Endocrine Module
Physiology (Lecture 5)
Hormonal Control of Calcium Metabolism

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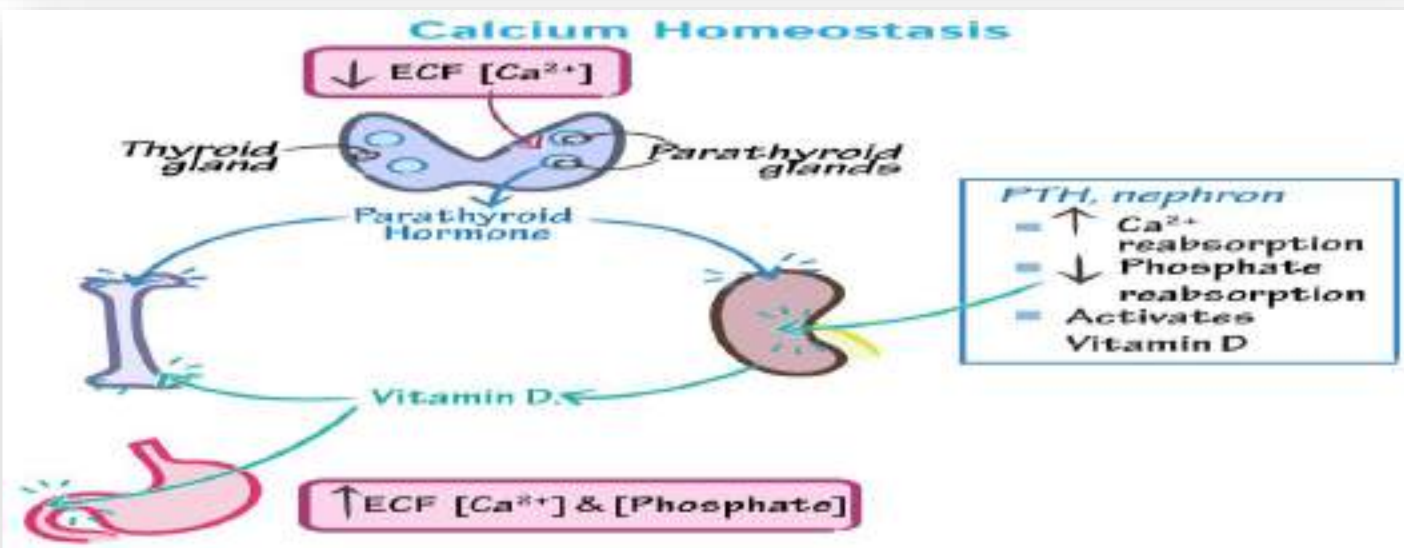


Calcium metabolism

- ✓ **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.

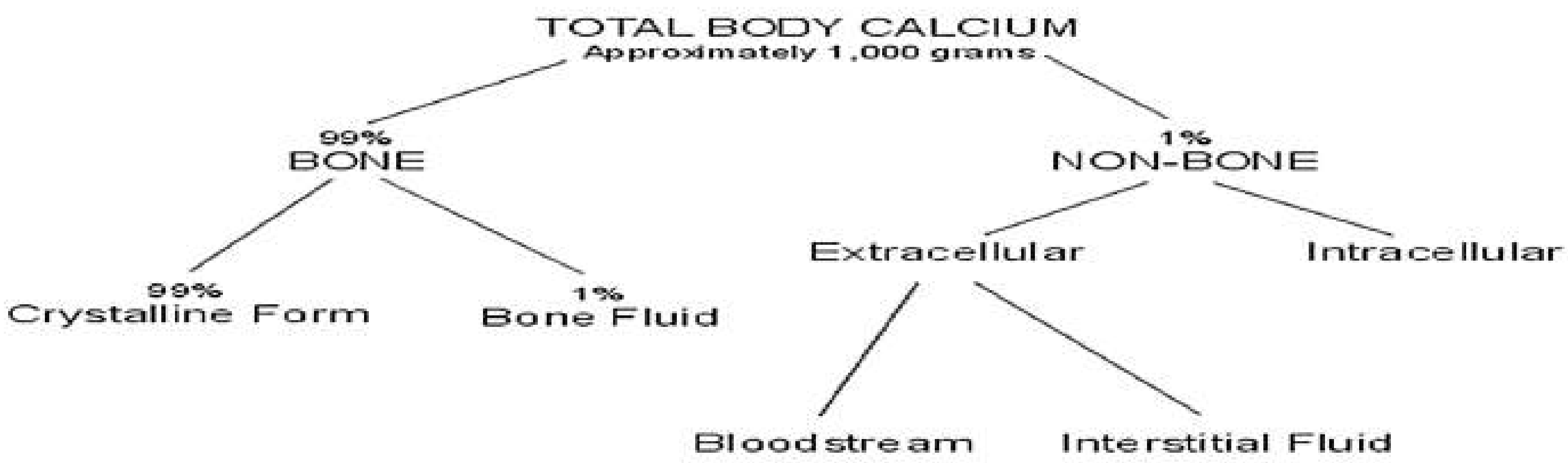
Calcium Content and Distribution in the Body

Total body calcium:

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

The 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**.

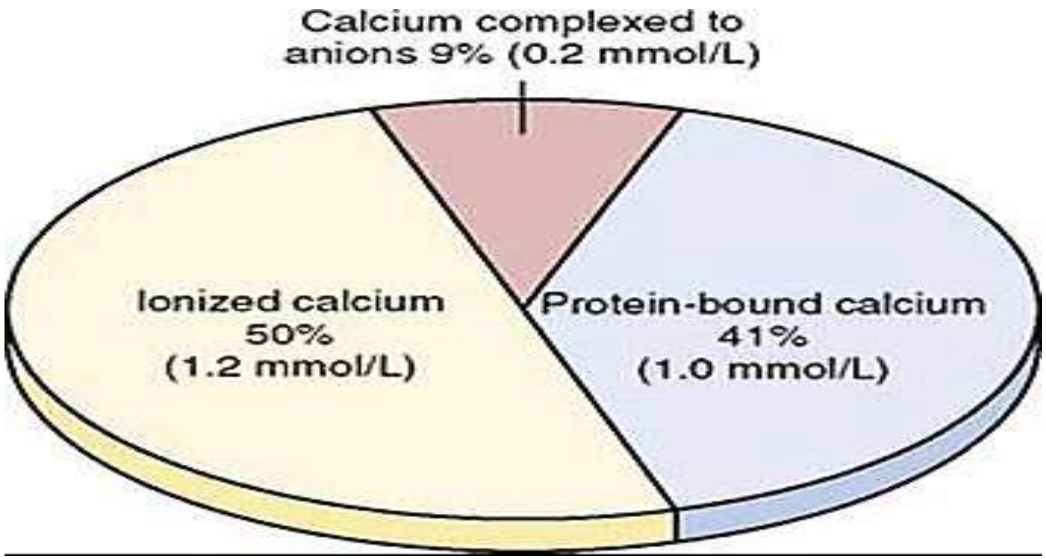


Calcium in plasma:

- 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**:

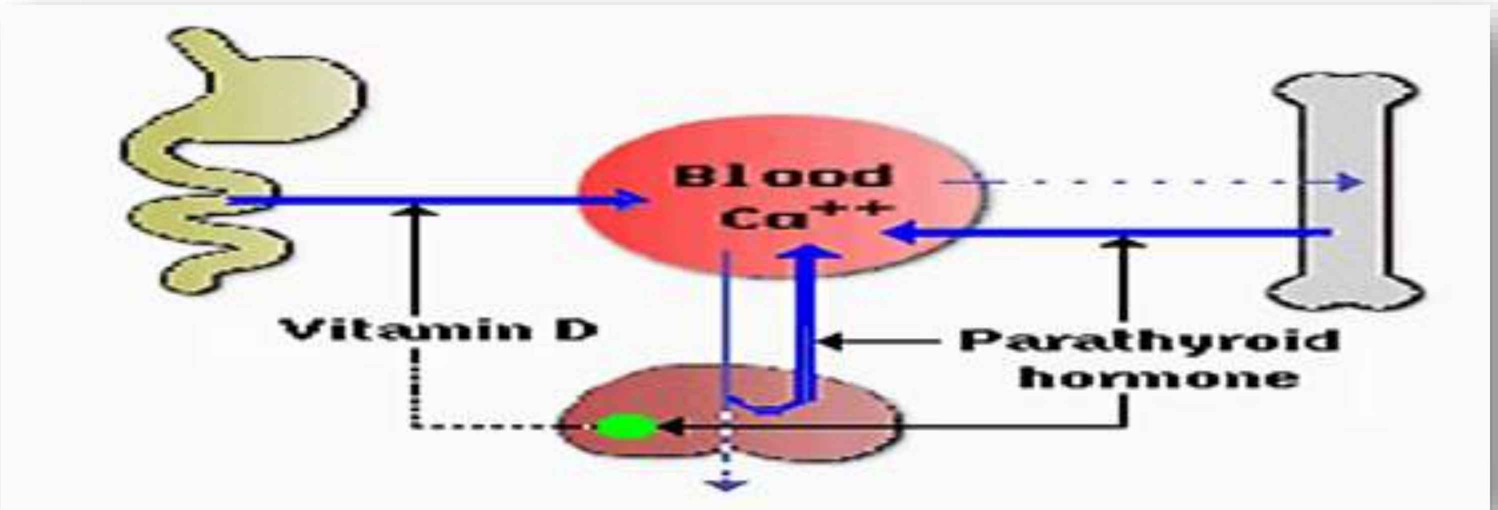
✓ **99.5%** is present **as stable salts (hydroxyapatite crystals)** that are very slowly exchangeable with plasma calcium.

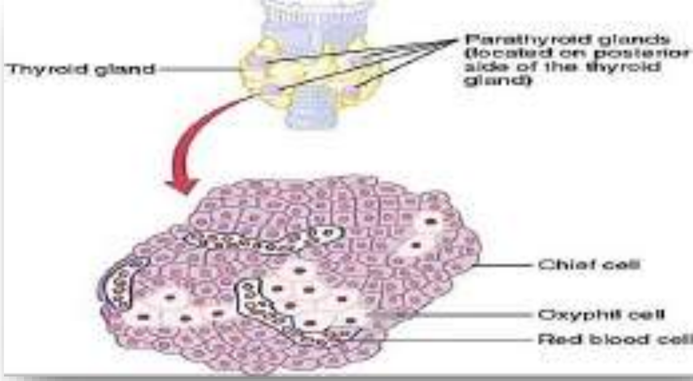
✓ **0.5% (about 5 gm) is readily exchangeable**. It **constitutes a reservoir** that is in equilibrium with the plasma calcium and keeps it constant at 7 mg% in absence of PTH.

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 ↑ plasma calcium level when decreased.**
2. **Calcitonin hormone: it ↓ plasma calcium level when increased.**
3. **Active vitamin D: it ↑intestinal absorption of calcium from GIT and ↑ 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 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 Ca^{2+} and inorganic phosphate (PO_4^{3-}) concentrations in body fluids.**
- **Normally, plasma PO_4^{3-} concentration is inversely related to plasma calcium concentration.**
- **$[PO4^{3-}] \propto 1/[Ca^{2+}]$**
- **$[Ca^{2+}] \times [PO4^{3-}] = K$ (constant)**
- **This constant K is known as the Solubility Product.**
- **The main function of PTH is to increase plasma Ca^{2+} level and decrease plasma PO_4^{3-} level** (so as to maintain the solubility product constant).

Mechanism:

PTH increases plasma 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 Ca^{2+} in the distal convoluted tubules → ↑ Plasma Ca^{2+} level (rapid physiological adjustment) and ↓Ca^{2+} excretion in urine.
2. PTH decreases the reabsorption of phosphates in the proximal convoluted tubule → ↑ excretion of phosphates in urine → ↓ plasma phosphate.

(2) Effect on Bones:

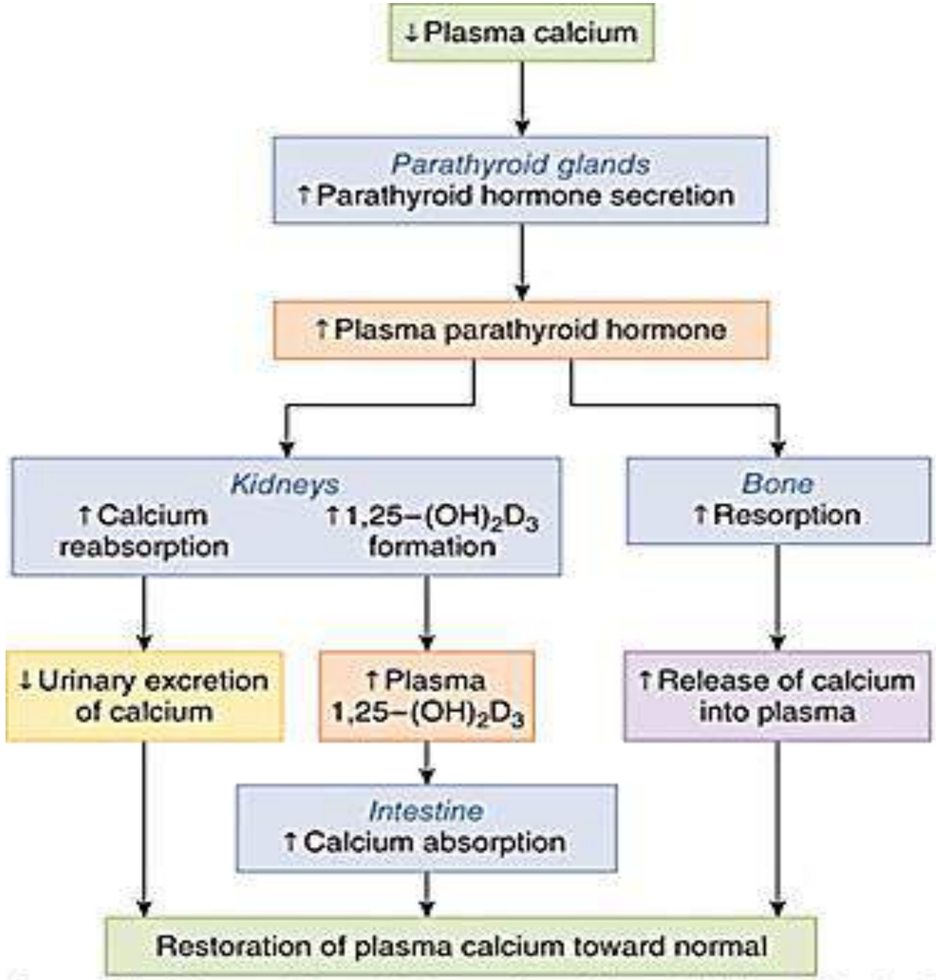
PTH stimulates the Ca^{2+} mobilization from bone into the plasma → ↑ plasma Ca^{2+} level by:

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

(3) Effect on Intestine:

PTH increases absorption of Ca^{2+} indirectly:

PTH activates the 1-α hydroxylase of the kidney responsible for transformation of 25, hydroxycholecalciferol into 1,25-dihydroxycholecalciferol (active vitamin D_3 metabolite) , thus it increases 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.
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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 Ca^{2+}** level which directly controls the parathyroid glands by **a negative feedback mechanism**:

- ↓ **Ionized Ca^{2+} stimulates PTH secretion while ↑ ionized Ca^{2+} inhibits PTH secretion.**

- Active form of vitamin D_3 (calcitriol): its increase → ↓ PTH and vice versa.
- Plasma PO_4^{3-} level: its increase → ↑ PTH secretion by lowering plasma 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 Ca^{2+} lowering effect if plasma Ca^{2+} level is raised above normal.**
- Its actions are mediated by increasing intracellular content of cAMP.

<u>Actions:</u>

- **Calcitonin decreases plasma 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 Ca^{2+}deposition in bones).**
- ✓ **It decreases the formation of new osteoclasts.**

Effect on the Kidney:

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

Regulation of Calcitonin

Calcitonin is regulated by:

- Plasma Ca^{2+} level: increased 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_3

- Vitamin D_3 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 1α-hydroxylation to produce 1,25 – dihydroxycholecalciferol (1,25 DHCC; Calcitriol); active metabolite. Its production in the kidney (in proximal convoluted tubule) is catalyzed by 1α -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_3 needs healthy liver and kidney with PTH.**

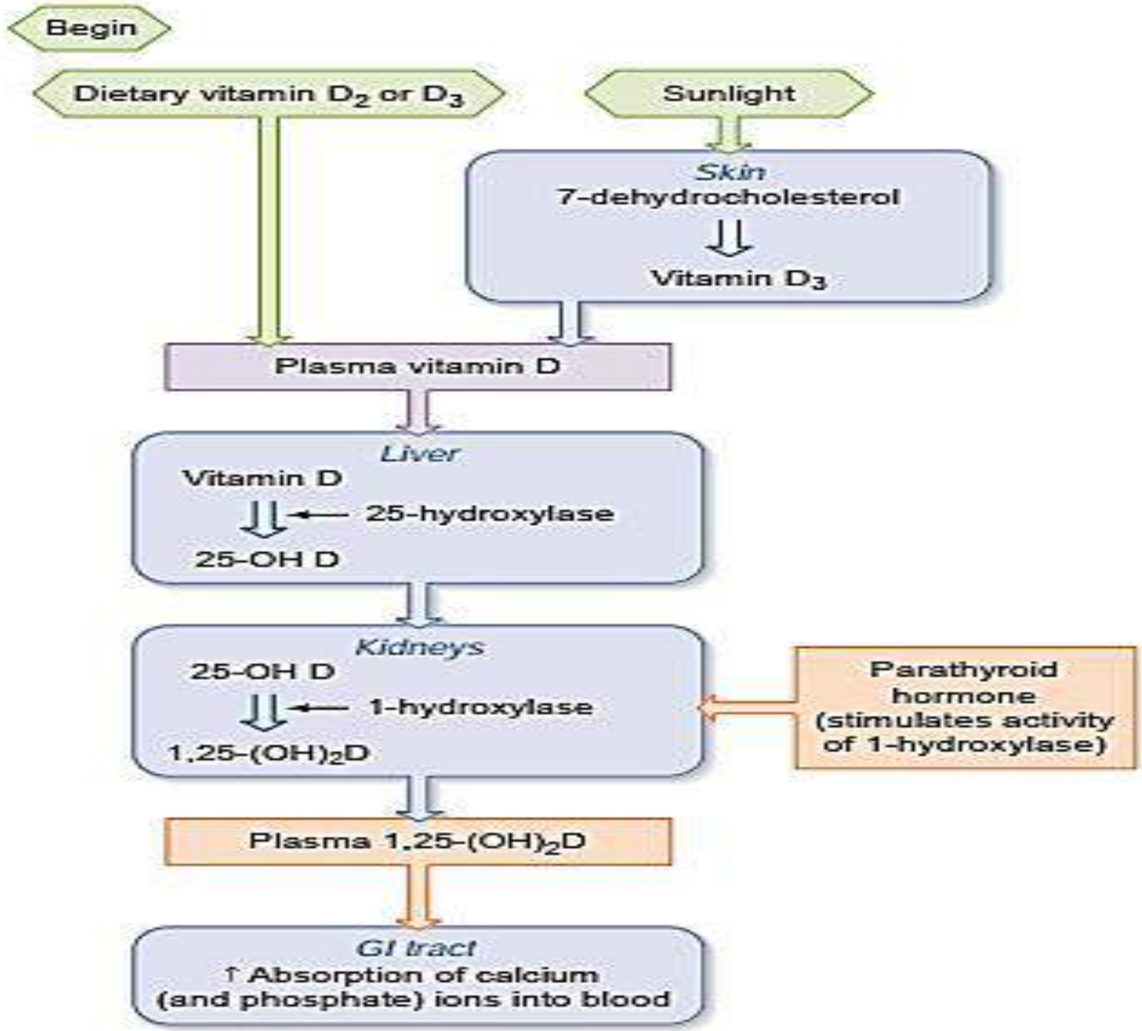


Figure 11.32 Metabolism of vitamin D to the active form, $1,25\text{-}(OH)_2D$.

Action of 1,25-dihydroxycholecalciferol (Calcitriol):

- **It increases Ca^{2+} absorption (and PO_4^{3-}) from intestine by:**
  - **Stimulating synthesis of a protein called calbindin-D that facilitates Ca^{2+} transport across the intestinal epithelium.**
  - **Increasing the Ca^{2+} - H^+ ATPase in the intestinal cells which is needed to pump Ca^{2+} into the ECF.**
- **It facilitates 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 Ca^{2+} and 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 increase calcitriol synthesis

- **Plasma Ca^{2+} 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.

- **Hormones:**

Growth hormone and calcitonin stimulate calcitriol synthesis.

- **Plasma calcitriol level:** its excessive increase leads to:

o Feedback inhibition of 1-α hydroxylase as well as PTH secretion.
o Stimulation of formation of relatively inactive metabolite 24,25 $(OH)_2CC$.

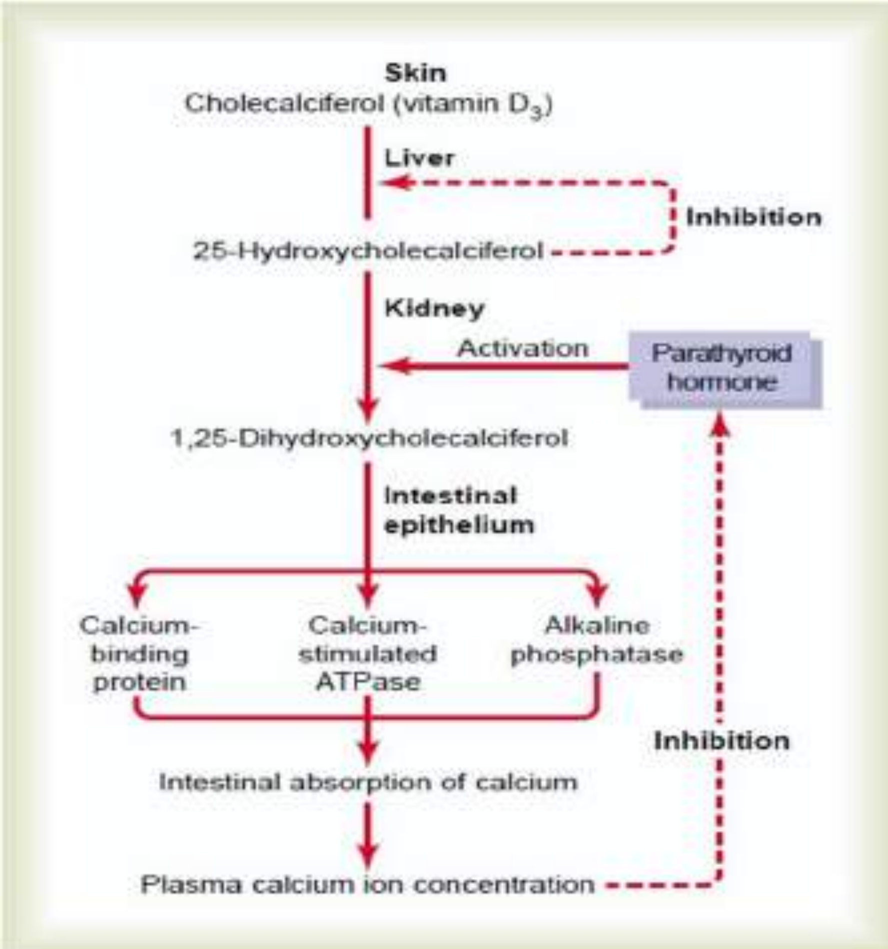
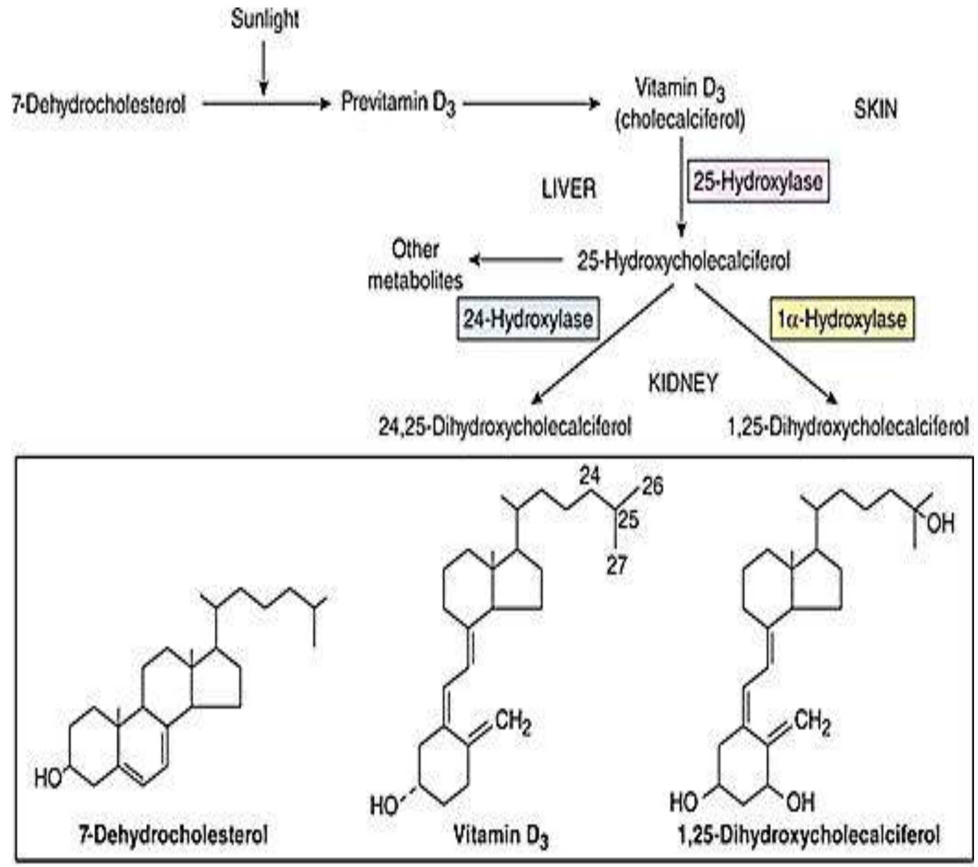


Figure 79–6

Activation of vitamin D_3 to form 1,25-dihydroxycholecalciferol and the role of vitamin D in controlling the plasma calcium concentration.



Source: Kim E. Barrett, Susan M. Barman, Scott Boitano, Heddwen L. Brooks: Ganong's Review of Medical Physiology, 25th Ed.
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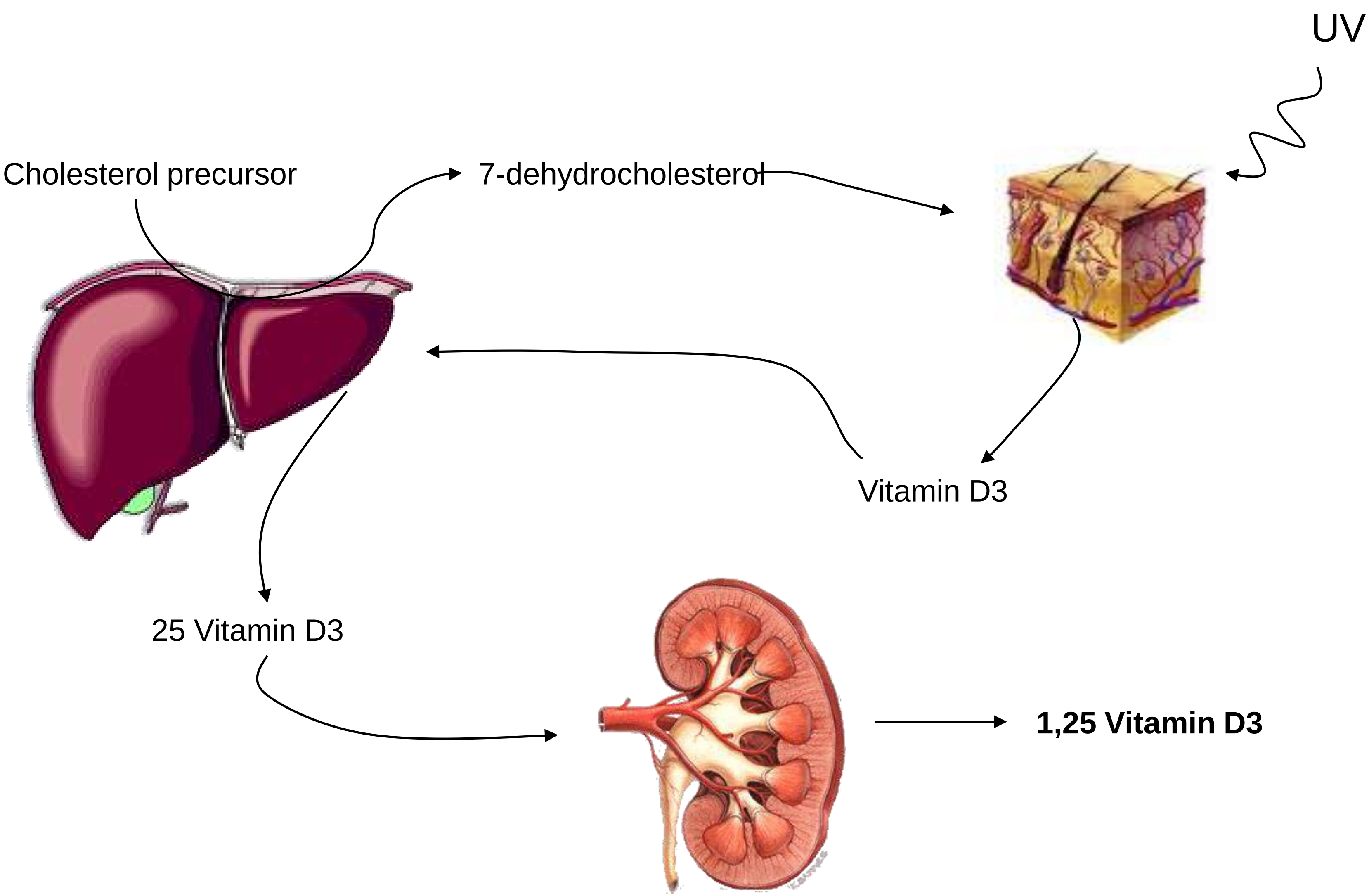
1,25 DHCC (Calcitriol)



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 Ca^{2+} level.

Causes: are the causes of hypocalcemia:

1. Hypoparathyroidism.
2. Vitamin D deficiency (decreases 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 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 Ca^{2+} level, there are 2 types of tetany:

1. Manifest tetany:

Occurs if the plasma 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:

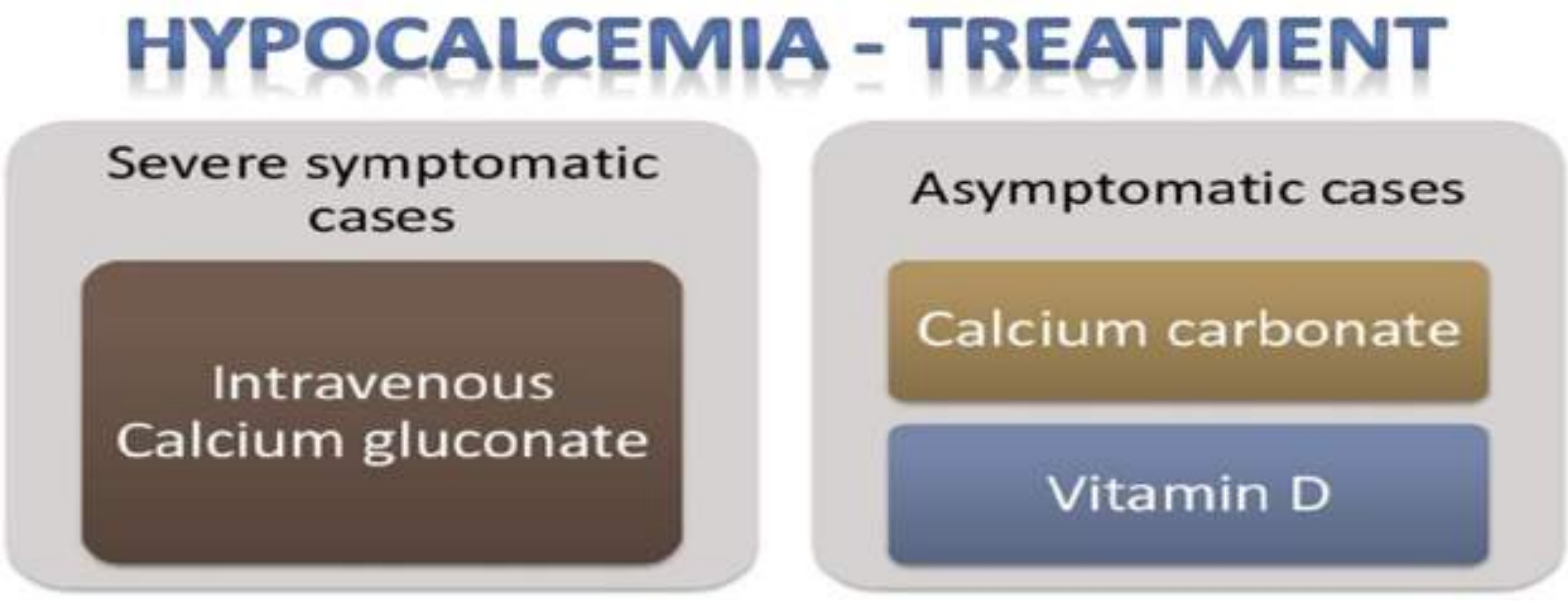
- Occurs if plasma Ca^{2+} level is above 7 mg %, but below 9 mg %.
- The manifestations of tetany are not apparent, but are liable to occur if any condition that tends to lower the plasma calcium occurred e.g. pregnancy, lactation, or hyperventilation.
- It can be diagnosed by measuring ionized Ca^{2+}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



OTHER HORMONES AFFECTING Ca^{2+} METABOLISM

Growth hormone: Promotes bone and cartilage growth and increases intestinal absorption of 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