**Calcium functions:**
- Bone & teeth maintenance
- Platelet adhesion
- Neuromuscular activity
- Blood coagulation
- Endocrine & exocrine functions
- Heart electrophysiology
- Smooth muscle electrophysiology

**Calcium distribution**

**Dietary sources of Ca**
- Dairy: cheese, yogurt, milk
- Protein: sardines, herring
- Veggies & fruit: spinach, kale, turnips, fortified orange juice
- Breads and cereals: enriched breads, grains, fortified cereals

**Calcium distribution**

- Normal total serum Ca: 2.1 – 2.6 mmol/L
- Normal ionized/active Ca: 1.1 – 1.4 mmol/L
- If patient has low albumin levels:
  - Request an ionized Ca level
  - Correction calc: \[ \text{Ca}_{\text{corr}} = \text{Ca}_{\text{meas}} + (40 – \text{albumin}) \times 0.02 \]

**Hormones and calcium homeostasis**

**Parathyroid hormone:** released when low \([Ca^{2+}]\) detected
- ↑ Ca release from bones (osteoclast activity)
- ↑ Ca reabsorption from kidney
- ↑ conversion of Vit D to active form
- Indirectly ↑ Ca and phosphate absorption in GIT (thru Vit D)

**Vitamin D:** intake from diet/supplements
- Conversion to calcitriol (active form) through sunlight, liver & kidney
- ↑ Ca release from bones (osteoclast)
- ↑ reabsorption by kidneys
- ↑ Ca absorption in GIT
- Negative feedback, decreases PTH release if supratherapeutic Ca

**Calcitonin:** released from thyroid when high \([Ca^{2+}]\) detected
- ↓ Ca release from bone (slows osteoclast activity)
- ↓ Ca reabsorption by kidneys

**Phosphate functions**
- Bone structure (hydroxyapatite)
- Intracellular structures, lipid bilayer
- Nucleic acids
- ATP: muscle contract, neuro fxn
- Metabolic processes (glycolysis)
- Acid-base buffer
- Coagulation cascade, platelet aggregation

**Phosphate Distribution**

- Major intracellular anion
- Closely linked to Ca
- Normal PO₄: 0.8 – 1.6
- Kidney major organ regulating PO₄ excretion

**Hormones &homeostasis**

**PTH:** decreases renal reabsorption when levels high (lowers phosphate levels)

**Vit D (Calcitriol)** | **Calcitonin** | **Fxns**
--- | --- | ---
↑ | ↓ | Release from bone (osteoclast)
| | Reabsorption by kidneys
| | Absorption in GIT

**High phosphate containing foods**
- Dairy products: milk, cheese, yogurt
- Proteins: organs, sardines, shellfish
- Veggies: dried beans & peas, lentils
- Breads and cereals: whole grains, nuts
- Beverages: ale, beer, colas, chocolate
**Goals of therapy**
- Improve & resolve S/S
- Correct underlying causes
- Normalize serum Ca
- Prevent further complications (renal failure)

**Disease causes**
- Malignancy: production of PTH-like peptides, ectopic PTH, calcitriol; metastatic cancers to bone
- Hyperparathyroidism: primary (adenoma), secondary (renal disease)
- Granulomatous diseases: sarcoidosis, tuberculosis
- Other: adrenal insufficiency, thyrotoxicosis, immobility

**Drug causes**
- Thiazide diuretics: reduces renal excretion of Ca
- Lithium carbonate: increases Ca threshold for suppression of PTH
- Tamoxifen: increased bone resorption
- Increased Ca absorption via intake/use (milk-alkali syndrome): calcium supplements, calcitriol/calcipotriol/Vit D, vitamin A, antacid overdose

**Normal Ca:**
- Total: 2.1 – 2.6
- Ion: 1.1 – 1.4

**Hypercacemia S/S:** “bones, stones, abdominal groans & psychic moans”
- CNS: fatigue, confusion, weakness, lethargy, seizures
- CV: bradycardia, changes on cardiac ECG (shortened QTc), arrhythmias
- MSK: weakness, tenderness, bone pain
- GI: anorexia, nausea, vomiting, constipation
- GU: kidney stones, polyuria → acute renal insufficiency

**General approach**
- Correct intravascular volume depletion
- Block body’s reabsorption of Ca
- Block osteoclast bone resorption

**Treatment algorithm**

<table>
<thead>
<tr>
<th>Mild</th>
<th>Mod</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>T: 2.6 – 3</td>
<td>T: 3 – 3.5</td>
<td>T: &gt; 3.5</td>
</tr>
<tr>
<td>Ion: 1.4 – 2</td>
<td>Ion: 2 – 2.5</td>
<td>Ion: &gt; 2.5</td>
</tr>
</tbody>
</table>

- Address underlying issues (ex/ drug-related causes)
- Volume repletion if needed
- Repletion with normal saline
- Bisphosphonate therapy
- Repletion with normal saline
- Bisphosphonate therapy
- Salmon calcitonin
- Dialysis (if indicated)

**Monitoring**
- Serum Ca levels: return to normal range in 12-48h
- Sx: decrease/absence
- Volume status: euvolemia, JVP, edema on exam
- Renal fxn: SCr normalizes or returns to baseline, good urine output

**Hypercalcemia: hyperparathyroidism** – Cinacalet
- Binds Ca receptor on parathyroid gland, sensitizes it to serum Ca levels & reduces PTH
- Used in CRF pts; symptomatic hypercalcemia in pts prior to or who cannot undergo parathyroidectomy

**Treatment options**

<table>
<thead>
<tr>
<th>Isotonic saline: restores intravascular volume, promotes Ca excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 L NS bolus, then 200-300 mL/h maintenance</td>
</tr>
<tr>
<td>Monitoring: urine output, JVP, overall volume status, SCr</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bisphosphonates: disrupts osteoclasts by binding to bone surface, toxic to osteoclasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use IV pamidronate or zoledronic acid</td>
</tr>
<tr>
<td>Onset 48-96 h and duration 10-35 days</td>
</tr>
<tr>
<td>Monitor: flu-like sx, PO4 and Mg levels, renal fxn, jaw osteonecrosis w/ prolonged/repeated used</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Salmon calcitonin: reduces calcium re-absorption, inhibits maturation of osteoclasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset 6 h BUT tachyphylaxis occurs quickly (2 days)</td>
</tr>
<tr>
<td>Use as temporary bridge therapy for symptomatic pts til bisphosphonates work</td>
</tr>
<tr>
<td>Monitor: avoid if fish allergy (anaphylaxis), watch phosphate level (can lower)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Furosemide IV: promotes Ca excretion &amp; removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only if hypervolemic as well</td>
</tr>
<tr>
<td>Monitor: volume status, SCr, K levels</td>
</tr>
<tr>
<td>Dialysis in severe cases</td>
</tr>
</tbody>
</table>
Hypocalcemia S/S
- CNS: irritability, confusion, fatigue, syncope, seizures
- CV: changes on cardiac ECG (prolonged QTc), arrhythmias, acute heart failure
- HEENT: difficulty swallowing
- MSK: cramps, weakness, spasms of hands and feet
- CHRONIC: coarse hair, dry skin, brittle nails, dental issues

Classic signs
- Trousseau sign: carpopedal spasm when inflating BP cuff above SBP for 3 minutes
- Chvostek sign: facial muscle twitches when tapping facial nerve anterior to the ear

Disease causes
- PTH deficiency: parathyroidectomy (hungry bone); genetic; autoimmune diseases; neck irradiation
- Hypoalbuminemia (malabsorption, malnutrition, chronic alcoholism): binding of Ca²⁺ to proteins
- Hyperphosphatemia: binding of Ca²⁺ to phosphate
- Pancreatitis

Drug causes
- Bisphosphonates
  - Reduces osteoclast activity
- Denosumab
  - Chelates with calcium (physical binding)
- Sodium citrate (blood transfusion)
  - Causes hypomagnesemia affecting Ca levels
- EDTA
- Cisplatin
- Aminoglycoside abx
- Cinacalcet
  - Inhibits PTH release
- Anticonvulsants (phenytoin, phenobarbital)
  - Increase Vitamin D catabolism

Goals of therapy
- Improve and resolve S/S
- Correct underlying causes
- Normalize serum calcium
- Prevent further complications (ex// tetany)

General approach
- Address underlying cause
- Replete with IV or PO calcium
- Resupplement other electrolytes, vit D

Drug-drug interactions with Ca
- Space Ca apart from oral alendronate, iron supplements, quinolones, oral phosphate, certain antacids, levothyroxine, bile acid sequestrants
- Watch for calcium’s effects on digoxin

Treatment algorithm (hypocalcemia T: < 2.1 Ion: <1.1)

<table>
<thead>
<tr>
<th>Mild/mod hypocalcemia</th>
<th>PO</th>
<th>Elemental Ca 1-2 g/day in 2-4 divided doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>Ca gluconate 1 g over 30 min PRN</td>
<td></td>
</tr>
<tr>
<td>Vitamin D supplement PRN</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute hypocalcemia or Sx present</th>
<th>IV</th>
<th>Ca gluconate 1-3 g in 50-100 mL fluid over 15-30 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>May follow</td>
<td>3-5 g of Ca gluconate in 500-1000 mL IV solution continuous infusion over 3-12 h</td>
<td></td>
</tr>
<tr>
<td>Vitamin D supplement PRN</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Vitamin D options
- Vitamin D3 (cholecalciferol) Tab 400, 1000, 10000 units
- Vitamin D2 (ergocalciferol) Capsule 50,000 units
- Calcium gluconate Tab 650 mg 60 mg
- Inject 100 mg/mL 9 mg/mL

Calcium options
- Salt | Form | Strength | Elemental Ca
- Ca acetate | Tab | 667 mg | 169 mg
- Ca carbonate | Tab | 500 mg | 200 mg
- 1000 mg | 500 mg | 1000 mg |
- 1500 mg | 600 mg |
- Ca chloride | Inject | 100 mg/mL | 27.3 mg/mL |
- Ca compound | Effervescent Tab | 500 mg | 500 mg |
- Tab | 1000 mg | 1000 mg |
- Liquid | 100 mg/5mL | 20 mg/mL |
- Ca gluconate | Tab | 650 mg | 60 mg |
- Inject | 100 mg/mL | 9 mg/mL |
- Vitamin D3 (cholecalciferol) Tab 400, 1000, 10000 units
- Alfacalcidol | Capsule | 0.25, 1 mcg |
- Solution | 2 mcg/mL |
- Calcitriol | Capsule | 0.25, 0.5 mcg |
- Injection | 1 or 2 mcg/mL |

Monitoring
- Ca²⁺: normal w/in 6-10 h (parenteral); 24-48 h (oral)
- Sx: decrease or absence; negative Chvostek/Trousseau
- Mg²⁺: maintained or returns to normal (0.6 – 1.2)
- Renal fxn: SCr normalizes or returns to baseline
### Hyperphosphatemia

| Normal: 0.8 – 1.6 |
| Mild: > 1.6 |
| Moderate: > 2.1 |
| Severe: >2.26 |

### Hyperphosphatemia S/S

- CNS: decreased levels of consciousness, seizures
- HEENT: band keratopathy, cornea calcification
- CVS: cardiac deposition of Ca/PO₄ precipitate; arrhythmias; prolonged QTc on cardiac ECG
- MSK: soft tissue calcification; weakness, cramps, tetanus
- GI/GU: precipitation in gastric mucosa & kidney; NVD; chronic renal failure

### Disease causes

- Renal disease: often in acute kidney insufficiency; almost always in chronic kidney disease
- Dietary intake: problem if impaired renal function
- Intracellular release: tumor lysis syndrome, rhabdomyolysis, hemolysis
- Hypoparathyroidism: increase in phosphate reabsorption by kidneys
- Transcellular shifts: acidosis (lactic, diabetic)

### Drug causes

<table>
<thead>
<tr>
<th>Increase serum phosphate</th>
<th>Phosphate-containing laxative and meds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vitamin D</td>
</tr>
<tr>
<td></td>
<td>Calcitriol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Causes nephrotoxicity can indirectly lead to hyperphosphatemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors/ARBs</td>
</tr>
<tr>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Amphotericin B</td>
</tr>
</tbody>
</table>

### Goals of therapy

- Improve and resolve S/S
- Correct underlying causes
- Normalize PO₄ levels
- Prevent further complications (ex// Ca/PO₄ deposits)

### General approach

- Intervene only if impaired renal function
- Dietary control and/or phosphate binders
- Enhanced elimination of phosphate

### Treatment options

<table>
<thead>
<tr>
<th>Oral phosphate binders</th>
<th>Binds phosphate in GIT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Insoluble compound not absorbed</td>
</tr>
</tbody>
</table>

| IV normal saline and/or furosemide | Dilutes serum phosphate and enhances renal elimination |

| Dialysis | Management in pts with CKD |

### Monitoring

- Serum PO₄ levels: return to normal w/in 24-48h (phosphate binders), 12h (dialysis)
- Sx: decrease/absence; signs of Ca deposits
- Ca levels: no S/S; w/in normal range
- Renal fxn: normalizes if patient has acute kidney injury

### Phosphate binders

| Ca acetate | Tab | 667 mg |
| Ca carbonate | Tab | 500 mg |
|             | Tab | 1250 mg |
|             | Tab | 1500 mg |
| Aluminum hydroxide | Tab | 600 mg |
| Sevelamer HCl | Tab | 400 mg, 800 mg |
| Sevelamer carbonate | Tab | 800 mg |
| Lanthum carbonate | Tab | 500 mg, 750 mg |
### Hypophosphatemia

<table>
<thead>
<tr>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.80 – 1.6</td>
<td>0.65 – 0.8</td>
<td>0.32 – 0.65</td>
<td>&lt; 0.32</td>
</tr>
</tbody>
</table>

### Hypophosphatemia S/S

- CNS: weakness, paresthesia, confusion, seizures
- RESP: resp. failure, hypoventilation
- CVS: decreased contractility (acute heart failure), reversible cardiomyopathy
- MSK: weakness, myalgias
- GI/GU: nausea, vomiting, acute kidney insufficiency
- HEME: hemolysis, thrombocytopenia

### Disease causes

<table>
<thead>
<tr>
<th>Internal redistribution (cellular shifts)</th>
<th>Respiratory alkalosis</th>
<th>Re-feeding syndrome (malnutrition)</th>
<th>Sepsis</th>
<th>Post-parathyroidectomy (hungry bone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased urinary excretion</td>
<td>Hyperparathyroidism</td>
<td>Renal tubular diseases</td>
<td>Chronic alcoholism</td>
<td></td>
</tr>
<tr>
<td>Decreased GI absorption</td>
<td>Malnutrition (decreased intake)</td>
<td>Vomiting diarrhea</td>
<td>Chronic alcoholism</td>
<td></td>
</tr>
</tbody>
</table>

### Drug causes

<table>
<thead>
<tr>
<th>Certain drug overdoses (insulin, ASA)</th>
<th>Drug overdoses w/ acid-base effects may cause PO₄₃⁻ redistribution from extra to intra-cellular compartments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>Increases urinary phosphate excretion</td>
</tr>
<tr>
<td>Oral phosphate binders</td>
<td>Decreases GI absorption of phosphate</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td></td>
</tr>
</tbody>
</table>

### Goals of therapy

- Improve and resolve S/S
- Correct underlying causes
- Normalize phosphate
- Prevent further complications (ex// acute resp/heart failure)

### General approach

- Phosphate replacement over several days
- Oral replacement limited by diarrhea
- IV replacement often used

### General approach

- Serum phosphate: normal w/in 24h (parenteral), 48 h (oral)
- Sx: decrease or absence; no signs of resp. or cardiac failure
- Serum Mg, K: follow if re-feeding syndrome
- Serum Ca: remains normal after repletion

### Treatment algorithm

<table>
<thead>
<tr>
<th>Mild and symptomatic</th>
<th>Oral</th>
<th>Phosphate solution 500 mg (4 mL) bid-qid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-mod &amp; asymptomatic</td>
<td>IV</td>
<td>Na phosphate 15 mmol IV via peripheral or central line</td>
</tr>
<tr>
<td>Severe and/or symptomatic</td>
<td>IV</td>
<td>K phosphate 15 mmol IV (higher doses require central line)</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Sodium phosphate 15-45 mmol IV</td>
</tr>
</tbody>
</table>