Regulation of Calcium Ion Level in the Blood
**Calcium**

The Total Body Calcium (1 100 g):

- **MAJORITY - BONES** (1 000 000 mg)
- **1 % - CELLS** (13 000 mg)
- **0,1% - EXTRACELLULAR FLUID** (1 300 mg):

**Phosphate**

TOTAL - 500-800 g:

- 85% - BONES
- 14-15% - CELLS
- 1% - EXTRACELLULAR FLUID:
  - $\text{HPO}_4^{2-}$ - 1.05 mmol/L
  - $\text{H}_2\text{PO}_4^-$ - 0.26 mmol/L

Expressed in terms of milligrams of phosphorus per deciliter of blood

- 3-4 mg/dL (adults)
- 4-5 mg/dL (children)

**Calcium level:**

2,25 – 2,75 mmol/L

(9-11 mg/dL)
Extracellular calcium ion concentration is regulated by hormones:

- Parathyroid hormone (PTH)
- 1,25-Dihydroxycholecalciferol (active form of vitamin D₃)
- Calcitonin
The four parathyroid glands lie immediately behind the thyroid gland. Almost all of the parathyroid hormone (PTH) is synthesized and secreted by the chief cells. The function of the oxyphil cells is uncertain, but they may be modified or depleted chief cells that no longer secrete PTH.
Figure 17.12  The Parathyroid Glands. There are usually four parathyroid glands embedded in the posterior surface of the thyroid gland.
Parathyroid gland

Thyroid gland
FIGURE 79-9

Histological structure of a parathyroid gland.
Effect of PTH and Calcitonin on Blood Calcium Level

High blood calcium
Stimulates
Thyroid
Calcitonin released
Inhibits
Low blood calcium
Stimulates
Parathyroid
Parathyroid hormone released
Stimulates
Release of calcium from bone
Absorption of calcium in intestines
Reabsorption of calcium in kidneys
Blood calcium reduced
Blood calcium increased
Actions of PTH are coordinated to produce

- an increase in serum [Ca^{2+}]
- a decrease in serum [phosphate]
Compensatory responses to decreased plasma ionized calcium concentration mediated by parathyroid hormone (PTH) and vitamin D.
Overview of Calcium Distribution - Bone

The bones can serve as large reservoirs, releasing calcium when extracellular fluid concentration decreases and storing excess calcium.
Bone – PTH Action
2. Slow Phase - Activation of Osteoclasts

- Requires several days or weeks to become fully developed
- **Osteoclastic reabsorption of the bone itself:**
- **Removal of calcium phosphate from hydroxyapatite crystals** - \( \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2 \)

1. Proteolytic enzymes digest or dissolve the organic matrix
2. Acids (citric, lactic) cause solution of the bone salts.
Overview of Calcium Distribution - Bone

Calcium salts in bone:

- Majority - hydroxyapatite crystals, bound tightly to collagen fibers
- 0.4 to 1 per cent – amorphous (noncrystalline) compounds

**Exchangeable calcium**
- A rapid **buffering mechanism**
- *In equilibrium* with the calcium ions in the extracellular fluids.
Bone – PTH Action

1. Rapid Phase - Activation of the Osteocytic Membrane System

A system of interconnected cells (osteoblasts and osteocytes) – a membrane that separates the bone itself from the extracellular fluid.

- pumps calcium ions from the bone fluid into the extracellular fluid
- mobilizes exchangable calcium
- PTH stimulates this pump - rapid phase begins in minutes, increases progressively for several hours.
Compensatory responses to decreased plasma ionized calcium concentration mediated by parathyroid hormone (PTH) and vitamin D.
Overview of Calcium Distribution

Kidney

Normally
- the renal tubules reabsorb 99 per cent of the filtered calcium
- about 1% -100 mg/day is excreted in the urine

- Normal calcium excretion –
  - <4 mg/kg body weight/day
  - < 200 mg/d (5 mmol/d)

- > 4 mg/kg body mass /day – hypercalciuria
Kidney - Calcium Reabsorption in the Renal Tubules

1). Proximal tubule

- Independent on PTH
- Usually parallels sodium and water reabsorption.
- Absorbed 65 per cent of the filtered calcium
Kidney - Calcium Reabsorption in the Renal Tubules

2). Thick ascending loops of Henle

- Dependent on PTH
- Absorbed 20-35 per cent of the filtered calcium
Calcium Reabsorption in the Renal Tubules

3). Distal and collecting tubules

- Dependent on PTH
- Absorbed 4-9 per cent of the filtered calcium
Kidney - Phosphate Reabsorption in the Renal Tubules

**Proximal tubule**
- Usually - continual excretion of phosphate into the urine
- Phosphate threshold = 0.8 mM/L
- $Tm = 0.1$ mM/min

**PTH**
- Inhibits phosphate reabsorption
- Increases phosphate excretion (phosphaturic effect)
  - Inhibits $Na^+$-phosphate cotransport
  - Lowers $Tm$
Bone resorption

\[ \text{PTH} \]

\[ + \text{1,25(OH)}_2\text{D}_3 \]

\[ \text{Excretion of } \text{PO}_4^{3-} \]

\[ \uparrow \text{Ca}^{2+} \quad + \quad \downarrow \text{PO}_4^{3-} \]
Kidney – Reabsorption in the Renal Tubules

- ↑ reabsortion of magnesium ions, hydrogen ions
- ↓ reabsortion of sodium, potassium, and amino acids
FIGURE 7-13 Hormonal regulation of Ca\(^{2+}\) metabolism. ECF = extracellular fluid; PTH = parathyroid hormone.
Actions of PTH

Compensatory responses to decreased plasma ionized calcium concentration mediated by parathyroid hormone (PTH) and vitamin D.
Activation of Vitamin D

Sunlight

7-Dehydrocholesterol $\rightarrow$ Previtamin D3 $\rightarrow$ Vitamin D3

(cholecalciferol)

LIVER $\rightarrow$ 25-Hydroxylase

25-Hydroxycholecalciferol $\leftarrow$ Other metabolites

25-Hydroxycholecalciferol $\rightarrow$ 24-Hydroxylase

24-Hydroxycholecalciferol

KIDNEY $\rightarrow$ 1α-Hydroxylase

1,25-Dihydroxycholecalciferol

$\downarrow$ [Ca $^+$], $\uparrow$ PTH, $\downarrow$ [phosphate]

Intestinal absorption of calcium
Activation of Vitamin D

Activation of vitamin D$_3$ to form 1,25-dihydroxycholecalciferol and the role of vitamin D in controlling the plasma calcium concentration.
Activation of Vitamin D

Figure 21-7. Formation and hydroxylation of vitamin D₃. 25-Hydroxylation takes place in the liver, and the other hydroxylations occur primarily in the kidneys. The formulas of 7-dehydrocholesterol, vitamin D₃, and 1,25-dihydroxycholecalciferol are also shown.
Effect of Plasma Calcium Level on Plasma 1,25-Dihydroxycholecalciferol Concentration

**Figure 79-8**

Effect of plasma calcium concentration on the plasma concentration of 1,25-dihydroxycholecalciferol. This figure shows that a slight decrease in calcium concentration below normal causes increased formation of activated vitamin D, which in turn leads to greatly increased absorption of calcium from the intestine.
**Table 7-11** Summary of Hormones that Regulate Ca^{2+}

<table>
<thead>
<tr>
<th>PTH</th>
<th>Vitamin D</th>
<th>Calcitonin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stimulus for secretion</strong></td>
<td>Serum [Ca^{2+}]</td>
<td>Serum [Ca^{2+}]</td>
</tr>
<tr>
<td></td>
<td>↓</td>
<td>↑ PTH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ Serum [phosphate]</td>
</tr>
<tr>
<td><strong>Action on:</strong></td>
<td><strong>Resorption</strong></td>
<td><strong>Resorption</strong></td>
</tr>
<tr>
<td>Bone</td>
<td>↑</td>
<td>↑ P reabsorption</td>
</tr>
<tr>
<td></td>
<td>↓ P reabsorption</td>
<td>↑ urinary cAMP</td>
</tr>
<tr>
<td></td>
<td>(↑ urinary cAMP)</td>
<td>↑ Ca^{2+} reabsorption</td>
</tr>
<tr>
<td>Kidney</td>
<td>↑ Ca^{2+} reabsorption</td>
<td>↑ Ca^{2+} reabsorption</td>
</tr>
<tr>
<td></td>
<td>↑ Ca^{2+} absorption</td>
<td>↑ Ca^{2+} absorption</td>
</tr>
<tr>
<td></td>
<td>(via activation of vitamin D)</td>
<td>(via calbindin D-28K)</td>
</tr>
<tr>
<td>Intestine</td>
<td>↑ Ca^{2+} absorption</td>
<td>↑ P absorption</td>
</tr>
<tr>
<td><strong>Overall effect on:</strong></td>
<td><strong>↑</strong></td>
<td><strong>↑</strong></td>
</tr>
<tr>
<td>Serum [Ca^{2+}]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum [phosphate]</td>
<td>↓</td>
<td></td>
</tr>
</tbody>
</table>

cAMP = cyclic adenosine monophosphate. See Table 7-1 for other abbreviation.
Effect of PTH and Calcitonin on Blood Calcium Level

High blood calcium

Stimulates

Calcitonin released

Inhibits

Thyroid

Low blood calcium

Stimulates

Parathyroid hormone released

Inhibits

Parathyroid

Release of calcium from bone
Absorption of calcium in intestines
Reabsorption of calcium in kidneys

Blood calcium reduced

Blood calcium increased
Case

Carl is a 53-year-old violinist with a local symphony orchestra. He has always been in excellent heath. However after two sets of tennis on a hot day, he suddenly experienced the worst pain in his life. The pain came in waves that started in his right flank and radiated into his groin. When he went to bathroom, he voided bright red urine.

His tennis partner drove him to the emergency room, where an ultrasonography showed several small stones in the right kidney and an enlarged ureter.

Carl was sent home with a prescription of narcotics and instruction to drink lots of water and „wait it out”. This evening he voided red urine and two brown stones.

There was nothing unusual in this history, except for constipation and his wife`s new „health kick” (She had convinced Carl to take multivitamins and Ca2+ supplementation).
<table>
<thead>
<tr>
<th>Laboratory Finding</th>
<th>Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total serum Ca(^{2+})</td>
<td>11.5 mg/dL</td>
<td>(normal, 9-11 mg/dL)</td>
</tr>
<tr>
<td>Serum ionized Ca(^{2+})</td>
<td>5.75 m/dL</td>
<td>(normal, 4-5.2 mg/d)</td>
</tr>
<tr>
<td>Serum phosphate</td>
<td>2 mg/dL</td>
<td>(normal, 3-4 mg/dL)</td>
</tr>
<tr>
<td>Serum PTH</td>
<td>125 pg/mL</td>
<td>(normal, 10-65 pg/mL)</td>
</tr>
<tr>
<td>Alkaline phosphate</td>
<td>Elevated</td>
<td></td>
</tr>
<tr>
<td>Urinary Ca(^{2+}) excretion</td>
<td>Elevated</td>
<td></td>
</tr>
</tbody>
</table>
Diagnosis?
<table>
<thead>
<tr>
<th>Disorder</th>
<th>PTH</th>
<th>1,25-Dihydroxycholecalciferol</th>
<th>Bone</th>
<th>Urine</th>
<th>Serum $[\text{Ca}^{2+}]$</th>
<th>Serum $[\text{P}]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperparathyroidism</td>
<td>↑</td>
<td>↑ (PTH stimulates $1\alpha$-hydroxylase)</td>
<td>↑ Resorption</td>
<td>↑ P excretion (phosphaturia)</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ Ca$^{2+}$ excretion (high filtered load of Ca$^{2+}$)</td>
<td>↑</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ urinary cAMP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humoral hypercalcemia of malignancy</td>
<td>↓</td>
<td>↓</td>
<td>↑ Resorption</td>
<td>↑ P excretion</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Surgical hypoparathyroidism</td>
<td>↓</td>
<td>↓</td>
<td>↓ Resorption</td>
<td>↓ P excretion</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Pseudohypoparathyroidism</td>
<td>↑</td>
<td>↓</td>
<td>↓ Resorption (defective $G_s$)</td>
<td>↓ P excretion</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ urinary cAMP (defective cAMP)</td>
<td></td>
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</tr>
<tr>
<td>Chronic renal failure</td>
<td>↑ $(2^\circ)$</td>
<td>↓ (caused by renal failure)</td>
<td>Osteomalacia (caused by ↓ 1,25-dihydroxycholecalciferol)</td>
<td>↓ P excretion</td>
<td>↓ $(caused by \downarrow 1,25$-dihydroxycholecalciferol)</td>
<td>↑ $(caused by \downarrow P$ excretion)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ Resorption (caused by ↑ PTH)</td>
<td></td>
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</tr>
</tbody>
</table>

cAMP = cyclic adenosine monophosphate; GFR = glomerular filtration rate. See Table 7-1 for other abbreviation.
Primary Hyperparathyroidism („stones, bones, and groans”)

• Cause
  - autonomous secretion of PTH (not inhibited by hypercalcemia)

  ➢ Single adenoma (85%)
  ➢ Parathyroid hyperplasia (15%)
  ➢ Parathyroid carcinoma (1%)

In 50-60% patients - only one manifestation!
Primary Hyperparathyroidism - $\uparrow$ PTH

$\uparrow$ Bone resorption

MILD - bone deposition can compensate for reabsorption

SEVERE - bone reabsorption outstrips deposition

- osteoporosis, osteolysis;
- subperiosteal resorption
- bone cysts, fractures
Figure 11-8 X-ray of hand showing marked evidence of hyperparathyroidism in a patient with renal failure and secondary hypersecretion of PTH. Note resorption of tips of distal phalanges and subperiosteal resorption on radial sides of phalanges from second and third fingers.
Kidney - Calcium Reabsorption in the Renal Tubules

Physiologic condition

*Primary Hyperparathyroidism - Excess PTH*

- Hypercalcemia
- ↑ filtered load of Ca$^{2+}$
- Despite increased Ca$^{2+}$ reabsorption, the filtered load of Ca$^{2+}$ eventually overwhelms the reabsorptive capacity of the kidney
- ↑ urinary Ca$^{2+}$ excretion

**Extreme tendency to form kidney stones**

- ↑ urinary phosphate excretion
Primary Hyperparathyroidism - Excess PTH

Renal Manifestations

- Nephrocalcinosis
- Kidney stones
**Primary Hyperparathyroidism - ↑PTH**

**GI Manifestations**

- Nausea, constipation
- Peptic ulcer
  - Calcium stimulates secretion of gastrin
- Pancreatitis — pathogenesis (?)
  - Calcium may activate pancreatic trypsinogen
  - Increased intravascular coagulation
  - Precipitation of calcium in alkaline pancreatic secretion
Primary Hyperparathyroidism - \( \uparrow \text{PTH} \)

Nervous and Muscular Systems

- First manifestation – calcium above about 12 mg/dL
- Marked manifestation – calcium level above 15 g/dL
- Calcium above 17 mg/dL - calcium phosphate crystals are likely to precipitate throughout the body

Depression of Nervous System and Muscle Activity

- Sluggish reflex activities
- Muscle weakness, atrophy
- Drowsiness, lethargy
- A great spectrum of psychiatric disorders (depression, memory impairment)
<table>
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<th>PTH</th>
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<th>Urine</th>
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<th>Serum [P]</th>
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<td>—</td>
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<td>↑ P excretion</td>
<td>↑</td>
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<td>malignancy</td>
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<td>↑</td>
<td>↓</td>
<td>↓ Resorption</td>
<td>↓ P excretion</td>
<td>↓</td>
<td>↑</td>
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<td></td>
<td></td>
<td></td>
<td>↓ (defective G&lt;sub&gt;α&lt;/sub&gt;)</td>
<td>↓ urinary cAMP (defective G&lt;sub&gt;α&lt;/sub&gt;)</td>
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<td>↓ (caused by ↓ 1,25-dihydroxycholecalciferol)</td>
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<td></td>
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<td></td>
<td>↑ Resorption</td>
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<td></td>
<td></td>
<td>(caused by ↑ PTH)</td>
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</tbody>
</table>

cAMP = cyclic adenosine monophosphate; GFR = glomerular filtration rate. See Table 7-1 for other abbreviation.
HYPOPARATHYROIDISM

Causes
- Idiopathic (parathyroid glands absent, hypoplastic),
- Surgical hypoparathyroidism (most common)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH level</td>
<td>↓</td>
</tr>
<tr>
<td>1,25 (OH)$_2$ D$_3$</td>
<td>↓</td>
</tr>
<tr>
<td>BONE</td>
<td>↓ resorption</td>
</tr>
<tr>
<td>URINE</td>
<td>↓ P excretion</td>
</tr>
<tr>
<td>Serum [P]</td>
<td>↑</td>
</tr>
<tr>
<td>Serum [Ca$^{2+}$]</td>
<td>↓ - HYPOCALCEMIA</td>
</tr>
</tbody>
</table>

Nervous System  
↑ permeability of neuronal membranes to Na$^+$ → ↑ excitability of nervous system → TETANY

Muscular system  
Muscle cramps, stiffness, contractions – “carpopedal spasm”: “obstetrical hand”, plantar flexion of toes

Latent tetany - positive results of provocative tests:
- Chvostek's sign – a twitch of facial and upper lip muscles produced by a sharp tap given over the facial nerve
- Trousseau's sign – “carpopedal spasm” induced by a sharp reduction of blood flow obtained with a blood pressure cuff
Figure 79–2

Hypocalcemic tetany in the hand, called carpopedal spasm.
Thank you