Metabolism Of Calcium and Phosphorus

*Three hormones crucially involved:

Vitamin D (1,25- (OH)2-D3)

Parathyroid hormone (PTH)

Calcitonin (CT)
Calcium is needed for:

- Bone Matrix (70% CaOH in form of Hydroxyapatite)
- Muscle Contraction
- Nerve Impulses
- Blood Clotting
- Cellular Metabolism

Importance of Maintaining Extracellular \([\text{Ca}^{2+}]\):

- Muscle contraction & relaxation
- Nerve conduction
- Blood clotting
- Bone and teeth formation
- Secretory activity of endocrine & exocrine cells
- Second messenger
The diagram illustrates the regulation of calcium (Ca) and phosphorus (P) balance in the body. Calcium and phosphorus are absorbed from the gut into the bloodstream, where they can be regulated by the parathyroid hormone (PTH) and calcitriol (CT). These hormones influence the balance of calcium and phosphorus in the serum, bone, and kidney. When the serum levels of calcium and phosphorus are high, PTH is released, increasing calcium and decreasing phosphorus. When levels are low, PTH decreases, allowing calcium and phosphorus to be reabsorbed from the gut and bone. The kidney plays a crucial role in this process, releasing or reabsorbing calcium and phosphorus based on the body's needs.
Calcitriol plays an important role in maintaining normal blood [Calcium]
Homeostasis of Calcium

Important for bone growth in children. It is now being given to older adults to help reverse osteoporosis.

Rising calcium level has not been shown to increase bone deposition by itself, but it makes it possible.

Other sources precede bone as a source of calcium.

Osteoclasts degrade bone matrix and release Ca^{2+} into blood

Parathyroid glands release parathyroid hormone (PTH)

Calcitonin stimulates calcium salt deposit in bone

Falling blood Ca^{2+} levels

Imbalance

Calcium homeostasis of blood 9-11 mg/100 ml

Rising blood Ca^{2+} levels

G cells in thyroid gland release calcitonin
Major Organs Regulate Calcium & Phosphate Balance

**Intestinal tract**

– the interface between Ca metabolism and the external environment  
– Ca is absorbed by passive diffusion and active transport.

Active absorption is stimulated by 1,25-(OH)2-D

– Ca enters ECF and into equilibrium within ECF, glomerular filtrate, and bone fluid

– Absorption increases during growth, pregnancy and lactation; Ca loss occurs during pregnancy and lactation

**Kidneys**

– 99% of Ca reabsorbed by renal tubules
– PTH increases Ca reabsorption
**Skeleton**

- Contains over 99% of body Ca
- Ca provides mechanical strength to the bones
- Bone serves as a reservoir for maintaining plasma Ca homeostasis

**Resorption:** Osteoclasts do this, using HCL and ACID PHOSPHATASE to dissolve bone matrix;

**Remodeling:** Ostoblasts do this, collagen fibers and hydroxyapatite matrix
Where do we get calcium (Ca)?

70 % inorganic matrix composed of Ca-salts in Hydroxyapatite Ca$_{10}$(PO$_4$)$_6$(OH)$_2$;

The skeleton is reservoir for the minerals Ca (and phosphorous);

Resorption – the process of dissolving bone and releasing its minerals into the blood for other uses;

The OSTEOCLAST secretes ACID PHOSPHATASE or sometimes HCL to digest bone matrix. (Secreted by lysosomes)
Calcium Pool

Three major pools of calcium in the body:
- intracellular calcium
- calcium in extracellular fluid and blood
- bone calcium

Adult body contains about 1kg calcium of which 99% is stored in skeleton.

About 1% of bone calcium is exchangeable with extracellular calcium pool.

Extracellular Calcium pool is in equilibrium with intracellular Calcium pool.

It is critical to maintain blood calcium concentrations within a tight normal range.

Deviations above or below the normal range frequently lead to serious disease.
Plasma Calcium Levels

<table>
<thead>
<tr>
<th></th>
<th>mg/dl</th>
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</thead>
<tbody>
<tr>
<td>Total calcium (Ca)</td>
<td>8.8 - 10.6</td>
</tr>
<tr>
<td>Ionized Ca</td>
<td>4.7</td>
</tr>
<tr>
<td>Protein bound-Ca</td>
<td>4.8</td>
</tr>
<tr>
<td>Complexed Ca (phosphate, citrate, etc)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Only free calcium is biologically active form!
VITAMIN D

The vitamin That Works
Like a hormone

Its Role in Calcium
Homeostasis
How Does ‘D’ Compare To Hormones?

- **Vitamin D3 is not** secreted by a classical endocrine gland, but its metabolite acts as a hormone by the mechanism similar to that of thyroid and steroid hormones - each of the forms of vitamin D is hydrophobic, and is transported in blood bound to carrier proteins; acts through nuclear receptors.

- The active form of the hormone is released from the kidney and acts at distant sites or locally.

- Only a very small proportion of vitamin D remains in a free form in the circulation and has a serum t1/2 of about 5 hours.

- **Sources of vitamin D**: produced in the skin by UV radiation (D3); ingested in the diet (D3 rich in fish, liver, milk; D2 rich in vegetables).
Warm Up and Hydroxylate 3X

Major source – sunlight

Skin
- Cholecalciferol (vitamin D₃)
- 7-Dehydrocholesterol

Liver
- 25-hydroxycholecalciferol (25-hydroxy vitamin D₃)
- 25-dihydroxyvitamin D₃

Kidney
- 1,25-dihydroxyvitamin D₃

Minor source – dietary intake
- Vitamin D₃ (fish, meat)
- Vitamin D₂ (vitamin supplements)

↑ Calcium absorption (small intestine)
↑ Urinary calcium re-absorption (kidney)
↑ Bone mineralisation

Maintains calcium balance in the body via the action of parathyroid hormone
Sunlight (290-310 nm) stimulates skin cell to produce previtamin D3 which is then converted to vitamin D3

Over exposure to sunlight converts previtamin D3 to inactive products

Vitamin D has very little intrinsic biological activity and must undergo successive hydroxylations in order to act as a hormone

In liver, it is hydroxylated to 25-OH-D which is transported to kidney to form 1,25-(OH)2-D or 24,25-(OH)2-D

1,25-(OH)2-D is the most potent vitamin D metabolite
Vitamin D helps...

to facilitate intestinal absorption of Ca, as well as to stimulate absorption of phosphate and magnesium ions – increases synthesis of Ca pump, Ca channel, calbindin: increases active absorption in the duodenum. **In the absence of vitamin D, dietary Ca is not absorbed efficiently.**

to regulate the proliferation and differentiation of both types of bone remodeling cells: those for bone breakdown or for reforming the bone anew (stimulating Ca and Pi resorption; providing Ca and Pi from old bone to mineralize new bone). **to retain Ca, although there is some proliferation of osteoclasts, the NET result is Ca absorption and remodelling outweighs resorption;**

to enhance Ca and Pi reabsorption in kidney
The vitamin D form, 1,25-dihydroxcholecalciferol [1,25(OH)2D3],

- stimulates the synthesis of the epithelial calcium channels in the plasma membrane calcium pumps, and

- induces the formation of the **calbindins**, which enhance Ca absorption

Ca absorption is transported across the epithelial cell, which is largely enhanced by the carrier protein **calbindin**, the synthesis of which is totally dependent on vitamin D
**Calbindins**

- A family of calcium-binding proteins

- Concentrations rise hours after Ca entry from intestinal lumen

- Free Ca across the intestinal cell and buffer the high Ca concentration and maintain a favorable gradient for Ca to enter across apical membrane

- Calbindins allow the intestinal cells to absorb large amounts of Ca while keeping free cytosolic Ca low
Slight decrease in [Ca2+] below normal causes marked formation of activated VD, which in turn leads to greatly increased absorption of Ca from intestine
Parathyroid Gland

- 4 Parathyroid glands are usually found *posterior to the* thyroid gland
- Total weight of parathyroid tissue is about 150mg
- Main cell type - chief cells, present throughout life
**Parathyroid Hormone (PTH)**

Polypeptide, synthesized as prepro-PTH

\[ \text{[PTH]} = 10\sim 50\text{ng/L}, \]

Half life: 20\sim 30 \text{ min}

**PTH Related Protein (PTHrp)**

Originally found as a product from cancerous tissue
Also produced by normal tissues: skin keratinocytes, lactating mammary epithelium, placenta, and fetal parathyroid glands

**Homology** - the PTHrp exhibits most effects of PTH on bone and kidney, via binding to PTH receptor- effects are different, since there is an additional receptor in the body that responds to PTH but not to PTHrP
PTH functions - mediated through cAMP mechanism

Major target organs

- bone (direct effect)
- kidney (direct effect)
- intestinal tract (indirect effect)

Overall effect

- increase plasma [Ca2+]
- decrease plasma [Pi]
- increase urinary cAMP
**PTH on Bone**

**Rapid action:** in minutes
- ↑ osteocyte membrane permeability for Ca2+ → liquid Ca of bone enters the cells → calcium pump transports Ca2+ to the extracellular fluid → ↑ Ca2+

**Delayed action:** in 12~14h
- ↑ osteolysis of osteoclast → ↑ Ca2+
- ↑ production of osteoclast → ↑ Ca2+
**PTH on Kidney**

*Increases reabsorption of Ca* from thick ascending limb and distal tubule by $\uparrow$ Ca$_2$+-ATPase and Na+-Ca$_2$+ antiporter

*Inhibits reabsorption of Pi* from proximal tubule $\rightarrow$ prevents precipitation

*Stimulates the synthesis of 1,25-(OH)$_2$-D*
  - cAMP mechanism
  - decrease Pi

*Therefore, PTH indirectly increases Ca absorption from intestine*
Sites of PTH Action:
Inverse Relationship between Plasma Ca\(^{2+}\) & PTH
1,25-(OH)2-D and PTH form negative feedback loop

Mg – chronic hypomagnesia inhibits PTH synthesis and impairs response of target tissues to PTH

[Pi]↑ → [Ca2+]↓ → PTH↑
Parathyroid glands

Increased calcium in blood

Parathyroid hormone

Bones

+ Calcium reabsorption

Kidneys

1,25 hydroxy-vitamin D

Intestines

+ Calcium absorption

+ Calcium reabsorption

+ Vitamin D hydroxylation
The Thyroid Gland - Calcitonin

a peptide hormone secreted by the parafollicular or “C” cells of the thyroid gland

synthesized as the preprohormone & released in response to high plasma Ca

acts on bone osteoclasts to reduce bone resorption; stimulates the secretion of calcium in the urine

Net result of its action is a decline in plasma Ca & phosphate

In order to maintain relatively constant blood calcium levels, calcitonin works with parathyroid hormone (PTH).
Function of Calcitonin

Major target cell – osteoclast (has calcitonin receptor); cAMP mechanism

Lowers blood Ca levels by inhibiting osteoclasts for bone resorption & stimulating Ca uptake by bones
inhibits synthesis and activity of osteoclasts → ↓ bone turnover
transitory action (‘escape’) due to down-regulation of its receptors

Effect on Ca: Antagonist to PTH - ↓ plasma Ca;
Effect on Pi: same as PTH - ↓ plasma Pi

Renal effect: mild phosphaturia and calciuresis

*Unlike parathyroid hormone and vitamin D, calcitonin plays no role in normal day-to-day regulation of plasma Ca regulation in humans*

Calcitonin is used in acute treatment of hypercalcemia, alternative of estrogen for treating osteoporosis in women; treat Paget disease (localized regions of bone resorption & reactive sclerosis)
实际上，对人类和其他陆栖类生物来说，CT在生理方面所起的作用并不重要。这一惊人的结论可通过两条证据来说明。首先，切除甲状腺（哺乳动物CT的惟一已知来源）对于钙和骨代谢并没有造成明显的影响；其次，在甲状腺髓样癌（一种C细胞恶性肿瘤）中降钙素的过程释放的过度也没有对盐代谢稳定造成明显影响。这说明，人类降钙素的功能仍需进一步探究。

CT有两方面的临床意义。首先，CT作为甲状腺髓样癌的一种肿瘤标志。其次，CT已被发现有几种治疗作用。通过肠道外给药或鼻喷雾降钙素可用治疗骨的Paget病、高血钙危象和骨质疏松症。
Effect of plasma [Ca2+] on plasma PTH and calcitonin
### Hormonal Regulation of $[\text{Ca}^{2+}]$

<table>
<thead>
<tr>
<th>Stimulus for secretion</th>
<th>PTH</th>
<th>Vitamin D</th>
<th>Calcitonin</th>
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<tbody>
<tr>
<td></td>
<td>↓ serum $[\text{Ca}^{2+}]$</td>
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</tr>
<tr>
<td></td>
<td>↑ PTH</td>
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<tr>
<td></td>
<td>↓ serum [phosphate]</td>
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<table>
<thead>
<tr>
<th>Action on:</th>
<th>PTH</th>
<th>Vitamin D</th>
<th>Calcitonin</th>
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</thead>
<tbody>
<tr>
<td>Bone</td>
<td>↑ resorption</td>
<td>↑ resorption</td>
<td>↓ resorption</td>
</tr>
<tr>
<td>Kidney</td>
<td>↓ P reabsorption (↑ urinary cAMP)</td>
<td>↑ P reabsorption</td>
<td>↑ Ca$^{2+}$ reabsorption</td>
</tr>
<tr>
<td></td>
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<table>
<thead>
<tr>
<th>Intestine</th>
<th>PTH</th>
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<th>Calcitonin</th>
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<tr>
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<td>↑ Ca$^{2+}$ absorption</td>
<td>↑ Ca$^{2+}$ absorption (Calbindin D-28K)</td>
<td>↑ P absorption</td>
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<tr>
<td></td>
<td>(via activation of vitamin D)</td>
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<table>
<thead>
<tr>
<th>Overall effect on:</th>
<th>PTH</th>
<th>Vitamin D</th>
<th>Calcitonin</th>
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<tbody>
<tr>
<td>Serum $[\text{Ca}^{2+}]$</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Serum [phosphate]</td>
<td>↓</td>
<td>↑</td>
<td></td>
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</table>
Ca$_2^+$ and Pi Homeostasis
Hypocalcemia

Plasma $[Ca^{2+}]$ falls below normal

$\uparrow$ neuronal membrane Na permeability

Initiation of action potentials

$\uparrow$ Excitability of nerve fiber

$\uparrow$ Excitability of brain

Tetanic muscle contraction

Seizures

damage to blood supply during thyroidectomy
Blood Ca too high - **Hypercalcemia**: sluggish nervous system, possible cardiac arrest

Blood Ca too low - **TETANY**: Inability for muscles to relax (muscles tremor i.e carpopedal spasms and laryngospasms…shuts off air… and can cause suffocation
Rickets: the consequences of inefficient Ca early in life?

Deficiency of vitamin D (dietary deficiency, insufficient sun exposure, liver/kidney diseases) causes inadequate mineralization of new bone matrix (lowered ratio of mineral/organic matrix)

Symptoms: decreased mechanical strength and distortion especially in the long bones of legs

The specific radiographic features:
the failure of cartilage calcification and endochondral ossification (best seen in the metaphysis of rapidly growing bones)
the metaphyses are widened, uneven, concave, or cupped and because of the delay in or absence of calcification, the metaphyses could become partially or totally invisible.
Later in Life….Osteoporosis and Osteomalacia

**Osteoporosis**: loss of bone density

**Osteomalacia**: lack of mineralization