

# Update in Internal Medicine

May 3, 2025



**UT Southwestern**  
Medical Center

## **Hypercalcemia and Hypocalcemia**



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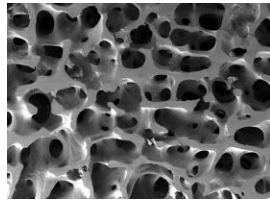
# Agenda



- Calcium Homeostasis
- Hypercalcemia
- Hypocalcemia

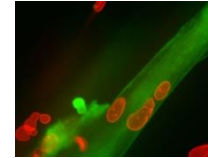
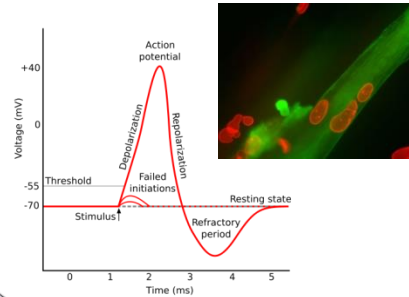
# Three pools of $\text{Ca}^{2+}$

Structural integrity

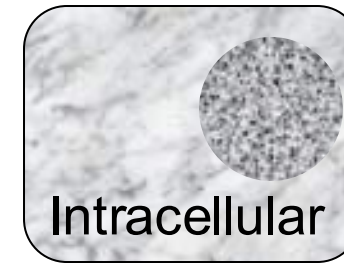
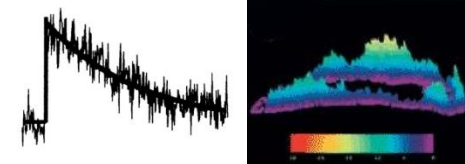


Bone

Excitability  
Coagulation  
Hormone



Cell signaling



Intracellular

Extracellular

$[\text{Ca}^{2+}]$

-

$10^{-3} \text{ M}$

$10^{-7} \text{ M}$

$\text{Ca}^{2+}$  content

$1.3 \times 10^6 \text{ mg}$

$\sim 3 \times 10^4 \text{ mmole}$

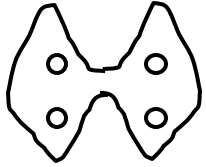
$10^3 \text{ mg}$

$\sim 25 \text{ mmole}$

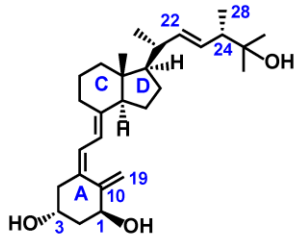
$< 0.1 \text{ mg}$

$< 0.0025 \text{ mmole}$

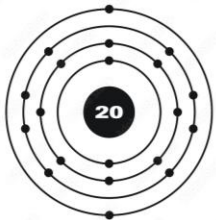
# Calcium Homeostasis



PTH

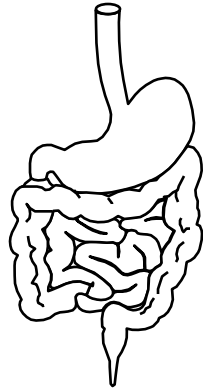


1,25(OH)<sub>2</sub>vitD



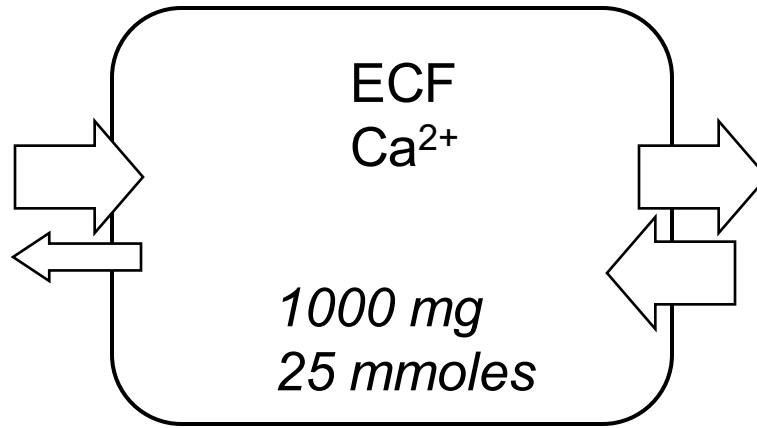
Ca<sup>2+</sup>

Ingest  
1000 mg  
25 mmoles

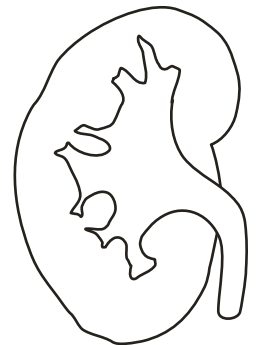


Net absorption  
200 mg  
5 mmoles

Stool  
800 mg  
20 mmoles



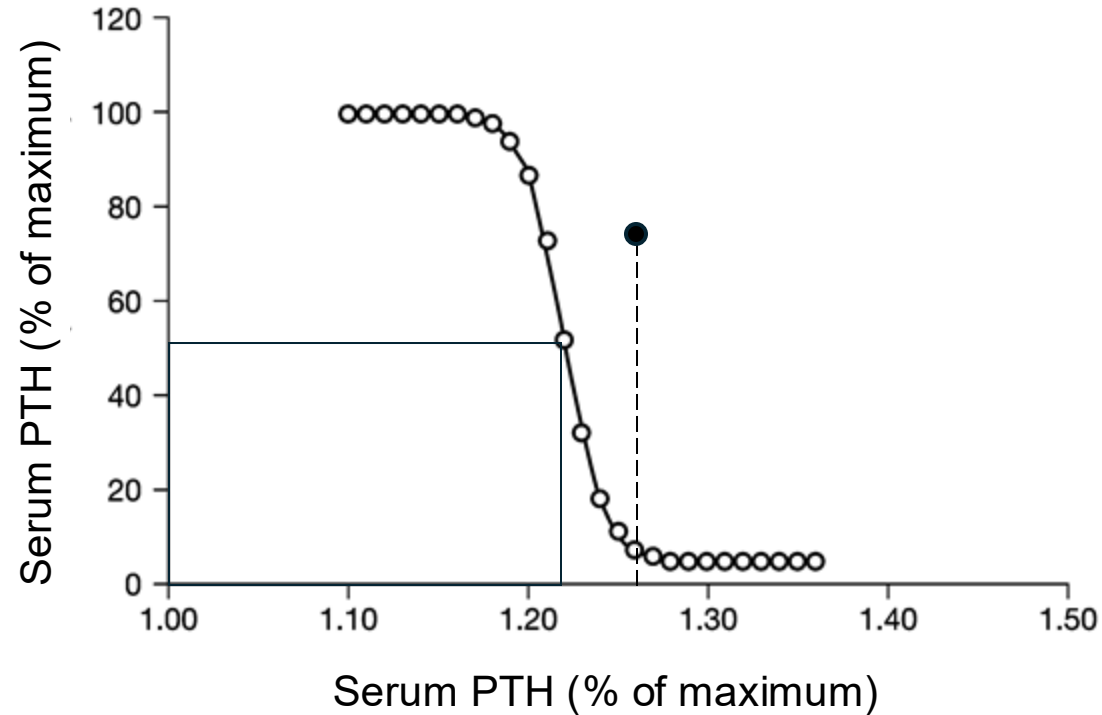
Bone turnover  
500 mg  
12.5 mmoles



Net excretion  
200 mg  
5 mmoles

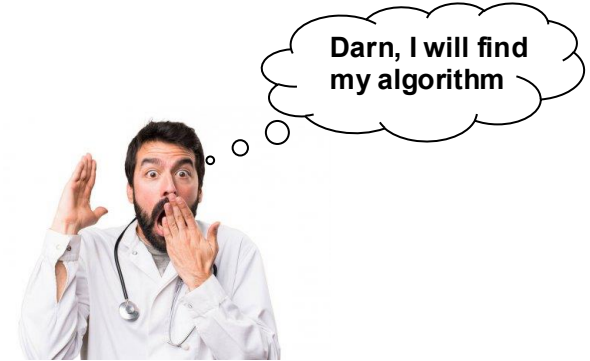
# Clinical Chemistry

## Laboratory parameter



Normal  
range

Report says "H"



I do not have to do anything

Report says "L"

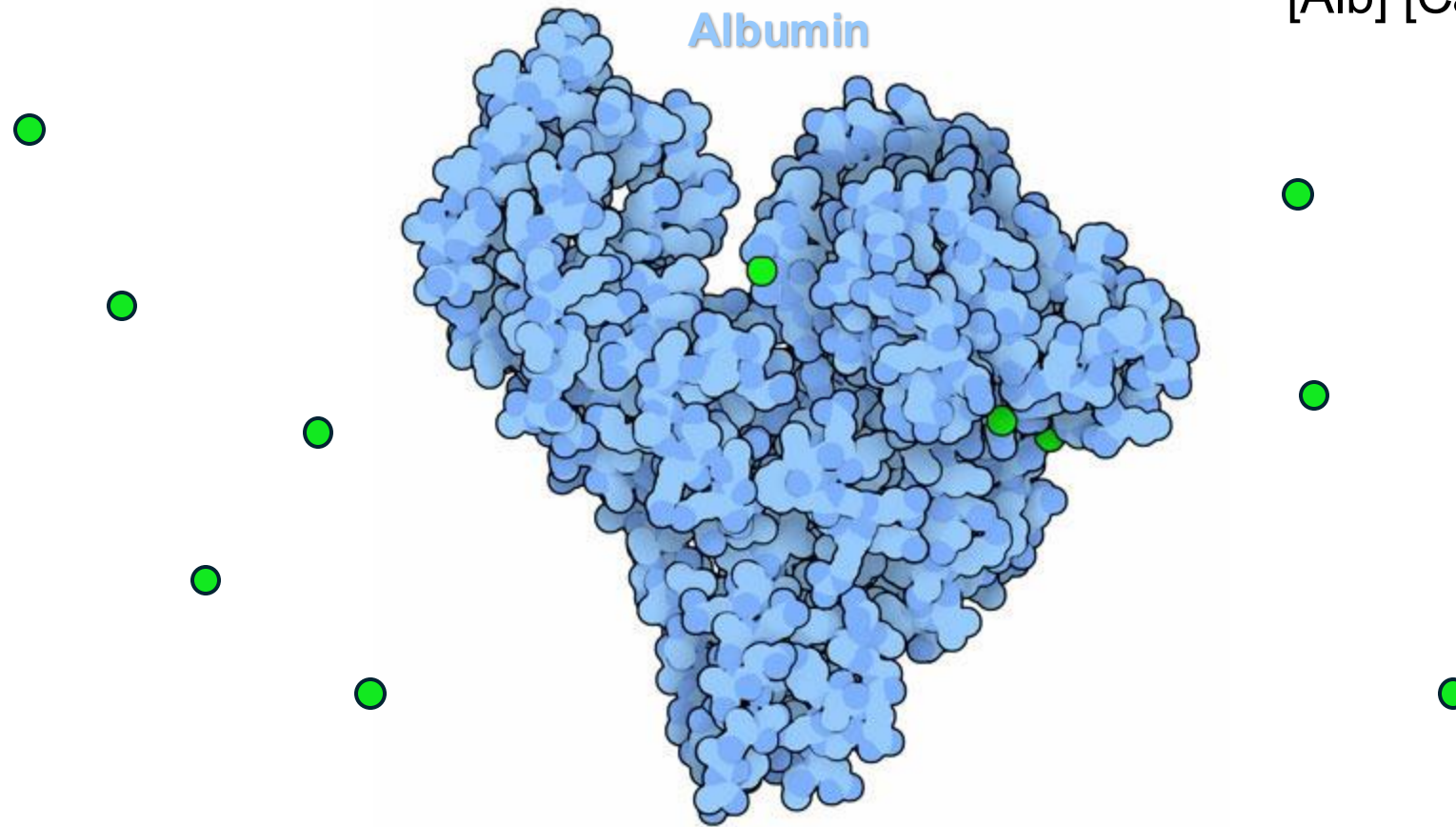


# Clinical Chemistry

12 ± 1 independent binding sites for  $\text{Ca}^{2+}$

$$K_{\text{Asso}} = \frac{[\text{Alb Ca}^{2+}]}{[\text{Alb}] [\text{Ca}^{2+}]}$$

90-100 litres/mole at 37 °C  
Unbuffered solutions  
pH 7.4  
Ionic strength 0.15–0.16.



# Clinical Chemistry

| Fraction         | mg/dl (mM)   | Percent of total (%) |
|------------------|--------------|----------------------|
| • Ionized        | 4.40         | 44                   |
| • Complexed      | 1.00         | 10                   |
| Total diffusible | 5.60         | 56                   |
| Protein-bound    | 4.60         | 46                   |
| <b>Total</b>     | <b>10.00</b> | <b>100</b>           |

## Fraction Excretion

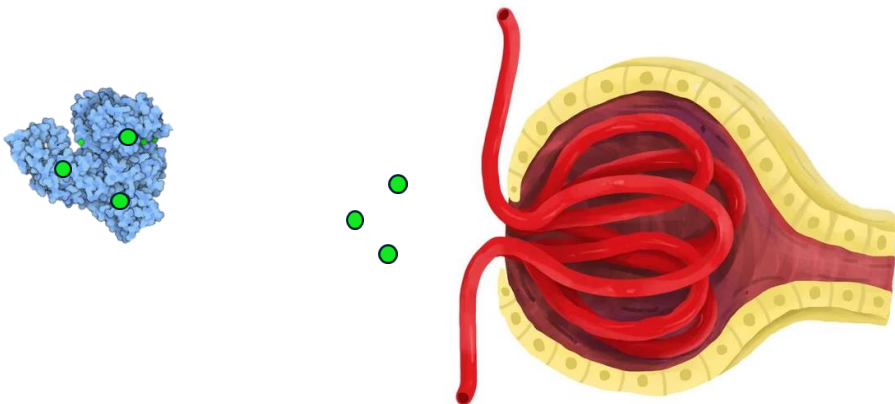
$$\frac{\text{Amount excreted}}{\text{Amount filtered}}$$

FENa

$$\frac{U_{\text{Na}} \cdot P_{\text{Cr}}}{P_{\text{Na}} \cdot U_{\text{Cr}}}$$

FECa

$$\frac{U_{\text{Ca}} \cdot P_{\text{Cr}}}{0.5 P_{\text{Ca}} \cdot U_{\text{Cr}}}$$



# Agenda



- Calcium Homeostasis
- Hypercalcemia
- Hypocalcemia



## Bone resorption

- A. Parathyroid hormone mediated
  1. Sporadic primary hyperparathyroidism
  2. Familial/inherited primary hyperparathyroidism
    - a. Multiple endocrine neoplasia
    - b. Familial isolated hyperparathyroidism
    - c. Hyperparathyroidism jaw-tumor syndrome
    - d. Familial hypocalciuric hypercalcemia (*CASR*, *GNA11*, *AP2S1* variants, etc)
    - e. Neonatal severe hyperparathyroidism (*CASR* variant)
  3. Parathyroid cancer
  4. Tertiary hyperparathyroidism
  5. Drugs—lithium
  6. Malignancy—ectopic parathyroid hormone production (rare)
- B. Non-parathyroid hormone mediated
  1. Malignancy
    - a. Humoral hypercalcemia of malignancy (parathyroid hormone-related protein)
    - b. Osteolytic metastases or myeloma
  2. Immobilization
  3. Vitamin A toxicity
  4. Hyperthyroidism
  5. Drugs—teriparatide, abaloparatide, rebound after denosumab discontinuation
  6. Jansen-type metaphyseal chondrodysplasia (activating *PTH1R* variant)
  7. Humoral hypercalcemia of benignancy (parathyroid hormone-related protein secretion by benign tissue)



## Gut absorption

- A. Vitamin D mediated
  1. Hypervitaminosis D
  2. 1,25-dihydroxyvitamin D mediated
    - a. Hematologic malignancies (increased 1 $\alpha$ -hydroxylase activity)
    - b. Granulomatous disorders
      - i. Infectious—tuberculosis, cat-scratch disease, histoplasmosis, cryptococcosis, candidiasis, leprosy, *Pneumocystis jirovecii*, etc
      - ii. Inflammatory—sarcoid, Wegener granulomatosis, Crohn disease, Blau syndrome, Langerhans cell histiocytosis, etc
      - iii. Foreign body—silicosis, talc, bacille Calmette-Guérin therapy, berylliosis, paraffin oil
      - iv. Other—subcutaneous fat necrosis of the newborn, lipid pneumonia
    - c. Drugs—calcitriol, activated vitamin D analog ingestion, 8-chloro-cyclic adenosine monophosphate
    - d. Congenital—*CYP24A1* variant, *SLC34A1* variant
- B. Non-vitamin D mediated
  1. Lactase deficiency
  2. Sucrase-isomaltase deficiency



## Renal excretion

- A. Drugs—thiazides
- B. Milk-alkali syndrome (concomitant with excess calcium carbonate ingestion)
- C. Acute kidney failure
- D. Bartter syndrome
- E. Adrenal insufficiency

## Others

- A. Reduced deposition of skeletal calcium
  1. Adynamic bone disease
  2. Hypophosphatasia
- B. Redistribution—rhabdomyolysis
- C. Other or unknown—acromegaly, pheochromocytoma, theophylline, ketogenic diet, kidney tubular acidosis, foscarnet, omeprazole, aromatase inhibitors, sodium-glucose cotransporter 2 protein inhibitors, immune checkpoint inhibitors, calcium-sulfate beads, COVID-19, Williams syndrome

# Patient: Hypercalcemia



27 yo black bisexual biologic 46XY male

CC: Fatigue, and constipation (previously good health)

PEx: Gluteal tenderness

|                  |                      |        |                     |
|------------------|----------------------|--------|---------------------|
| Cr               | 12.8 mg/dl           | iCa    | 7.25 mg/dl (1.8 mM) |
| tCO <sub>2</sub> | 18 mM                | PTH    | 8 pg/ml             |
| tCa              | 14.5 mg/dl (3.63 mM) | 25 D   | 12 ng/ml            |
| P                | 6 mg/dl              | 1,25 D | 78 pg/ml            |
| WBC              | 11.8                 | FECa   | 19%                 |

4 yrs ago- Gluteal silicone injections and implants

MRI- Soft tissue swelling

OR:

Noncaseating granuloma.

Infiltrate lymphocytes, eosinophils, neutrophils, plasma cells.

No giant cells

1-hydroxylase: IHC negative; RT-PCR positive

# Patient: Hypercalcemia

27 yo black bisexual biologic 46XY male

CC: Fatigue, and constipation (previously good health)

PEx: Gluteal tenderness

Calcitonin



Removal prosthesis



Saline + furosemide

Prednisone

| Time  | 0    | 4hr  | 8 hr | 24 hr | 1 d post op | 2 d post op |
|-------|------|------|------|-------|-------------|-------------|
| tCa   | 12.8 | 11.5 | 9.5  | 9.4   | 8.9         | 8.2         |
| iCa   | 7.25 | 6.15 | 4.6  | 4.5   | 4.5         | 4.0         |
| Cr    | 9.2  | 7.7  | 7.0  | 5.6   | 3.1         | 2.0         |
| 25, D | 12   |      | 13   | 11    | 17          | 15          |
| 1,25D | 78   |      | 62   | 50    | 45          | 32          |

# Hypercalcemia: Acute Rx

| Agent                   | Mechanism of action                                                      | Dose                                                            | Onset of action                  | Duration of action | Adverse reactions                                                            |
|-------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------|----------------------------------|--------------------|------------------------------------------------------------------------------|
| <b>Saline</b>           | Volume expansion decreases PT Ca reabsorption                            | 200–500 ml/h                                                    | < 1 h                            | hrs                | Volume overload                                                              |
| <b>Loop natriuretic</b> | Inhibit TAL Ca absorption                                                | 40-120 mg bolus<br>Repeated boluses<br>Drip                     | < 1 hr                           | hrs                | Hypokalemia<br>Volume depletion                                              |
| <b>Calcitonin</b>       | Inhibits OC activity;<br>Increases calciuresis<br>Inhibits GI absorption | 4–8 units/kg im./sc.<br>Q12 h for 2–3 days                      | ~2 h                             | 6–8 h              | Flushing. Nausea<br>site reaction<br>Hypersensitivity<br>Hypocalcemia        |
| <b>Pamidronate</b>      | Inhibits OC activity                                                     | 60–90 mg iv. over<br>2–6 h <sup>†</sup> (one dose)              | ~24 h                            | 7–14 days          | Fever<br>Hypocalcemia<br>Hypophosphatemia<br>Nephrotoxicity<br>Osteonecrosis |
| <b>Zoledronic acid</b>  | Inhibits OC activity                                                     | 4 mg iv. over 15–30<br>min <sup>†</sup> (one dose) <sup>‡</sup> | 24–48 h                          | 32 days            | Same as pamidronate                                                          |
| <b>Denosumab</b>        | Inhibits RANKL binding to RANK<br>Inhibits OC activity                   | 120 mg sc. q4 weeks                                             | 9 days (median time to response) | 100 days           | Fatigue. Nausea<br>Hypophosphatemia<br>Hypocalcemia<br>Dermatitis/rash       |

# Patient: Hypercalcemia

55 yo white female with pulmonary sarcoid

tCa 10.8-12.0 mg/dl

Cr 1.9 mg/dl (baseline 0.8)

PTH

25 (OH) D

1,25 (OH)<sub>2</sub>D

U<sub>Ca</sub>V

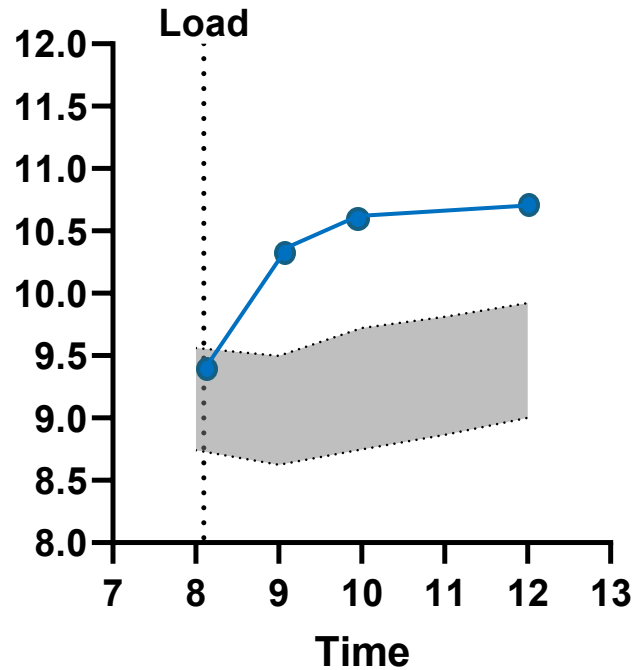
14 pg/ml (10-70)

31 ng/ml (20-40)

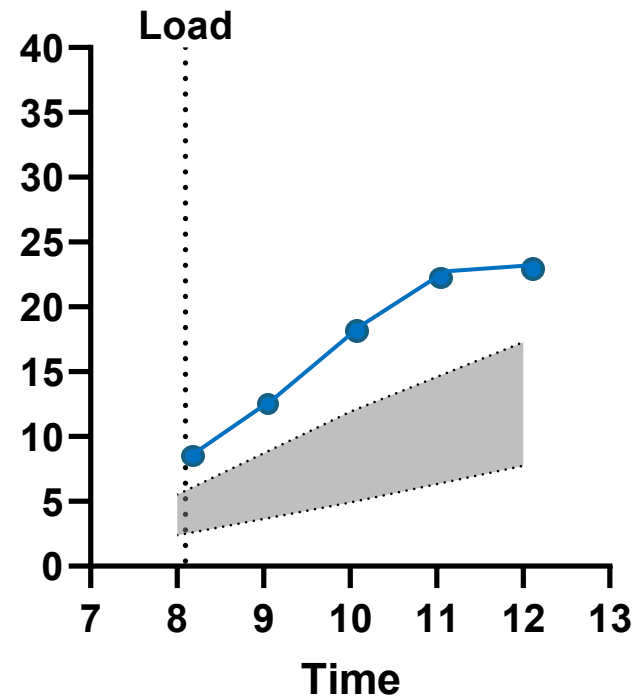
89 pg/ml (18-78)

310 mg/day (<200)

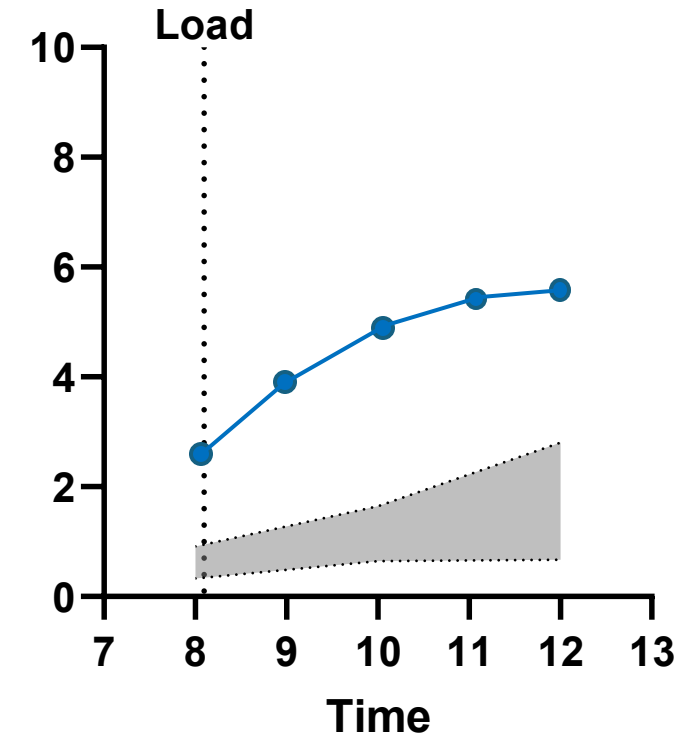
**Serum Calcium (mg/dL)**



**Calcium excretion rate (mg/hr)**



**FECa (%)**

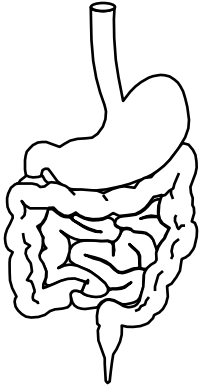


# Agenda



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- Hypercalcemia
- Hypocalcemia

# Hypocalcemia

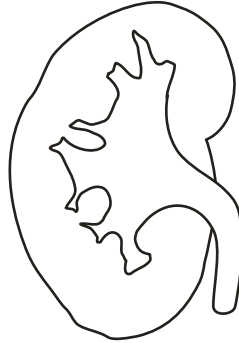


## Decreased gut absorption

Hypoparathyroidism\*  
Malabsorption  
Ca binding by fat  
Vit D deficiency  
Vit D resistance

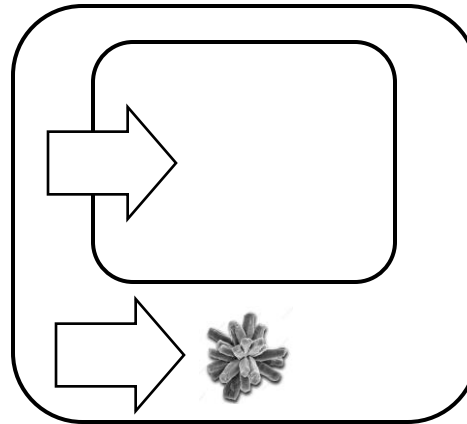
\*

Surgical  
Autoimmune  
Infiltrative  
Congenital



## Renal leak

Hypoparathyroidism  
PseudohypoPTH  
PseudopseudohypoPTH  
Prox tubule dysfxn-Fanconi



## Increased sequestration

Hyperphosphatemia  
Acute pancreatitis  
Massive transfusion



## Increased bone uptake

Blastic metastasis  
Anti-resorptive  
Bisphosphonate  
Denosumab  
Hungry bone  
Calcimimetc

## Increased cell uptake

Rhabdomyolysis  
Acute hyperventilation

# Patient: Hypocalcemia

39 yo healthy white female

3.5 gland parathyroidectomy age 28

Ca citrate

Vit D

Little details of medical records

Stone passage x 4-5 yrs

Radio-opaque

ESWL x2

URS x3

tCa 8.7-9.2 mg/dl

Phos 4.3-4.5 mg/dl

25 D 50 ng/ml

1,25D 23 pg/ml

PTH 0 pg/ml

| <i>Ad lib</i> diet |         |
|--------------------|---------|
| Calcium            | 368 mg  |
| Oxalate            | 38 mg   |
| Uric Acid          | 520 mg  |
| Citrate            | 646 mg  |
| pH                 | 6.2     |
| TV                 | 2.5 L   |
| Na                 | 105 mEq |
| K                  | 72 mEq  |
| SO <sub>4</sub>    | 34 mEqs |
| P                  | 1009 mg |
| Mg                 | 69 mg   |
| NH <sub>4</sub>    | 28 mEq  |
| Creatinine         | 1200 mg |

NCCT scan Non-obstructing stones (3 R, 2 L)

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39 yo healthy white female

3.5 gland parathyroidectomy age 28

Ca citrate

Vit D

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tCa 8.7-9.2 mg/dl

Phos 4.3-4.5 mg/dl

25 D 50 ng/ml

1,25D 23 pg/ml

PTH 0 pg/ml

2-5K/yr PTH (1-34) Teriparatide

25K/yr PTH (1-84) Palopegteriparatide



| <i>Ad lib</i> diet |         |         |
|--------------------|---------|---------|
| Calcium            | 368 mg  | 201 mg  |
| Oxalate            | 38 mg   | 34 mg   |
| Uric Acid          | 520 mg  | 420 mg  |
| Citrate            | 646 mg  | 702 mg  |
| pH                 | 6.2     | 6.8     |
| TV                 | 2.5 L   | 3.0 L   |
| Na                 | 105 mEq | 97 mEq  |
| K                  | 72 mEq  | 76 mEq  |
| SO <sub>4</sub>    | 34 mEqs | 30 mEq  |
| P                  | 1009 mg | 976 mg  |
| Mg                 | 69 mg   | 60 mg   |
| NH <sub>4</sub>    | 28 mEq  | 24 mEq  |
| Creatinine         | 1200 mg | 1170 mg |

NC CT scan Non-obstructing stones (3 R, 2 L)

# Patient: Hypocalcemia

48 yo female ESRD on HD

Hypertension Obesity

ESRD on HD x two years

Poorly controlled secondary PTH : 950-1300 pg/ml

Parathyroidectomy considered

Admission:

Hypotension

Calcium 5.9 mg/dl iCa 3.7 mg/dl

PTH 107<-> 154 pg/ml

Vit D 16.4 <->18.5 pg/ml

CT neck negative

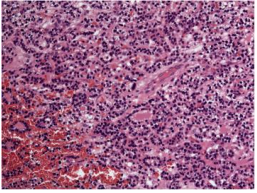
Rx: Hold Cinacalcet

Calcium Citrate

Calcitriol

Maintained Ca 7.5-8.1 mg/dl

# Patient: Hypocalcemia



## Parathyroid apoplexy

Hyperplasia/hypertrophy outstrips blood supply  
More often with Calcimimetic

### Systemic

- Spontaneous resolution hyperparathyroidism
- Hypocalcemia
- Hyperphosphatemia
- Low vitamin D

### Local

- Neck pain/swelling
- Recurrent laryngeal nerve
- Airway compromise

Rx: Ca/vit D

Monitor:

PTH

Blood and urine Ca

25D, 1,25D

Bone turnover markers

DEXA

PTH (1-34) Teriparatide (Forteo)

PTH (1-84) Palopegteriparatide (Yorvipath)

- Stabilize plasma calcium, phosphate
- Reduce urine excretion of calcium
- Protect bone

# Summary

- Three pools of calcium with highly diverse concentration, quantity, and functions
- Three organs and multiple hormones are involved in calcium homeostasis
- Clinical disorders = derangements in one or more of these organs and hormones
- Management: Restoration and target underlying etiology

# Update in Internal Medicine

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