Calcium disorders

Distribution in body

- 99% mineralized in bones, 1% ICF&ECF, <0.5% serum
- Normal total serum Ca: 8.5-10.5 mg/dL
- Normal ionized serum Ca: 4.4-5.4 mg/dL

Ca regulation

PTH | parathyroid hormone

- Most important Ca regulator
- Excreted when low serum Ca: ↓Ca → ↑PTH
- Ca levels detected by Ca-sensing receptor (CaSR)
- Secreted indirectly by high phosphate levels
- Targets cells in bone & kidneys
- Regulates Ca by 3 processes:
    - Bone: (+)osteoclasts → resorption from bone → release Ca to ECF
      (–)osteoblasts → (–)Ca incorporation into bone → (–)bone formation
    - Kidneys: ↑distal tubular reabsorption of Ca → ↓Ca excretion
    - Intestines: ↑calcitriol activation → ↑Ca absorption in small intestine
      ↑phosphate absorption
      ↑Hydroxylation of 25(OH)D_3 → 1,25$(OH)_2D_3$

Vit D: endogenous calcitriol, helps ↑Ca absorption in gut

Calcitonin: (–)osteoclastic bone resorption

	PTH	Vit D
(+) Ca release from bone	Directly	Indirectly
↓Ca renal elimination	Directly	Indirectly
↑Ca absorption in GI	Indirectly	Directly

Ca absorption

- Absorbed in intestines + reabsorbed in kidneys
- ↑Ca absorption: endogenous Vit D (calcitriol) or exogenous Vit D & analogues (calcitriol, doxercalciferol, paricalcitol)
- ↓Ca absorption: malabsorption, renal failure
- Reabsorption in kidneys: 50-70% in proximal tubules (Na dependent) + 10% in distal tubules (PTH dependent)

HYPOCALCEMIA

Etiology

- ↓Ca intake: dietary intake, renal insufficiency, or complexed (phosphates, citrates, sulfates, oxalates, phytates)
- ↓Vit D: ↓dietary Vit D, ↓sunlight exposure, ↓absorption (pancreatitis, biliary cirrhosis, GI bypass surgery, malabsorption syndromes), ↓synthesis, ↓activation
    - ↓Vit D synthesis: [insert diagram here]
    - ↓Vit D activation: [insert diagram here]
- ↑Ca elimination: hypo-PTH, loop diuretics, saline infusions

Calcium measurements

Total serum Ca	Measures ECF bound & unbound Ca Normal: 8.5-10.5 mg/dL
Corrected Ca	Ca is bound to albumin → approximates & adjusts for low albumin levels Corrected Ca = total serum Ca + 0.8 x (4 – serum albumin) May overestimate Ca → need ionized Ca if pt critically ill or total serum Ca low
Ionized Ca	Alkalosis → ↑pH → ↓ionized Ca …….. Acidosis → ↓pH → ↑ionized Ca Rate of fall > actual serum level → need to look at trend lab values Ionized Ca (corrected for pH) = total serum Ca + 0.12/ (0.1 x [7.4 – pH])

Chronic hypocalcemia

- CKD → GFR < 60 ml/min/m2 → ↓calcitriol activation via 1α-hydroxylase
- Hypo-PTH → ↓PTH secretion
- Vit D deficiency: due to poor dietary intake, malabsorption, short bowel, cirrhosis (↓calcidiol synthesis), kidney disease (↓calcidiol activation)

Vitamin D supplements

	Type	Onset of action	Duration of action	Dose
Ergocalciferol, cholecalciferol	Inactive	10-14 days	4-12 weeks	Ergo: 50,000 U/wk Chole: 400-1000 U/day
Calcitriol, doxercalciferol, paricalcitol	Active	2-6 hrs	3-5 days	Dose ratio 1:2:4

Vitamin D supplements: safety

- Monitoring parameters: serum Ca, serum PO_4, S&S of hypercalcemia/hypocalcemia, Vit D levels
- Early SE due to ↑Ca: headache, N/V/C, weakness, anorexia
- Late SE due to ↑Ca: hypertension, CNS, arrhythmias, polyuria, polydipsia, renal failure
- Drug interactions: phenytoin, phenobarbital, mineral oil, cholestyramine

Vitamin D

Normal serum levels: 30-80 ng/ml
Depleted by: phenytoin, phenobarbital, alcohol

Vitamin D in CKD

CKD	Agent	Purpose	Dosing
Stage 3-4	Calcitriol or an active Vit D analog	Bone/mineral metabolism + replacement	PO daily or 3x/week
	Ergocalciferol (inactive)	Immune/cardiac fxn + bone/mineral metabolism	Dosed according to serum Vit D levels
Stage 5	Calcitriol or an active Vit D analog	Bone/mineral metabolism only	IV or PO 3x/week
	Ergocalciferol (inactive)	Immune/cardiac fxn only	Dosed according to serum Vit D levels

Hypocalcemia signs & symptoms

Acute symptoms

	Presentation	Tests
Neurological	Seizures	EEG
Neuromuscular	Spasms, numbness, tetany	Chvostek's sign, Trousseau's sign
Cardiovascular	Hypotension, impaired contractility, prolonged QT interval	BP monitoring, EKG

Chronic symptoms: bone, psychiatric, dermatologic

Treatment

Goal: 200-300mg elemental Ca
IV bolus over 5-10 min → repeat until symptoms resolve → elemental Ca 0.5-2mg/kg/hr until ionized Ca normalizes → 0.3-0.5 mg/kg/hr infusion to maintain Ca
Monitor: ionized Ca

Parenteral calcium

- Agents:
  - CaGluc: preferred, 9% elemental Ca
  - CaCl: irritating to veins, possible extravasation & skin necrosis, 27% elemental Ca
- Avoid rapid administration: possible hypotension, bradycardia, asystole
- Drug interaction: digoxin + parenteral Ca → arrhythmias
- Therapeutic interventions: loop diuretics → thiazide diuretics; replace Mg if hypomagnesemia

Hungry bone syndrome

- Parathyroidectomy → post-surgery leads to shift from serum to bone → drop in both serum Ca and PO4
- Like unclogging the drain
- Treatment: IV Ca if acute drop ± symptoms, IV/PO calcitriol to sustain low Ca levels, outpatient calcitriol po qd

Oral calcium supplements

	%Elemental
Calcium **carbonate**	40%
Calcium **acetate**	25%
Calcium **citrate**	21%
Calcium **lactate**	13%
Calcium **gluconate**	9%

Treatment: 1-2g elemental Ca daily
Prevention: 0.5-1g elemental Ca daily
Take in divided doses → best absorption if taken 1-1.5 hrs before or after meals

HYPERCALCEMIA
Serum Ca > 10.5 mg/dL

Etiology

- Two main causes: 1° hyperparathyroidism, malignancy
- Other causes: 2° hyperparathyroidism in CKD, granulomatous diseases, milk-alkali syndrome
- Mechanisms: ↑bone resorption into ECF, ↑GI absorption, ↓renal elimination, malignancy
    - Malignancy: malignant cells → ↑osteoclasts + ↑humoral substance secretions (e.g. PTH-related hormone, Vit D, PGEs, Ifs, TNF, granulocyte-stimulating factor)
- Drug induced: thiazides, lithium, antiestrogens, Vit D toxicity, Vit A toxicity

Signs & Symptoms

- S&S not correlated with Ca levels → more important to look at rate of rise

	Acute ↑Ca	**Chronic ↑Ca**
1° Hyperparathyroidism	X	X
2° Hyperparathyroidism		X
Malignancy (except breast cancer & multiple myeloma)	X	

Therapy

- Acuity of rise in Ca levels determines therapy
- Cinacalcet: treats 2° hyperparathyroidism
- Acute hypercalcemia: 0.9% NS + furosemide
- Calcitonin: when NS is contraindicated, short term management
- Bisphosphonates: hypercalcemia secondary to malignancy, rehydration first, calcitonin if need rapid ↓Ca
- Gallium nitrate: (–)osteoclast activity, only if all else fails, extremely nephrotoxic
- Prednisone: chronic treatment of granulomatous diseases (sarcoidosis), multiple myeloma, Vit A & Vit D toxicity

Nephrolithiasis

- Prevention: KCitrate, NaCitrate, HCTZ, indapamide, chlorthalidone, Calcibind, low Ca diet
- Mainstay of therapy: hydration hydration hydration