Physiology Team 439

MED439
KING SAUD UNIVERSITY

Revised & Approved

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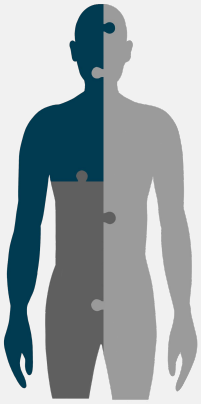


# Calcium Homeostasis & Hypo and Hyperparathyroidism

# 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
- Understand hypo and hyper-parathyroidism
- Identify the normal range of dietary calcium and phosphate intake, distribution in the body, and routes of excretion.
- Know the cells of origin for parathyroid hormone,
- List the target organs and cell types for parathyroid hormone and describe its effects on each.
- Describe the functions of the osteoblasts and the osteoclasts in bone remodeling.
- Describe the regulation of parathyroid hormone secretion and the role of the calcium-sensing receptor.
- Understand the causes and consequences of a) over-secretion, and b) under-secretion of parathyroid hormone, as well as its therapeutic use.
- Identify the sources of vitamin D and the organs involved in modifying it to the biologically active 1,25(OH2)D3 (1-25 dihydroxycholecalciferol). 8. Identify the target organs and cellular mechanisms of action for vitamin D.
- Describe the negative feedback relationship between parathyroid hormone and the biologically active form of vitamin D [1,25(OH2)D3].
- Describe the consequences of vitamin D deficiency and vitamin D excess.
- Name the stimuli that can promote secretion of calcitonin, and its actions.

**Color index:**

- Important.
- Girls slide only.
- Boys slide only.
- Dr's note.
- Extra information.

**Editing File**

# Introduction Of **Bone Composition**

## Bone composition*

### Organic matrix 30%

What is bone **Resorption/ Reabsorption**?
When osteoclast dissolve the bone, so that the calcium will dissolve from the bone to the ECF(blood).

#### Cells 2%

1. **Osteoblasts.** (bone/collagen forming cells)
2. **Osteocytes.** (osteoblasts trapped/ surrounded by calcified matrix)
3. **Osteoclasts.** bone eroding/dissolving Cell (resorping) (phagocytic)

Remodeling of Bone Bone is continually being deposited by osteoblasts, and it is continually being resorbed where osteoclasts are active

#### matrix 98%

**Components**:
-Collagen Fibers (95%)
-Ground Substance (5%): (ECF, Proteoglycans)

**Provide:**
Tensile force (قوة شد) provided by collagen.
If there was no collagen → the bone will break easily

Think of **collagen** like iron (in buildings) → **Tensile force**

Think of **calcium** like cement (in buildings) → **Compressional force**

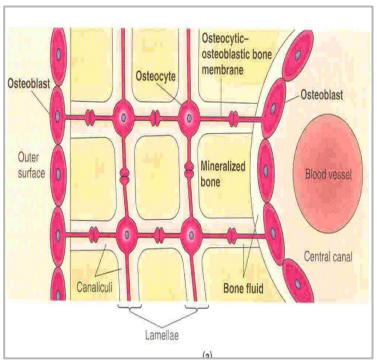
### Inorganic matrix (Mineral salts) 70%

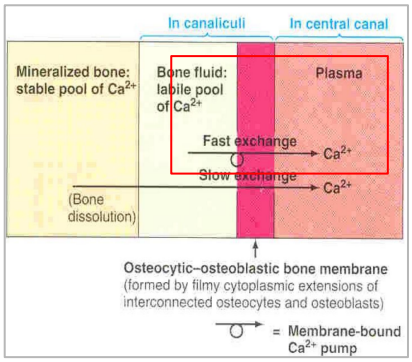
**Components**:
1. Salts of Ca++ & PO4- In the form of **Hydroxyapatite crystals** (99%): [In the form of Hydroxyapatite crystals $Ca_{10}(PO_4)_6(OH)_2$]
2. **Mg, Na, K, Carbonate ions**
3. **Amorphous salts:** A type of exchangeable calcium. Play role in rapid **regulation** of ionized Ca++ level in ECF. 0.4-1% of total bone Ca++ always in equilibrium with Ca in ECF

**Provide:**
Compressional force
If there was no salt → the bone will bend easily

## Mechanical Stress (Wolff's Law):*

- States that bone in a healthy person or animal will adapt to the loads under which it is placed. If loading on a particular bone increases, the bone will remodel itself over time to become stronger to resist that sort of loading.
- For example, the bones of athletes become considerably heavier than those of nonathletes. Also, if a person has one leg in a cast but continues to walk on the opposite leg, the bone of the leg in the cast becomes thin and as much as 30% decalcified within a few weeks, whereas the opposite bone remains thick and normally calcified.
- Patients who have been in hospital beds for weeks can develop hypercalcemia due to bone decalcification from the absence of mechanical stress




If plasma calcium levels decrease, the **very first line** response will be releasing Amorphous salts from bony fluid canaliculi to **quickly** restore normal levels. |||| If that was insufficient to restore normal levels, other mechanism that involve dissolving **Hydroxyapatite crystals** from mineralized bone will start (**slower** response)

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And if plasma calcium levels increased on the other hand, the first response will be precipitating the excess calcium as amorphous salts ||||| If it was insufficient, precipitation as Hydroxyapatite crystals will start.

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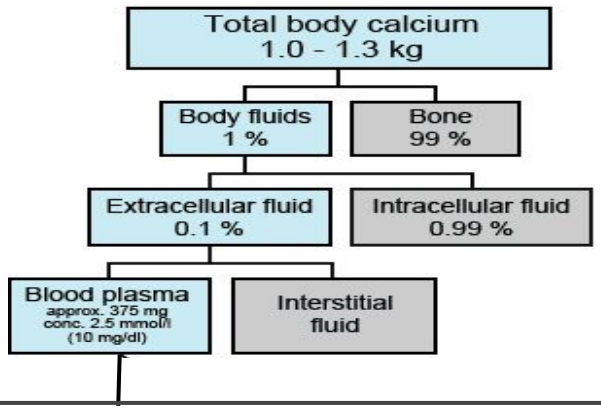
If none of these mechanisms was sufficient to establish homeostasis, other mechanisms will kick in (hormonal.. etc).

# Distribution of Ca++ in Body

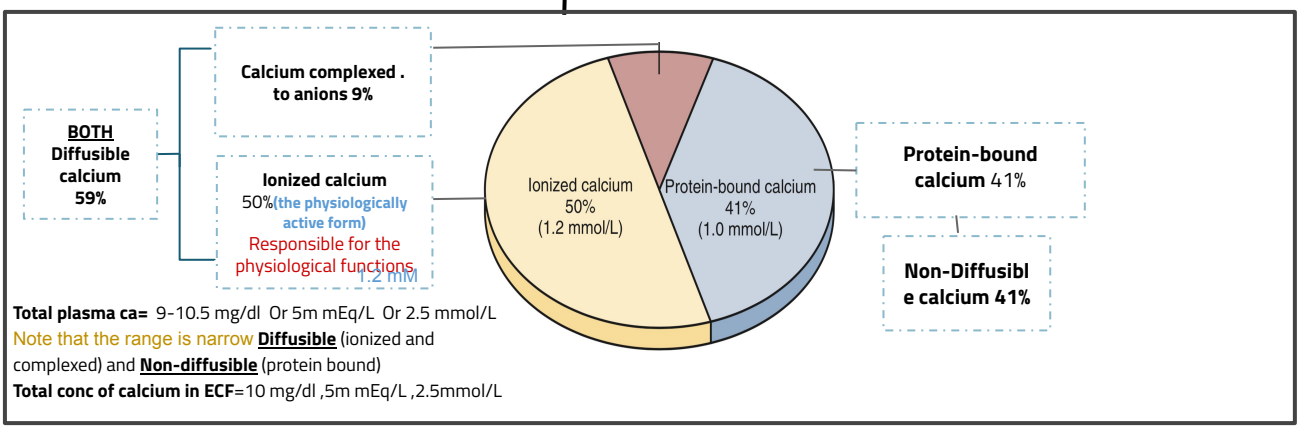
**TABLE 40.1 Forms of Ca and $P_i$ in Plasma**

| 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.




You have to differentiate between total calcium and ionized calcium
(ionized calcium = 50% of total calcium)




**Total plasma ca=** 9-10.5 mg/dl Or 5m mEq/L Or 2.5 mmol/L
Note that the range is narrow **Diffusible** (ionized and complexed) and **Non-diffusible** (protein bound)
**Total conc of calcium in ECF**=10 mg/dl ,5m mEq/L ,2.5mmol/L

## 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:
  Alkalosis ⇒ ↓Ionized $Ca^{2+}$
  Acidosis ⇒↑Ionized $Ca^{2+}$

**Acidemia**:
We have high plasma hydrogen ion levels (low pH). These protons displace protein bound Calcium and move it to the blood causing an **increase in Ionized calcium**

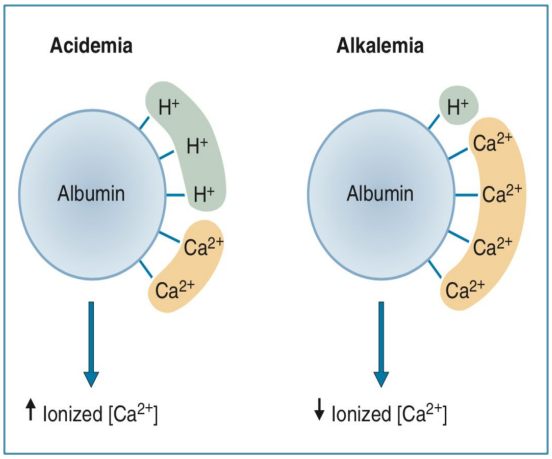
**Alkalemia:**
We have low plasma hydrogen ion levels (high pH). Albumin will have room for more calcium to bind to it which will take away the ionized calcium in the blood. **Decreasing Ionized calcium.**

**In both conditions, if we measure the Total Ca++ levels, it will be similar,** however the ionized Ca++ won't be the same

- ↑Albumin levels → ↓Ionized Ca++

## Phosphate*

- Approximately 85 % of the body's phosphate is stored in bones,14-15 % is in the cells.
- Less than 1% is in the extracellular fluid.
- Although extracellular fluid phosphate concentration is not nearly as well regulated as calcium concentration, phosphate serves several important functions and is controlled by many of the same factors that regulate calcium.



# Calcium*

## Physiological importance

(all maintained by **ionized** 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 :
–Neuromuscular excitability – Hormonal secretion – Enzymatic regulation
– Blood coagulation – Second messenger

Remember GIT: calcium was an important cofactor in several steps of the coagulation cascade (e.g. conversion of prothrombin to thrombin). In hospital laboratories, we prevent clotting of blood samples by adding coagulation inhibitors (such as Citrate) to the test tube (Citrate will bind to calcium and precipitate it. This will prevent it from facilitating the coagulation cascade). If calcium levels in someone's body are low (as low as 5mg/dl), he will bleed to death (because no calcium = no coagulation).

## Source

- Milk ,dairy products ,Fish

## Daily Requirement

- Infants & adults: 12.5 -25 mmol/day will be doubled in pregnancy & after menopause.
- Pregnancy, lactation ,after menopause: 25-35 mmol/day

## Absorption

- Duodenum: active transport In general, calcium is poorly absorbed from GIT
- Small intestine: concentration gradient

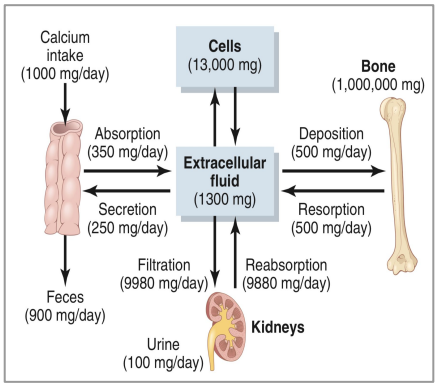
## Metabolism

- 1000-350=650

الفكرة الرئيسية هنا أن تركيز الكالسيوم في ECF يكون ثابت

**▪ Calcium metabolism:**

- 1000mg a day intake(equals calcium amount in 1L of milk), **350** absorbed and **650** lost (depending on Vit D). Out of the 350mg, 250 secreted.
-**Total excretion =900mg (250+650) | Total absorption =100mg.**
- Cellular and extracellular calcium is constantly exchanging
- Kidney: the filtered calcium is the diffusible kind (ionized and anions bound) 60% of total Ca, 99% will be reabsorbed and 1% is excreted **(100mg)**.
**- Total excretion (urine 100) + (feces 900) equals the intake (1000).**
**Imp** Female Dr: these are the only numbers that you need to memorize
- 500mg deposited and reabsorbed in bones is due to constant remodeling of bones. This process depends on calcium,Vit D, PTH levels in the blood.
- In case of deficiency or increased Ca levels, the kidney will selectively increase/decrease its filtration to compensate.




## Regulation

- ➢ Changes in Plasma Concentrations of Free Calcium
- ➢ Hormonal Mechanisms Provide High-Capacity, Long-Term Regulation of Plasma Calcium and Phosphate Concentrations
- ➢ [Ca2+] < 9-10.5 mg/dl → **Tetany** + seizures + **excitation** of the nervous system
- ➢ [Ca2+] > 9-10.5 mg/dl → **Renal stones** + **depression** of the nervous system

- Decrease in **intracellular/Endoplasmic reticulum** calcium = decrease in contractility (as u might have known from previous blocks).
- However, in this case, we are talking about **extracellular** calcium; decrease in its levels will lead to increase Na permeability & influx inside the cells → more tissue excitability = tetany!
- Vice versa.. Increase in extracellular calcium → less Na permeability & influx → less excitability = depression of CNS.

## Regulated by

### Phosphate

Phosphorus is an essential mineral necessary for ATP and cAMP second messenger systems

- Phosphate plasma concentration is around 4 mg/dL.
- Forms: - Ionized (diffusible) around 50% of total (The functional form)
- Un-ionized (non-diffusible ) and protein- bound (50%)
- **Calcium is tightly regulated with Phosphorus in the body.**

### Hormones

- Parathyroid hormone(from p
- Calcitonin*
- Vitamin D

*no physiological importance, It's more important in children and pregnant ladies. (Thyroidectomy patients don't need calcitonin replacement)

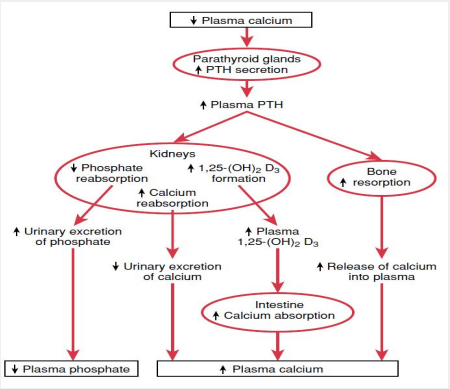
# Hormones regulate $Ca^{++}$

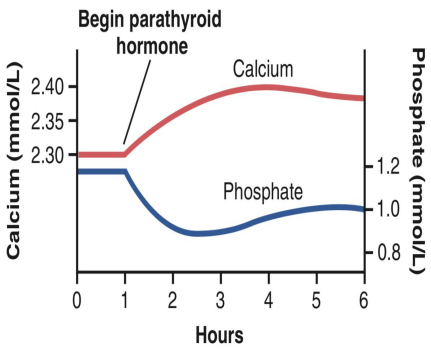
| | Parathyroid hormone | Calcitonin | Vitamin D |
|---|---|---|---|
| **Source** | Secreted by chief cells of parathyroid gland | Secreted by the parafollicular cells (C cells) of the thyroid gland. | 1--Sunlight: (7-Dehydrocholesterol > **Vit D3** aka; **cholecalciferol**) inactive<br>2--Dietary intake:<br>Vit D3 (fish, meat).<br>Vit D2(supplements)<br>**Liver** take up the Vit D forms> converted to **25-hydroxyvitamin D3** By 25α-hydroxylase<br>**Kidneys** take up 25-hydroxyvitamin D3 and is converted into **1-25 dihydroxyvitamin D3** (active form) by the enzyme **1α-hydroxylase**<br>(this enzyme is activated by **parathyroid hormone**) |
| **General** | - Polypeptide hormone: (84 aa)<br>- Molecular Weight: 9500<br>- Half Life: 10 min<br>Not important | - Nature: 32 amino acid peptide.<br>- Stimulus for secretion: Increased plasma calcium concentration. | |
| **Mechanisms of action** | Acts via 2nd messenger mechanism utilizing cAMP<br>Operates in tissues via GPCR | Decrease blood Ca++ level very rapidly within minutes.<br>Opposite effect to PTH | |
| **Site of action** | Bone, Kidney and Intestine | Bone and Kidney | Bone, kidney and Intestinal tract |
| **Function (actions)** | - **increases** calcium levels in blood<br>- **decreases** phosphate levels<br>ماشين عكس بعض<br>**-On bone:**<br>1. Stimulates the Formation of new osteoclasts.<br>2.Increases Calcium and Phosphate Absorption from the Bone<br>3.. Activation of osteoclasts (because it causes resorption of bone and release of Ca to blood)<br>4.. Depression of Osteoblastic activity<br>**On kidney**<br>1. ↓phosphate reabsorption from the proximal convoluted tubules (phosphaturic action). Which leads to ↑Phosphate excretion in the urine and ↓ plasma phosphate concentration<br>2. ↑ Ca++ & Mg ions reabsorption from the distal convoluted tubules, collection ducts and ascending loop of Henle.important to prevent bone deterioration<br>3. ↑ Formation of 1,25 vit D3 in the Kidney.<br>**On intestine:** ↑ absorption of calcium and phosphate indirectly through stimulating formation of 1,25 – (OH)2-D3 in kidney(Increases Calcium and Phosphate Absorption from the Bone • Existing osteocytes stimulated (minutes to hours) to transport calcium - calcium pumps • Existing osteoclasts activated and new osteoclasts formed (days to weeks) to digest bone and release calcium and phosphate Stimulated indirectly by osteoblasts: osteoblasts express RANKL which binds to RANK on osteoclasts leading to its activation.) | - **decrease** calcium levels in blood<br>**On bone:**<br>1.↑Ca++ deposition of bone (decrease it in blood)<br>(Effect to decrease calcium is not permanent)<br>2. Inhibits Bone resorption by inhibition of osteoclasts.<br>↓ formation of osteoclasts.<br>3. Causes reduced bone turnover.<br>**On kidney:**<br>↓↓ Ca++ reabsorption and ↑↑ Ca++ excretion (in addition to phosphate)<br>(Effect to decrease calcium is transitory Causes reduced bone turnover Has weak effect in kidney and intestines) | - **increases** calcium levels in blood<br>- **increases** phosphate levels<br>ماشين بنفس الاتجاه<br>Vitamin D in the form of **1,25 Dihydroxycholecalciferol** increases calcium blood level by:<br>**-on Bone &** Its Relation to **Parathyroid Hormone Activity.**<br>-Vitamin D in smaller quantities : promotes bone calcification (by↑calcium and phosphate absorption from the intestine and enhances the mineralization of bone)<br>- The administration of extreme quantities of vitamin D causes absorption of bone:<br>• by facilitating PTH action on bones.<br>• number & activity of osteoclasts.<br>**-On Intestinal tract.**<br>has a potent effect to increase calcium **and** phosphate absorption. (increases synthesis of calcium binding proteins)<br>**-On kidney:**<br>↑Renal calcium and phosphate absorption.<br>**-On immunity**:<br>stimulates differentiation of immune cells |
| **Abnormalities** | Hypoparathyroidism<br>Hyperparathyroidism | Osteomalacia<br>Osteoporosis | |
| | | | Control of vit D: 1- low Ca++ ions<br>2- prolactin<br>3- PTH<br>All stimulate renal **1,alpha hydroxylase**. |

cont...

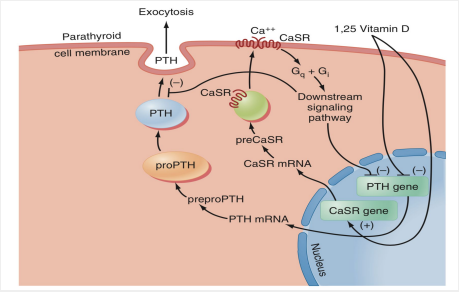
# Hormones regulate $Ca^{++}$

## Effect of PTH on Calcium level




▪ PTH: increases excretions of Phosphate and increases reabsorption of calcium (decreasing excretion) Among the diffusible calcium, 60% is reabsorbed in PCT, 30% in loop of Henle, and 10% in rest of the kidney. PTH works mainly on DCT and to a lesser extent Ascending loop of henle. PTH adjusment of reabsorption is very small because we need fine adjustment of Ca levels PTH Decreases Phosphate reabsorption in PCT ▪ In Hyperparathyroidism we see Hypercalcemia and Hypophosphatemia

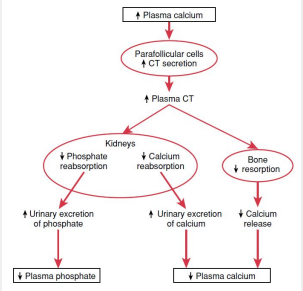


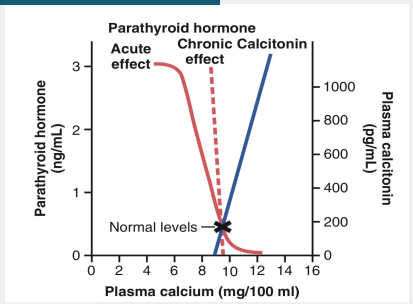

CaSR is Calcium sensing receptor, It suppresses PTH Gene expression.

-Low Serum Ca → CaSR is inactivated → PTH gene is no longer suppressed →Increased PTH production and secretion →Increase resorption in bones by activating osteoclasts. + Activate Vit D in kidneys by activating 1α-hydroxylase.

-Vit D enters parathyroid gland →Increase CaSR gene expression → increased production of CaSR (Negative feedback for Vit D activation).
-Vit D Suppress PTH gene (negative feedback for Vit D activation)

## Effect of calcitonin on Calcium level

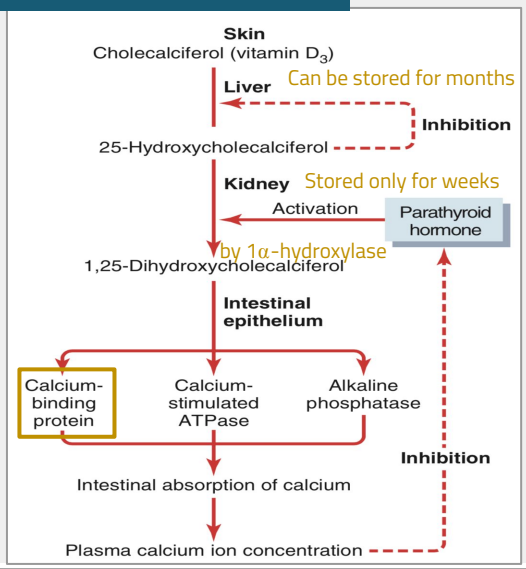



Normally Ca should be around 9.5 Ca> 9, Calcitonin secretion. Ca <9, PTH secretion.

## Effect of Vit D on calcium level

Trigger of PTH → low Ca
Trigger of Vit D → PTH

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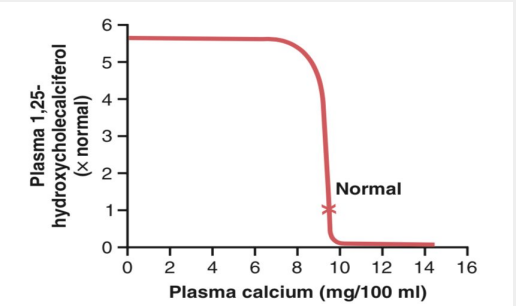
Main mechanism

Important mechanism because Ca cannot be absorbed without its binding protein




Vit D decreases dramatically when calcium is around 8-9 mg / dl

# Disorders of **Bones**

| Disease name | Rickets<br>لين العظام / الكساح | Osteomalacia<br>Adult Rickets (Rare) | *Osteoporosis |
|---|---|---|---|
| Cause | • Lack of vitamin D **leading** to calcium/phosphate deficiency in ECF<br>• Occurs In the spring (because vitamin D levels decreased in winter) | Poor absorption of vitamin D and calcium | • lack of physical stress<br>• malnutrition<br>• lack of vitamin C<br>•postmenopausal lack of estrogen (one of estrogen function is depressing the osteoclastic activity )<br>• old age •Cushing's syndrome |
| General* | positive Chvostek's sign is facial nerve irritability/spasms elicited by tapping the nerve | • serious deficiencies of both vitamin D and calcium occasionally occur as a result of **steatorrhea** (failure to absorb fat)<br>Almost never proceeds to the stage of tetany but often is a cause of severe bone disability | • Osteoporosis is the most common of all bone diseases in adults, especially **in old age.** |
| Features | • Low plasma calcium and phosphate<br>• Weak bones<br>• Tetany<br>(only shows in late stages due to the effect of compensating mechanisms)<br>Normal formation of the collagen matrix BUT Incomplete mineralization (poor calcification), lead to Soft Bones , CLINICALLY: Bone Deformity | Problem in bone slats<br>**No compression force**<br>demineralization (poor calcification) of preexisting bones which leads to more susceptibility to fractures | Results from equal loss of both organic bone **matrix and minerals** resulting in loss of total bone mass and strength.<br>The cause of the diminished bone:<br>• the osteoblastic activity in the bone is usually less than normal so the rate of bone osteoid deposition is depressed.<br>• excess osteoclastic activity. |
| Treatment | • supplying adequate calcium and phosphate in the diet and, administering large amounts of vitamin D | - | - |

| | Tetany in rickets<br>Early stage | Osteomalacia<br>*Renal Rickets (Rare) | |
|---|---|---|---|
| | **Early stage:** no tetany<br>• (PTH stimulate osteoclastic absorption of bone)<br>• ECF Calcium level is normal<br>When the bones finally become exhausted of calcium Calcium level falls rapidly. blood level of calcium falls below 7 mg/dl → signs of tetany: (positive Chvostek's sign)<br>→Death: tetanic respiratory spasm | It is a type of Osteomalacia due to **prolonged kidney disease**<br>• **Failure of the damaged kidney to form alpha hydroxylase enzyme** | - |

# Bone composition

## Hyperparathyroidism

### 1 -primary Hyperparathyroidism

mainly tumors

Affects approximately 100,000 patients a year (in the US). ▪ Prevalence: 0.1 to 0.3% of the general population. ▪ More common in women (1:500) than in men (1:2000). ▪ Patients with single adenoma (~90%): minimally invasive surgery

**causes:**

- Adenoma (90%)
- Multiple gland enlargement (10%)
- Familial hyperparathyroidism
- Carcinoma (<1%)
- Familial benign hypercalcemia (FBH).

**Manifestations:**

- Hypercalcemia (↑Ca2+), Hypercalciuria.
- Hypophosphatemia (↓PO-4), Hyperphosphaturia(Parathyroid hormone causes phosphaturia and a decrease in serum phosphate)
- Demineralization of bone forming multiple bone cysts (osteitis fibrosa cystica).
- Broken bones.
- ↑ Alkaline phosphatase.
- CNS depressed and peripheral nervous system depressed.
- Muscle weakness.
- Constipation, abdominal pain, peptic ulcer & decrease appetite.
- Depressed relaxation of the heart during systole.
- Calcium containing stones in kidney.
- **Parathyroid poisoning**: Precipitation of calcium in soft tissues occur when Ca2+ → >17 mg/dl → lead to death.
- Most serious complication is the deposition of calcium in the kidney tubules resulting in impaired renal function.
- **Treatment** of Hypercalcemia(severe):

Indications for therapy:1- Symptoms of hypercalcemia
2-Plasma [Ca] >14 mg/dl.
Principles of therapy:- Expand ECF volume, Increase urinary calcium excretion, Decrease bone resorption, NS(normal saline) bolus to restore volume; then 100 – 200 ml/hr, Bisphosphonates (onset 24-48 hrs), Calcitonin 4 – 8 IU q6-8 hrs (onset immediate, resistance develops in 24-48 hrs), Surgery for adenoma.

**Common causes of hypercalcemica**

▪ PTH mediated
▪ Primary hyperparathyroidism ▪ Non-PTH mediated
▪ Parathyroid hormone–related peptide (PTHrP): certain tumors secrete high levels of PTHrP, which causes hypercalcemia of malignancy.
▪ Vitamin D intoxication, granulomatous disorders, osteolytic bone metastases, malignancy
▪ Immobility ▪ Dehydration ▪ Medications
▪ Lithium, thiazide diuretics

**Clinical Manifestations of Hypercalcemia**

▪ Nausea, vomiting ▪ Anorexia, weight loss ▪ constipation ▪ Lethargy and Fatigue ▪ Confusion, stupor, coma ▪ Impaired concentration and memory ▪ Depression & anxiety ▪ Reduced neuromuscular excitability and muscle weakness ▪ Easy fatigability and muscle weakness more common in hyperparathyroidism than other hypercalcemic conditions ▪ Cardiac arrhythmias ▪ Vascular calcification ▪ shortening of the QT interval.

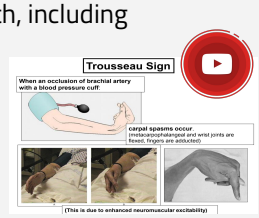
## Hypoparathyroidism hypocalcemia

**causes:**

- Injury to the parathyroid glands (surgery).
- Autoimmune.
- Magnesium deficiency.
- PTH resistance (pseudohypoparathyroidism): Normal PTH levels but deficient receptors.
- Vitamin D deficiency or resistance.
- Lack of 1α hydroxylase, no vit D3 activation.
- Other: renal failure, pancreatitis, tumor lysis.

**symptoms:** (due to hypocalcemia)

- Tingling in the lips, fingers, and toes.
- convulsions
- Dry hair, brittle nail, and dry coarse skin.
- Muscles cramps and pain in the face, hand, legs, and feet.
- Cataracts of the eyes.
- Malformation of the teeth, including weakened tooth enamel.
- Loss of memory.
- Headaches.




**Signs:**

- Tetany can be overt or latent.
- Positive Chvostek's sign (facial muscle twitch): tapping the facial nerve as it emerge from the parotoid gland in front of the ear causes contraction of facial muscles.
- Positive Trousseau's sign (carpal spasm): arresting (stopping) blood flow to the forearm for few minutes (e.g. by sphygmomanometer), causes flexion at the wrist, thumb, and metacarpophalangeal joints.
- Delayed cardiac repolarization with prolonged of the QT interval. (arrhythmia)
- Paresthesia.

**Treatment:**

- Calcium carbonate and vitamin D supplements.

### 2 Secondary (compensatory) Hyperparathyroidism

- **(Due to low Ca2+ in ECF)**

**Causes:**

1- Low calcium diet.
2- Pregnancy.
3- Lactation.
4- Rickets.
5- Osteomalacia.
6- Chronic renal failure. (↓1,25 (OH) - D3 Synthesis )

# MCQ & SAQ:

**Q1: All of the following are hormones that regulate calcium except:**

A. Vitamin D
B. Prolactin
C. Parathyroid hormone
D. Calcitonin

**Q2: Which of the following occurs when administering extreme quantities of Vitamin D?**

A.↓Renal calcium
B.↑Renal excretion
C. Bone resorption
D. Bone absorption

**Q3: which of the following increases ionized calcium?**

A. inhibition of parathyroid hormone
B. Calcitonin
C. Acidosis
D. Alkalosis

**Q4: which one of the following is refers to an abnormal reaction to the stimulation of the facial nerve?**

A. Trousseau's sign
B. Brudzinski's Sign
C. Chvostek's sign
D. Kernig sign

**Q5: Which of the following is true about the early stage of tetany in rickets:**

A. Calcium level increases
B. Calcium level falls rapidly.
C. ECF Calcium level is normal.
D. Nothing change

**Q6: Which one of the following is a manifestation of Hypoparathyroidism?**

A. Hypercalcemia
B. Tetany
C. Increased alkaline phosphate
D. shortened QT interval

answer key:
1:B
2:D
3:C
4:C
5:C
6:B

**1- what is the physiological importance of calcium?**

**2- How is renal 1$\alpha$-Hydroxylase stimulated?**

**3-what are the causes of Osteoporosism?**

**4- Mention 4 Manifestations for primary Hyperparathyroidism?**

**A1:** 1. in bone: provide structural integrity of the skeleton
2. in extracellular and cellular fluids: is essential to normal function for the biochemical processes :
–Neuromuscular excitability – Hormonal secretion
– Enzymatic regulation – Blood coagulation
– Second messenger

**A2: Stimulation of renal 1$\alpha$-Hydroxylase occurs by low calcium ions, prolactin, and PTH.**

**A3:** • lack of physical stress • malnutrition • lack of vitamin C •postmenopausal lack of estrogen • old age •Cushing's syndrome

**A4:** • Hypercalcemia • Hypercalciuria • Hypophosphemia • ↑ Alkaline phosphatase.

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