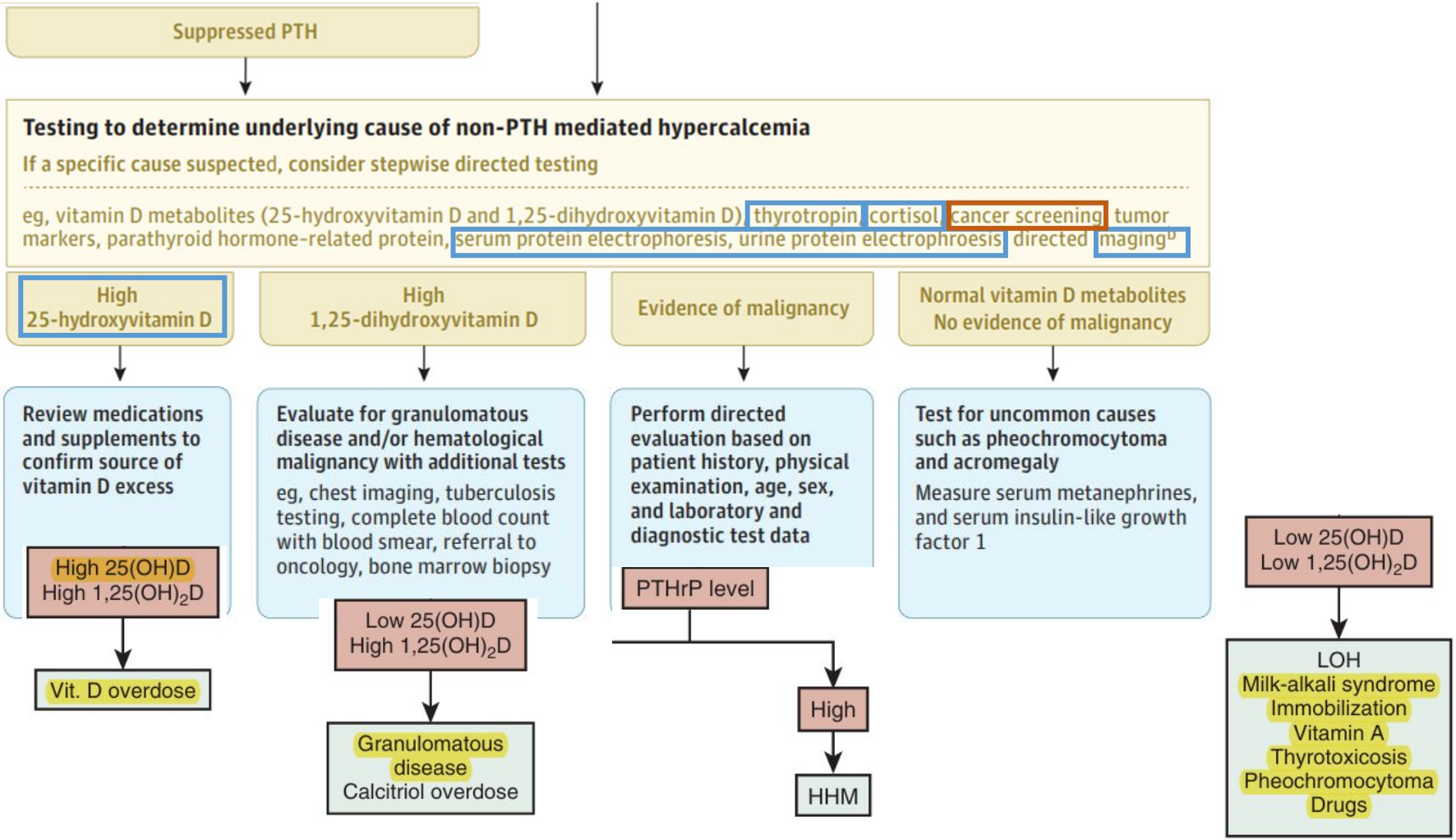
Measure intact parathyroid hormone (PTH) and serum calcium on same day

Elevated or normal PTH

Confirm primary hyperparathyroidism

- Consider familial hypocalciuric hypercalcemia if onset is at younger age (<40 y), there is family history of hypercalcemia, or urine fractional calcium excretion is <0.01




Suppressed PTH
Testing to determine underlying cause of non-PTH mediated hypercalcemia
If a specific cause suspected, consider stepwise directed testing
eg, vitamin D metabolites (25-hydroxyvitamin D and 1,25-dihydroxyvitamin D), thyrotropin, cortisol, cancer screening, tumor markers, parathyroid hormone-related protein, serum protein electrophoresis, urine protein electrophoresis, directed imaging[b]
High 25-hydroxyvitamin D
High 1,25-dihydroxyvitamin D
Evidence of malignancy
Normal vitamin D metabolites No evidence of malignancy
Review medications and supplements to confirm source of vitamin D excess
High 25(OH)D
High 1,25(OH)2D
Vit. D overdose
Evaluate for granulomatous disease and/or hematological malignancy with additional tests
eg, chest imaging, tuberculosis testing, complete blood count with blood smear, referral to oncology, bone marrow biopsy
Low 25(OH)D
High 1,25(OH)2D
Granulomatous disease
Calcitriol overdose
Perform directed evaluation based on patient history, physical examination, age, sex, and laboratory and diagnostic test data
PTHrP level
High
HHM
Test for uncommon causes such as pheochromocytoma and acromegaly
Measure serum metanephrines, and serum insulin-like growth factor 1
Low 25(OH)D
Low 1,25(OH)2D
LOH
Milk-alkali syndrome
Immobilization
Vitamin A
Thyrotoxicosis
Pheochromocytoma
Drugs

Typical Biochemical Profile, Pathophysiology of Various Etiologies of Hypercalcemia

Condition	Relative frequency[52]	Pathophysiology	Laboratory tests				Specific treatment
			Calcium	PTH	Phosphorus	Urine calcium	
Primary hyperparathyroidism[a]	54%	Excess PTH increases bone resorption, kidney calcium reabsorption, calcitriol production, gastrointestinal absorption	Usually mild elevation[b]	High or normal	Normal or low	Normal or high	Parathyroidectomy or observation; cinacalcet can be used for severe chronic hypercalcemia in patients who are not surgical candidates
Malignancy	35%						
Humoral hypercalcemia of malignancy		Tumors secrete parathyroid hormone-related protein, which has actions similar to PTH	Moderate to severe elevation	Low	Normal or low	Normal or high	Control underlying malignancy to extent possible; hydration; bisphosphonates; denosumab
Osteolytic metastases		Tumors cause focal increases in bone resorption	Moderate to severe elevation	Low	Normal or high	Normal or high	Zoledronic acid and denosumab
Calcitriol-producing lymphomas		Ectopic 1,25-dihydroxyvitamin D production increases gastrointestinal calcium absorption and bone resorption	Moderate to severe elevation	Low	High	Normal or high	Treat underlying malignancy; steroids
All other causes	11%						
Familial hypocalciuric hypercalcemia		Variants in calcium-sensing receptor increase set point for serum calcium	Mild elevation	Normal or high normal	Normal or low	Low	No treatment typically required
Vitamin D intoxication[c]		Increased gastrointestinal calcium absorption	Elevated	Low	High	Normal or high	Discontinue vitamin D ingestion; steroids if severe or recurrent hypercalcemia
Sarcoid[d]		Ectopic 1,25-dihydroxyvitamin D production increases gastrointestinal calcium absorption, and bone resorption	Elevated	Low	High	Normal or high	Steroids; limit dietary calcium and vitamin D and sun exposure
Milk-alkali syndrome		High calcium intake increases gastrointestinal absorption and reduces kidney clearance of calcium	Elevated	Low	Normal or low[e]	Low	Discontinue calcium supplement ingestion

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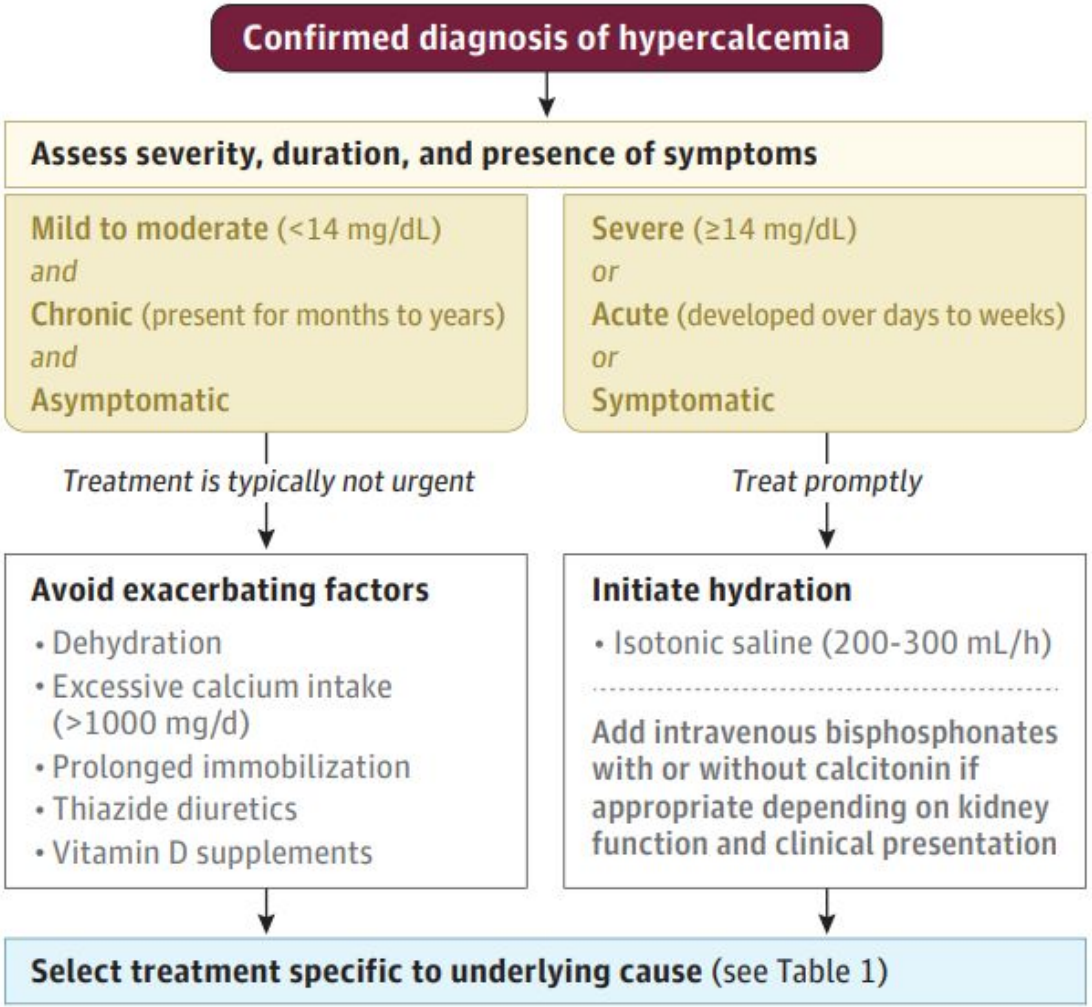
Approach to Treatment of Hypercalcemia



Treatment specific to underlining cause

What Are the Indications for Parathyroidectomy in Patients With PHPT?

Parathyroidectomy is recommended for patients with classic features of PHPT such as symptoms of hypercalcemia, kidney stones, or osteitis fibrosa cystica. Parathyroidectomy is also recommended for asymptomatic patients with any 1 of the following: (1) serum calcium of greater than 1 mg/dL (0.25 mmol/L) above the upper limit of normal; (2) bone mineral density T score of −2.5 or lower at any site; (3) vertebral fracture on spine imaging; (4) creatinine clearance of less than 60 mL/min/1.73 m^2; (5) nephrocalcinosis or nephrolithiasis by ultrasound or x-ray; (6) urinary calcium excretion of greater than 250 mg/d (>6.2 mmol) for women or greater than 300 mg/d (>7.48 mmol) for men; and (7) age less than 50 years.

How Is Primary Hyperparathyroidism Diagnosed?

Primary hyperparathyroidism is diagnosed when there is an elevated serum total (corrected for albumin) or ionized calcium level and a concomitant serum parathyroid hormone (PTH) level that is above normal. PTH levels within the normal range are also consistent with PHPT because hypercalcemia should suppress PTH secretion. For patients with hypercalcemia and PTH levels close to the lower limit of the normal range, other causes of hypercalcemia should be investigated.

How Should Severe Hypercalcemia Be Managed?

Severe hypercalcemia (serum calcium ≥14mg/dL or 3.5 mmol/L) is managed with saline hydration, calcitonin, and intravenous zoledronic acid (5 mg over 15 minutes), which should be administered with or soon after initiation of hydration. If serum creatinine is elevated, consider slower infusion rates (30-60 minutes) or lower doses of zoledronic acid or consider denosumab, which is not cleared by the kidney, instead of zoledronic acid.

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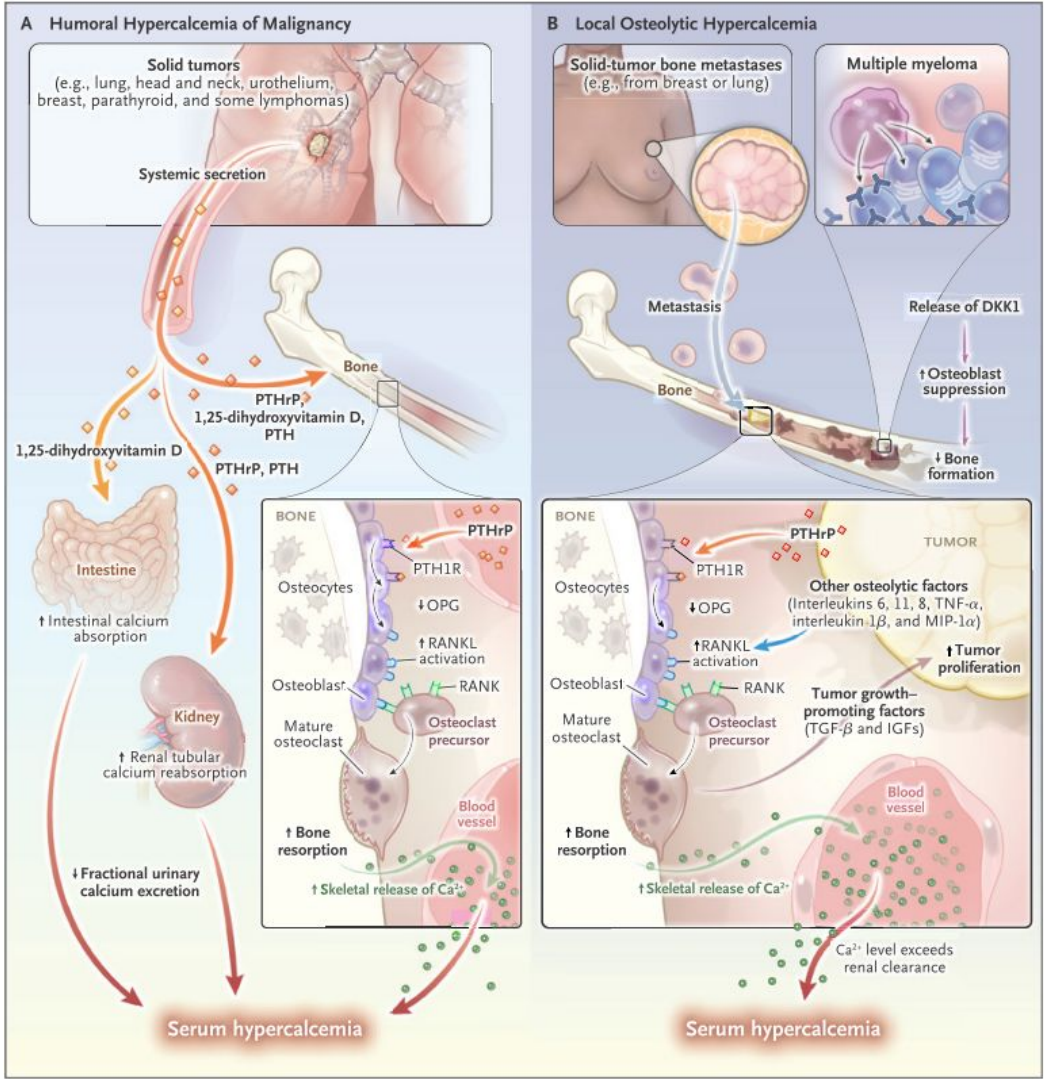
Cancer-associated hypercalcemia

Four subtypes:
(1) Humoral,
(2) Local osteolytic,
(3) 1,25-dihydroxyvitamin D–mediated,
(4) Ectopic hyperparathyroidism

- Malignancy was the most common identifiable cause of hypercalcemia (40%) among inpatient hypercalcemia
- lung cancer (20%), multiple myeloma (14%) and renal cell carcinoma (11%) being the main cancer types.

https://doi.org/10.57187/smw.2023.40069



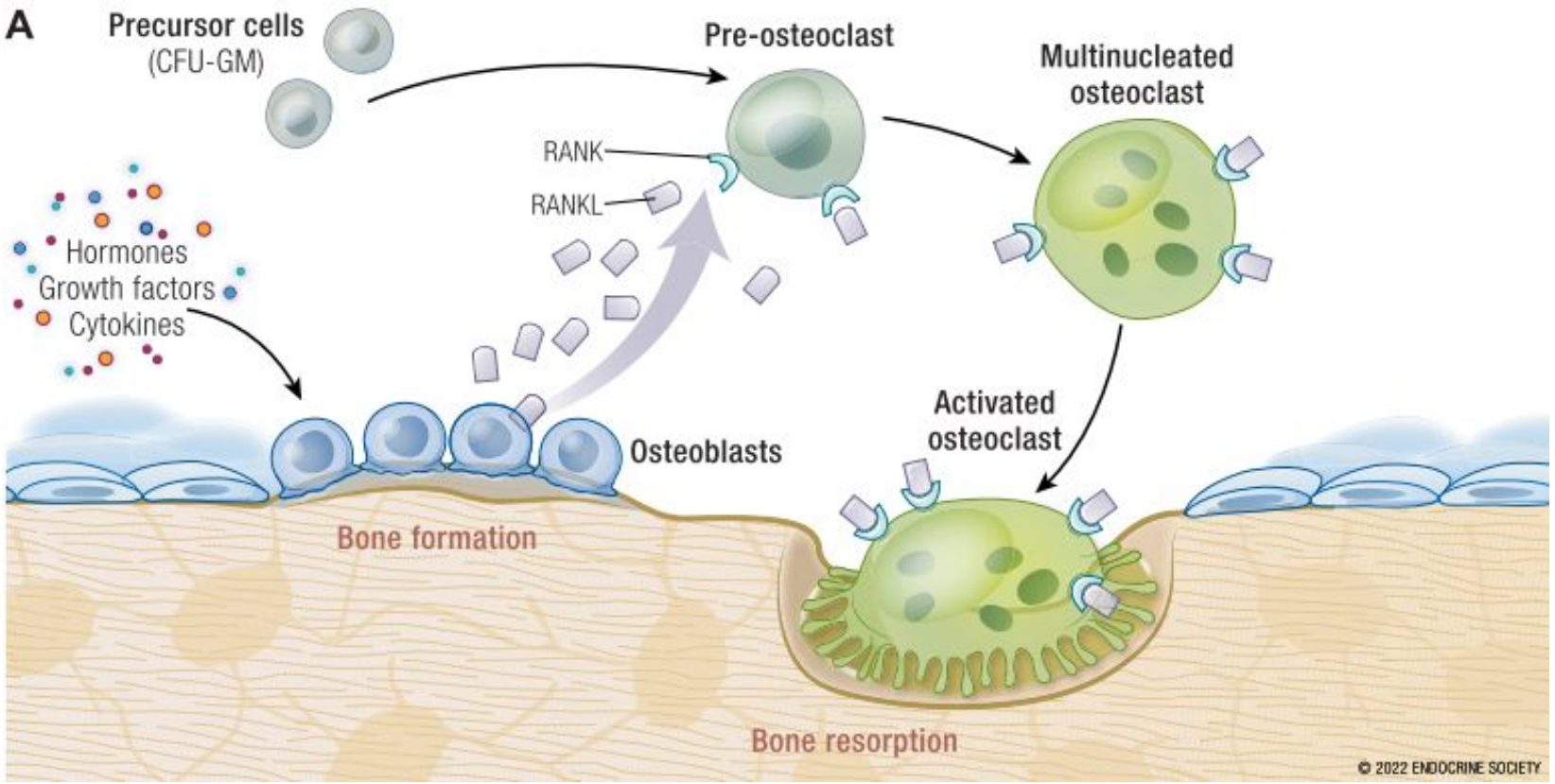
Classification of types of cancer-associated hypercalcemia

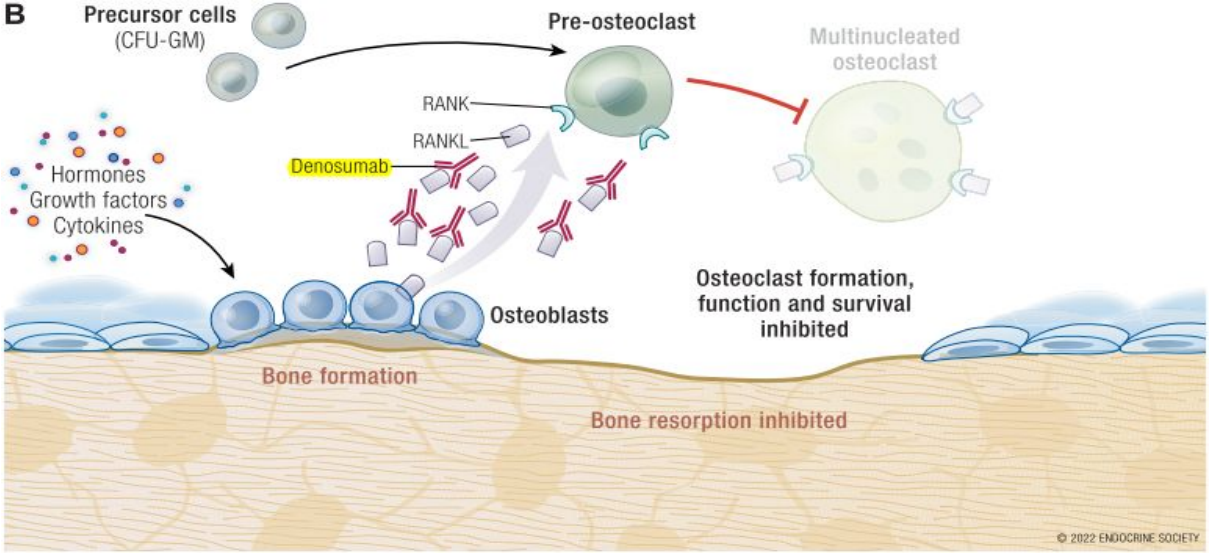
Feature	Humoral Hypercalcemia			Local Osteolytic Hypercalcemia	
Mediator	PTHrP	1,25 dihydroxy-vitamin D	Parathyroid hormone	TNF, interleukin-6, interleukin-1, macrophage inhibitory protein, and others	PTHrP, TNF, interleukin-6, interleukin-1, and others
Tumor type	Lung, breast, renal, and many others	Hematologic cancer, T-cell lymphoma	Parathyroid cancer, neuroendocrine, ovarian, and others	Myeloma or lymphoma in bone	Breast, lung, kidney
Bone metastases, tumor in bone	None or few	None or few	None or few	Extensive	Extensive
Parathyroid hormone	Low	Low	High	Low	Low
PTHrP	High or normal	Low	Low	Low	Variable
1,25-dihydroxyvitamin D	Variable	High	High	Variable	Low
Phosphorus	Low	High	Low	Variable	Variable
Osteoclast activity	High	High	High	High	High

Head & Neck
Prostate

Prostate

Osteoclast formation, activity, and pharmacologic inhibition




B
Precursor cells
(CFU-GM)
Pre-osteoclast
Multinucleated
osteoclast
RANK
RANKL
Denosumab
Hormones
Growth factors
Cytokines
Osteoblasts
Osteoclast formation,
function and survival
inhibited
Bone formation
Bone resorption inhibited
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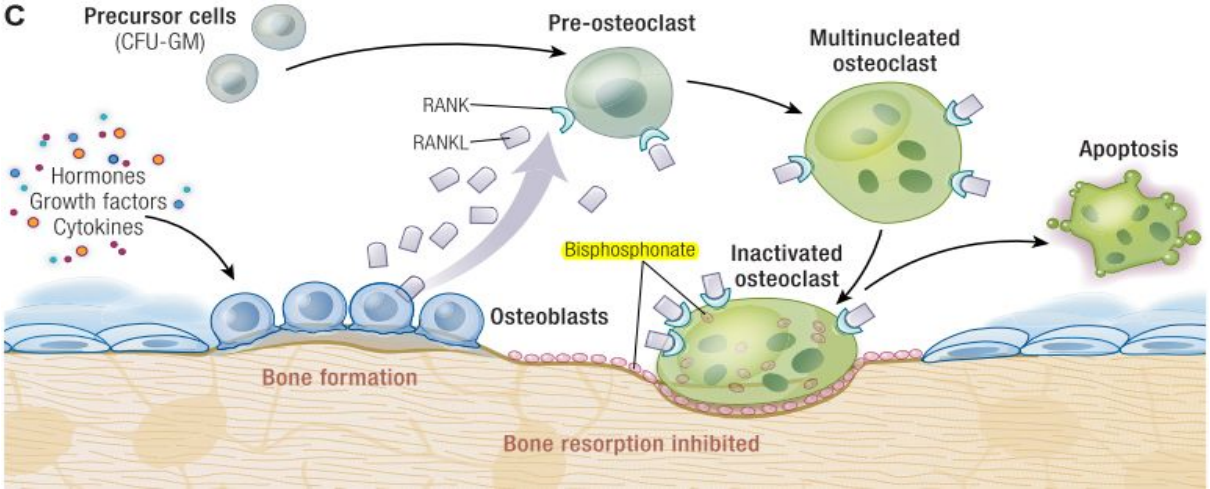
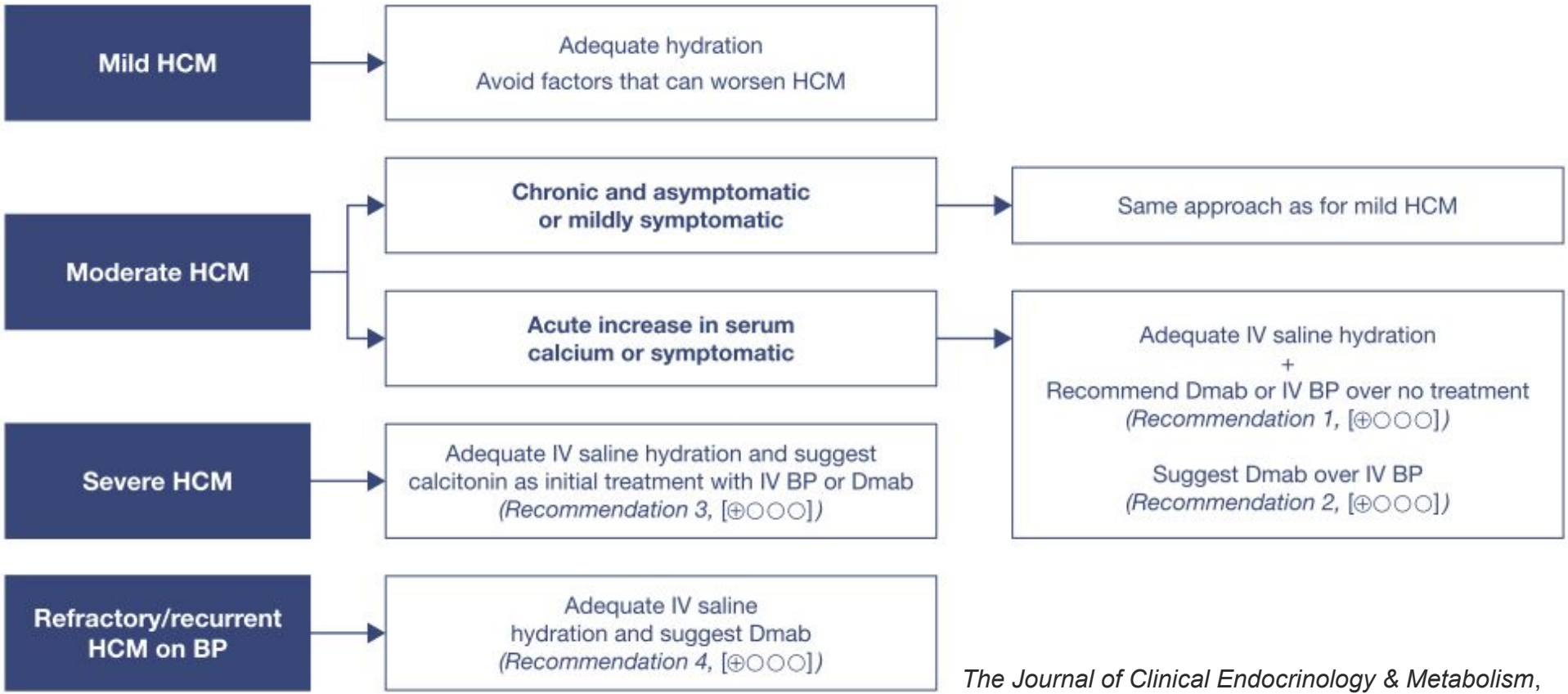

C
Precursor cells
(CFU-GM)
Pre-osteoclast
Multinucleated
osteoclast
RANK
RANKL
Apoptosis
Hormones
Growth factors
Cytokines
Bisphosphonate
Inactivated
osteoclast
Osteoblasts
Bone formation
Bone resorption inhibited

Suggested workflow for the management of HCM



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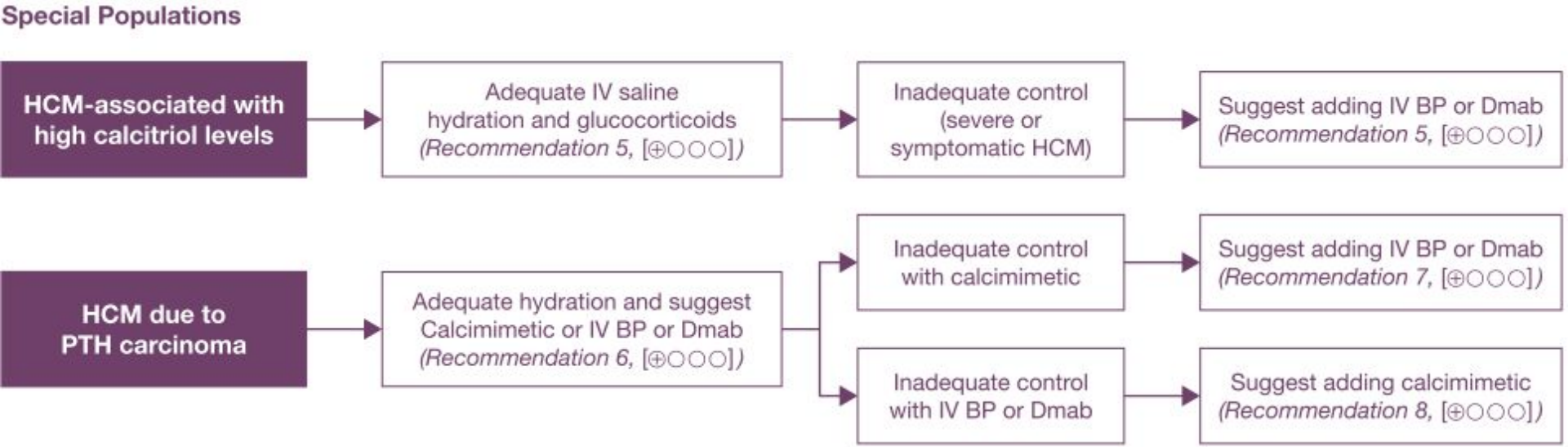

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Ungraded good practice statements

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Ungraded good practice statement (UGPS) definition: Necessary actionable and clear guideline statements that are supported only by overwhelming indirect evidence. The supporting direct evidence is either unavailable or considered inappropriate for a systematic review process. UGPS should describe the population and intervention options and, if appropriate, comparator components of the recommendation (28, 29).

The panel reviewed the criteria for UGPSs and makes the following UGPSs for patients with HCM:

UGPS 1: In adults with HCM, adequate hydration with intravenous (IV) fluids is first-line therapy while awaiting the effect of antiresorptive drugs. Therapy should be tailored according to cardiac function.

UGPS 2: In adults with HCM, dental hygiene and oral health, including visual examination of the mouth, should be monitored in the context of the provision of antiresorptive therapy.

UGPS 3: To avoid hypocalcemia in adults with HCM who receive antiresorptive therapy, vitamin D levels should be monitored and managed in accordance with Endocrine Society vitamin D guidelines. These guidelines are however not specific to patients with HCM.

UGPS 4: In adults with HCM, renal function (creatinine clearance or estimated glomerular filtration rate [eGFR]) should be assessed prior to administration of IV BPs.

UGPS 5: In adults with HCM and renal insufficiency (defined as creatinine clearance <60 mL/min) who are treated with IV BPs, administer renal BP dosing of zoledronic acid over 30 to 60 minutes or renal BP dosing of pamidronate over 2 to 24 hours.

UGPS 6: In adults with HCM, serum magnesium and phosphorous levels should be monitored and repleted if determined to be low.

UGPS 7: In adults with HCM, clinical oncology consultation for treatment of the underlying malignancy should be undertaken.

UGPS 8: In adults with hypercalcemia due to parathyroid carcinoma, surgical consultation should be pursued for definitive treatment.

Adequate IV hydration. Aware HF.
Dental hygiene. Visual exam of the mouth.
To avoid hypocalcemia, monitor VitD. level.
Check Ccr before IV BPs.

If Ccr<60, IV BPs (Zoledronic A> 30-60ms)
Monitor serum Mg and P.
Oncologist consultation for malignancy survey
If parathyroid CA -> surgical consultation

KEY CLINICAL POINTS

CANCER-ASSOCIATED HYPERCALCEMIA

- Hypercalcemia complicates the course of a variety of cancers when tumor factors overwhelm normal calcium and bone homeostasis.
- Cancer-associated hypercalcemia often occurs late in the course of solid-tumor development and portends a poor prognosis.
- Hypercalcemia in the context of cancer may have nonmalignant causes, such as primary hyperparathyroidism; this possibility should be ruled out with the use of appropriate clinical assessment and laboratory testing.
- Because patients with cancer-associated hypercalcemia typically present with profound dehydration, the initial treatment should involve the administration of intravenous fluids.
- Increased osteoclastic bone resorption is almost always responsible for hypercalcemia, regardless of tumor type or mediator; after hydration, the use of bone-resorption inhibitors (most commonly intravenous bisphosphonates) to lower calcium levels is the mainstay of treatment.
- Successful treatment of cancer-associated hypercalcemia ultimately depends on treatment of the underlying cancer.

Treatment of Hypercalcemia of Malignancy in Adults: An Endocrine Society Clinical Practice Guideline

Intervention/dose frequency	Mode of action	Onset of action	Median duration of action/ effect/proportion of subjects achieving normocalcemia	Adverse events/comments
Isotonic saline hydration/ Bolus of 1 to 2 L then 200 to 500 mL/hour to maintain urine output at 100 to 150 mL/hour.	Restores depleted intravascular volume. Enhances urinary calcium excretion.	Immediate	During infusion. Lowers calcium by 1 to 1.5 mg/dL (0.25 to 0.375 mmol/L) over first 24 hours.	Carefully assess for volume overload.
Loop diuretics*/ Furosemide 160 mg/d to 100 mg/h intravenously, or 40 to 60 mg/d orally only to be administered after volume repletion.	Increase urinary calcium excretion by inhibiting renal calcium reabsorption in the thick ascending loop of Henle, and proximal and distal renal tubules. Interferes with the chloride cotransport system.	Within 3 to 60 minutes	2 hours if bolus. During therapy if IV drip. Lowers calcium by 0.5 to 1.0 mg/dL (0.125 to 0.25 mmol/L) after resolution of volume depletion.	Volume depletion, and worsening HCM. May be useful in patients at risk for volume overload/congestive heart failure.
Salmon Calcitonin/CT 4 to 8 units/kg Intramuscular or SQ every 6 to 12 hours for 48 to 72 hours.	Inhibits bone resorption by interfering with osteoclast function. Promotes urinary calcium excretion, as well as that of magnesium, sodium, potassium and phosphate.	4 to 6 hours	6 to 8 hours. Rapidly lowers calcium by 1 to 2 mg/dL (0.25 to 0.50 mmol/L).	Tachyphylaxis may occur after 48 to 72 hours.

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Intervention/dose frequency	Mode of action	Onset of action	Median duration of action/ effect/proportion of subjects achieving normocalcemia	Adverse events/comments
Bisphosphonates/BPs	Pamidronate and zoledronic acid are nitrogen-containing BPs that inhibit bone resorption by inhibiting farnesyl pyrophosphate synthase (FPPS) within osteoclasts to cause osteoclast apoptosis. They also interfere with osteoclast recruitment and function.			
Pamidronate/APD 60 to 90 mg IV over 2 to 24 hours. Can be repeated every 2 to 3 weeks.		48 to 72 hours	7 to 14 days; may last 2 to 4 weeks. Normalizes calcium in 60% to 70% of patients.	May cause kidney damage especially if glomerular filtration rate <30 to 35 mL/minute. Acute-phase response relatively common; hypocalcemia; renal insufficiency possible if decreased glomerular filtration rate; Atypical femoral fractures are rare and ONJ occurs infrequently.
Zoledronic acid/ZLN 3 to 4 mg IV over 15 to 30 minutes. Can be repeated in 7 days, if desirable calcium level not achieved, and every 3 to 4 weeks thereafter.		48 to 72 hours	4 to 6 weeks. Normalizes calcium in 80% to 90% of patients.	May cause kidney damage especially if glomerular filtration rate <30 to 35 mL/minute. Dose adjustment required if glomerular filtration rate <60 mL/min, and administer over 30 to 60 minutes.

Intervention/dose frequency	Mode of action	Onset of action	Median duration of action/ effect/proportion of subjects achieving normocalcemia	Adverse events/comments
Glucocorticoids 200 to 400 mg hydrocortisone IV/day for 3 to 5 days. 60 mg/day of prednisone for 10 days, or 10 to 20 mg/day for 7 days.	Decrease intestinal calcium absorption. Inhibits 1α-hydroxylase and limits 1,25-dihydroxyvitamin D production by mononuclear cells in patients with granulomatous diseases or lymphoma.	2 to 5 days	As long as on therapy.	Hyperglycemia, altered mental status, and hypertension.
Denosumab/Dmab 120 mg SQ. Repeat 1, 2 and 4 weeks later, then monthly thereafter.	Inhibits bone resorption via inhibition of RANKL. Dmab is an antibody to RANKL. Upon binding to RANKL, Dmab blocks the interaction between RANKL and RANK (receptor on osteoclast surfaces) and prevents osteoclast formation and thus bone resorption.	3 to 10 days	Time to complete response 23 days. Median duration of effect 104 days. Normalizes calcium in at least 70% of patients.	Acute-phase response rare; Atypical femoral fractures are rare and ONJ occurs infrequently. Rebound osteoclastogenesis may occur with discontinuation. Patients with GFR < 30 mL/min have a higher risk of hypocalcemia, and a lower dose should be considered.
Calcimimetics Oral: Initial: 30 mg twice daily; increase dose incrementally every 2 to 4 weeks (to 60 mg twice daily, 90 mg twice daily, and 90 mg 3 to 4 times daily) as necessary to normalize SCa levels.	Calcium-sensing receptor agonist, reduces parathyroid hormone secretion, and may decrease renal calcium reabsorption.	2 to 3 days	During therapy. Reduces calcium by at least 1 mg/dL (0.25 mmol/L) in approximately 60% of patients.	Nausea, vomiting, headache, and fractures. Case reports indicate reduction of calcium levels in patients with refractory HCM related to non–small-cell lung, neuroendocrine, breast, or renal cancer.

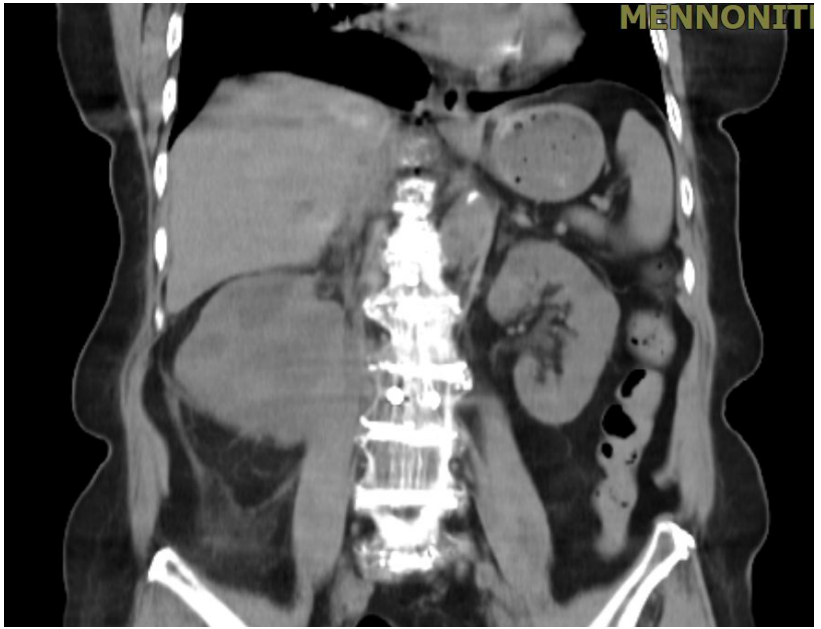
Case

This 79-year-old has DM and HTN.

Right flank pain along with general weakness and poor appetite since 2024 Jan.

Abdominal CT at Mennoite hospital showed right renal tumor with IVC thrombosis on 2024/01/25. She was admitted on 2024/02/01 for CT-guided biopsy on 2024/02/01.

Nephrologist was consulted for hypercalcemia on 2024/02/02.



檢驗項目	檢驗報告	單位
PTH-intact	4.1	pg/mL

檢驗項目	檢驗報告	單位
25-(OH)D3	32.4	ng/mL

檢驗項目	檢驗報告	單位
Na	131	mmol/L
K	4.1	mmol/L
Ca	2.68	mmol/L
I P	1.6	mg/dL
Mg	1.8	mg/dL

Zoledronic A.

Hydration.
Furosemide.

1130223	1130219	1130216	1130214	1130207	1130205	1130203	1130201
2.47	2.67	2.80	2.93	2.56	2.51	2.68	3.08

Pathology: high grade infiltrating urothelial carcinoma

Feature	Humoral Hypercalcemia			Local Osteolytic Hypercalcemia	
Mediator	PTHrP	1,25 dihydroxy-vitamin D	Parathyroid hormone	TNF, interleukin-6, interleukin-1, macrophage inhibitory protein, and others	PTHrP, TNF, interleukin-6, interleukin-1, and others
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Bone metastases, tumor in bone	None or few	None or few	None or few	Extensive	Extensive
Parathyroid hormone	Low	Low	High	Low	Low
PTHrP	High or normal	Low	Low	Low	Variable
1,25-dihydroxyvitamin D	Variable	High	High	Variable	Low
Phosphorus	Low	High	Low	Variable	Variable
Osteoclast activity	High	High	High	High	High

Head & Neck
Prostate

Prostate

Breast PE.
Neck LNs.

B symptoms.
LNs.

Thyroid PE.
Ovarian PE.

CXR
Mammography
Renal ultrasound
H&N CT(C+)
PSA

Thyroid ultrasound
GYN untrasound

Serum and Urine
PEP/IFE.