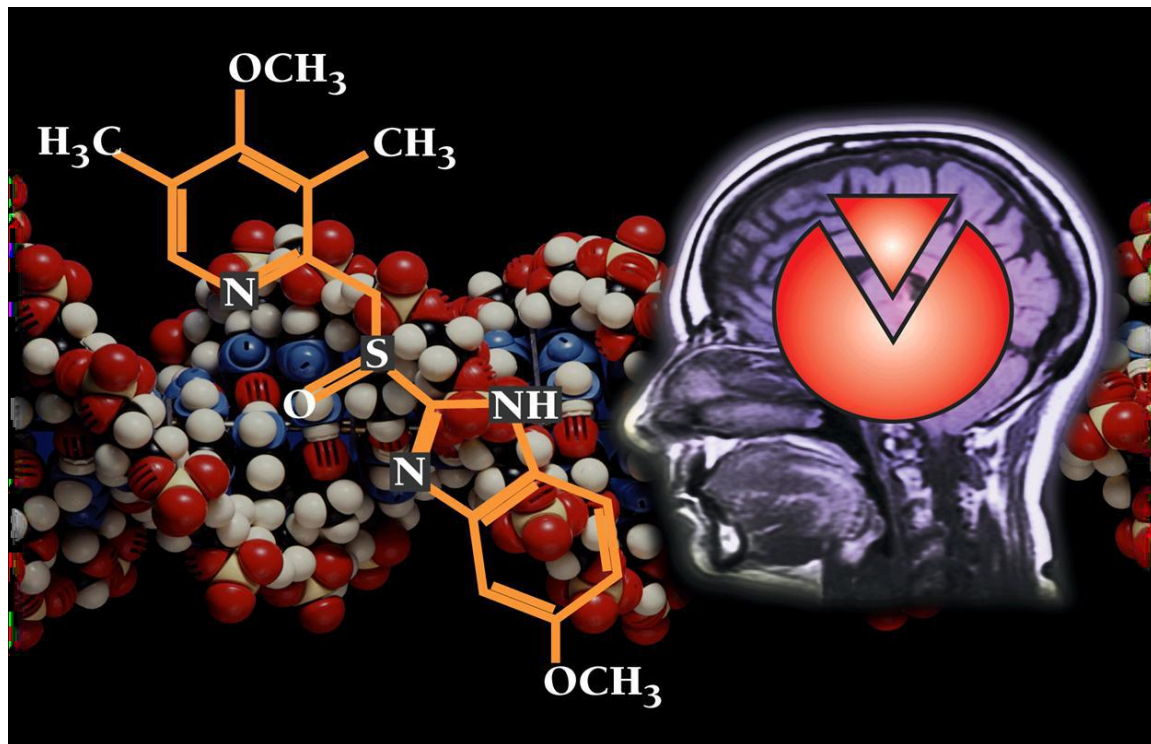


# 04-Pharmacology of drugs used in calcium & vitamin D disorders



**Note:** First page is an introduction, text in Red are important points, and textboxes with thick light blue margins are additional info

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## Introduction :

**BONE:** Is a dynamic organ undergoes continuous **remodeling** process involving **resorption** of old bone by **osteoclast** & **formation** of new bone by **osteoblast**

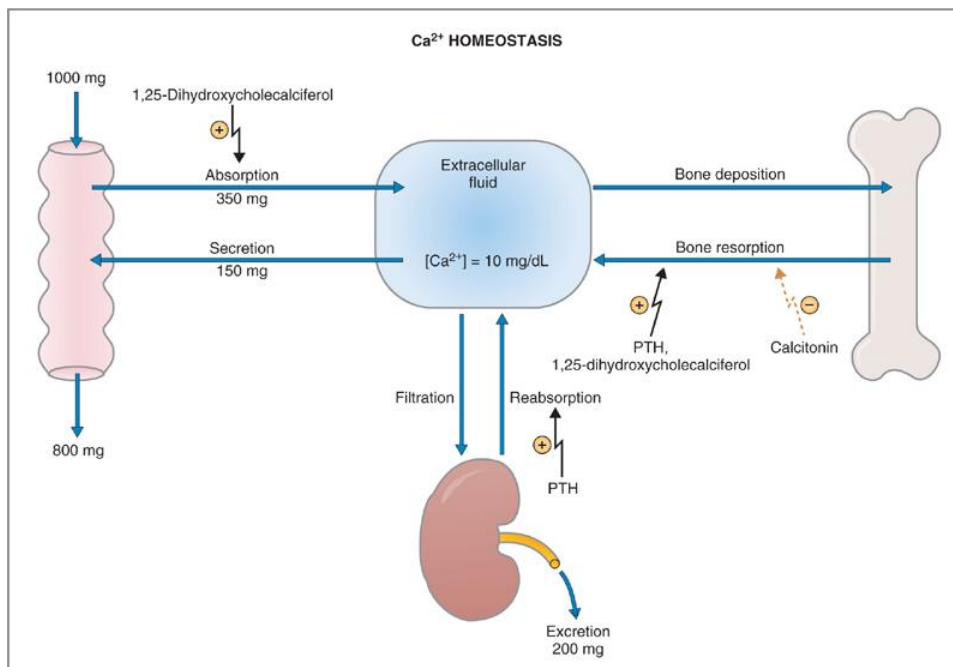
If there is any disturbance in this balance → Pathological conditions occur.

The principal factors involved in calcium metabolism & bone remodeling are:

- Parathyroid hormone ( PTH)
- calcitonin
- vitamin D

The target tissues for **PTH, calcitonin & vitamin D** :

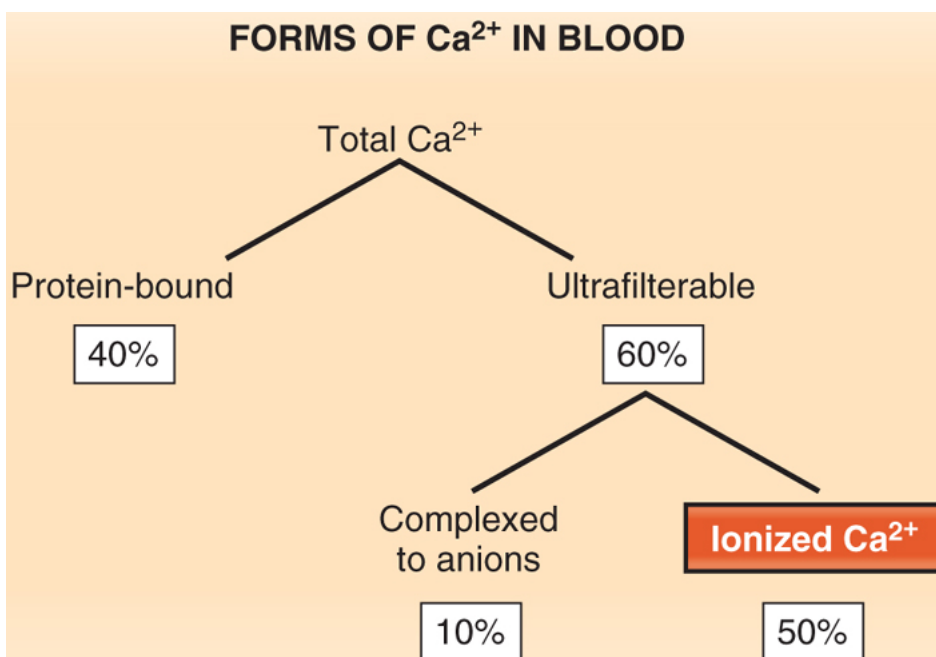
- Bone
- kidney
- Intestine.



**In the GIT:** Vitamin D stimulates the absorption of Ca (Increase Ca in blood)

**In bone deposition:** Ca is consumed ( Decrease Ca in blood)

**In bone resorption:** Ca is released to the blood. ( Ca increase)



40% of Ca is bound to proteins e.g. Albumin

The remaining is either free ionized calcium or complexed to anions (e.g. phosphates)

## 1-Parathyroid Hormone :

Is released from the parathyroid gland in **response to low plasma  $\text{Ca}^{2+}$  level**

### Effects of PTH:

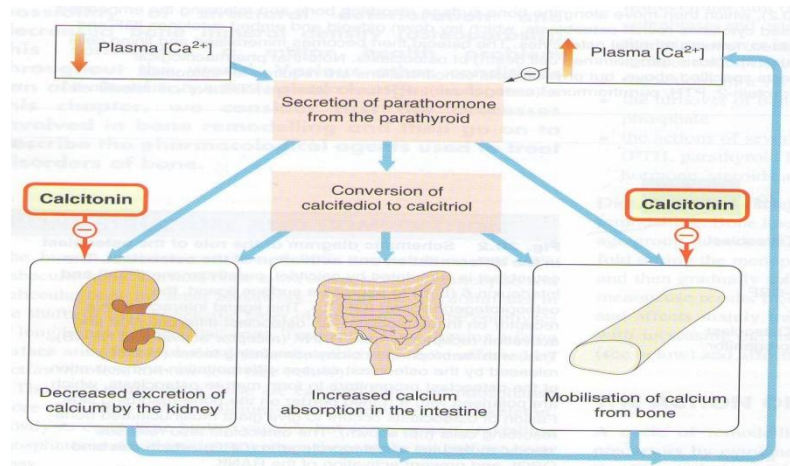
**1-BONES:** Mobilization of  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$  from bone in response to **hypocalcemia**, PTH stimulates osteoclast cells to **increase the outward flux of calcium** to restore serum calcium level.

### 2-kidneys:

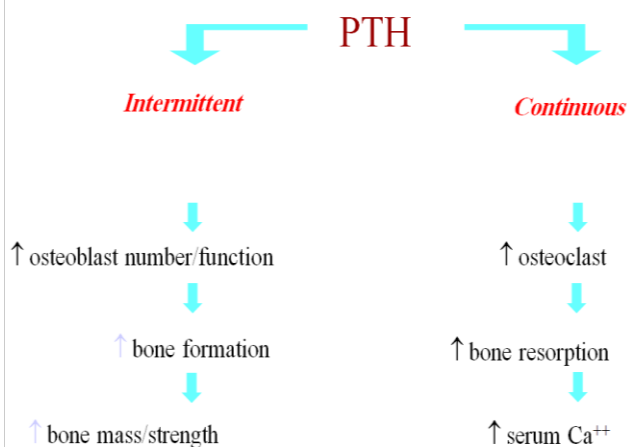
- $\uparrow \text{Ca}^{2+}$  reabsorption
- $\uparrow$  formation of **calcitriol** (1,25-dihydroxycholecalciferol) which is the active form of vitamin D

**3-GIT :**  $\uparrow$  absorption of  $\text{Ca}^{2+}$  (effect mediated via stimulation of the enzyme responsible for converting vitamin D to its active form)

Daily, **intermittent** administration of PTH for 1 to 2 hours / day leads to a **net stimulation of bone formation** -  
Continuous exposure to elevated PTH leads to **bone resorption**.



### SKELETAL RESPONSE TO PTH



The skeletal effects of **teriparatide** (Synthetic polypeptide PTH) analogue depend upon the pattern of systemic exposure. Once-daily administration of **teriparatide** stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of **osteoblastic** activity over **osteoclastic** activity. In monkey studies, **teriparatide** improved trabecular microarchitecture and increased bone mass and strength by stimulating new bone formation in both cancellous and cortical bone. **In humans**, the anabolic effects of **teriparatide** are manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. By contrast, continuous **excess of endogenous PTH**, as occurs in hyperparathyroidism, may be detrimental to the skeleton because **bone resorption** may be stimulated more than **bone formation**.

### Clinical uses:

- Treatment of **severe osteoporosis** - Cases failed to respond to other medications (not 1<sup>st</sup> line)

## 2-Teriparatide

- Synthetic polypeptide PTH analogue. **Bone forming drug: it acts mainly on osteoblast : increase bone formation and density .**
- Given, once / daily / subcutaneous injection
- Affect calcium homeostasis
- **Used to treat severe cases osteoporosis in people who have a risk of getting fracture ( increase bone mass & strength )**

People at risk of getting fracture:

- Post menopausal women
- On steroid drugs
- Men with hypogonadism

## Side effects

- Diarrhea, heart burn, nausea
- headache, leg cramps
- Hypotension when standing can occur.
- Elevated serum calcium can occur **in some** cases can lead to kidney stones

## Contraindications

- **Should not be used by people with increased risk for bone tumors (osteosarcoma)** –because it has high incidence of forming bone tumor - including :
  - People with **Paget's disease** of bone.(Elevated serum **alkaline phosphates** usually occurs in this disease)
  - People who had radiation treatment involving bones.
  - Elevated serum **alkaline phosphatase**

Recent Studies suggest using it in treatment of osteoarthritis because it promotes formation of new cartilages. (The only drug has such effect)

**Paget's disease** : A bone disorder, of unknown origin, characterized by excessive bone destruction and disorganized repair. Complications include skeletal deformity, musculoskeletal pain, kidney stones, and organ dysfunction secondary to pressure from bony overgrowth

## Comparison between PTH & Teriparatide

### PTH

- Acts through a mechanism named **remodeling- based formation**
- ( stimulate bone formation through an increase in the bone remodeling rate-ongoing gains in the amount of bone tissue, including trabecular thickness )

### Teriparatide

- Acts through a mechanism named **modeling-based formation** .
- stimulating formation directly without a need for prior resorption
- Increase trabecular bone in thickness & connectivity

## 3-Vitamin D

- Refers to **cholecalciferol ( vitamin D3) & ergocalciferol ( vitamin D2) .**
- **Vitamin D2** is the prescription form of vitamin D & is also used as food additive.
- **Vitamin D3** is usually for vitamin D- fortified milk & foods & also available in drug combination products.

## Sources of Vitamin D

- Diet : D2
  - milk
  - egg yolk
  - fish oils
- **Sunshine** : Cholecalciferol (D3) : Generated in the skin from **7- dehydrocholesterol** by the action of ultraviolet radiation (sunshine).

## Vitamin D Metabolism

- The initial transformation of D3 occurs in **liver** to 25-(OH)D3 ( calcifediol )
- In the **kidney** : **parathyroid hormone** stimulates the formation of active form of vitamin D (**calcitriol**) { 1,25-(OH)<sub>2</sub> D3 }

## Effects of Vitamin D

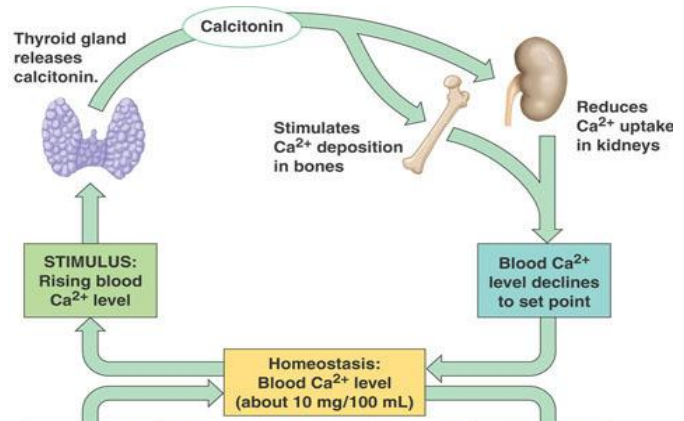
- **Bone** : Activation of **osteoblast** cells
- **Kidney** : Increased **reabsorption** of  $\text{Ca}^{2+}$  &  $\text{PO}_4$ .
- **GIT** : Increased **absorption** of  $\text{Ca}^{2+}$

## 4-Calcitonin

- Produced by the **parafollicular cells (C cells)** of the thyroid gland . It is **released when there is an elevated level of  $\text{Ca}^{2+}$  in the blood.**
- **calcitonin salmon** : synthetic form given by nasal spray

### Effects of calcitonin

- **Bone** : Decrease bone resorption by inhibiting **osteoclast activity**
- **Kidney** : Decreases reabsorption of  $\text{Ca}^{2+}$  &  $\text{PO}_4$  , thus increasing their excretion



### Clinical uses of Calcitonin

- **Osteoporosis**
- **Hypercalcemia**

### Routes of administration

- S.C.
- Nasal spray ( calcitonin salmon )

### Adverse effects

- Nausea
- local inflammation ( injection )
- **Flushing of face & hands**
- Nasal irritation (Nasal spray)

## Summary

- The principal factors involved in calcium metabolism & bone remodeling are: **parathyroid hormone (PTH)**, **teriparatide**, **calcitonin**, and **vitamin D** . And they are targeting **bone, kidney, and intestine**.
- **Parathyroid hormone** is released from the parathyroid gland in response to **low plasma  $\text{Ca}^{2+}$  level**. It causes mobilization of  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$  from bone, it stimulates osteoclast cells to increase the outward flux of calcium , increase  $\text{Ca}^{2+}$  reabsorption and formation of **calcitriol** in the kidney, and increase absorption of  $\text{Ca}^{2+}$  from GIT in order to restore **serum calcium level**.
  - **Daily , intermittent administration of PTH for 1 to 2 hours / day leads to a net stimulation of bone formation , while continuous exposure to elevated PTH leads to bone resorption.**
  - **It used in Treatment of severe osteoporosis - Cases failed to response to other medications.**
- **Teriparatide** : Synthetic polypeptide PTH analogue
  - **Used to treat osteoporosis in people who have a risk of getting fracture ( increase bone mass & strength )**
  - **Side effects** : Diarrhea, heart burn, nausea , headache, leg cramps ,hypotension when standing can occur, **and kidney stones due to elevated serum calcium.**
  - **Should not be used by people with increased risk for bone tumors (osteosarcoma)** e.g :people with **Paget's disease** or who had radiation treatment involving bones.
- **Vitamin D** : Refers to cholecalciferol ( vitamin D3) & ergocalciferol ( vitamin D2) .
  - The initial transformation of D3 occurs **in liver** to 25-(OH)D3 ( calcifediol ) . **In the kidney:** parathyroid hormone stimulates the formation of active form of vitamin D (calcitriol) { 1,25-(OH) $_2$  D3 }
  - **It Activates osteoblast cells**, increases **reabsorption of  $\text{Ca}^{2+}$  &  $\text{PO}_4$**  from **the kidney**, and Increases absorption of  $\text{Ca}^{2+}$  in GIT
- **Calcitonin** produced **by the parafollicular cells (C cells)** of the thyroid gland . It is released when there is an **elevated level of  $\text{Ca}^{2+}$**  in the blood. **Calcitonin salmon** : synthetic form given by nasal spray
  - It decreases bone resorption by **inhibiting osteoclast activity** , and decreases reabsorption of  $\text{Ca}^{2+}$  &  $\text{PO}_4$  from the kidney , thus increasing their excretion
  - Used in **Osteoporosis and hypercalcemia**
  - **Its common SE is flushing of face & hands**