

# Endocrine Module

## Physiology (Lecture 5)

### Hormonal Control of Calcium Metabolism

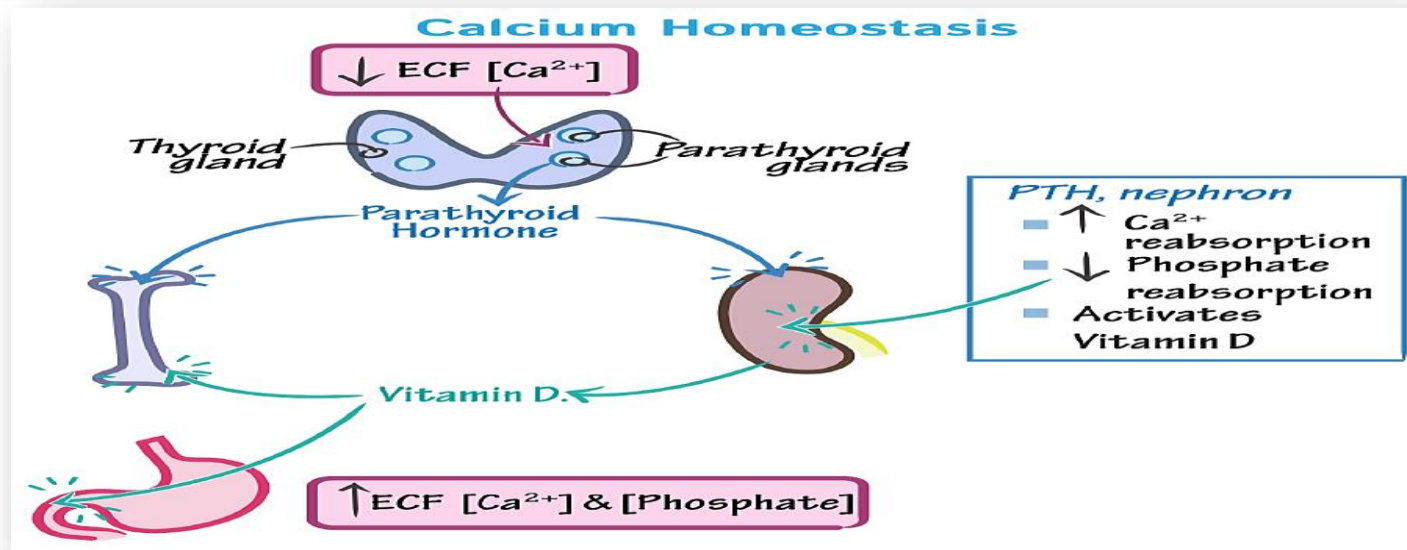
By

Dr. Fatma Farrag Ali

Associate Professor of Medical Physiology

Faculty of Medicine – Mutah University

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# Calcium metabolism

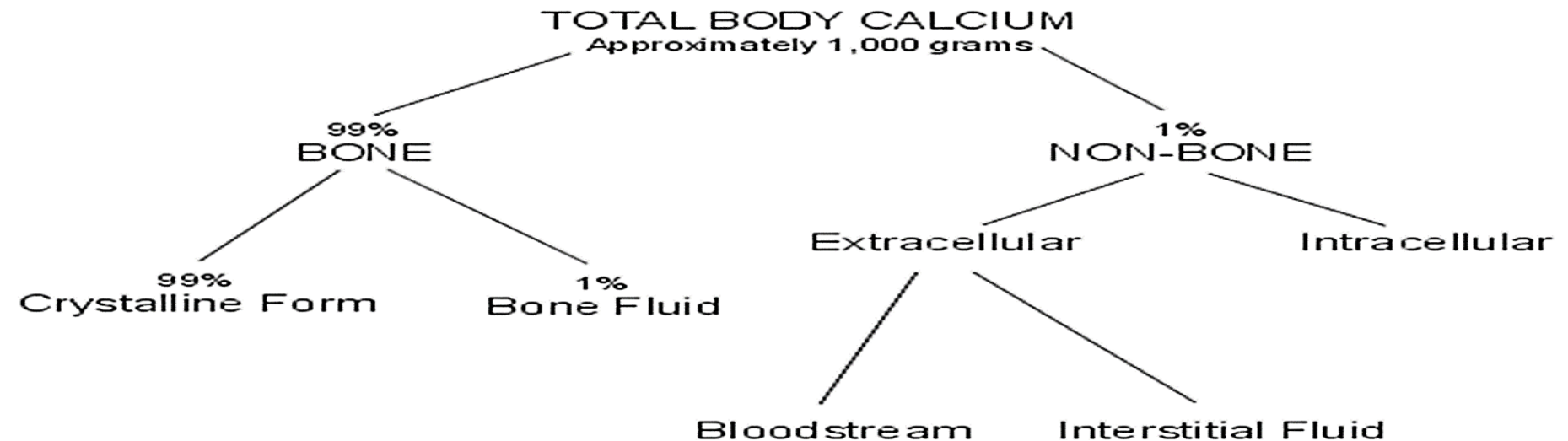
- ✓ **Calcium is an essential element.**
- ✓ **Calcium is important for many physiological functions in the body as:**
  1. It maintains normal excitability of nerves and muscles.
  2. It is important in neuromuscular transmission.
  3. It is essential for muscle contraction.
  4. It is essential for release of most neurotransmitters.
  5. It is a second messenger in many hormonal actions.
  6. Bone and teeth mineralization.
  7. It is essential for blood coagulation.

# Calcium Content and Distribution in the Body

## Total body calcium:

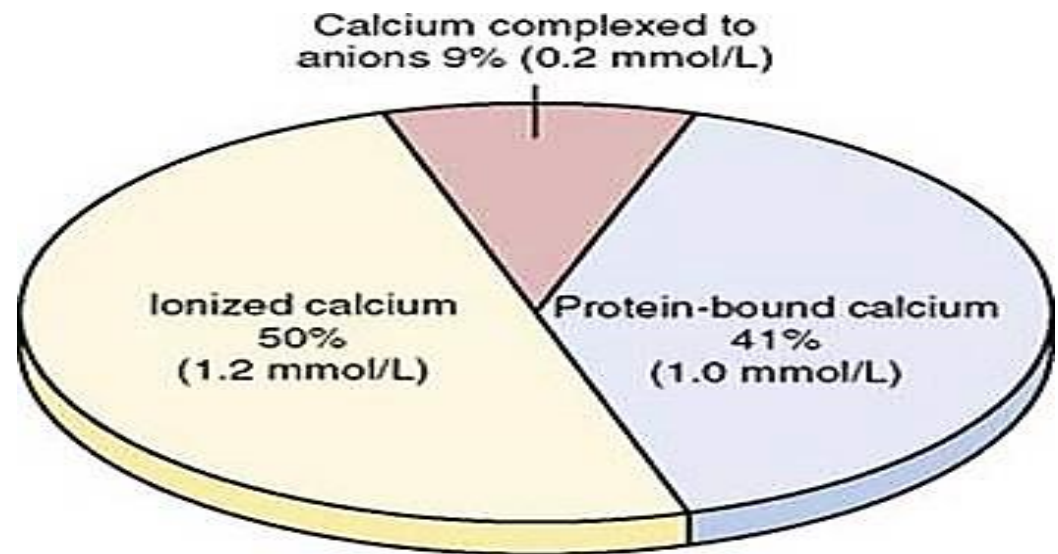
The average adult human body contains about 1000-1100 gm calcium.

The  $\text{Ca}^{2+}$  present in **intracellular and extracellular fluids** represents about **1%** of the total calcium content of the body. The remaining **99%** is present in the **bone**.



## Calcium in plasma:

- Normal plasma calcium level averages **10 mg% ( 9-11 mg%)**.
- Plasma calcium is present in **3 forms**:
- **50% (about 5 mg%) ionized** and diffusible. It is the **biologically active fraction** that is important for most functions of calcium in the body.
- **50%:**
  - **41% is bound to plasma proteins** (albumin and globulins, specially albumin) and is **non-diffusible** through cell membranes (about 4.5 mg%). It is **biologically inactive**.
  - **9% forming complexes** with citrates and phosphates and can diffuse with difficulty (**diffusible**). About 0.5 mg%

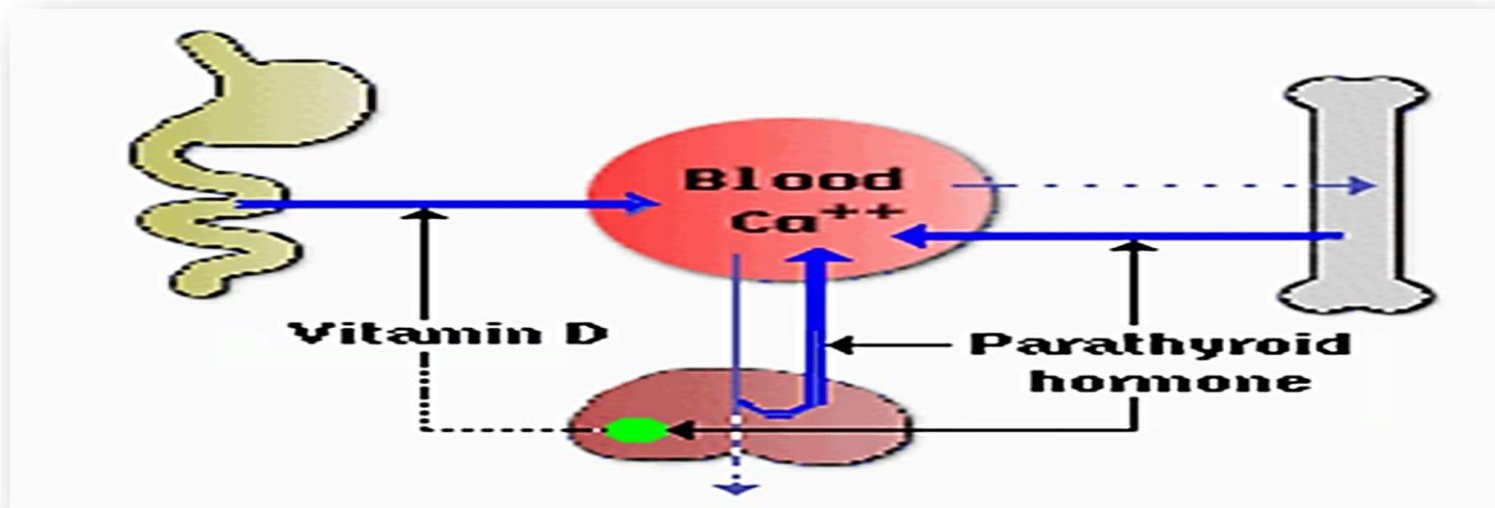


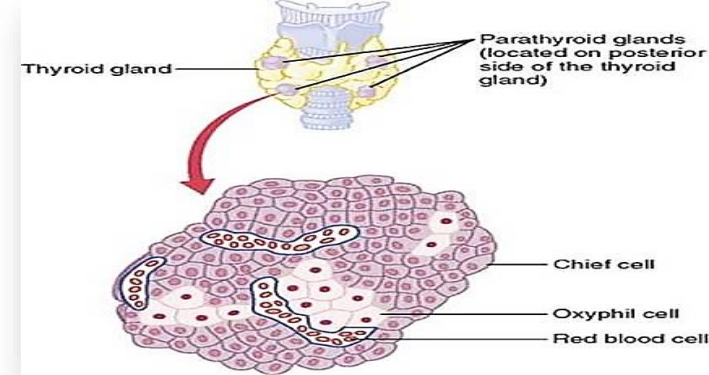
## Calcium in bones:

- **Bones contain about 99% of total body calcium, which is 2 types:**
- ✓ **99.5%** is present as **stable salts (hydroxyapatite crystals)** that are very slowly exchangeable with plasma calcium.
- ✓ **0.5% (about 5 gm) is readily exchangeable.** It **constitutes a reservoir** that is in equilibrium with the plasma calcium.

# Calcium Homeostasis

- Normal plasma calcium level is about 9-11 mg% (averages 10 mg%).
  - Plasma calcium level is kept constant mainly by the action of three hormones:
1. Parathyroid hormone (PTH): it  $\uparrow$  plasma calcium level when decreased.
  2. Calcitonin hormone: it  $\downarrow$  plasma calcium level when increased.
  3. Active vitamin D: it  $\uparrow$  intestinal absorption of calcium from GIT and  $\uparrow$  calcium deposition in bone.





## Parathyroid Hormone (PTH)

- Parathyroid hormone or parathormone (PTH) is a polypeptide hormone (containing 84 amino acids) which is secreted by parathyroid glands.
- The primary function of PTH is regulation of  $\text{Ca}^{2+}$  concentration in ECF, and for this it is essential to life. PTH is the primary hormone regulating plasma calcium concentration.

### Actions:

- Normally, PTH is a major regulating factor for both  $\text{Ca}^{2+}$  and inorganic phosphate ( $\text{PO}_4^{3-}$ ) concentrations in body fluids.
- Normally, plasma  $\text{PO}_4^{3-}$  concentration is inversely related to plasma calcium concentration.
- $[\text{PO}_4^{3-}] \propto 1/[\text{Ca}^{2+}]$
- $[\text{Ca}^{2+}] \times [\text{PO}_4^{3-}] = K$  (constant)
- This constant K is known as the Solubility Product.
- The main function of PTH is to increase plasma  $\text{Ca}^{2+}$  level and decrease plasma  $\text{PO}_4^{3-}$  level (so as to maintain the solubility product constant).

## **Mechanism:**

### **PTH increases plasma $\text{Ca}^{2+}$ level by 3 mechanisms:**

- 1. Effect on the kidney.**
- 2. Effect on bones.**
- 3. Effect on intestine.**

#### **(1) Effect on Kidney:**

1. PTH increases the reabsorption of  $\text{Ca}^{2+}$  in the distal convoluted tubules  $\rightarrow$   $\uparrow$  Plasma  $\text{Ca}^{2+}$  level (rapid physiological adjustment) and  $\downarrow$   $\text{Ca}^{2+}$  excretion in urine.
2. PTH decreases the reabsorption of phosphates in the proximal convoluted tubule  $\rightarrow$   $\uparrow$  excretion of phosphates in urine  $\rightarrow$   $\downarrow$  plasma phosphate.

## **(2) Effect on Bones:**

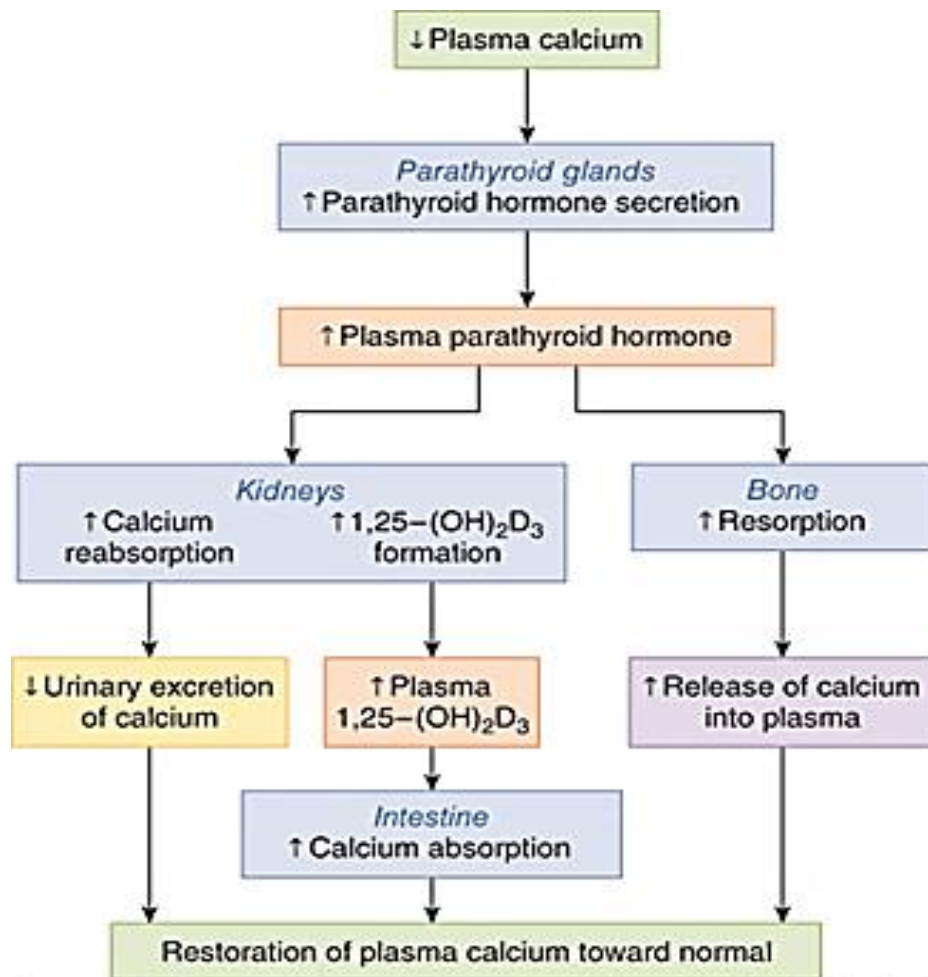
**PTH stimulates the  $\text{Ca}^{2+}$  mobilization from bone into the plasma  $\rightarrow \uparrow$  plasma  $\text{Ca}^{2+}$  level by:**

- ✓ Increased osteoclastic (bone eating cells) activity  $\rightarrow$  which destroy bone by releasing  $\text{H}^+$  and protease enzymes resulting in bone resorption and  $\text{Ca}^{2+}$  mobilization into bloodstream  $\rightarrow$  increased plasma  $\text{Ca}^{2+}$ .
- ✓ Formation of new osteoclasts.

## **(3) Effect on Intestine:**

**PTH increases absorption of  $\text{Ca}^{2+}$  indirectly:**

**PTH activates the 1- $\alpha$  hydroxylase of the kidney** responsible for transformation of 25, hydroxycholecalciferol into 1,25-dihydroxycholecalciferol (active vitamin  $\text{D}_3$  metabolite), thus it increases  $\text{Ca}^{2+}$  absorption from the intestine.



Source: Kim E. Barrett, Susan M. Barman, Scott Boitano, Heddwen L. Brooks: Ganong's Review of Medical Physiology, 25th Ed. [www.accessmedicine.com](http://www.accessmedicine.com)  
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## **Mechanism of PTH action:**

It acts mainly through increasing cAMP content in target cells.

## **Regulation (Control ) of PTH secretion:**

- **No tropic hormone from the anterior pituitary to control PTH secretion.**
- **The main regulating factor for PTH secretion is plasma ionized  $\text{Ca}^{2+}$  level which directly controls the parathyroid glands by a negative feedback mechanism:**
  - **$\downarrow$  Ionized  $\text{Ca}^{2+}$  stimulates PTH secretion while  $\uparrow$  ionized  $\text{Ca}^{2+}$  inhibits PTH secretion.**
- **Active form of vitamin  $\text{D}_3$  (calcitriol):** its increase  $\rightarrow$   $\downarrow$  PTH and vice versa.
- **Plasma  $\text{PO}_4^{3-}$  level:** its increase  $\rightarrow$   $\uparrow$  PTH secretion by lowering plasma  $\text{Ca}^{2+}$  level.

# CALCITONIN

- It is a **calcium-lowering** peptide **hormone** (containing 32 amino acids ).
- It is **secreted by the parafollicular cells (C cells ) of the thyroid gland.**
- **Calcitonin has a  $\text{Ca}^{2+}$  lowering effect if plasma  $\text{Ca}^{2+}$  level is raised above normal.**
- Its actions are mediated by increasing intracellular content of cAMP.

## Actions:

- **Calcitonin decreases plasma  $\text{Ca}^{2+}$  level through acting on bones and kidneys.**
- **Calcitonin acts mainly and directly on bones.**

### **Effect on bones:**

- ✓ **Calcitonin inhibits bone resorption by reducing activity of osteoclasts (thus it helps  $\text{Ca}^{2+}$  deposition in bones).**
- ✓ **It decreases the formation of new osteoclasts.**

### **Effect on the Kidney:**

**Calcitonin increases urinary excretion of  $\text{Ca}^{2+}$  by inhibiting its reabsorption from the renal tubules.**

# Regulation of Calcitonin

## Calcitonin is regulated by:

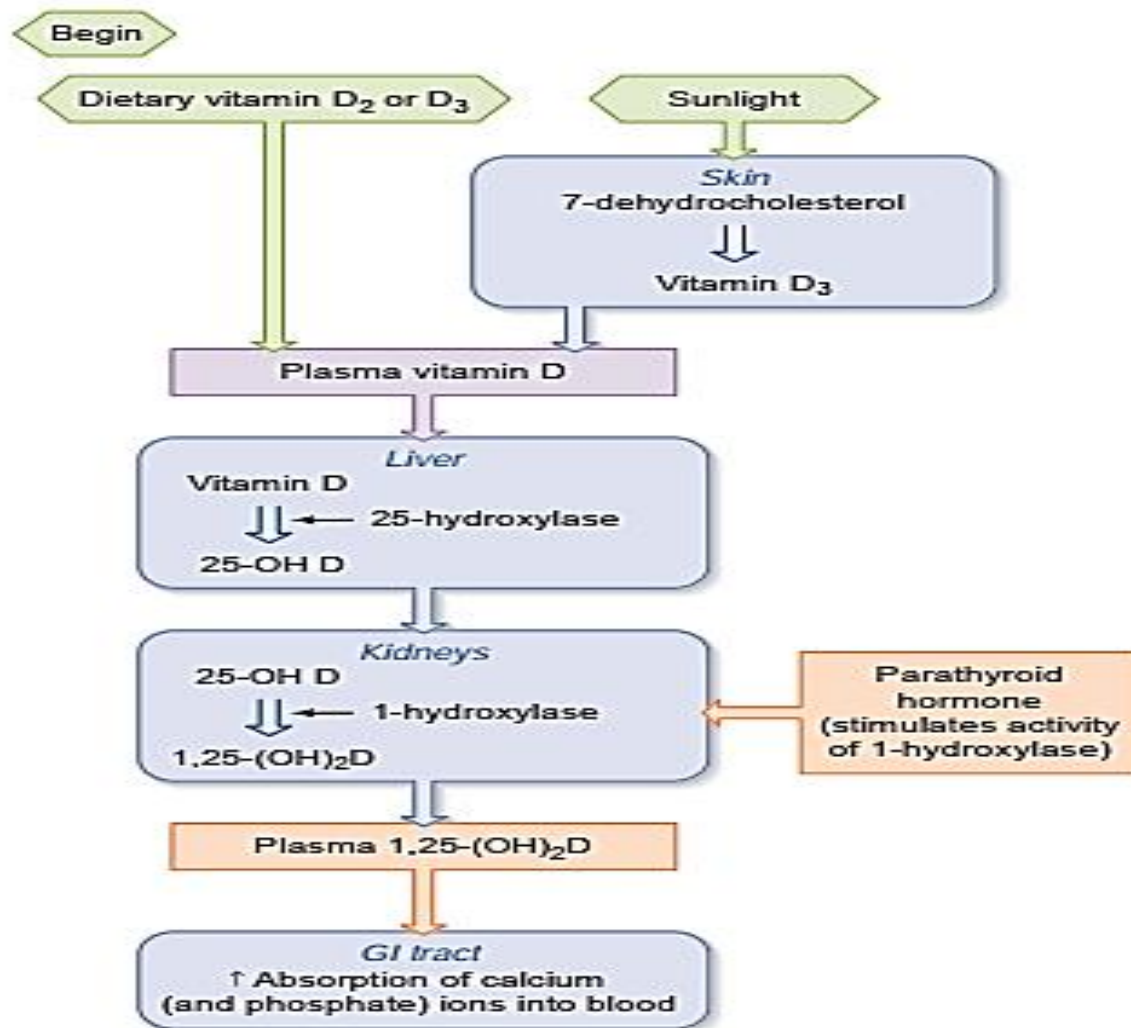
- Plasma  $\text{Ca}^{2+}$  level: increased  $\text{Ca}^{2+}$  level stimulates calcitonin secretion and vice versa.
- GIT hormones as gastrin, secretin and CCK stimulate calcitonin secretion: Its release following meals helps prevention of postprandial hypercalcemia.

## Importance of calcitonin:

- Its plasma level is more in children than in adults, which helps bone growth and development of the skeleton.
- It is used in treatment of bone diseases which is characterized by excessive osteoclastic activity.

## ACTIVE FORM OF VITAMIN D<sub>3</sub>

- Vitamin D<sub>3</sub> is one of fat soluble vitamins.
- It is naturally present in certain foods especially fish liver oil.
- **Its provitamin 7-dehydrocholesterol is present under skin of man.**
  
- **UV sunlight penetrates the skin to convert 7-dehydrocholesterol to cholecalciferol.**
- **It is activated as follows:**
  - ✓ In the liver, cholecalciferol undergoes 25-hydroxylation to yield 25(OH) cholecalciferol (25-HCC; calcidiol).
  - ✓ In the kidney , 25(OH) cholecalciferol undergoes further 1 $\alpha$ -hydroxylation to produce 1,25 – dihydroxycholecalciferol (1,25 DHCC; Calcitriol); active metabolite. Its production in the kidney (in proximal convoluted tubule) is catalyzed by 1 $\alpha$  -hydroxylase enzyme (activated by PTH).
- 1,25 - dihydroxycholecalciferol is transported in the bloodstream.
- **It is considered to be a steroid hormone** (and similar to these hormones, it also acts on intracellular receptors that induce transcription of mRNA).
- **Activation of vitamin D<sub>3</sub> needs healthy liver and kidney with PTH.**



**Figure 11.32** Metabolism of vitamin D to the active form, 1,25-(OH)<sub>2</sub>D.

## **Actions of 1,25-dihydroxycholecalciferol (Calcitriol):**

- **It increases  $\text{Ca}^{2+}$  ( and  $\text{PO}_4^{3-}$ ) absorption from intestine by:**
  - **Stimulating synthesis of a protein called calbindin-D that facilitates  $\text{Ca}^{2+}$  transport across the intestinal epithelium.**
  - **Increasing the  $\text{Ca}^{2+}$  -  $\text{H}^+$  ATPase in the intestinal cells which is needed to pump  $\text{Ca}^{2+}$  into the ECF.**
- **It facilitates  $\text{Ca}^{2+}$  reabsorption in distal tubules of the kidneys.**
- **It is necessary for bone development (by increasing the activity of osteoblasts) as well as calcification of bone matrix. However, in high concentrations, it mobilizes  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$  from bone (by secondary increase in activity of osteoclasts).**

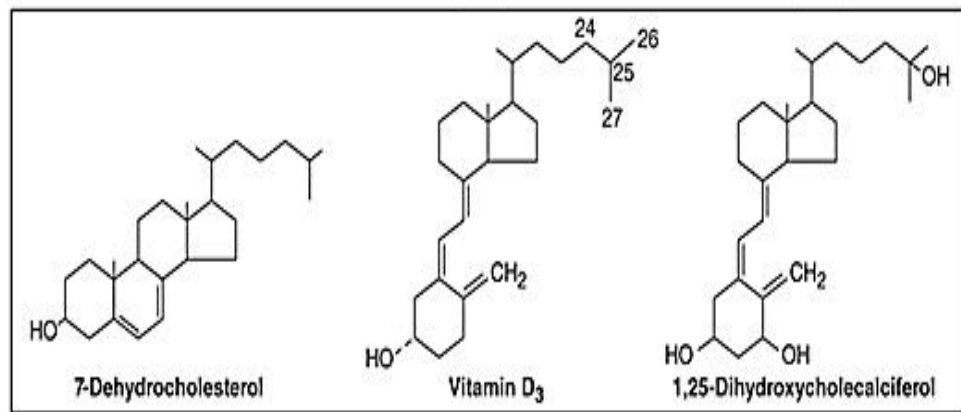
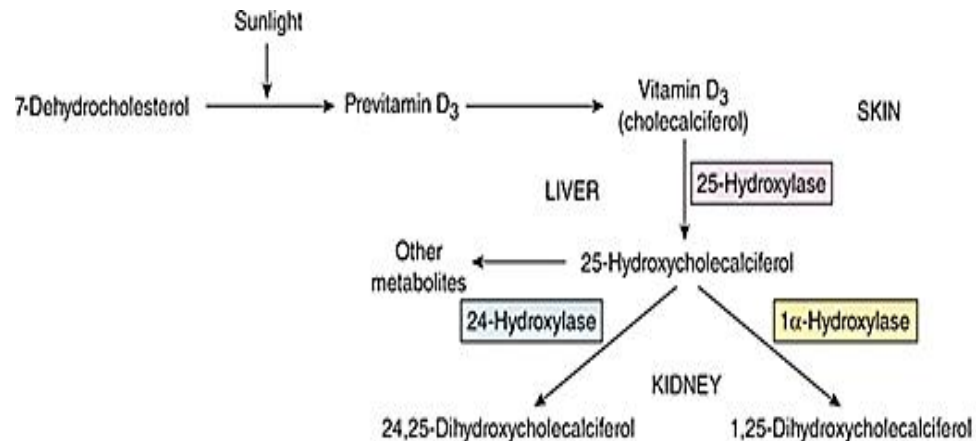
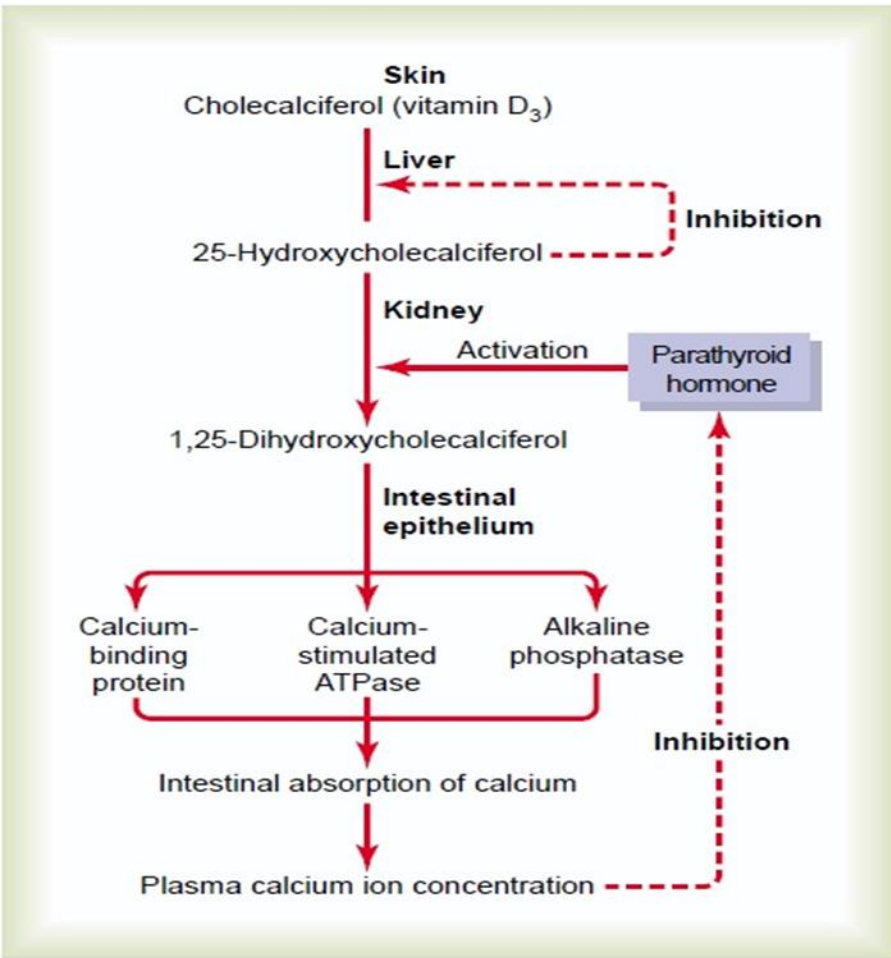
## Regulation (Control) of 1,25-dihydroxycholecalciferol (Calcitriol):

Activity of 1- alpha hydroxylase enzyme is the main factor in regulation of calcitriol synthesis.

Factors that stimulate 1- alpha hydroxylase enzyme increase calcitriol synthesis and vice versa.

### These factors include:

- **PTH:** it stimulates 1- alpha hydroxylase enzyme thus increases calcitriol synthesis.
- **Plasma Ca<sup>2+</sup> level:**  
When plasma calcium level is high, the secretion of PTH decreases and little calcitriol is synthesized. The opposite occurs when plasma calcium level is low.
- **Plasma calcitriol level:** its excessive increase leads to:
  - Feedback inhibition of 1- $\alpha$  hydroxylase as well as PTH secretion.
  - Stimulation of formation of relatively inactive metabolite 24,25 (OH)<sub>2</sub>CC.

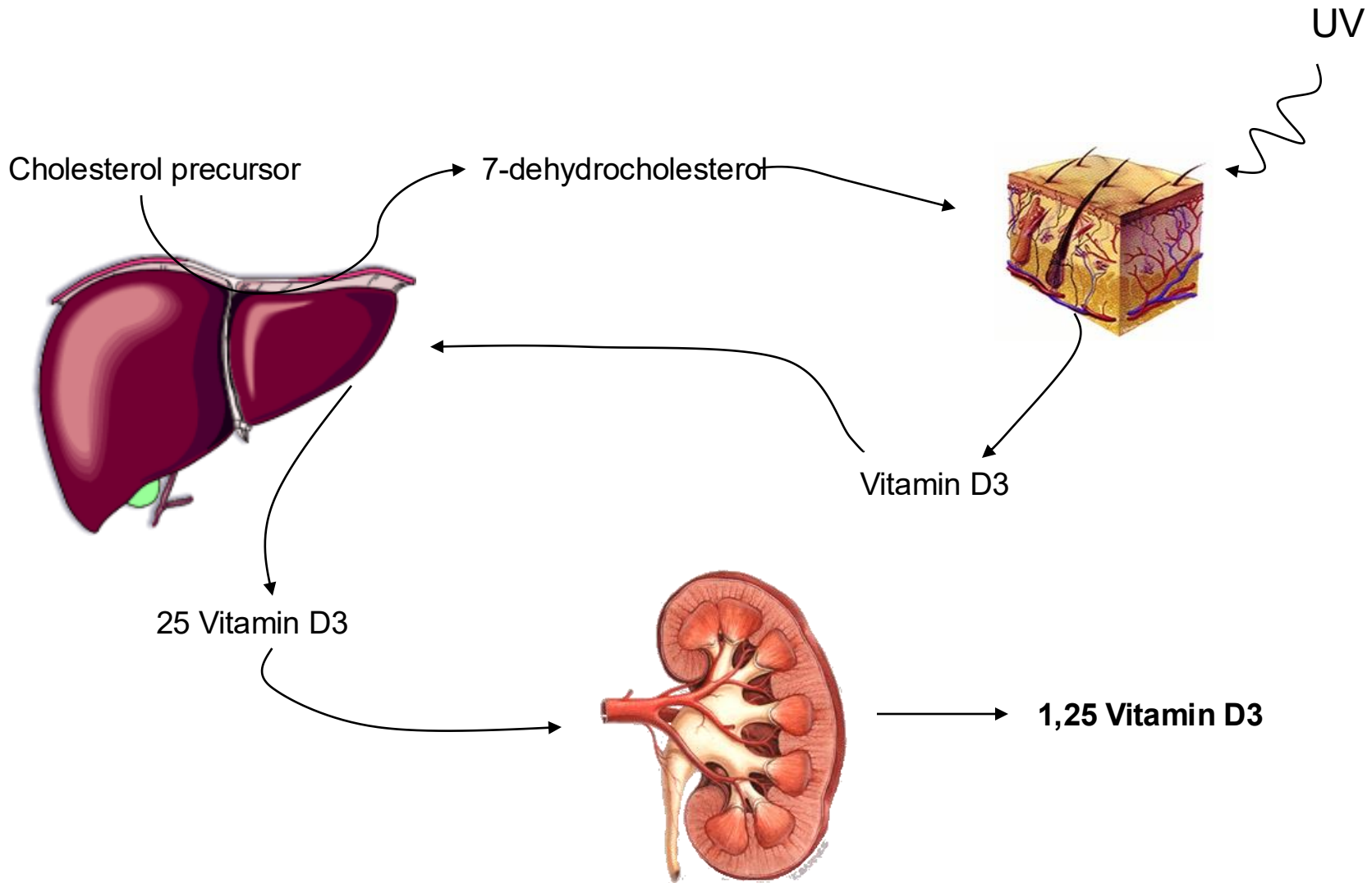


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**Figure 79-6**

Activation of vitamin D<sub>3</sub> to form 1,25-dihydroxycholecalciferol and the role of vitamin D in controlling the plasma calcium concentration.

# 1,25 DHCC (Calcitriol)



# TETANY

## Definition:

It is a state of spastic contraction of skeletal muscles due to increased neuromuscular excitability resulting from a decrease in the ionized plasma  $\text{Ca}^{2+}$  level.

## Causes: are the causes of hypocalcemia:

1. Hypoparathyroidism.
2. Vitamin D deficiency (decreases  $\text{Ca}^{2+}$  absorption from intestine).
3. Low calcium content in diet or diets that combine with calcium and form unabsorbable calcium compounds.
4. Alkalosis  $\rightarrow$  precipitation of  $\text{Ca}^{2+}$ .
5. Renal failure (due to decreased formation of 1,25-DHCC as well as calcium reabsorption in the distal convoluted tubules).

# Types and manifestations of tetany

Depending on plasma  $\text{Ca}^{2+}$  level, there are 2 types of tetany:

## 1. Manifest tetany:

Occurs if the plasma  $\text{Ca}^{2+}$  level drops below 7 mg %. The manifestations of tetany are quite apparent.

- Spasmodic contractions of skeletal muscles:
  - **In the hands & feet → carpopedal spasm.**
  - **Carpal spasm (Obstetrician's hand):** There is flexion of the wrist and metacarpophalangeal joints with extension of the interphalangeal joints. The thumb is adducted.
  - **Pedal spasm: the feet and toes are plantar flexed.**
- In severe conditions: generalized convulsions may occur.
- In the laryngeal muscles → asphyxia.

## 2. Latent tetany:

- Occurs if plasma  $\text{Ca}^{2+}$  level is above 7 mg %, but below 9 mg %.
- The manifestations of tetany are not apparent, but are liable to occur if any condition that tends to lower the plasma calcium occurred e.g. pregnancy, lactation, or hyperventilation.
- It can be diagnosed by measuring ionized  $\text{Ca}^{2+}$  plasma level.

## Carpal spasm



## Treatment of tetany

1. During the attack: I.V. calcium salts (gluconate or chloride) must be given very slowly to avoid calcium rigor.
2. In between the attacks or for cases of latent tetany:
  - Oral calcium + vitamin D.

## HYPOCALCEMIA - TREATMENT

Severe symptomatic cases

Intravenous  
Calcium gluconate

Asymptomatic cases

Calcium carbonate

Vitamin D

## OTHER HORMONES AFFECTING $\text{Ca}^{2+}$ METABOLISM

**Growth hormone:** Promotes bone and cartilage growth and increases intestinal absorption of  $\text{Ca}^{2+}$ .

**Thyroid hormones:** Increased thyroid hormones cause hypercalcemia, hypercalciuria and **osteoporosis**.

### **Glucocorticoids:**

Decrease plasma calcium level by decreasing intestinal absorption and increase the renal excretion (anti-vitamin D).

Prolonged administration of glucocorticoids stimulates osteoclasts causing **osteoporosis**.

**Estrogens:** Promote bone growth and development by stimulating osteoblasts and inhibiting osteoclasts. When estrogens are reduced at menopause, **osteoporosis** is accelerated.

**Testosterone:** stimulates bone and cartilage growth.

**Insulin:** stimulates bone growth by its anabolic effect.



Thank  
you