



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

Calcium Cases

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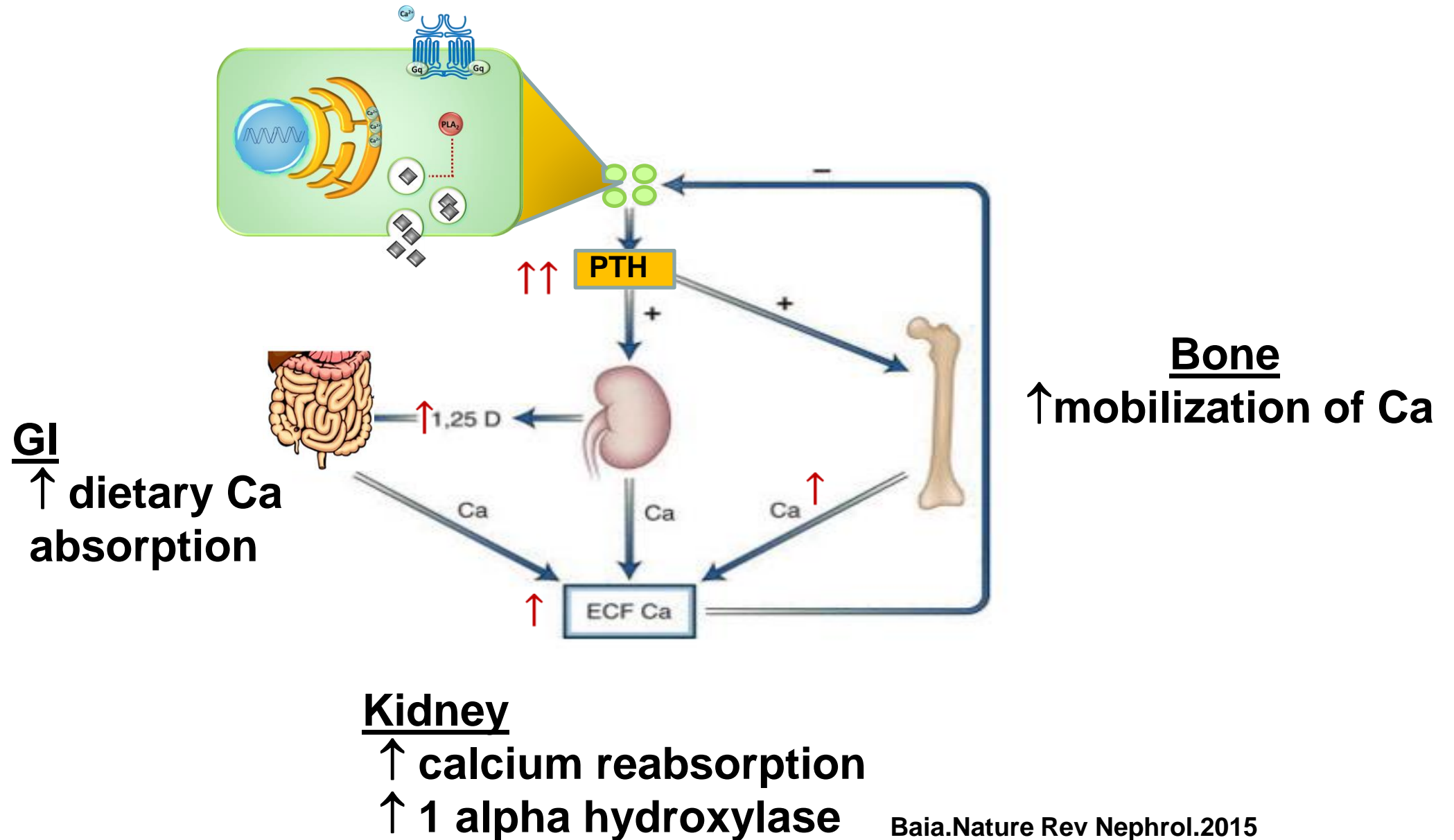


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- **Medicine Residency & Chief Resident at Massachusetts General Hospital**
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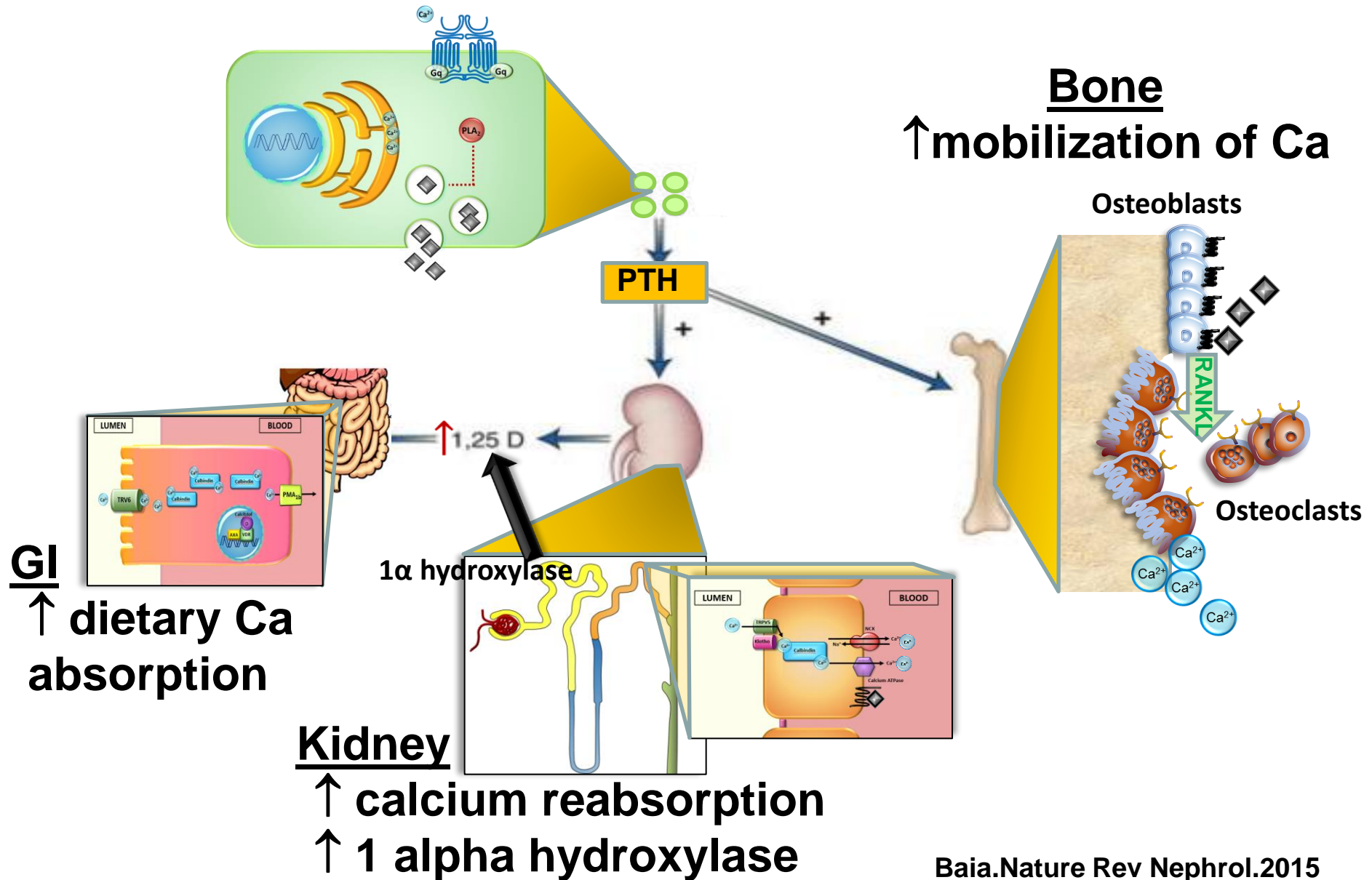
Disclosures

- **UpToDate**
 - Author
- **Alexion Pharmaceuticals –**
 - Site PI for Global Hypophosphatasia Registry
- **Ensho Health**
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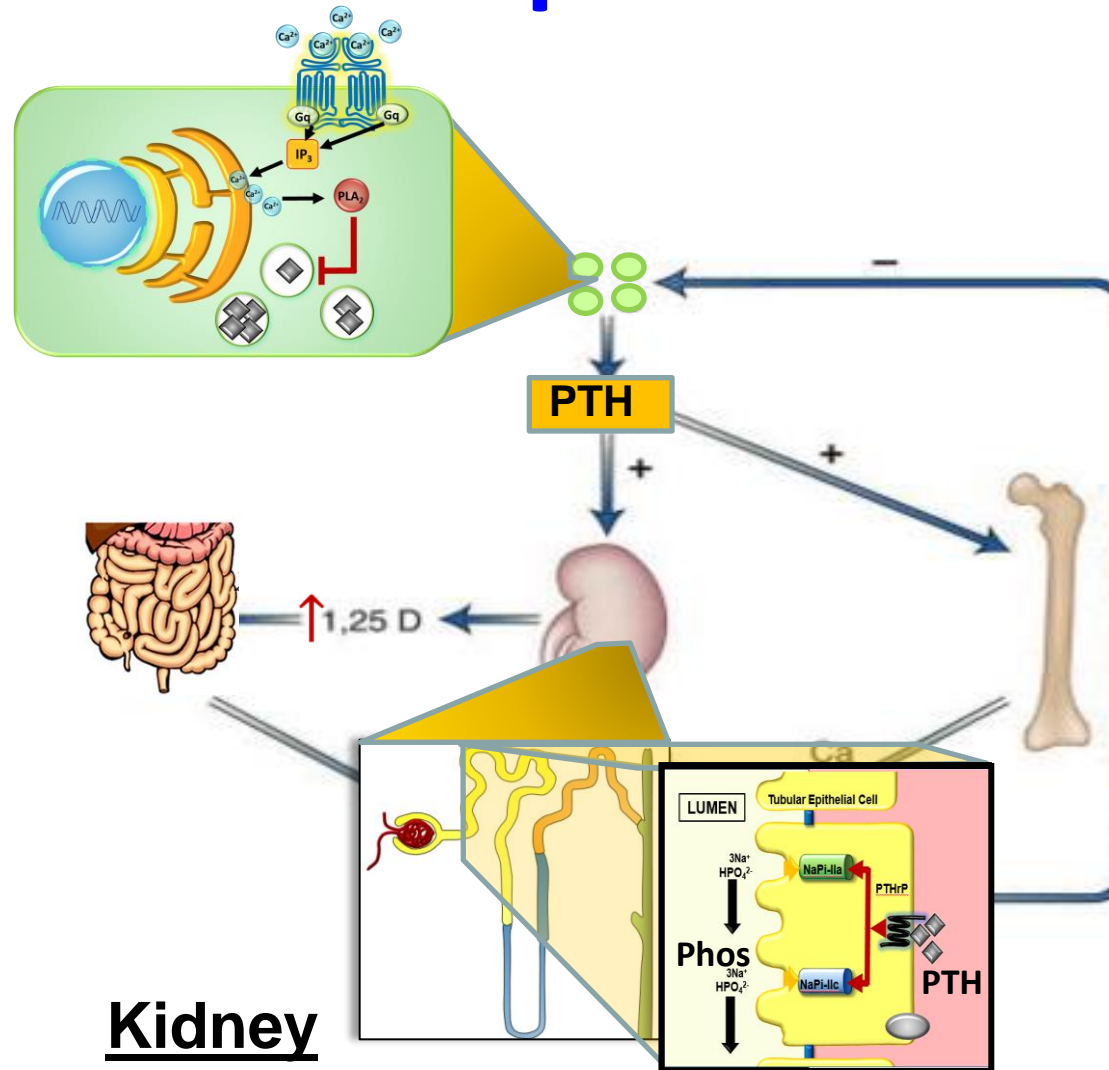
Calcium Homeostasis



Calcium Homeostasis



Calcium & Phosphate Homeostasis

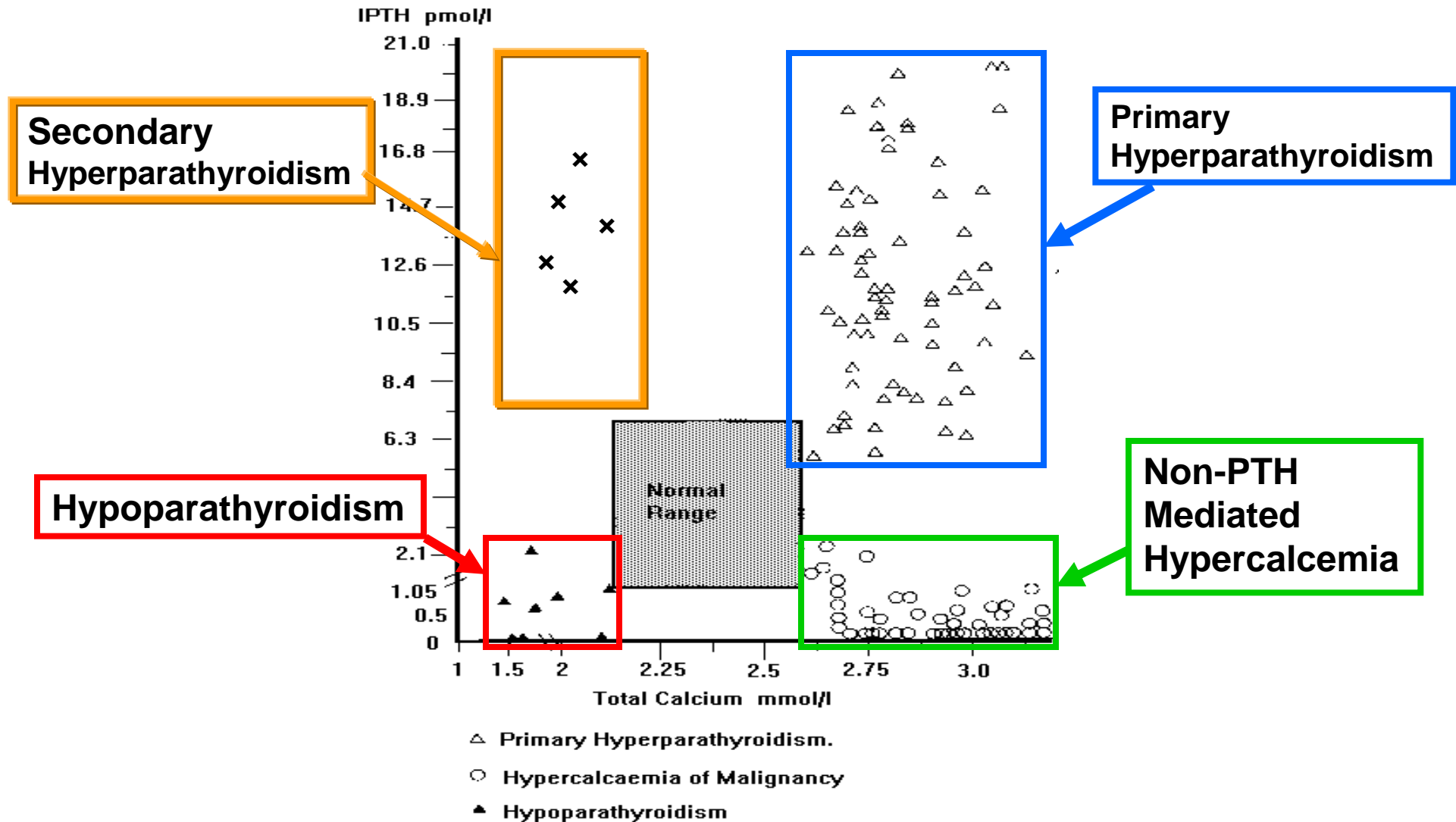


Kidney

PTH decreases serum Phos

\uparrow 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 m² (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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- D. Repeat serum calcium and PTH in 6 months**

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**

POLLING: What Would Be Your Best Next Step?

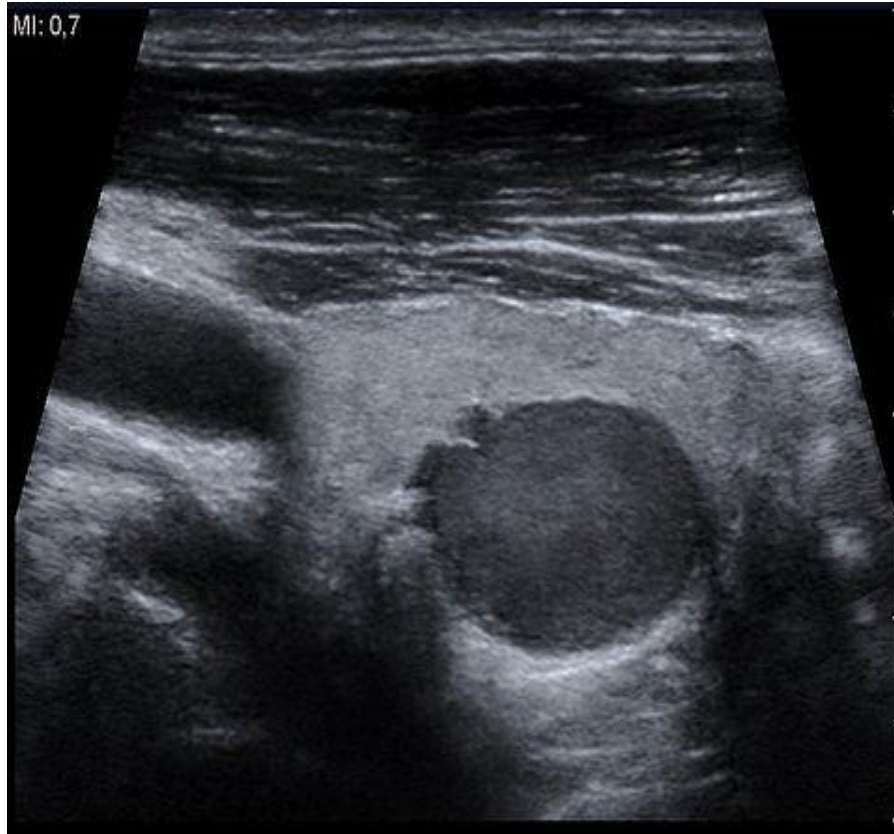
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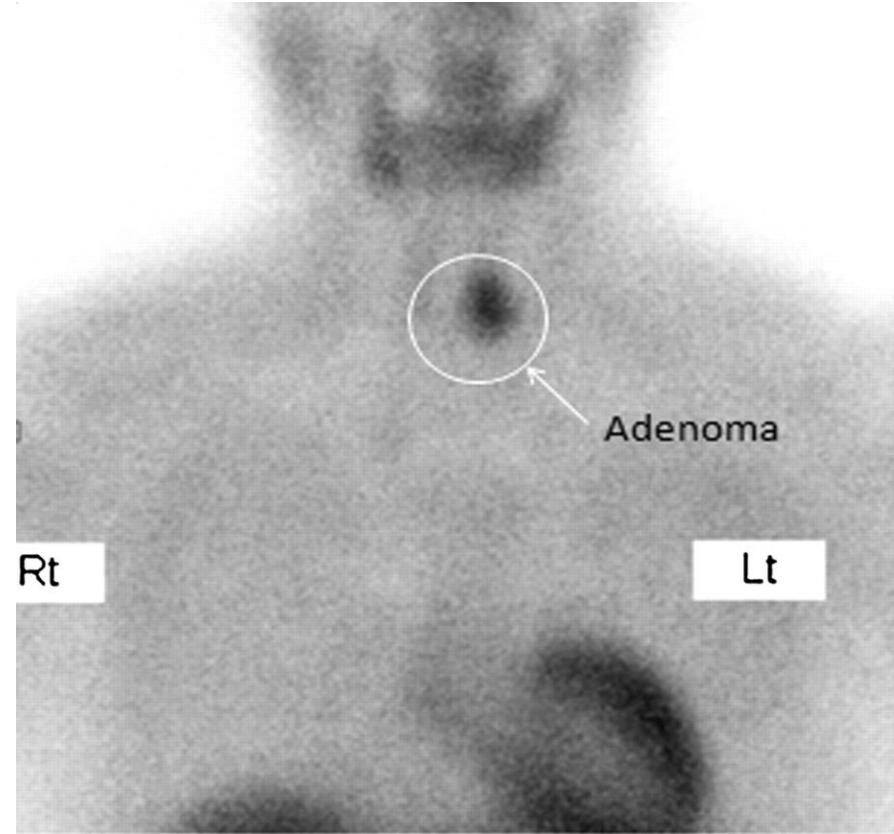
- A. Parathyroid imaging studies
- B. Cinacalcet
- C. Calcitriol
- D. Recheck serum Ca/PTH in 1 yr

- 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)



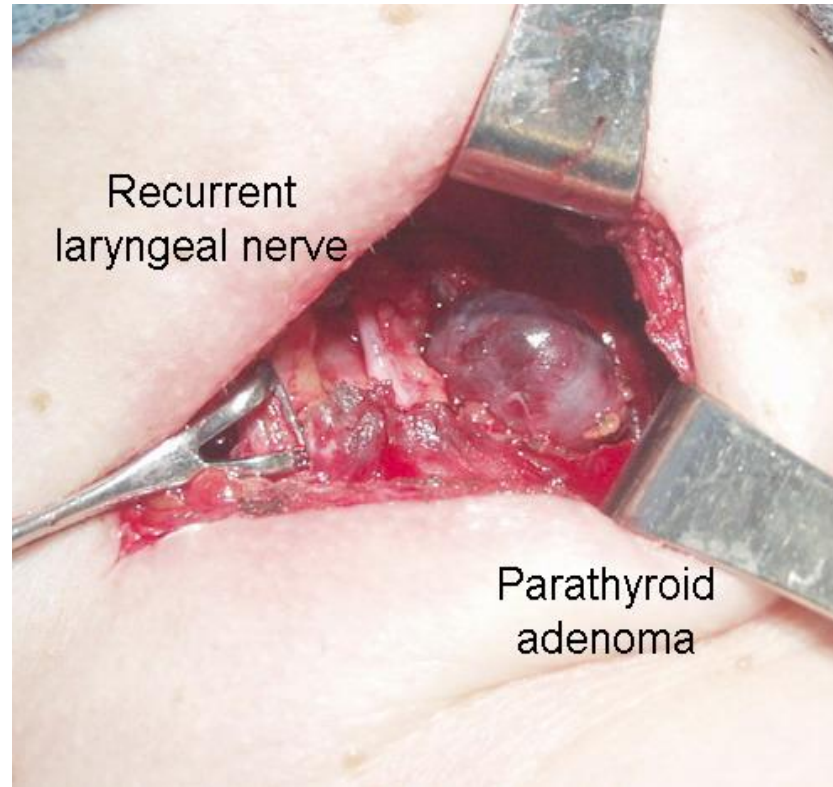
Ultrasound



Sestamibi Scan

Sporadic PHPT (>90%): Surgical Findings

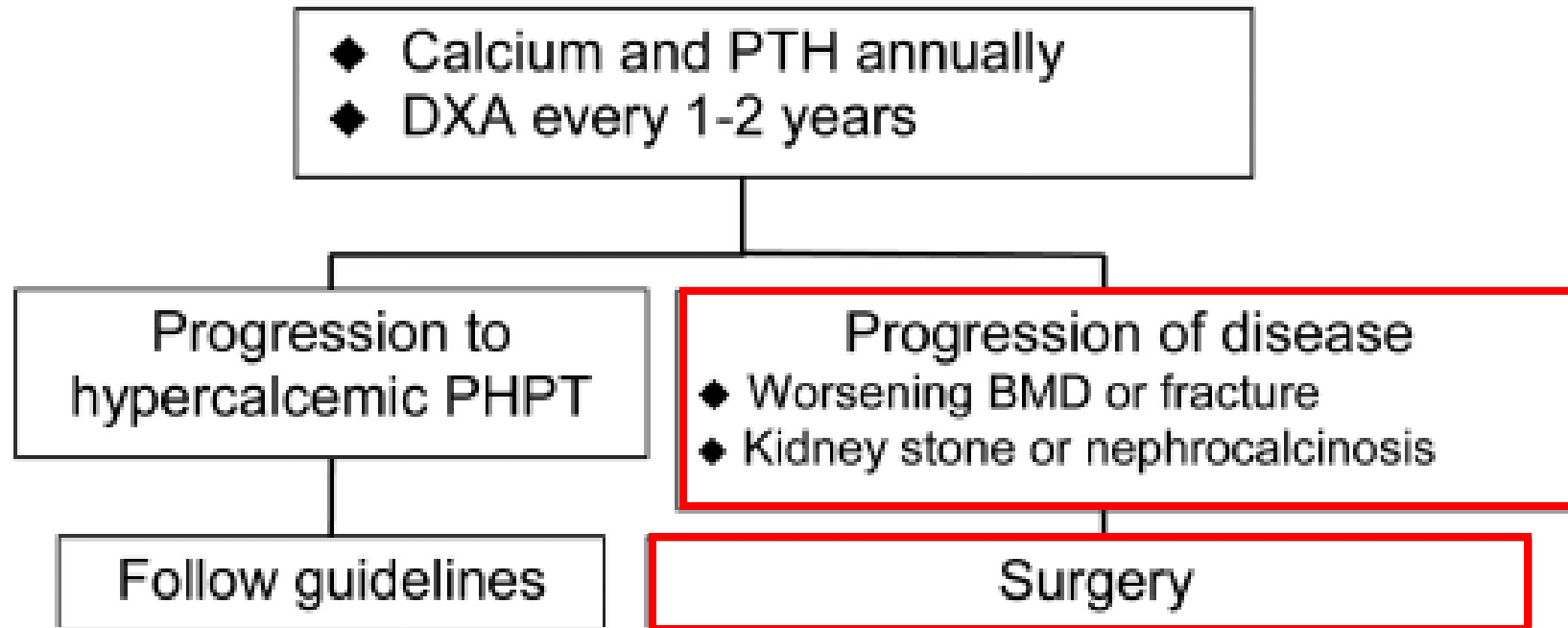
- 80-85% solitary adenoma
- 10-15% 4-gland hyperplasia
- 2-4% multiple adenomas
- <0.5% parathyroid carcinoma



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 and nephrolithiasis, similar to classic PHPT.

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⁺ **3.1 (↓)**,
- HCO₃ **37 (↑)**
- Creatinine **2.0 (↑)**
- Intact PTH **< 10**
- 25OHD **28 ng/ml**
- 1,25(OH)₂D **< 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.

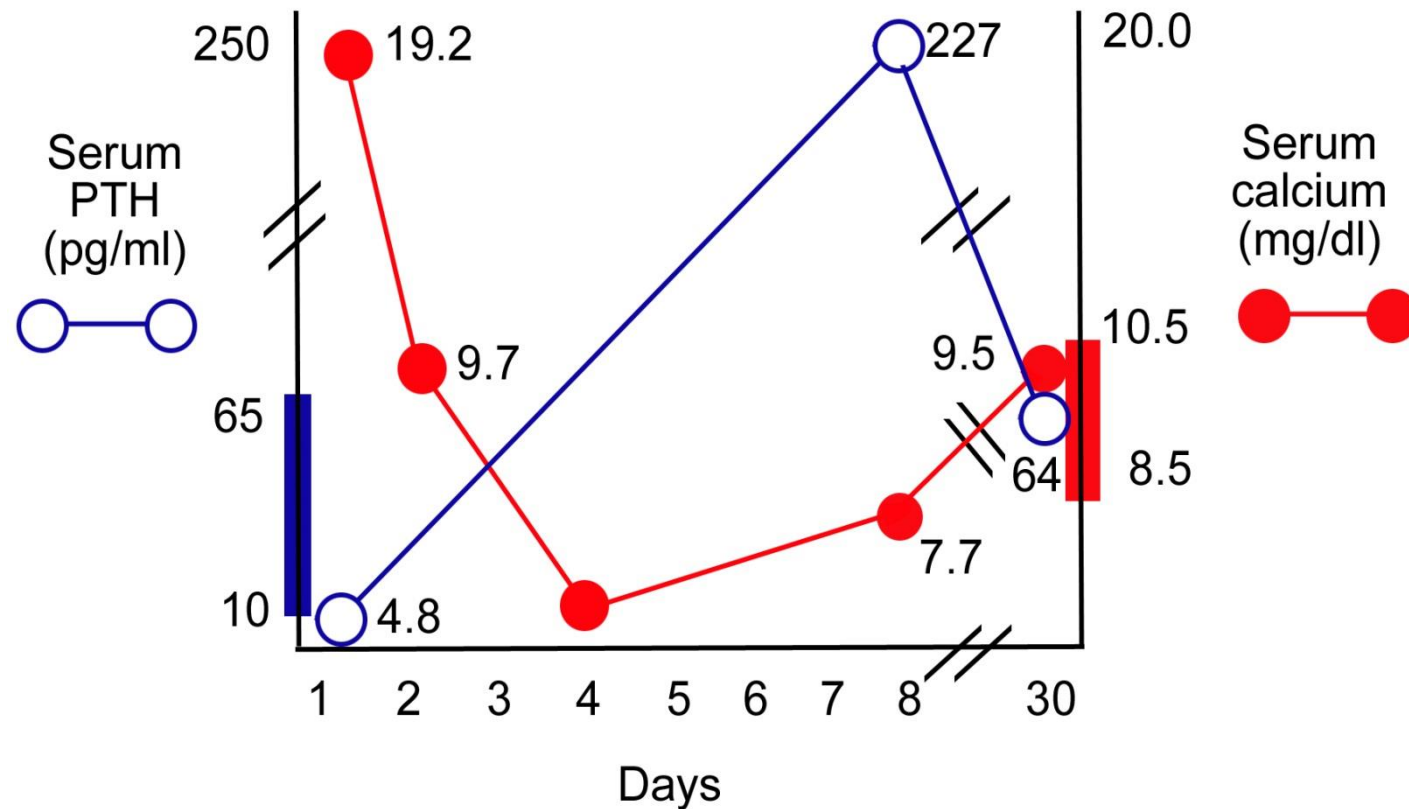


Teaching Points

- 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** 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)₂ 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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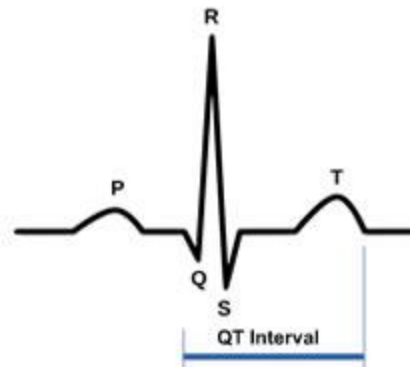
- Symptomatic hypocalcemia may occur in patients receiving potent antiresorptive agents (eg. zoledronic acid and denosumab) when there are certain **preconditions**:
 - Profound vitamin D and/or Ca deficiency
 - Hypoparathyroidism
 - **Renal insufficiency**
- Check serum Ca 7-10 days post-denosumab
- 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

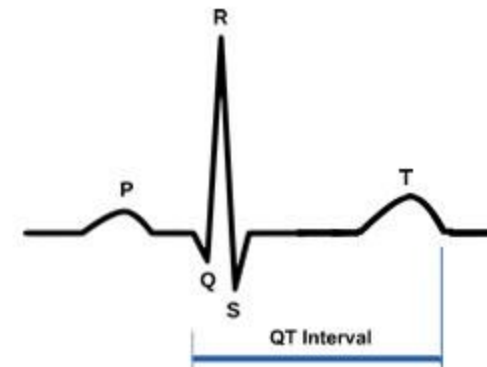
- Paresthesias of fingers, toes, circumoral
- Tetany, carpopedal spasm, muscle cramps
- Laryngospasm
- Bronchospasm
- Seizure
- Chvostek sign
- Trousseau's sign
- Prolonged QT
- Basal ganglia calcifications



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.

References

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THANK YOU!!!!

Calcium Homeostasis

