Disorders of Calcium and Phosphate Metabolism
Major Mediators of Calcium and Phosphate Balance

- Parathyroid hormone (PTH)
- Calcitriol (active form of vitamin D$_3$)
- Calcitonin
In parathyroid cells – 115 amino acid pre-pro-PTH – cleaved to 90 aa pro-PTH – cleaved again:

1-84 aa full molecule = **INTACT PTH** – is excreted – this is 4 to 35 % of total PTH.

**BUT** further cleavage in cells also gives carboxyl fragments: 7-84 aa = inactive PTH-C – also excreted with half-life 24-36 h !!

Amino terminal fragments presumably have short half-life – also active
Role of PTH

- Stimulates renal reabsorption of calcium
- Inhibits renal reabsorption of phosphate
- Stimulates bone resorption
- Inhibits bone formation and mineralization
- Stimulates synthesis of calcitriol

Net effect of PTH ➔

↑ serum calcium
↓ serum phosphate
Parathyroid glands

Low unbound plasma Ca

PTH promotes:
1. Bone resorption
2. Renal tubular reabsorption
3. 1,25 DHCC synthesis
4. Calcium absorption from gut
Regulation of PTH

Low serum $[\text{Ca}^{+2}]$ $\rightarrow$ Increased PTH secretion

High serum $[\text{Ca}^{+2}]$ $\rightarrow$ Decreased PTH secretion
Role of Calcitriol

- Stimulates GI absorption of both calcium and phosphate
- Stimulates renal reabsorption of both calcium and phosphate – contrast PTH
- Can stimulate bone mineralisation (as well as resorption) – contrast PTH – only resorption

Net effect of calcitriol → ↑ serum calcium
                          ↑ serum phosphate
Regulation of Calcitriol

7-dehydrocholesterol

In skin

cholecalciferol (vitamin D3)

In liver

25-hydroxycholecalciferol (25-hydroxy vitamin D)

In kidney

1,25-dihydroxycholecalciferol (1,25-dihydroxy vitamin D)

Active form of vitamin D

Diet → Cholecalciferol (Vitamin D3)

UV Light

25-hydroxylase (located in liver)

25 (OH) cholecalciferol (calcidiol)

1α-hydroxylase (located in kidney)

1,25 (OH)₂ cholecalciferol (calcitriol)

Calcitriol, ↑ serum [phosphate]

PTH, ↓ serum [phosphate]
Different Forms of Calcium

At any one time, most of the calcium in the body exists as the mineral hydroxyapatite, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$.

Calcium in the plasma:
- 45% in ionized form (the physiologically active form)
- 45% bound to proteins (predominantly albumin)
- 10% complexed with anions (citrate, sulfate, phosphate)

To adjust the total calcium in states of hypoalbuminemia:

$$[\text{Ca}^{2+}]_{\text{Corrected}} = [\text{Ca}^{2+} \text{ mg/dl}]_{\text{Measured}} + [0.8 \times (4 - \text{Albumin (g/dL)})]$$

$$[\text{Ca}^{2+}]_{\text{Corrected}} = [\text{Ca}^{2+} \text{ mM}]_{\text{Measured}} + [0.02 \times (47 - \text{Albumin (g/L)})]$$
Normal

Lab measures total calcium (bound and unbound)

Ca = 2.4 mmol/l
Alb = 47 g/l
Normal result

Low albumin

No symptoms of hypocalcaemia

Hypocalcaemia

Parathyroid glands are unable to maintain Ca^{2+} in normal limits

Symptoms of hypocalcaemia
Spectrum of Hypercalcemia

Total serum calcium level, mg/dL (mmol/L)

8 (2) 10 (2.5) 12 (3) 14 (3.5) 16 (4)

- Normocalcemia
- Mild hypercalcemia
- Moderate hypercalcemia
- Hypercalcemic crisis
Etiologies of Hypercalcemia

Increased GI Absorption
- Milk-alkali syndrome
  - Elevated calcitriol
  - Vitamin D excess
  - Excessive dietary intake
  - Granulomatous diseases
- Elevated PTH*
- Hypophosphatemia

Decreased Bone Mineralization
- Elevated PTH*
- Aluminum toxicity

Increased Loss From Bone
- Increased net bone resorption
  - Elevated PTH*
  - Hyperparathyroidism
- Malignancy*
  - Osteolytic metastases
  - PTHrP secreting tumor
- Increased bone turnover
  - Paget’s disease of bone
  - Hyperthyroidism

Decreased Urinary Excretion
- Thiazide diuretics*
- Elevated calcitriol
- Elevated PTH*
- Familial
  - Hypocalciuric hypercalcemia
Possible causes of hypercalcemia

- elevated PTH
- malignancy
- Vit. D
- Granulomatous disease
- Thyrotoxicosis
- Diuretic therapy
- Immobilization
- Renal disease
- Calcium therapy
- Milk-alkali syndrome
Representative Normogram for Interpreting Serum Intact PTH Levels

- **Intact PTH (pg/mL)**
  - 500
  - 200
  - 150
  - 100
  - 50
  - 6 (1.5)
  - 8 (2)
  - 10 (2.5)
  - 12 (3)
  - 14 (3.5)
  - 16 (4)

- **Total serum calcium level, mg/dL (mmol/L)**

- **Primary hyperparathyroidism**
- **Hypoparathyroidism**
- **Normal**
- **Malignancy**

- Data points for various conditions are plotted on the graph to illustrate the normogram.
Etiologies of Hypocalcemia

Decreased GI Absorption
- Poor dietary intake of calcium
- Impaired absorption of calcium
  - Vitamin D deficiency
    - Poor dietary intake of vitamin D
    - Malabsorption syndromes
- Decreased conversion of vit. D to calcitriol
- Liver failure
- Renal failure
- Low PTH eg. via low Mg.
- Hyperphosphatemia

Increased Urinary Excretion
- Low PTH eg. via low Mg.
  - thyroidectomy
  - s/p I131 treatment
  - Autoimmune hypoparathyroidism
- PTH resistance
- Vitamin D deficiency / low calcitriol

Decreased Bone Resorption/Increased Mineralization
- Low PTH (aka hypoparathyroidism) eg. via low Mg.
- PTH resistance (aka pseudohypoparathyroidism)
- Vitamin D deficiency / low calcitriol
- Hungry bones syndrome
- Osteoblastic metastases
<table>
<thead>
<tr>
<th></th>
<th>Calcium Deprivation</th>
<th>Calcium Loading</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parathyroid hormone</strong></td>
<td>Secretion stimulated</td>
<td>Secretion inhibited</td>
</tr>
<tr>
<td><strong>Vitamin D</strong></td>
<td>Production stimulated by increased parathyroid hormone secretion</td>
<td>Synthesis suppressed due to low parathyroid hormone secretion</td>
</tr>
<tr>
<td><strong>Calcitonin</strong></td>
<td>Very low level secretion</td>
<td>Secretion stimulated by high blood calcium</td>
</tr>
<tr>
<td><strong>Intestinal absorption of calcium</strong></td>
<td>Enhanced due to activity of vitamin D on intestinal epithelial cells</td>
<td>Low basal uptake</td>
</tr>
<tr>
<td><strong>Release of calcium and phosphate from bone</strong></td>
<td>Stimulated by increased parathyroid hormone and vitamin D</td>
<td>Decreased due to low parathyroid hormone and vitamin D AND CALCITONIN !!</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>Calcium Deprivation</td>
<td>Calcium Loading</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>of calcium</td>
<td>Decreased due to enhanced tubular reabsorption stimulated by elevated parathyroid hormone and vitamin D; hypocalcemia also activates calcium sensors in loop of Henle to directly facilitate calcium reabsorption</td>
<td>Elevated due to decreased parathyroid hormone-stimulated reabsorption.</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>Strongly stimulated by parathyroid hormone; this phosphaturic activity prevents adverse effects of elevated phosphate from bone resorption</td>
<td>Decreased due to hypoparathyroidism</td>
</tr>
<tr>
<td>of phosphate</td>
<td></td>
<td></td>
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<tr>
<td>General Response</td>
<td>Typically see near normal serum concentrations of calcium and phosphate due to compensatory mechanisms. Long term deprivation leads to bone thinning (osteopenia).</td>
<td>Low intestinal absorption and enhanced renal excretion guard against development of hypercalcemia.</td>
</tr>
</tbody>
</table>
Calcium Deprivation

Summary

Calcium Loading
Etiologies of Hyperphosphatemia

Increased GI Intake
   Fleet’s Phospho-Soda

Decreased Urinary Excretion
   Renal Failure
   Low PTH (hypoparathyroidism)
      s/p thyroidectomy
      s/p I\textsuperscript{131} treatment for Graves disease or thyroid cancer
   Autoimmune hypoparathyroidism

Cell Lysis
   Rhabdomyolysis
   Tumor lysis syndrome
Etiologies of Hypophosphatemia

**Decreased GI Absorption**
- Decreased dietary intake (rare in isolation)
- Diarrhea / Malabsorption
- Phosphate binders (calcium acetate, Al & Mg containing antacids)

**Decreased Bone Resorption / Increased Bone Mineralization**
- Vitamin D deficiency / low calcitriol
- Hungry bones syndrome
- Osteoblastic metastases

**Increased Urinary Excretion**
- Elevated PTH (as in primary hyperparathyroidism)
- Vitamin D deficiency / low calcitriol
- Fanconi syndrome

**Internal Redistribution (due to acute stimulation of glycolysis)**
- Refeeding syndrome (seen in starvation, anorexia, and alcoholism)
- During treatment for DKA
HPT

- The symptoms of hyperparathyroidism can be remembered by the rhyme "moans, groans, stones, bones, and psychiatric overtones":
  - "moans" (complaints of not feeling well)
  - "groans" (abdominal pain, gastroesophageal reflux)
  - "stones" (kidney)
  - "bones" (bone pain)
  - "psychiatric overtones" (lethargy, fatigue, depression, memory problems).
### Clinical Manifestations of Hypercalcemia

<table>
<thead>
<tr>
<th>Renal “stones”</th>
<th>Neuromuscular “psychic groans”</th>
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<tbody>
<tr>
<td>Nephrolithiasis</td>
<td>Impaired concentration and memory</td>
</tr>
<tr>
<td>Nephrogenic diabetes insipidus</td>
<td>Confusion, stupor, coma</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Lethargy and fatigue</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>Muscle weakness</td>
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<th>Skeleton “bones”</th>
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<th>Cardiovascular</th>
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<tbody>
<tr>
<td>Bone pain</td>
<td>Osteitis fibrosa cystica in hyperparathyroidism (subperiosteal resorption, bone cysts)</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Arthritis</td>
<td></td>
<td>Shortened QT interval on electrocardiogram</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td>Cardiac arrhythmias</td>
</tr>
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<tr>
<th>Gastrointestinal “abdominal moans”</th>
<th>Other</th>
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<tbody>
<tr>
<td>Nausea, vomiting</td>
<td>Itching</td>
</tr>
<tr>
<td>Anorexia, weight loss</td>
<td>Keratitis, conjunctivitis</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
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<tr>
<td>Abdominal pain</td>
<td></td>
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<tr>
<td>Pancreatitis</td>
<td></td>
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<tr>
<td>Peptic ulcer disease</td>
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