



**Brigham and Women's Hospital**  
Founding Member, Mass General Brigham

# Calcium Cases

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# J. Carl Pallais, MD, MPH

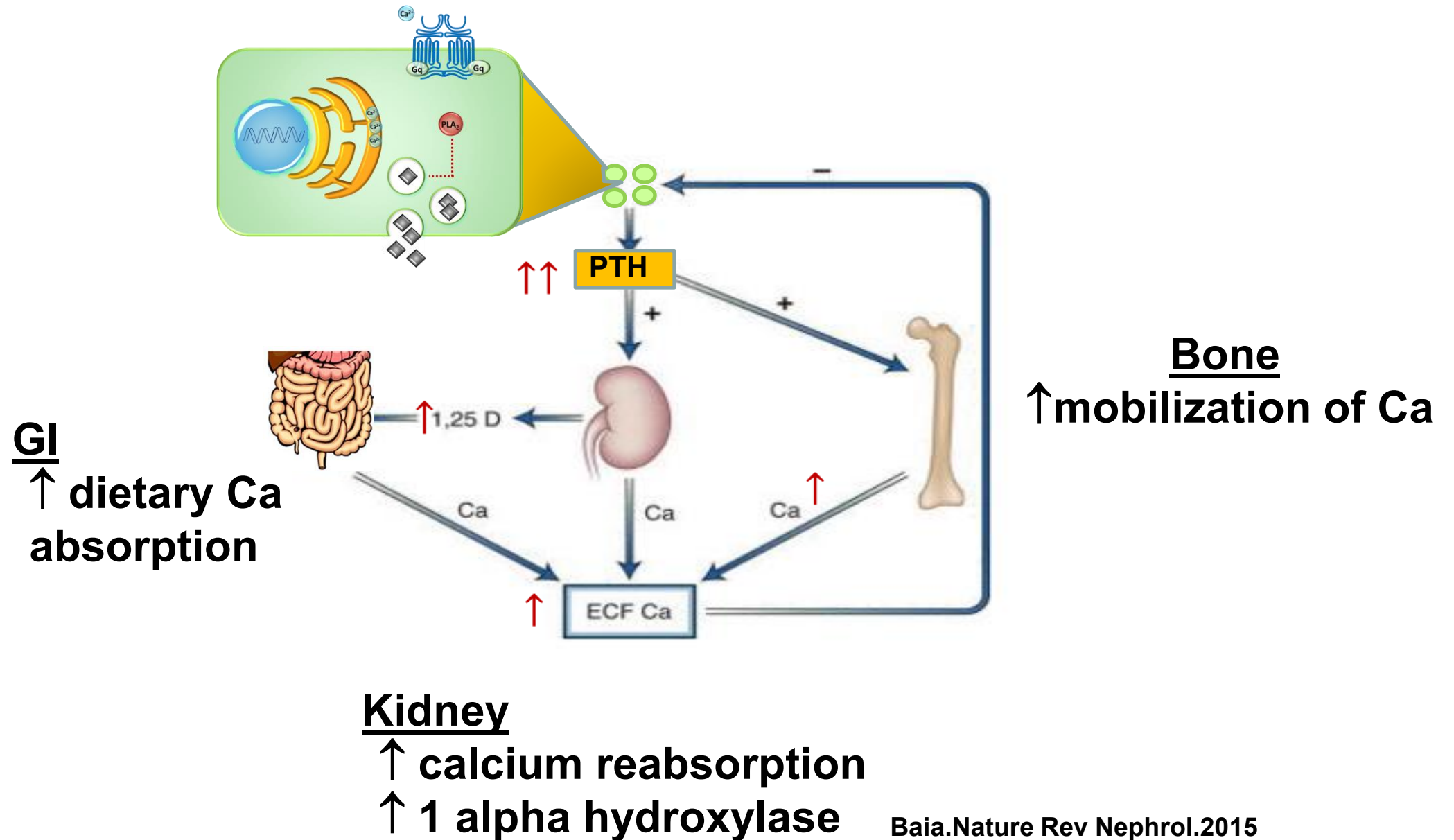


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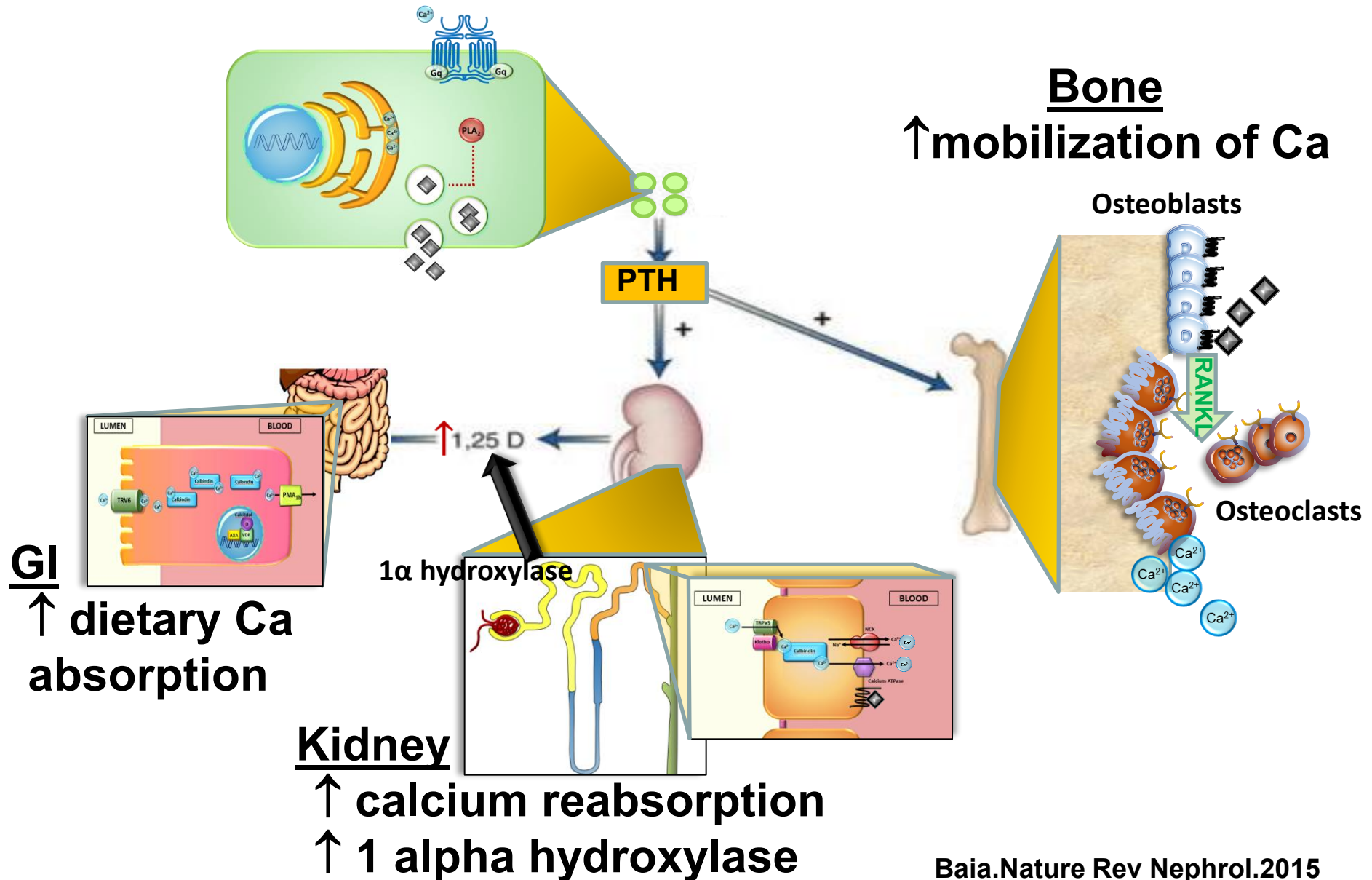
# Disclosures

- **UpToDate**
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- **Alexion Pharmaceuticals**
  - Site PI for Global Hypophosphatasia Registry
- **Alesta Therapeutics**
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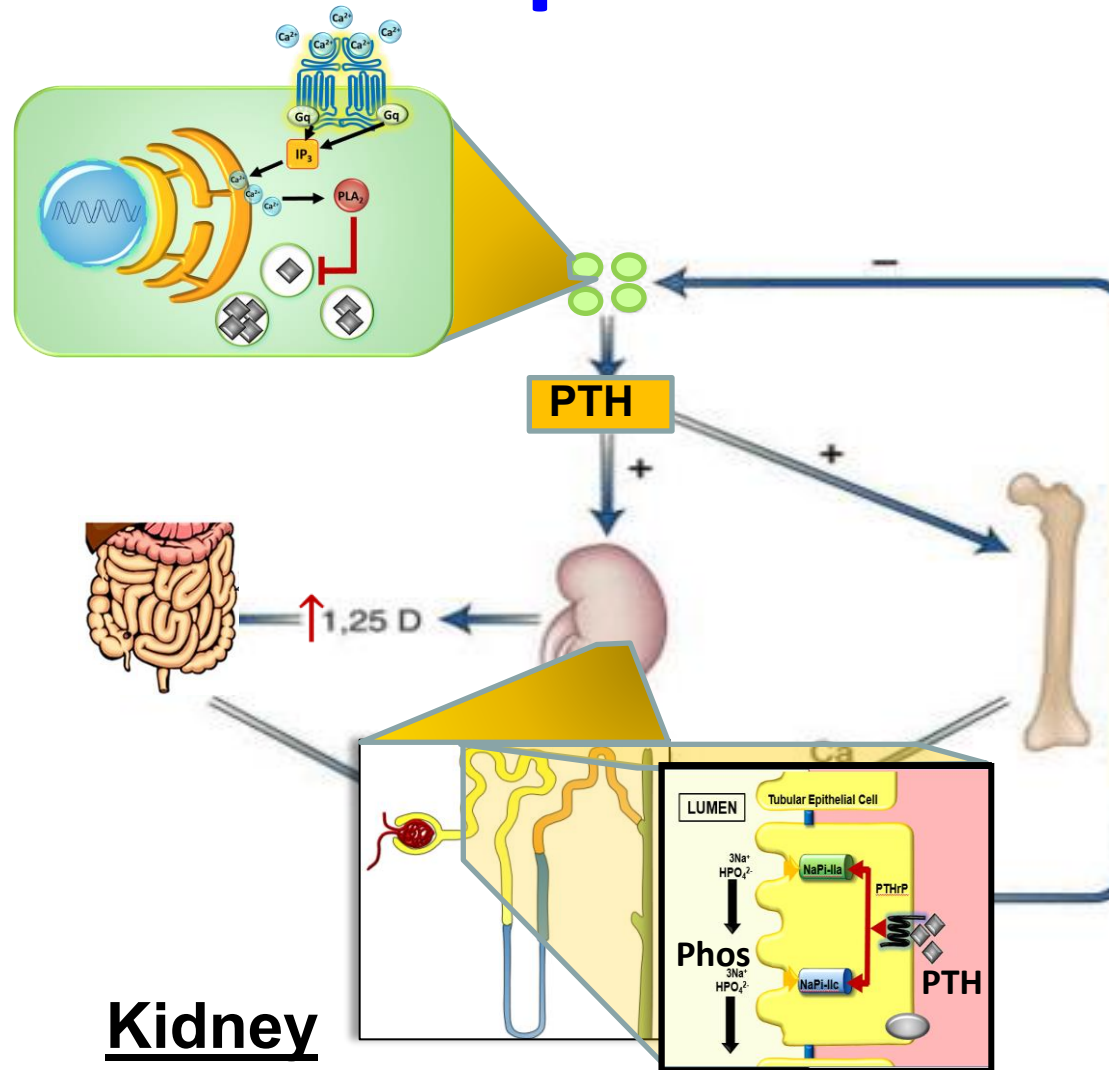
# Calcium Homeostasis



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# Calcium & Phosphate Homeostasis

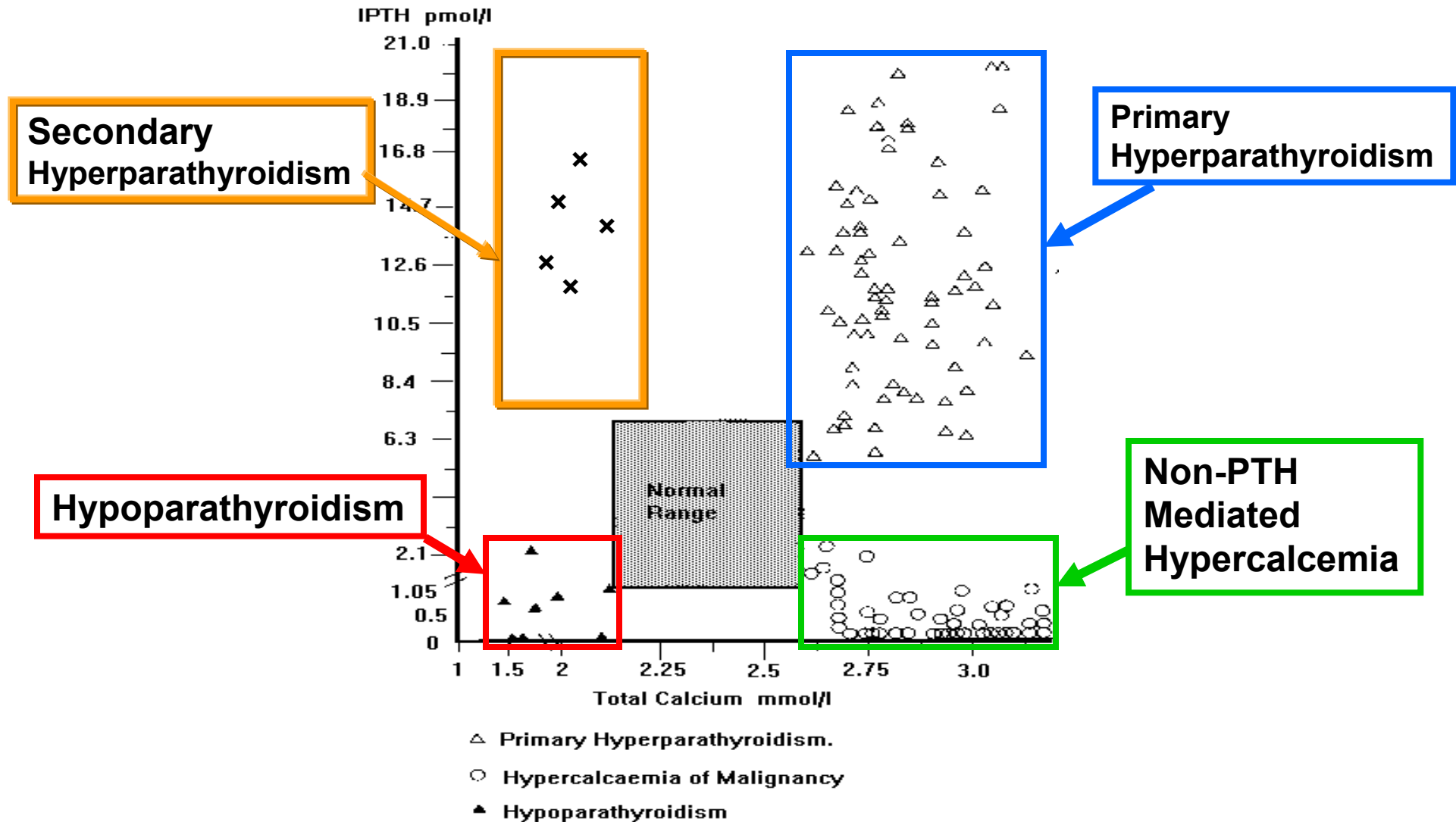


**Kidney**

**PTH decreases serum Phos**

**↑ Urinary Phos excretion**

# Serum Calcium-PTH Nomogram



# Case 1

- A 65-year-old woman with HTN and Stage 3 CKD has hypercalcemia: serum Ca 10.6 – 11.0 mg/dL (ref 8.2 – 10.2 mg/dL).
- Serum intact PTH = 90 pg/mL (ref 10 – 65 pg/mL);
  - Repeat is 98 pg/mL.
- Serum creatinine = 1.4 mg/dL (ref 0.7 – 1.1 mg/dL).
- eGFR = 39 ml/min per 1.73 m<sup>2</sup> (ref > 60 ml/min).
- 25-hydroxy-vitamin D = 30 ng/mL (ref 25- 50 ng/mL).
- Urinary calcium = 188 mg/24 hrs (ref 100 – 300 mg/24 hrs).



# Additional Data

- Meds: lisinopril
- DXA (including 1/3 distal radius) shows lowest T-score is -2.6 at the **distal radius**.
- No symptoms, fractures, or history of kidney stones.
- Neck ultrasound → negative.
- Sestamibi parathyroid scan → “non-localizing.”

# **POLLING: Which of the Following is the Best Next Step?**

- A. Treat with cinacalcet**
- B. Send for 4-gland parathyroid exploration**
- C. Measure serum 1,25-dihydroxy-vitamin D**
- D. Repeat serum calcium and PTH in 6 months**

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# Teaching Points

- A. Cinacalcet
- B. 4-Gland parathyroid surgery**
- C. 1,25(OH)2-Vit D
- D. Repeat Ca/PTH in 6 mos

- A. Cinacalcet can normalize calcium levels but does not prevent bone loss.
- B. This patient meets criteria for surgery for PHPT due to low eGFR and osteoporosis. Without pre-op localization, 4-gland parathyroid exploration is necessary.**
- C. Measurement of 1,25-dihydroxy-vitamin D is not part of the evaluation of PHPT.
- D. Repeating calcium and PTH in 6 - 12 months is not appropriate because of the synergistic effects of CKD and PHPT on accelerating bone loss can worsen osteoporosis.

# Evaluation of Asymptomatic PHPT

- Check Ca, phos, alk phos, BUN, Cr, intact PTH, 25(OH)-vitamin D levels
- 24 hr urine for Ca, Cr, CCCR
- BMD by DXA (spine, hip, 1/3 distal radius)

- Vertebral spine imaging: Xray, VFA
- Stone risk assessment (pending 24-hr urine if > 250 mg Ca in women or > 300 mg Ca in men)
- Abdominal imaging

# Surgical Criteria for Asymptomatic PHPT

- Age < 50 years
- Serum Ca > 1 mg/dL above normal
- CrCl < 60 cc/min
- DXA: T-score of -2.5 or lower at spine, hip, or 1/3 distal radius

- Vertebral fracture on imaging
- High kidney stone risk (> 250 mg Ca in women/> 300 mg Ca in men and increased risk on comprehensive urine analysis)
- Nephrolithiasis/calcinosis on imaging

# Surgical Criteria for Asymptomatic PHPT

- Serum Ca > 1 mg/dL above normal
- **DXA: T-score of -2.5 or lower** at spine, hip, or **1/3 distal radius**
- **CrCl < 60 cc/min**
- **Age < 50 years**

Due to low eGFR and osteoporosis at the wrist , our patient needs parathyroid surgery. Without + localization, the only approach is 4-gland parathyroid exploration.

# Medical Management of PHPT

- Antiresorptive therapy for osteoporosis: bisphosphonates; denosumab; (ERT; SERMs).
- Cinacalcet (Sensipar) for **symptomatic** hypercalcemia but will **not** improve osteoporosis.
- Maintain calcium intake (800-1000 mg/d) and vitamin D3 (to > 30 ng/ml).



# Differential Diagnosis of Primary Hyperparathyroidism

- Sporadic (> 90%)
- Drugs (lithium, thiazides)
- Genetic forms (~10%)
  - MEN 1, 2, & 4
  - Hyperparathyroidism jaw tumor syndrome
  - Familial isolated HPT
  - Familial hypocalciuric hypercalcemia (FHH)

## Case 2

A 64 yo F has a DXA after falling and breaking her right humerus.

- DXA: T-score -2.4 at LS, **-2.7 at FN, -2.5 at TH.**
- Labs reveal: normal total and ionized calcium levels with high PTH levels of **75, 86, 82 pg/ml** (ref 10-65 pg/mL).
- Serum creatinine, eGFR, 25(OH)-vitamin D, phosphate, and 24 hour urine Ca excretion are normal.
- She is on no medications and feels well.

## **POLLING: What is the Most Likely Diagnosis?**

- A. Secondary hyperparathyroidism**
- B. Normocalcemic primary hyperparathyroidism**
- C. Renal leak hypercalciuria**
- D. Occult malabsorption**

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# Teaching Points

- A. Secondary hyperparathyroidism
- B. Normocalcemic hyperparathyroidism
- C. Renal leak hypercalciuria
- D. Malabsorption

- Normocalcemic PHPTHism = persistently normal albumin-adjusted total serum Ca and ionized Ca with **elevated PTH x 2 over 3-6 mo.**
- Must exclude:
  - **CKD** (eGFR < 60 ml/min)
  - **Drugs**: thiazides, lithium, bisphosphonates, denosumab
  - **Malabsorption** (eg. celiac → hypocalciuria)
  - **Vitamin D deficiency** (aim for 30 ng/ml [75 nmol/L] or greater)
  - **Low calcium intake**
  - **Hypercalciuria**

# **POLLING: What Would Be Your Best Next Step?**

- A. Parathyroid imaging studies**
- B. Cinacalcet**
- C. Calcitriol**
- D. Recheck serum Ca and PTH in 6-12 months**

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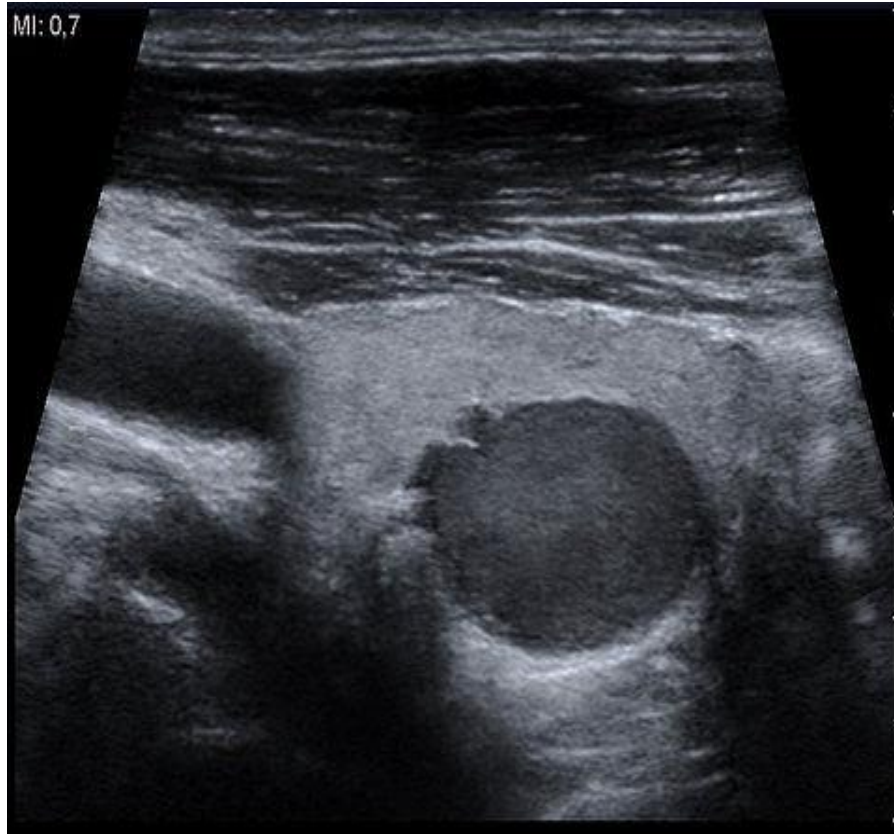
# Teaching Points

- A. Parathyroid imaging studies
- B. Cinacalcet
- C. Calcitriol
- D. Recheck serum Ca/PTH in 1 yr

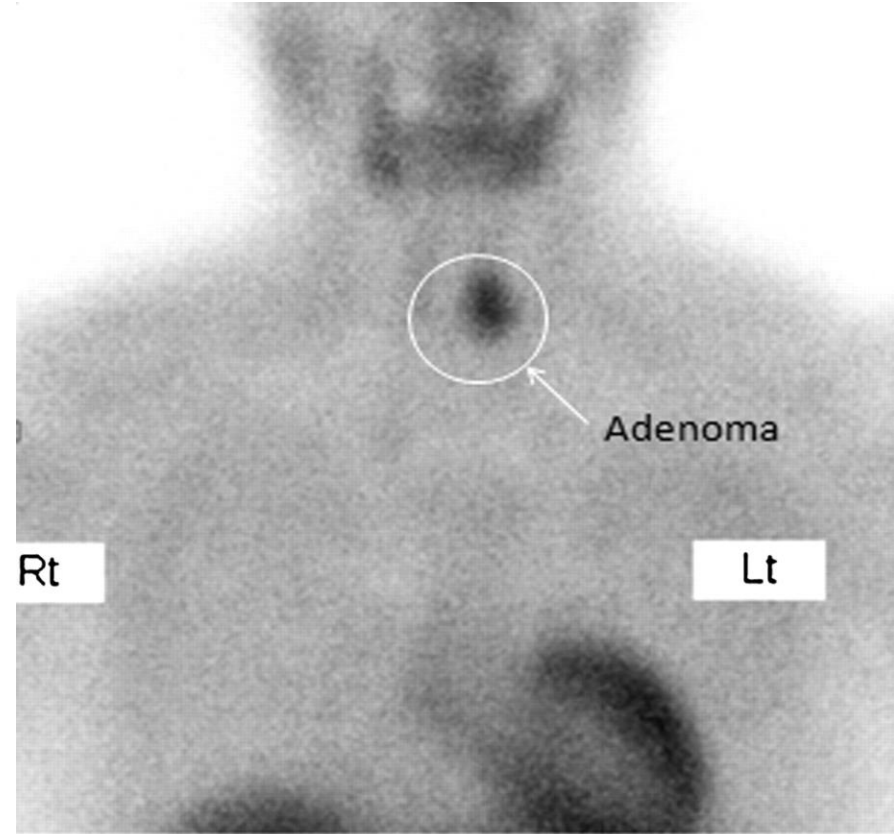
- A. Patients with osteoporosis, fractures, or stone disease are surgical candidates. **Parathyroid imaging is the best next step prior to surgical intervention to allow minimally invasive parathyroidectomy.**
- B. Cinacalcet lowers PTH but does not improve BMD or lower fracture risk.
- C. Calcitriol will lower PTH and potentially increase serum Ca but is not a definitive therapy for her osteoporosis nor for the normocalcemic PHPTism.
- D. Because of limited data, **no specific guideline exist** to guide the management of normocalcemic primary hyperparathyroidism. Monitoring levels **while treating osteoporosis** may be reasonable.



# Preoperative Imaging to Localize Parathyroid Adenoma(s)



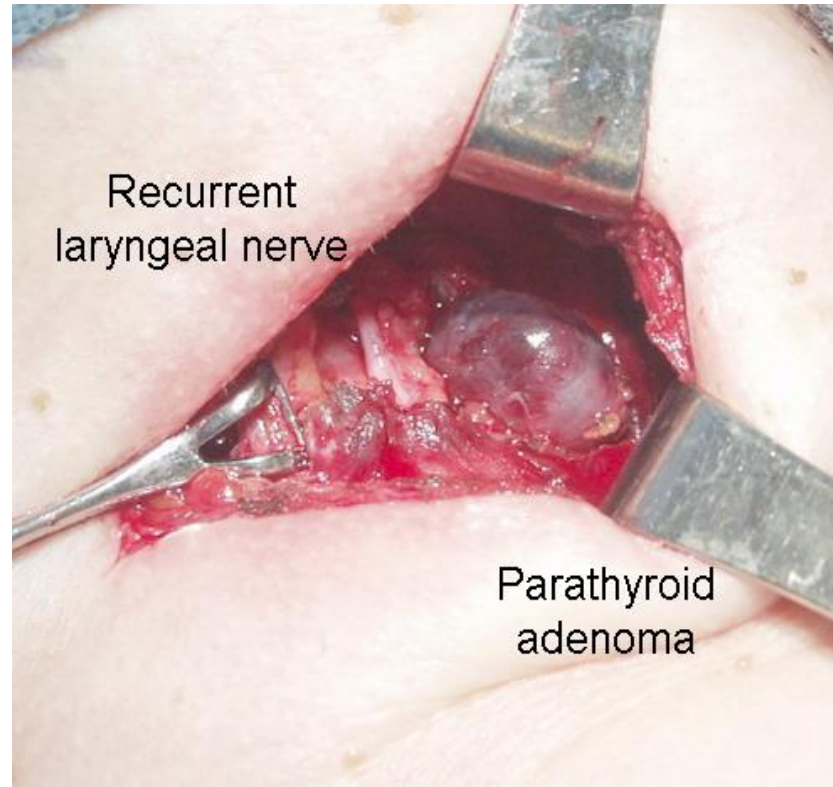
Ultrasound



Sestamibi Scan

# Sporadic PHPT (>90%): Surgical Findings

- 80-85% solitary adenoma
- 10-15% 4-gland hyperplasia
- 2-4% multiple adenomas
- <0.5% parathyroid carcinoma

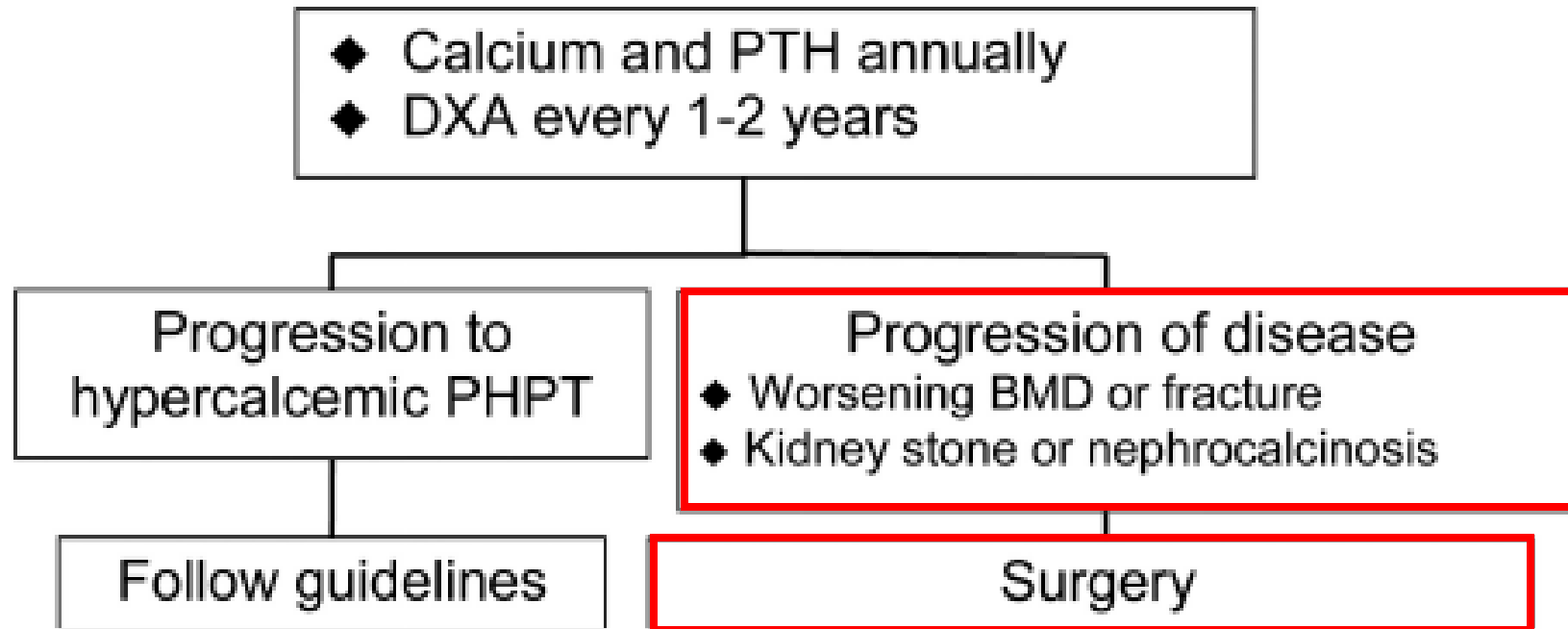


# Comparing Normocalcemic PHPT vs “Classic” Hypercalcemic PHPT

- The sensitivity of all localization studies is lower in normocalcemic disease compared to classic PHPT.
- At surgery, multigland involvement is more common in normocalcemic disease compared to classic PHPT.
- Surgery in normocalcemic PHPT patients may result in improvements in BMD, similar to classic PHPT, but improvements in nephrolithiasis vary.

Cusano NE et al. 2018. Best Pract Res Clin Endocrinol Metab 32:837;  
Bilizekian JP et al. 2022. J Bone Miner Res. 37:2293  
Liu et al. 2025. J Clin Endocrinol Metab. 110:e868.

# Monitoring Patients with “Normocalcemic PHPT”



## Question 3

A 45-year-old man is admitted with altered mental status after 72 hours of N/V, and epigastric pain.

- While on vacation, he drank a lot of alcohol, then developed severe abdominal pain.
- PMH: peptic ulcer disease and GERD
- Meds: unknown
- In the ER, his total serum calcium is **16.2 mg/dl** (nl 8.7 – 10.4)
- PE: BP 140/100, he is lethargic and disoriented with epigastric tenderness; otherwise, negative.

# Labs

- Calcium **16.2 (↑↑)**
- Ionized Ca **1.75 (↑↑)**
- K<sup>+</sup> **3.1 (↓)**,
- HCO<sub>3</sub> **37 (↑)**
- Creatinine **2.0 (↑)**
- Intact PTH **< 10**
- 25OHD **28 ng/ml**
- 1,25(OH)<sub>2</sub>D **< 15**
- Amylase **1300 (↑)**
- Lipase **1800 (↑)**

**POLLING: In Addition to Analgesia, Vigorous IV Hydration, and Making the Patient NPO, What Else Would You Recommend?**

- A. Zoledronic acid 5 mg IV**
- B. Pamidronate 30 mg IV**
- C. Denosumab 120 mg SQ**
- D. Close monitoring**

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# Further history

- During several days prior to admission, he consumed multiple bottles of calcium carbonate and sodium bicarbonate due to abdominal pain from gastritis and pancreatitis.

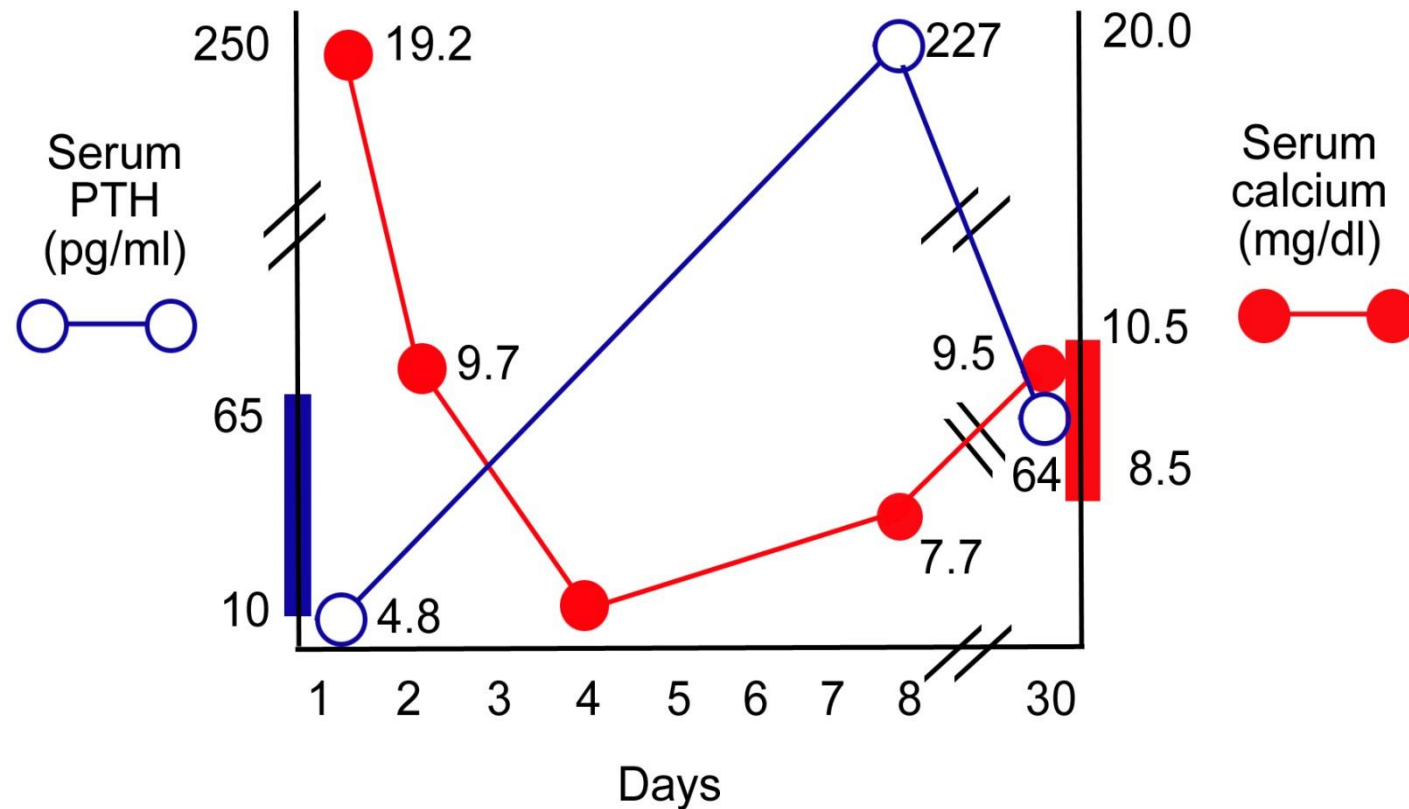


# Teaching Points

- A. Zoledronic acid
- B. Pamidronate
- C. Denosumab
- D. Close monitoring

- Classic triad of hypercalcemia, renal insufficiency, and metabolic alkalosis is the hallmark of calcium-alkali syndrome resulting from ingestion of large amounts of calcium and absorbable alkali.
- Intake of **10 – 15 gm calcium carbonate (>4 g of elemental calcium)** per day is often needed for the syndrome.
- Treatment: stop Ca and bicarb, give IV hydration → rapid resolution of hypercalcemia.

# Typical Response of Ca and PTH in Calcium-Alkali Syndrome



# Differential Diagnosis of Non-PTH-Mediated Hypercalcemia

## ABSORPTIVE

- Excess exogenous vitamin D\*
  - Vitamin D intoxication
- Excess endogenous vitamin D\*
  - Granulomatous
  - Neoplasms (lymphomas, renal cell carcinoma)
- Excess calcium
  - Calcium/milk-alkali syndrome

## RESORPTIVE

- Malignant osteolytic bone disease
  - PTHrP-mediated
    - Squamous cell CA
    - Renal cell CA
  - Local metastases
    - Breast CA
    - Multiple myeloma
- Immobilization (Paget's)
- Hyperthyroidism
- Excess vitamin A

\* Involves excess resorption also

# Work-up for Non-PTH Mediated Hypercalcemia

## HISTORY AND PHYSICAL EXAM ARE KEY!

- SPEP, UPEP
- 25(OH) vitamin D
- 1,25(OH)<sub>2</sub> vitamin D
- PTHrP
- Cortisol
- Vitamin A (if indicated)
- CXR
- Bone scan
- Mammography
- CT scan of chest, abdomen, pelvis
- Lymph node or tissue biopsy

## Question 4

- A 76-year-old woman with chronic kidney disease slips on ice and fractures her right hip.
- DXA shows generalized osteoporosis.
- Pertinent labs include:
  - ✓ Serum Ca 8.6 mg/dL (ref 8.2 – 10.2 mg/dL)
  - ✓ Albumin 4.0 g/dL (normal)
  - ✓ Creatinine **3.8 mg/dL** (0.6 – 1.5 mg/dL)
  - ✓ 25-hydroxy-vitamin D 32 ng/mL (normal)
- One month after surgical repair of the hip fracture, you treat her with denosumab 60 mg SQ.

**POLLING: Which of the Following is the Most Likely Adverse Effect of This Therapy?**

- A. Symptomatic hypocalcemia**
- B. Decline in renal function**
- C. Osteonecrosis of the jaw**
- D. Impaired fracture healing**

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# Teaching Points

- A. Symptomatic hypocalcemia
- B. Decline in renal function
- C. Osteonecrosis of the jaw
- D. Impaired fracture healing

- Symptomatic hypocalcemia may occur in patients receiving potent antiresorptive agents (eg. zoledronic acid and denosumab) when there are certain **preconditions**:
  - Profound vitamin D and/or Ca deficiency
  - Hypoparathyroidism
  - **Renal insufficiency**
- Check serum Ca 7-10 days post-denosumab
- To prevent: Treat with calcitriol and extra calcium for 2-4 weeks post-denosumab to help prevent hypocalcemia in CKD (no guidelines!)

# Neuromuscular Signs and Symptoms of Hypocalcemia

- Paresthesias of fingers, toes, circumoral
- Tetany, carpopedal spasm, muscle cramps
- Laryngospasm
- Bronchospasm
- Seizure
- Chvostek sign
- Trousseau's sign
- Prolonged QT
- Basal ganglia calcifications

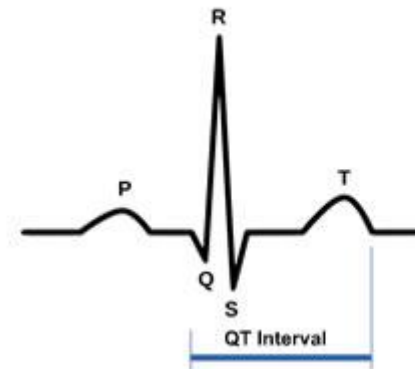
Chvostek sign



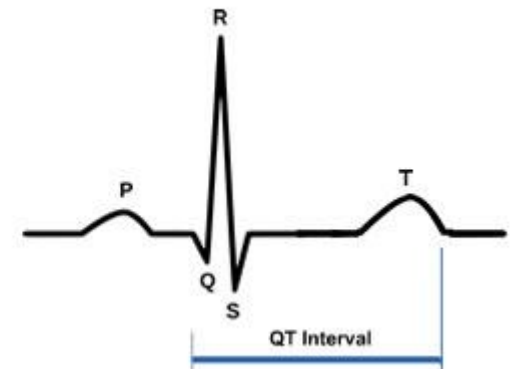
Trousseau's sign



Normal ECG



Long-QT



## Question 5

- A 60-year-old woman with T2DM and ESRD on hemodialysis for many years, presents with excruciatingly painful lesions on her shins.
- Labs: HgbA1C 9.5%, serum Ca 9.5 mg/mL (nl 8.2 – 10.2), Phos 6.1 mg/mL (nl 2.3 – 4.7), intact PTH 586 pg/mL (nl 10 – 65).
- PE: Obese with tender erythematous, necrotic lesions on both lower extremities.

# POLLING: What Is the Most Likely Diagnosis?

- A. Pyoderma gangrenosum
- B. Erythema nodosum
- C. Necrobiosis lipoidica
- D. Calciphylaxis



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# Teaching Points

- A. Pyoderma gangrenosum
- B. Erythema nodosum
- C. Necrobiosis lipoidica
- D. Calciophylaxis

- Calciophylaxis results from decreased arteriolar blood flow due to calcification, fibrosis, and thrombus formation in the arterioles of the skin.
- It is most commonly found in pts with ESRD associated with secondary HPTism, activated vitamin D treatment, hyperphosphatemia, and elevated Ca x Phos product.
- Diabetes, obesity, hypercoagulable states, glucocorticoid use, and connective tissue disorders are risk factors.
- Treatments (sodium thiosulfate; parathyroidectomy; hyperbaric oxygen; cinacalcet, and bisphosphonates) are not always effective.

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**THANK YOU!!!!**



# Calcium Homeostasis

