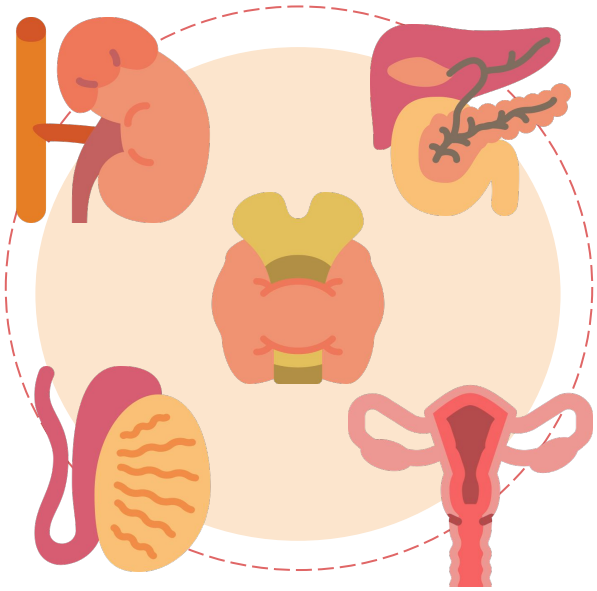

Calcium homeostasis

Objectives:

- List the functions of calcium
- Describe calcium metabolism
- Describe physiology of bone
- Understand and explain hormonal regulation of calcium metabolism
  - Parathyroid hormone
  - Calcitonin
  - Vitamine D

Revised By
Hadeel Awartani
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- Renad AlSwailmy, Sultan AlAqil
- Wejdan AlShamery

Colour index:
- Important
- Numbers
- Extra

Distribution of Ca^{++} in Body

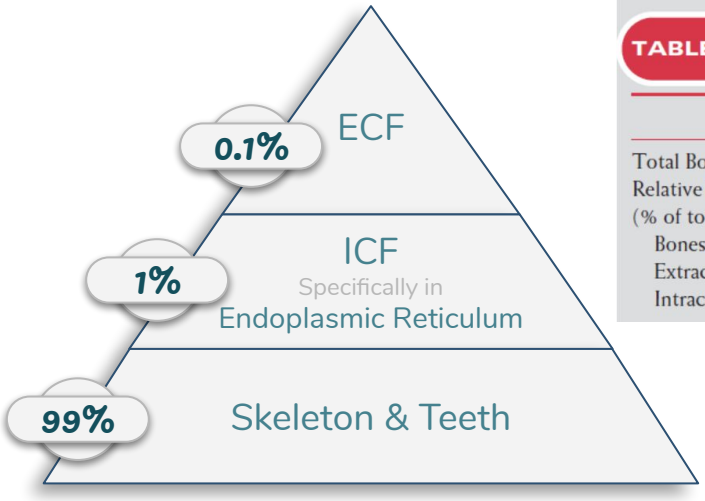


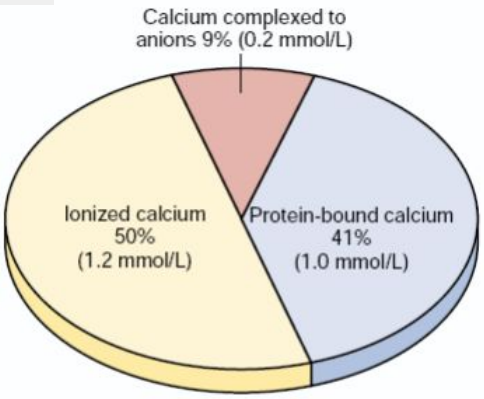
TABLE 36.1 Body Content and Tissue Distribution of Calcium and Phosphorus in a Healthy Adult

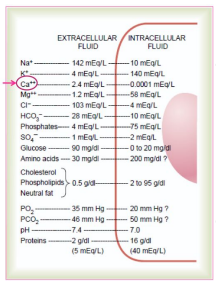
	Calcium	Phosphorus
Total Body Content	1,300 g	600 g
Relative Tissue Distribution (% of total body content)		
Bones and teeth	99%	86%
Extracellular fluid	0.1%	0.08%
Intracellular fluid	1.0%	14%

Great video for lecture 8

Distribution of Ca^{++} in ECF/Plasma

- Total concentration of calcium in ECF =
  - 9-10.5 mg/dl
  - Or 5m mEq/L
  - Or 2.5 mmol/L
- Non Diffusible = 41%
- Diffusible = 59%
  - Complexed 9%
  - Ionized 50%





Ca^{+2} : **ECF** = 2.4 mE\L
ICF = 0.0001.
How the Ca inside the cell is low?
- The amount measured in the cytoplasm only, the rest is in the ER.

Most of Ca^{+2} [1]***in bone 99%***
[2]**ECF: (*plasma +IF*)= 0.1 %** = in mg\dl **9-10.5**
Now we are talking about this 0.1% in three form in ECF:
1. Ca^{+2} bound to protein **41**% = non-diffusible
2. Ca^{+2} bound to anion citrate **9**%=**diffuse**
3. Ionized calcium **50**% = free and can **diffuse** and give the physiological function. If it's increase = acidosis ,If it's decrease = alkalosis

So, *How much do we have **diffusible** plasma* Ca^{+2}? :**59%**

Protein-bound calcium

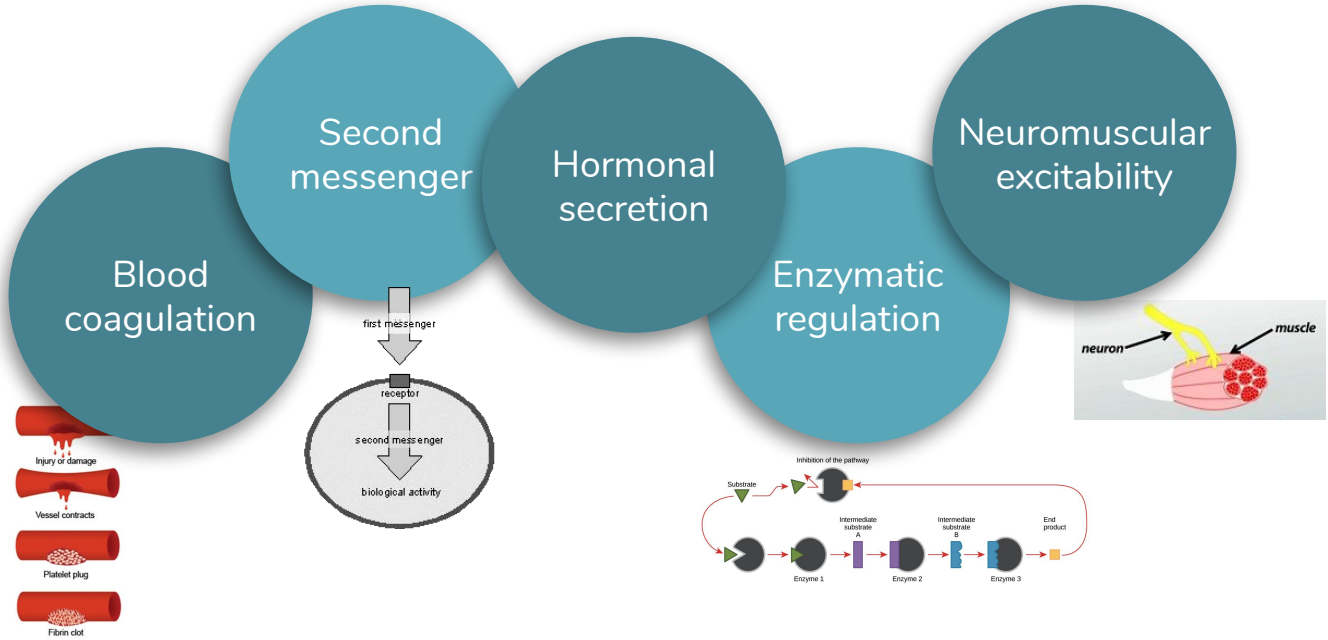
- Most of this calcium is bound to albumin & much smaller fraction is bound to globulin.
- Binding of calcium to albumin is pH-dependent.
- Acute respiratory alkalosis increases calcium binding to protein thereby decreases ionized calcium level.

Acidosis ⇧ Ionized Ca^{2+}

Alkalosis ⇩ Ionized Ca^{2+}

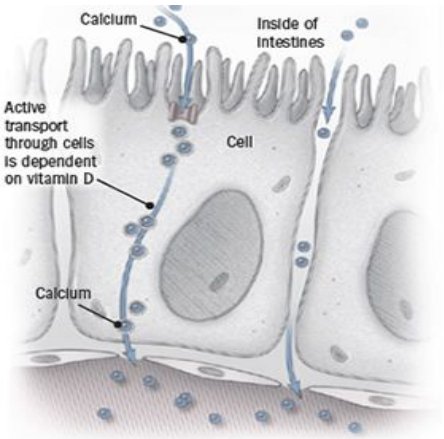
Physiological Importance of Calcium

- Calcium salts in bone provide structural integrity of the skeleton.
- Calcium ions in extracellular and cellular fluids is essential to normal function for the biochemical processes, like:



Calcium Source

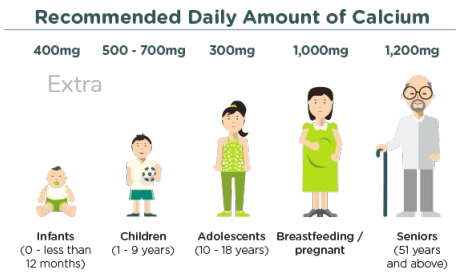
Absorption



- Duodenum:
  - Active transport
- Small intestine
  - concentration gradient

Daily requirements

- 12.5-25 mmol/day:
  - Infants
  - Adults
- 25-35 mmol/day
  - Pregnancy
  - Lactating
  - After menopause



Phosphate

- Phosphorous is an essential mineral necessary: for ATP and cAMP second messenger systems.
- Phosphate plasma concentration is around 4 mg/dL.
- Calcium is tightly regulated with Phosphorus in the body.

- Forms:

TABLE 40.1 Forms of Ca and P_i in Plasma

Ion	mg/dL	Ionized	Protein Bound	Complexed
Ca	8.5–10.2	50%	45%	5%
P_i	3–4.5	84%	10%	6%

Ca^{++} is bound (i.e., complexed) to various anions in plasma, including HCO_3^-, citrate, and SO_4^{2-}. P_i is complexed to various cations, including Na^+ and K^+.
From Koeppen BM, Stanton BA. *Renal Physiology.* 4th ed. Philadelphia: Mosby; 2007.

Bone Cells

Osteocytes

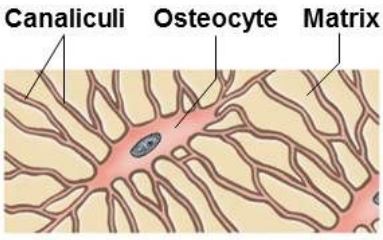
- It's an osteoblasts surrounded by calcified matrix

Osteoclasts

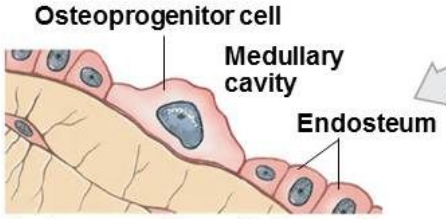
- It's a bone eroding (resorping) cells

Osteoblasts

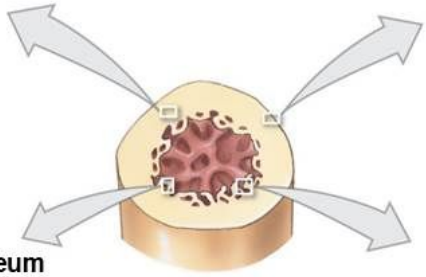
- It's a bone forming cells

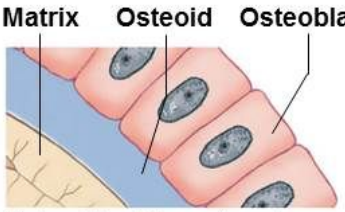


Osteocyte: Mature bone cell that maintains the bone matrix

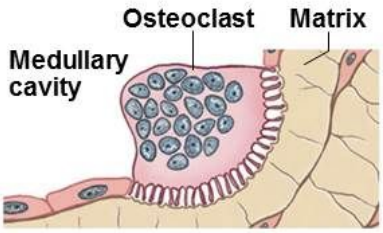


Osteoprogenitor cell: Stem cell whose divisions produce osteoblasts





Osteoblast: Immature bone cell that secretes organic components of matrix



Osteoclast: Multinucleate cell that secretes acids and enzymes to dissolve bone matrix

Notes:

Metabolism of Ca : الأرقام حفظ !!
نفترض شربنا حليب وكانت كمية الكالسيوم فيه 1000مج ايش راح يصير لهذه الكمية في جسمنا ؟
لكن قبل مانشرح ننتبه لشغله صغيرة وهي أنه أصلا في الدم عندنا نسبة الكالسيوم ثابته وهي 1300 مج
فلو اخذت 1000 مج من الحليب وكان في الدم عندي 1300 الجسم بيطلع 1000 نفسها ليش ؟ لأنه مايحتاجها
طيب متى راح يمتصها الجسم أو يطلع كمية أكبر ؟ إذا كان نسبة الكالسيوم في الدم مو الرينج الطبيعي هذا 1300
فلو كانت أكبر بنطلعه وإذا كانت أصغر من هذه الكمية فبتزيد نسبة الامتصاص

الان الشرح اللي نشرحه هذا عبارة لو كانت نسبة الكالسيوم في الدم بالرينج الطبيعي 1300 مج واخذنا حليب فيه له 1000 مج من الكالسيوم ايش راح يصير ؟

- Absorbed from intestine to blood only 350 , remain 650 - will be excreted -
الان فيه كمية كالسيوم راح تفرز من الأمعاء نفسها اللي هي
Gastric juices secreted Ca = 250 so the total now 650+ 250 = 900 excreted in the feces
الان تكلمنا عن Feces
- Now we will explain how it will be excreted into urine = after secretion of 250 from 1300 = remaining 1050 + 350 that have been absorbed = 1400 (from this 1400 kidney will take only 9980 to filter it and reabsorb 9880 so the total amount excreted now is = 100 mg \ day
-
لسا ملخبطين ؟ اعتبروا ال 1300 هي الحصالة اللي نجمع فيها فلوس وماتقدر تأخذ منها ولا تزود عليها لأنها محدودة
و 1000 هي العيدية فتقدر تأخذ من العيدية ومن الحصالة لكن نهاية اليوم ترجع لازم تكون 1300 موجودة في الحصالة لا زيادة ريال و لانقصان

Bone cells :
- Osteoblast (produce collagen)
- this Precipitate collagene called = osteoid

When osteoblast done from its function it's trapped we called it = osteocyte
- Precipitate of calcium called = calcified bone matrix
- Function of the osteoclast is bone resorption = it means the Ca travel from bone to blood but when we talk about Ca absorption from intestine to blood

Regulation of Ca : 9-10.5 (0.1%)

Hypocalcemia in blood :
Tetany , excitability of neuromuscular junction why ? when we have low Ca level the Na permeability increase which lead to depolarize the cell then the cell become excitable

"High ca" Hypercalcemia in blood :
Decrease Na permeability , decrease Na permeability , the cell is less excitable .

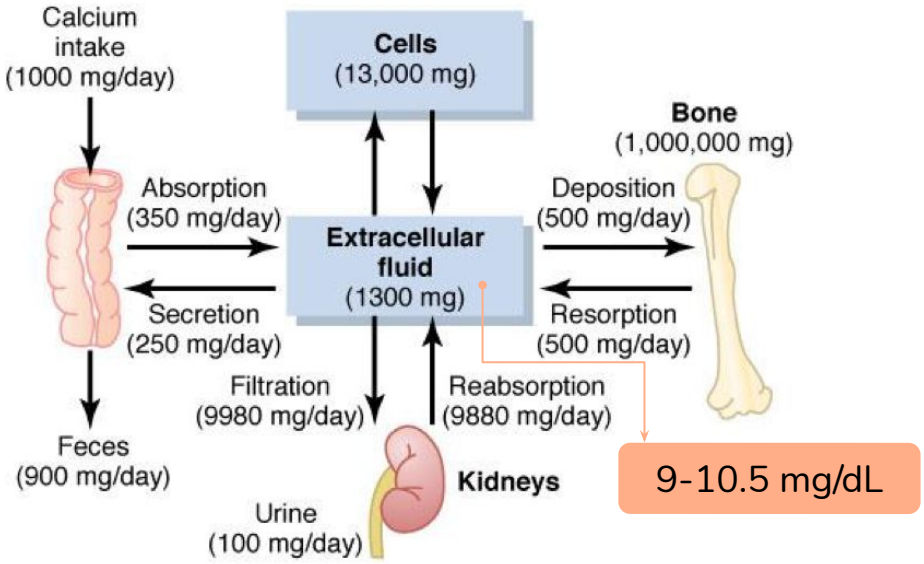
Regulation of Calcium Level

Regulation of Plasma Calcium and Phosphate Concentrations:

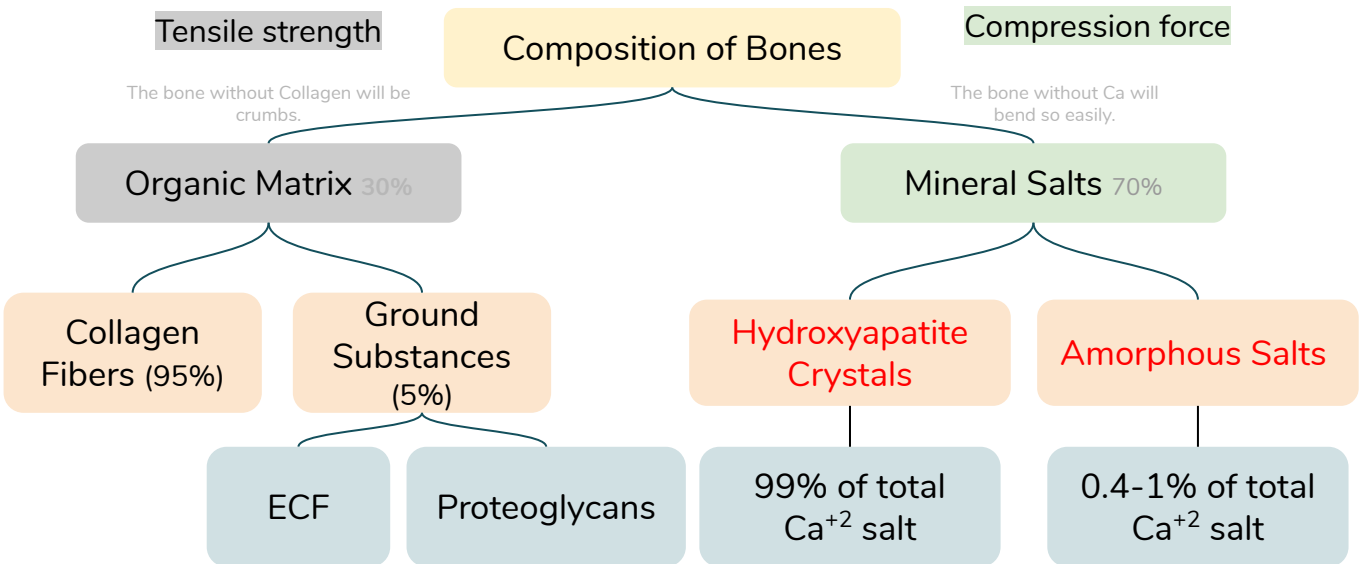
- **Non-Hormonal mechanisms** can rapidly buffer small changes in plasma concentrations of free calcium.
- **Hormonal Mechanisms provide** high-capacity, long-term regulation of plasma calcium and phosphate concentrations.

Tetany ⟷ 9-10.5 mg/dL ⟷ Renal stone

Calcium Metabolism in an Adult Human



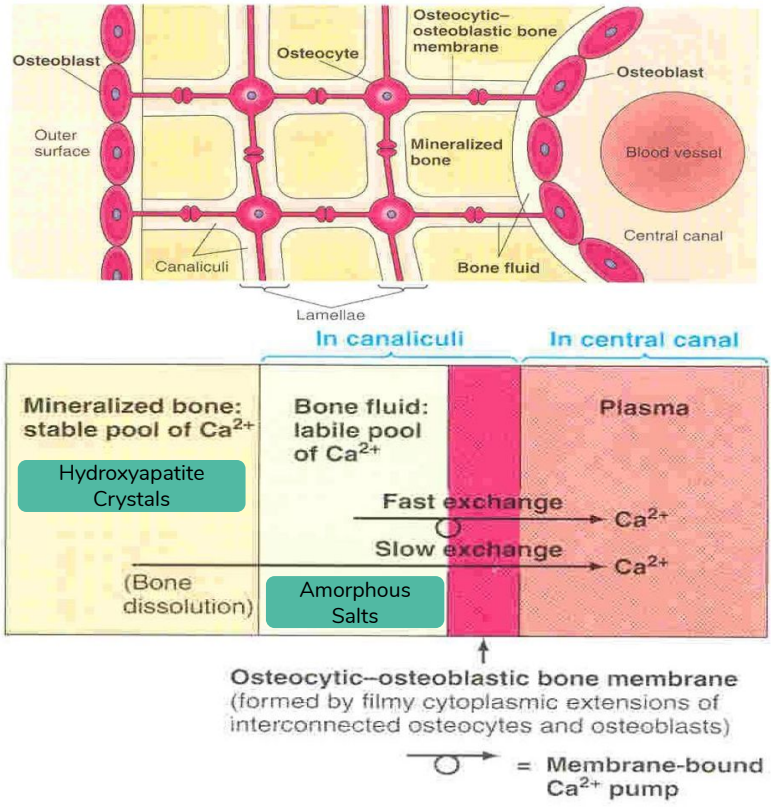
Composition of Bones



Composition of Bones Cont.

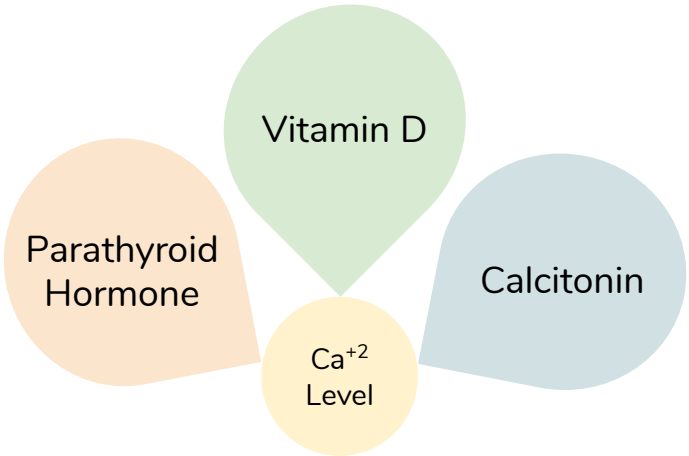
(2) Bone Salts

- **Hydroxyapatite crystals.**
  - In the form of Hydroxyapatite crystals $Ca_{10}(PO_4)_6(OH)_2$
- **Mg, Na, K, Carbonate ions.**
- **Amorphous salts:**
  - A type of exchangeable calcium.
  - Play role in rapid regulation of ionized Ca^{+2} level in ECF.
  - 0.4-1% of total bone Ca^{+2}.
  - Always in equilibrium with Ca^{+2} in ECF.



First of all the bone is highly vascularized. This picture present osteon basic unit.
Let's suppose the level of the Ca is decreased 8 so the first line to exchange is the **amorphous salt** (fast exchange)
Let's suppose the level of the Ca is increase 12 = the Ca come back to the amorphous and storage there, If this doesn't work will go to other line :
Hormonal mechanism give high capacity long term plasma and concentration =parathyroid, vit D, calcitonin hormone

Three Hormones (That contribute to the Regulation of Calcium)



Vitamin D

Vitamin D

Ca^{+2} Level

1,25 Dihydroxycholecalciferol

1.Intestinal tract

Has a potent effect to increase calcium & phosphate absorption

2.Renal

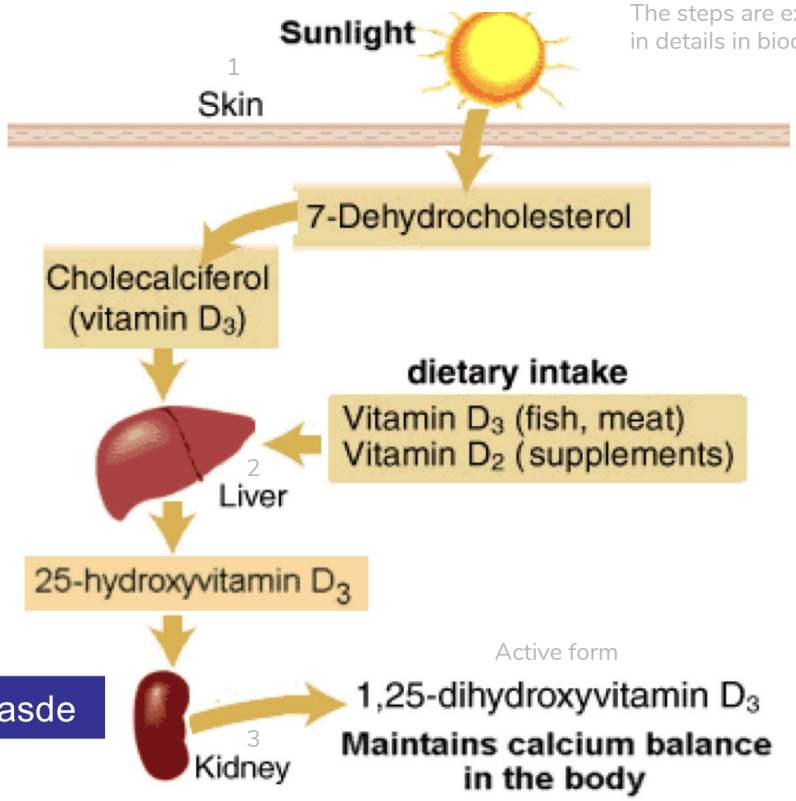
Increases Renal calcium and Phosphate absorption

3.Bones

Bone absorption

Increase calcium blood level

4.stimulates differentiation of immune cells.



The steps are explained in details in biochemistry

Effects of Vitamin D on Bone & Its Relation to Parathyroid Hormone Activity

Vitamin D

Ca^{+2} Level

- Vitamin D in <u>smaller</u> quantities :
- Promotes **bone calcification** by ↑ **calcium and phosphate absorption from the intestine and enhances the mineralization of bone.**
- The administration of <u>extreme</u> quantities of vitamin D causes **absorption of bone**:
  - By facilitating PTH action on bones.
  - Number & activity of osteoclasts.

Imp.

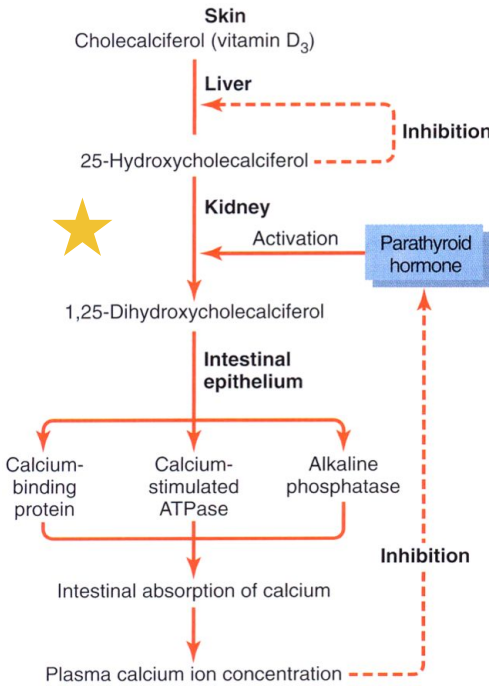
Control of Vit D

Low Ca^{+2} ions

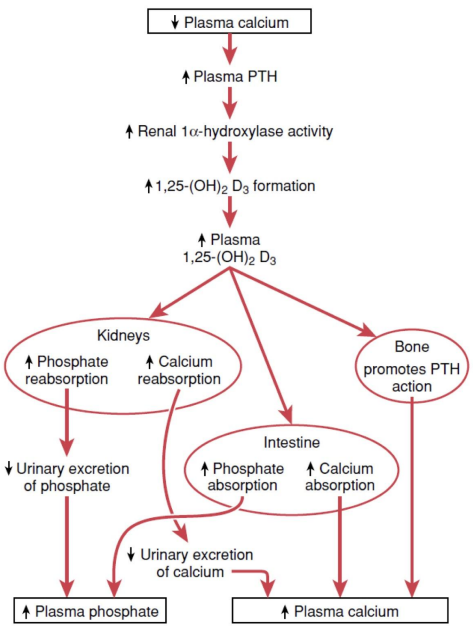
Prolactin

PTH

All stimulate renal **1,alpha hydroxylase.**

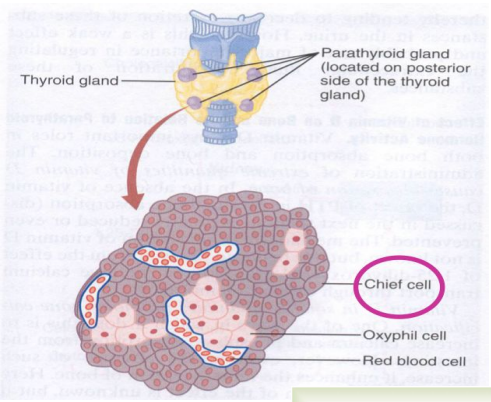


Regulation of calcium level



Parathyroid hormone (PTH)

- Source: Parathyroid gland
- Polypeptide hormone: (84 AA) Molecular Weight: 9500
- Half Life: 10 min
- Overall Effect:
  ↑ **plasma Ca^{++} level**
  ↓ **phosphate level**
- Mechanism of action: acts via 2nd messenger mechanism utilizing **cAMP**



PTH

Ca^{+2} Level

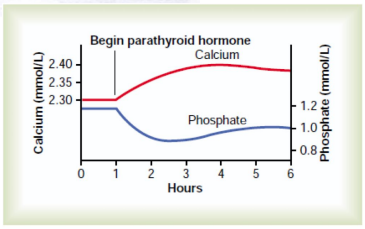


Figure 79–10

Approximate changes in calcium and phosphate concentrations during the first 5 hours of parathyroid hormone infusion at a moderate rate.

Act on

Intestine

↑ absorption of calcium and phosphate indirectly through stimulating formation of 1,25 – $(OH)_2$-D3 in kidney

Bones

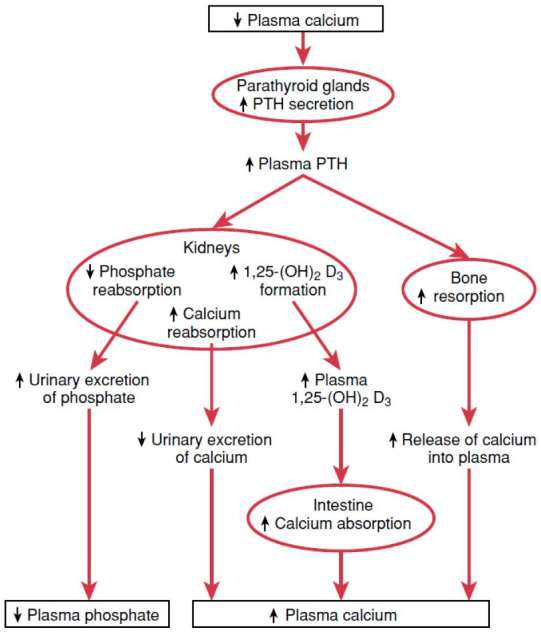
Increase calcium resorption from the bone via:

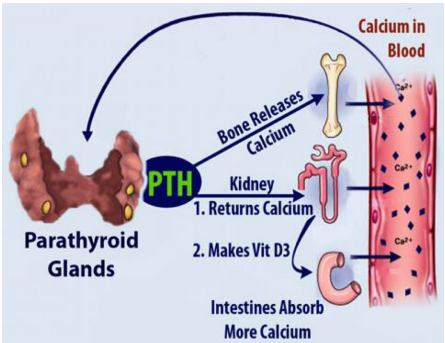
1. Stimulates the formation of new osteoclasts
2. Depression of osteoblastic activity
3. Activation of osteoclasts

Kidney

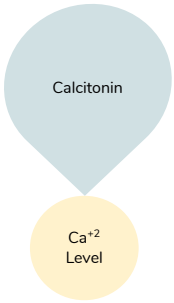
1. ↓ Phosphate reabsorption from the proximal convoluted tubules (phosphaturic action). Leading to :
   ↑Phosphate excretion in the urine
   ↓plasma phosphate concentration
2. ↑ Ca^{+2} & Mg ions reabsorption from the distal convoluted tubules, collection ducts and ascending loop of Henle.
3. ↑ Formation of 1,25 vit D3 in the kidney.

Effect of Calcium level on PTH





Calcitonin



- Source Secreted by the **parafollicular cells (C cells)** of the thyroid gland.
- Natur 32 amino acid peptide.
- Function
  ↓ **blood Ca^{+2} level** very rapidly within minutes.
  (Opposite effect to PTH)
- Stimulus for secretion Increased plasma calcium concentration

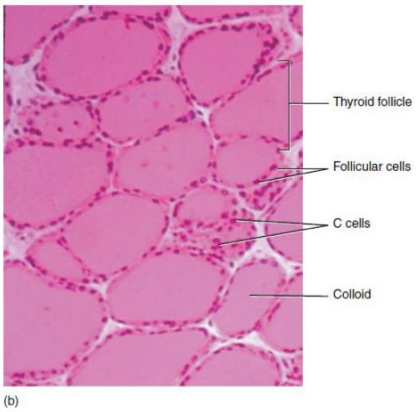
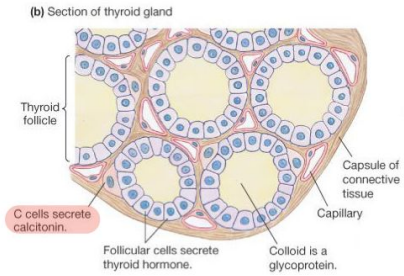


Figure 17.8 The Thyroid Gland. (a) Gross anatomy; (b) histology.



Actions of Calcitonin

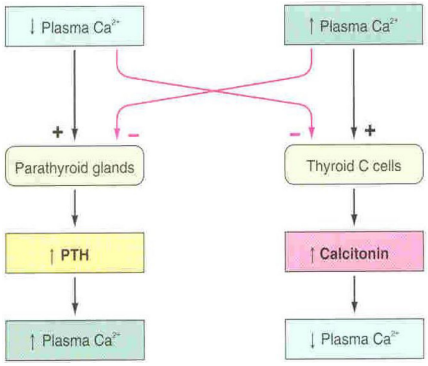
On bone

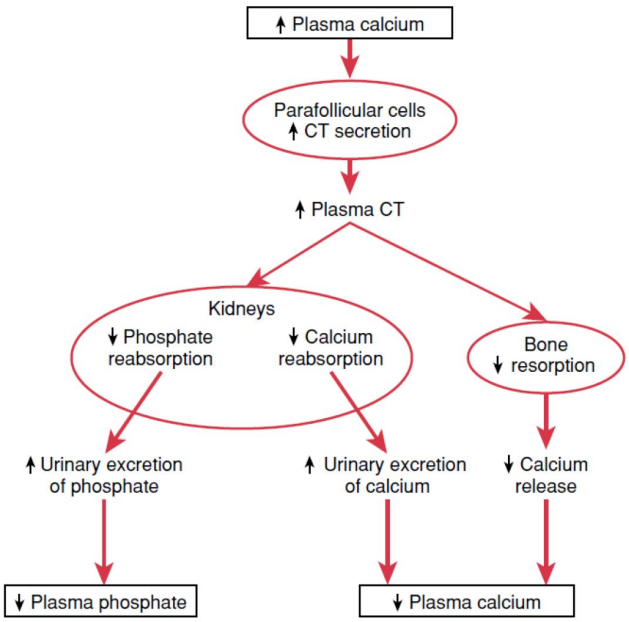
- ↑Ca^{+2} deposition of bone
- Inhibits Bone resorption via:
  - Inhibition of osteoclasts
  - ↓ formation of osteoclasts

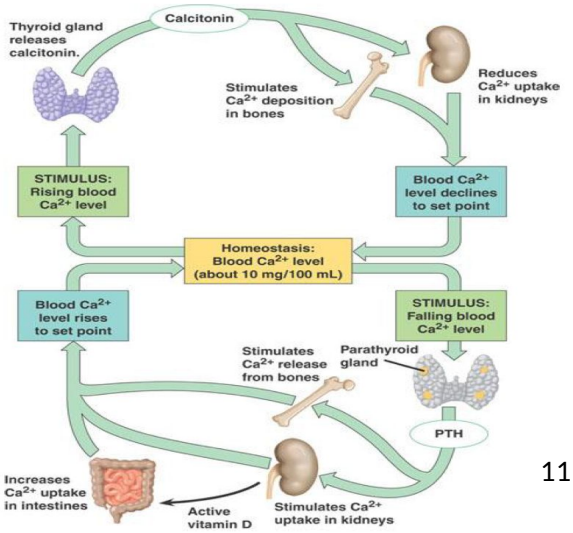
On kidney

- ↓↓ Ca^{++} reabsorption
- ↑↑ Ca^{++} excretion (in addition to phosphate)

Effect of Calcium level on Calcitonin







Summary

Importance of Calcium

Calcium salts in bone provide Structural integrity of skeleton.
Calcium ions: Blood coagulation - 2nd messenger - Hormonal secretion - Enzymatic regulation - Neuromuscular excitability

Regulation of Calcium

- **Non-Hormonal mechanisms** can rapidly buffer small changes in plasma concentrations of free calcium.
- **Hormonal Mechanisms** provide high-capacity, long-term regulation of plasma calcium and phosphate concentrations.

Protein bound calcium

Alkalosis	**Acidosis**
Increases calcium binding to protein. **Ionized Ca levels Decrease**	Decreases Calcium binding to proteins. **Ionized Ca levels Increase**

Calcium level

Less leads to **Tetany**	9-10.5 mg/dL	More leads to **Renal Stones**

Hormones Regulating Calcium Levels

Calcitonin	Vitamin D 1,25 Dihydroxycholecalciferol	Parathyroid Hormone
↓ blood Ca+2 level very rapidly within minutes. (Opposite effect to PTH)	In small quantities: it promotes bone calcification In Extreme quantities: it causes absorption of bone by enhancing effect of PTH and increasing number & activity of osteoclasts	↑ plasma Ca++ level ↓ phosphate level
	Control	
	↓Ca ions - Prolactin- PTH All stimulate 1,alpha hydroxylase	

MCQs

1.Exposure to UV light directly facilitates which of the following?
A) Conversion of cholesterol to 25-hydroxycholecalciferol
B) Conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol
C) Transport of calcium into the extracellular fluid
D) Storage of vitamin D3 in the liver

2.Parathyroid hormone directly
A) controls the rate of 25-hydroxycholecalciferol formation
B) controls the rate of calcium transport in the mucosa of the small intestine
C) controls the rate of formation of calcium binding protein
D) controls the rate of formation of 1, 25-dihydroxycholecalciferol

3.Extracellular ionic calcium activity will be decreased within 1 min by which of the following?
A) Increase in extracellular phosphate ion activity
B) Increase in extracellular pH
C) Decrease in extracellular Pco2
D) All of the above

4.Which of the following increases the rate of excretion of calcium ions by the kidney?
A) Decrease in calcitonin concentration in the plasma
B) Increase in phosphate ion concentration in the plasma
C) Decrease in the plasma level of parathyroid hormone
D) Metabolic alkalosis

5.Which of the following stimulates the secretion of parathyroid hormone (PTH)?
A) Increase in calcitonin concentration
B) Respiratory acidosis
C) Increased secretion of PTH-releasing hormone from the hypothalamus
D) None of the above

6.Which of the following decreases the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol?
A) A diet low in Ca2+
B) Hypocalcemia
C) Chronic renal failure
D) Hyperparathyroidism

Answers
1. A
2. D
3. D
4. C
5. D
6. C