# *Calcium homeostasis

- **Plasma calcium:-**
  - Concentration: - 9 – 11 mg% (average 10 mg %).
  - Forms:-
    1) Ionized: - 50%.
    2) Non ionized (bound):-
       a. 40% bound with albumin (non diffusible).
       b. 10% bound with citrate and phosphate (diffusible).
- **Calcium absorption:-**
  - From upper part of small intestine (mainly from duodenum) by active process.
  - Controlled by the most active form of vitamin D (1,25 dihydroxy vitamin D), which is formed in the kidney under effect of parathormone.
  - Increased by : - 1. Acids. 2. Proteins. 3. Citrates.
  - Decreased by :- 1. Alkali. 2. Fat. 3. Oxalate.
- **Functions of calcium:-**
  1) **Bone and teeth mineralization.**
  2) **Blood coagulation:** - $Ca^{2+}$ is needed for all steps of blood coagulation except the first 2 steps in intrinsic pathway.
  3) **In neuromuscular system:** - $Ca^{2+}$ is important for:-
     a. Normal excitability of the nerve.
     b. Release of neurotransmitters from synaptic knobs at nerve terminals.
     c. Excitation contraction coupling.
  4) **In endocrine system:-** Important for:-
     a. Release of hormones.
     b. Hormone action: - It acts as a second messenger for some hormones.
  5) **Cellular activity:-** Important for:-
     a. Oxidative phosphorylation and ATP formation in mitochondria.
     b. ATP utilization, because it affects the activity of many cellular enzymes.
     c. Normal cell membrane permeability.
- **Calcium homeostasis:-** The level of ionized calcium is controlled by:-
  1) **Blood level of inorganic phosphate ($PO_4^{-3}$)**
     - Total plasma phosphate is 12 mg %. 2/3 is in the organic compounds (non ionized) as ATP, GTP etc. 1/3 (4 mg%) is found in the inorganic (ionized) form.
     - The product of plasma ionized calcium and phosphate is constant at any given PH and is called solubility product.

$Ca^{2+} \times PO^{3-}_4$ = solubility product = constant.

- Thus at constant PH ↑ $PO^{3-}_4$ in plasma →↓ $Ca^{2+}$ and vice versa.

**(2) PH of blood:-**

- Acidosis (↓ PH) →↑ both ionized calcium and phosphate →↑ solubility product.
- Alkalosis has an opposite effect.

**(3) Hormones:-** (hormonal control of calcium homeostasis). Calcium homeostasis is regulated by 3 hormones:-

1. Parathormone: It raises $Ca^{++}$ level in plasma.
2. calcitonin: It lower $Ca^{++}$ level in plasma.
3. Active form of vitamin D (Vitamin D metabolite) (1, 25 dihydroxy vitamin D): It raises $Ca^{++}$ level in plasma.

## * Parathormone (PTH) *

- PTH is secreted by the chief cells of the parathyroid glands.
- PTH is a polypeptide acts through cAMP.
- Inactivation of PTH takes place in the liver and to a lesser extent in the kidney.

**Biological effects of PTH:**

PTH increases Ca ions level in plasma by action on bone, kidney and intestine.

a. **Effect on bone:-**

PTH stimulates bone resorption, releasing calcium into extra cellular fluid.

- PTH inhibits osteoblasts. (Bone forming cell).
- PTH stimulates osteoclasts. (Bone destroying cell).

b. **Effect on kidney:**

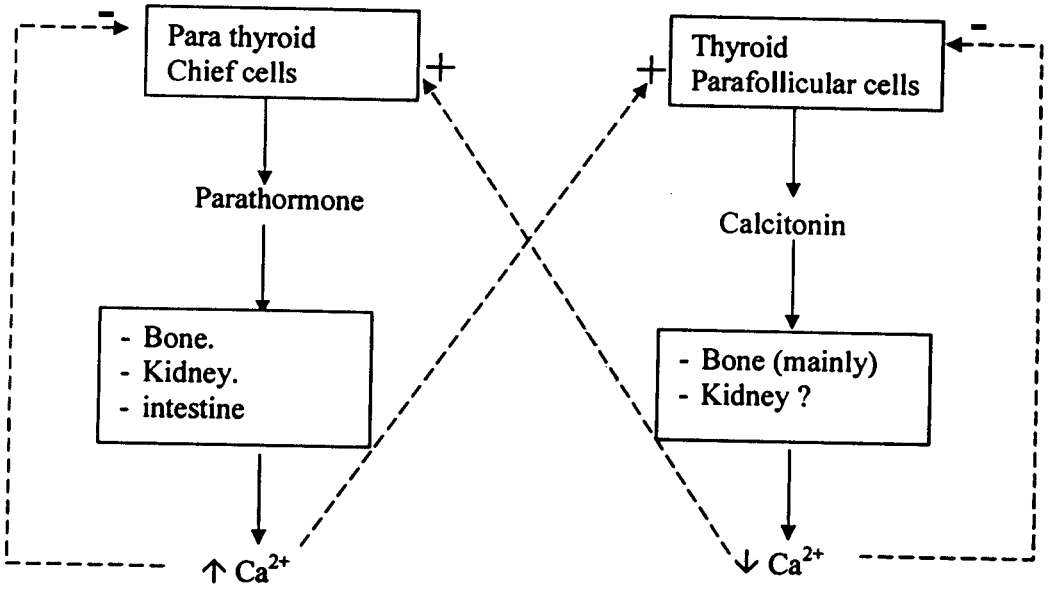
PTH has three main effects on the kidney:

1. PTH stimulates calcium reabsorption in the distal convoluted tubules and collecting ducts.
2. PTH decreases phosphate reabsorption in the proximal convoluted tubules, leading to increased urinary excretion of phosphate. The phosphate level in plasma is decreased →↑ Plasma $Ca^{2+}$.
3. PTH and hypophosphataemia stimulate the formation of 1,25 dihydroxy vit.D, the latter increases the absorption of calcium and phosphate from the intestine.

c. **Effect on intestine:-** Stimulate absorption of calcium and phosphate from intestine indirectly by stimulation of formation vit.D in kidney.

**Regulation of PTH secretion:** Controlled by plasma $Ca^{2+}$

- There is a negative feed back control between the calcium level in the plasma and PTH secretion i.e. **decreased Ca ion level** →↑ PTH
- The maximum rate of PTH secretion occurs below a plasma calcium concentration of 7 mg%.
- Increasing the plasma calcium above 14mg% does not lead to further decrease in the rate of PTH secretion.




## Calcitonin (CT)

- CT is secreted by the parafollicualr (c) cells of the thyroid gland.
- CT is a polypeptide and acts through second messenger system other than c AMP (mainly) however some action may be mediated by cAMP.

### Biological effect of CT:

CT decreases Ca ions level in plasma through effect on:-

1. **Bone:** (main effect). CT decreases bone resorption by inhibiting osteoclasts. This action of CT results in a decrease of plasma $Ca^{2+}$.
2. **kidney:** (minor effect):- CT inhibits the tubular reabsorption of calcium and phosphate. Thus, CT is used in diseases accompanied by hypercalcaemia e.g. paget's diseae.
3. **Intestine:-** (minor effect). It decreases $Ca^{2+}$ absorption from intestine.

### Regulation of CT secretion:

1. **Plasma calcium level:** CT secretion increase when plasma calcium rises (above 9 mg) and ↓ when plasma $Ca^{2+}$ decreases.

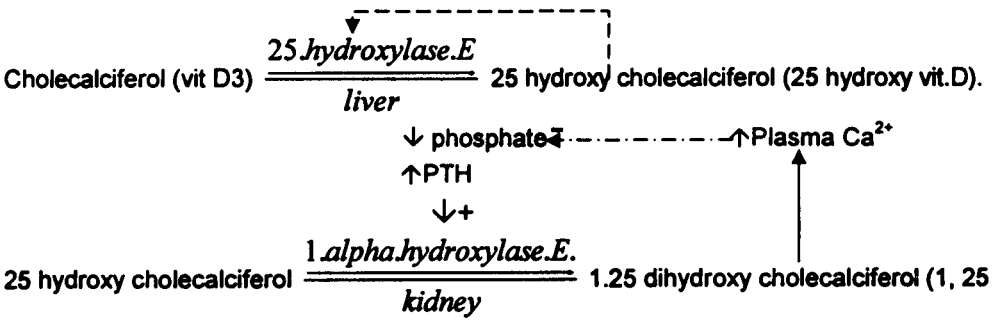
2.**Gastrointestinal hormones:** Gastrin and CCK released during digestation of food stimulate CT secretion which allows efficient utilization of dietary calcium and prevents postprandial hypercalcaemia.

# Vitamin D

- **Source and biosynthesis:-**
  - It refers to a group of compounds derived from sterols and closely related both in structure and function.
  - The most important of these is vitamin D3 (chole calciferal), most of it is formed in the skin by the effect of sunlight (ultravidot rays) on 7-dehydro cholesterol (a substance present normally in the skin).

$$\text{7 dehydrocholesterol} \xrightarrow[skin]{ultraviolet(in\ sunlight)} \text{Cholecalciferol (vitamin } D_3\text{)}$$

  - Additional vitamin D compounds taken with food are mainly identical to vit $D_3$ and are absorbed in ileum under effect of bile salts.
- **Activation:-** Vit. $D_3$ is a prohormone which is converted into 1, 25 dihydroxy vit. D ( the most active form of vit.D) As follows:-




dihydroxy Vit.D).

- **Transport:-** Vit. D is transported in plasma bound to a specific Vit. D binding protein.
- **Mechanism of action:** - As steroid hormones it acts on cytoplasmic receptors.
- **Regulation of the formation of 1,25 dihydroxy vit.D.**

  The hydroxylation of 25 hydroxy vit D. at position 1 in the kidney is catalysed by 1 alpha hydroxylase enzyme. The activity of this enzyme is increased by:-
  a. A decrease in the level of plasma $Ca^{2+}$.
  b. A decrease in the level of plasma phosphate.
  c. An increase in the rate of secretion of parathormone.

d. Growth hormone, prolactin and insulin.

**Note:** Estrogens increase the formation of vitamin D binding globulin.

- **Biological effects of 1.25 dihydroxy vit.D.**

1. **On the small intestine:**
   - It stimulates absorption of calcium and phosphate.
   - It helps $Ca^{2+}$ absorption from intestine by 3 mechanisms:-
     1. Stimulate formation of calcium binding protein that help absorption of $Ca^{2+}$ at brush border of intestinal epithelial cells then $Ca^{2+}$ is transported at basolateral border by facilitated diffusion.
     2. stimulate formation of calcium stimulated ATpase at brush border in epithelial cells.
     3. Stimulate formation of alkaline phosphate
2. **On the bone:**

   It is important for bone mineralization. It stimulates osteoblasts to deposit $Ca^{2+}$ and $PO^{3-}$ in bone.

**Notes:** - In high doses vit.D causes bone resorption.

3. **On the kidney:** It simulates calcium reabsorption in the distal convoluted tublules.
4. It may play a role for mineral transfer in certain organs as mammary gland, placenta and skin.

## Disturbances of calcium homeostasis

## I-Hypocalcemia: (Tetany).

- **Definition:** A state of increased neuromuscular excitability caused by a decrease in the level of ionized calcium in blood.
- **Causes:** conditions which lower the ionized calcium level in blood.
  1. Hyoparathyroidism: due to :-
     a. Accidental surgical removal during thyroidectomy.
     b. Destruction by autoimmune disease.
  2. Vitamin D deficiency.
  3. Alkalosis: Threshold of tetany is PH 7.6. It ↓ solubility product.
  4. Administration of large amount of citrate or oxalate.
  5. Renal failure because of phosphate retention →↓ $Ca^{2+}$ to keep solubility product constant.
- **Types:**

**A. Manifest tetany:**

- It occurs when plasma calcium level is below 7 mg %.
- The condition is characterized by:

**a.** Attacks of spasmodic muscle contraction or cramps that usually affect the extremities giving a characteristic appearance of the

hands and feet known as carpopedal spasm. Carpal spasm or acchucheur's hand, there is flexion of the wrist and metacarpophalangeal joints while interphalangeal joints are extended and the thumb is adducted in the palm. Pedal spasm occurs in the feet in the same manner.

b. Attacks of generalized convulsions might occur specially in children.
c. Attacks of spasmodic contractions of laryngeal and respiratory muscles might occur specially in children which result in cyanosis and asphyxia.
d. Inbetween the attacks skeletal muscles show fibrillary twitches and stiffness.

**B. Latent tetany:**

- It occurs when plasma calcium level is from 7 to 9 mg%.
- The tetanic manifestations do not appear during rest, but only during stresses e.g., emotions and exercise.
- Latent tetany can be diagnosed by:-
  a. Blood tests for serum ionized calcium.
  b. Certain tests which show the increased neuromuscular excitability e.g.
     1. Subthreshold galvanic current is enough to excite motor nerves. 4 instead of 8 milliampers. (Erb's test).
     2. Tapping of facial nerve in front of the ear leads to twitches of the facial muscles.( Chvostek's test).
     3. Placing a tourniquet (sphygmomanometer cuff) on the upper arm i.e, ischaemia of the peripheral nerves leads to carpal spasm of the hand. (Trousseau's test).

**- Treatment:**

a. Manifest tetany: Calcium 10% slowly intravenously.
b. Latent tetany and inbetween attacks of manifest type:
   1. Oral calcium preparation: milk and its products.
   2. vitamin D to help calcium absorption.
   3. acidifying salt to help ionization of calcium.
   4. Antitetanic 10 (At 10) (dihydrotachysterol) in hypoparathyroidism. It gives the same effect as parathormone.

**Notes:**

1. PTH is not used for treatment of hypoparathyroidism. This is because, PTH is a polypeptide.
   - If PTH is taken orally, it will be digested.

- If PTH is injected, it will stimulate the formation of antibodies which inactivate the hormone.

2. Effect of hypocalcaemia:

7 –9 mg %→ Latent tetany.

4 – 7 mg % →Manifest tetany.

4 mg %→ Death from tetany (asphyxia).

Below 4mg% →Failure of clotting mechanism.

3. Thus, coagulation defect can not be produced by calcium deficiency because the patient would die from tetany before the $Ca^{2+}$ level is low enough to cause failure of clotting.

II- **Hypercalcemia:-** Occur when $Ca^{2+}$ increases more the 12 mg %.

- **Causes:-**

1. Hyperparathyroidism.
2. Hypervitaminosis D.
3. Acidosis →↑ solubility product.

- **Mainfestations**

1. Decrease neuromuscular excitability and muscle weakness.
2. Increased urinary excretion of calcium → renal stones.
3. Metastatic calcification:- deposition of $Ca^{2+}$ in abnormal sites as arteries, lungs and thyroid.
4. In case of hyperparathyroidism bone resorption occur leaving cavities or cysts in bone (osteitis fibrosa cystica) which makes bone weak and fragile.