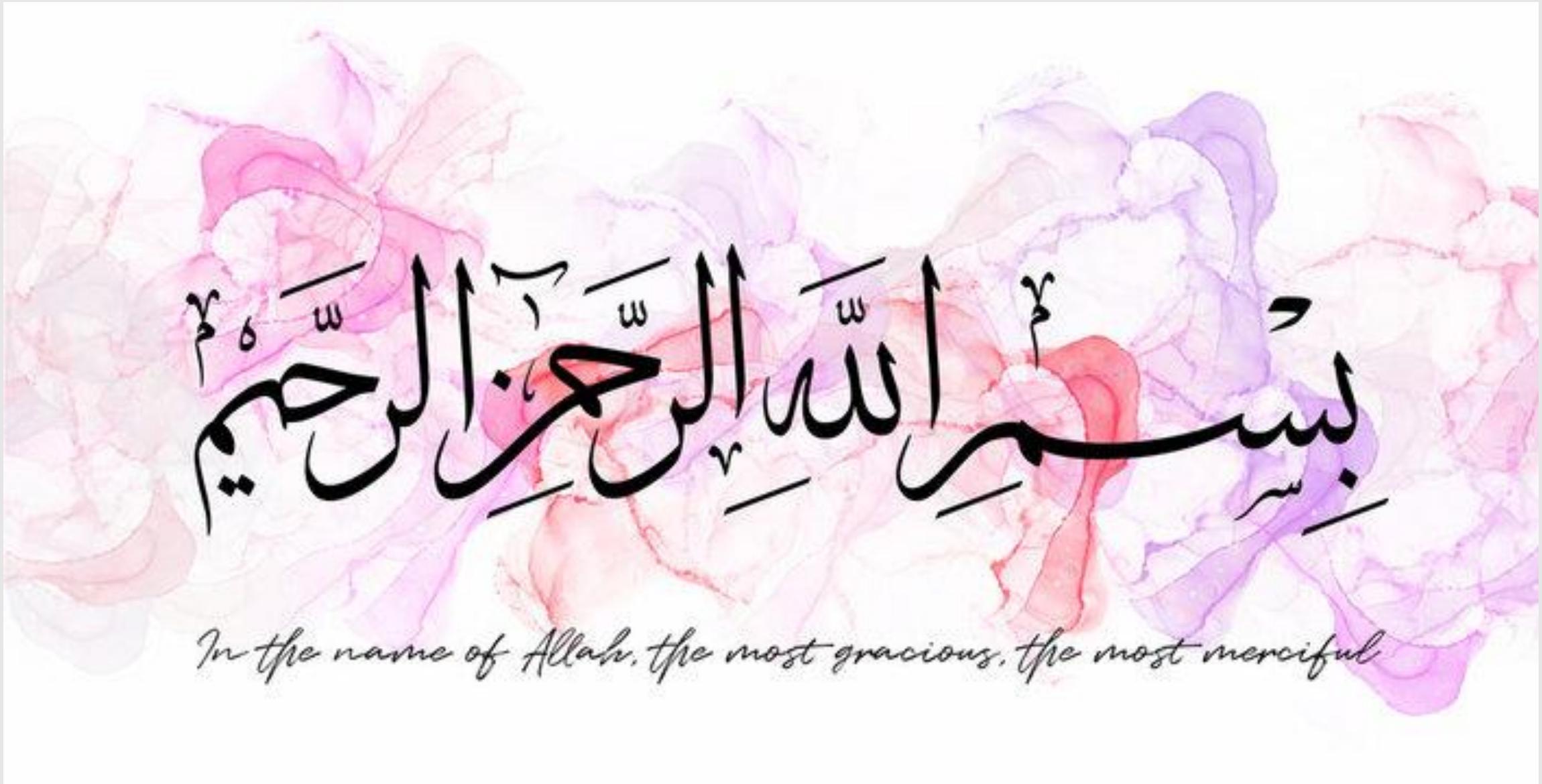

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ
In the name of Allah, the most gracious, the most merciful

Hormonal Control of Calcium & Phosphate Metabolism

Dr Zubia Shah

Learning Objectives

- **Explain the role of Vit D in Calcium and phosphorus metabolism.**
- **Explain the mechanism of action PTH.**
- **Describe the effect of Parathyroid Hormone on Calcium and Phosphate concentrations.**
- **Describe the control of Parathyroid Secretion.**

Maintenance of blood Calcium level

Normal blood calcium level = 9-11 mg/dl

3 hormones are important in calcium homeostasis

1. Parathyroid hormone

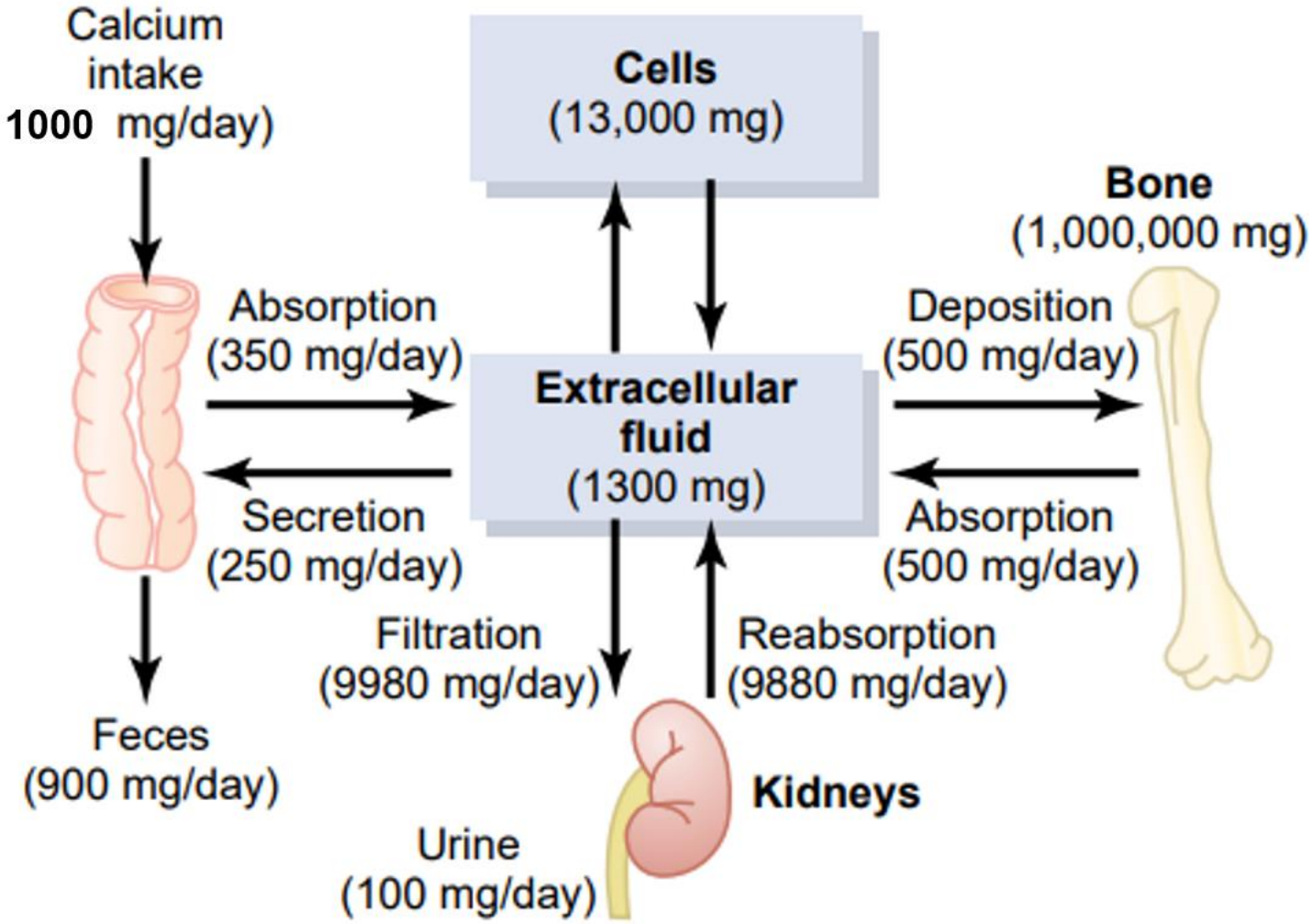
2. 1, 25 dihydroxycholecalciferol

3. Calcitonin

Normal Distribution of Calcium in mmol/L

Total diffusible		**1.34**
Ionized (Ca^{2+})	1.18	
Complexed to HCO_3^-, citrate, etc	0.16	
Total nondiffusible (protein-bound)		**1.16**
Bound to albumin	0.92	
Bound to globulin	0.24	
Total plasma calcium		**2.50**

Absorption And Excretion Of Calcium And Phosphate



Normal Distribution of Inorganic Phosphate in ECF

- Phosphate Ions → HPO_4^{-2} & $H_2PO_4^-$
- Average total quantity of inorganic phosphorus represented by both phosphate ions is 4mg/dL of blood
- 3-4mg/dL in adults
- 4-5mg/dL in children

Phosphate levels 2-3 times above or below normal → no major effects on the body

Easily absorbed from gut except for that excreted in feces with non-absorbed calcium

Phosphate

- Bones and teeth - made of crystalline calcium phosphate

Medical and biological research uses

- The medicinal type (salt) of phosphorus is phosphate
- help cure many urinary tract infections - urine more acidic
- avoid the development of calcium stones in the urinary tract

Why Calcium concentration must be diligently regulated?

Regulation of Calcium

- 99% of Ca^{2+} in the body (1000 g) is in crystalline form (skeleton & teeth)
- 0.9% (9 g) is intracellular - soft tissues
- less than 0.1% (1 g) is in the ECF
- half of the ECF Ca^{2+} is bound to plasma proteins (plasma) or is complexed with PO_4^{3-} and not free to participate in chemical reactions
- The other half of ECF Ca^{2+} is freely diffusible and can readily pass from the plasma into the interstitial fluid and interact with the cells
- **Only this free ECF Ca^{2+} is biologically active and subject to regulation; it constitutes less than one thousandth of the total Ca^{2+} in the body**

Functions of Calcium

Free ECF Ca^{2+} is Biologically Active

1. Neuromuscular excitability –

A **fall in free Ca^{2+}** results in overexcitability of nerves and muscles Fall in free Ca^{2+} ↑ Na^{+} permeability - threshold. Hypocalcemia → excitation

While **↑ free Ca^{2+}** depresses neuromuscular excitability - Hypercalcemia is also life threatening →cardiac arrhythmias and generalized depression of NM excitation

2. **Excitation contraction Coupling in cardiac & smooth muscles**

3. **Stimulus secretion coupling –** secretion of neurotransmitters by nerve cells and hydrophilic hormones by endocrine cells

Free ECF Ca^{2+} is Biologically Active

4. **Excitation–secretion coupling**

In pancreatic ß cells - Ca^{2+} influx from the ECF → insulin secretion

5. **Maintenance of tight junctions** between some cells by acting as cement

6. **Clotting of blood** - serves as a cofactor in cascade of reactions → clot formation

7. Second messenger in many cells

8. Cell motility & ciliary action

9. Bone & teeth integrity

Bone

Depot for 99% of body's Calcium

Bone Is a Living Tissue

Tough organic matrix or osteoid - precipitated calcium phosphate salts ($Ca_3(PO_4)_2$)

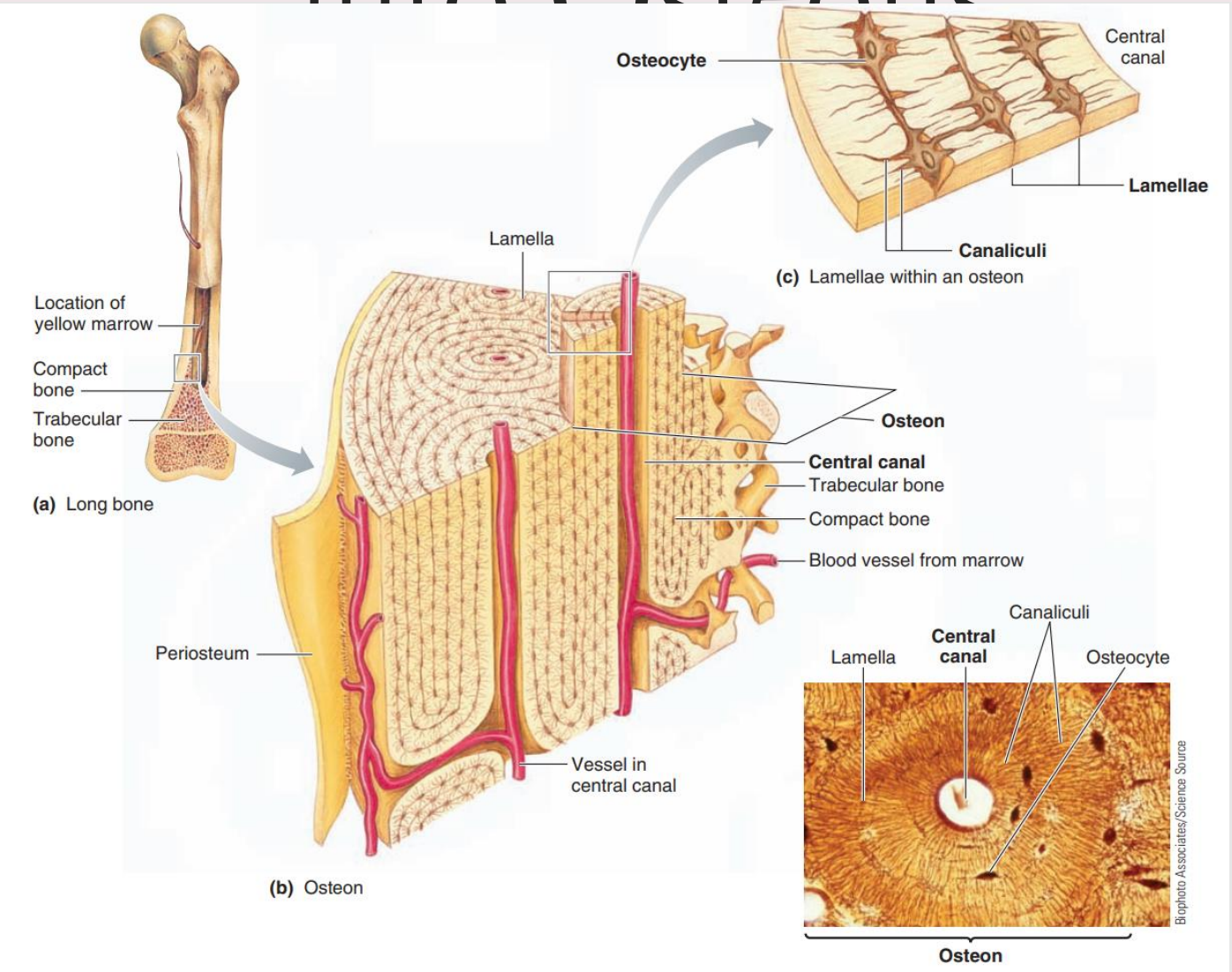
($Ca_3(PO_4)_2$)salts are in solution in the ECF and precipitate (crystallize) around the collagen fibres in the matrix

Organic matrix is 90-95% collagen fibers and remaining ground substance

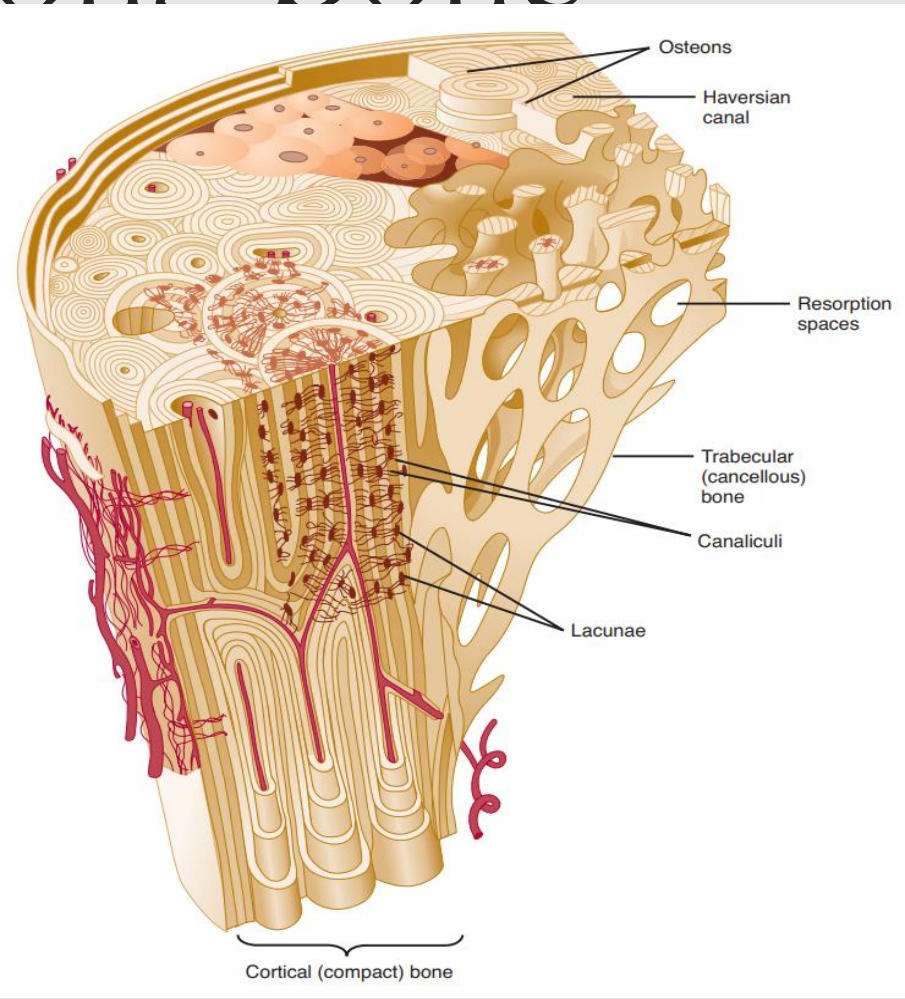
Ground substance = ECF + proteoglycans (chondroitin sulphate & hyaluronic acid)

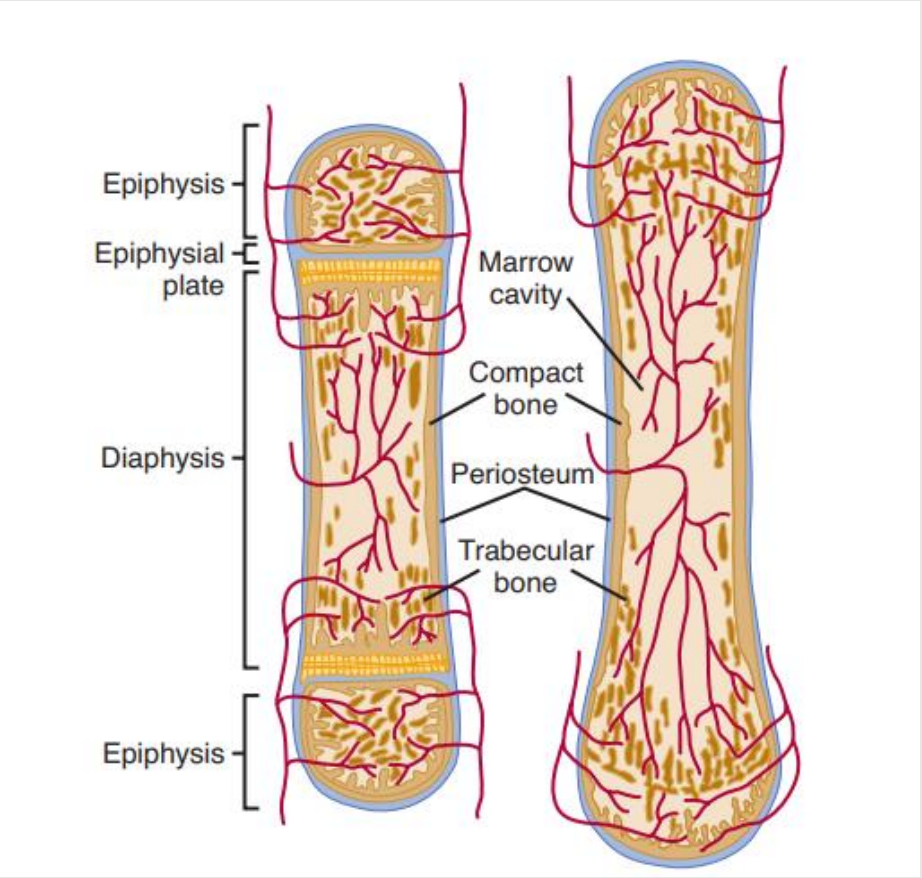
Bone continuously undergoes remodelling

Organization of Compact Bone into Osteons



Compact & Trabecular bone
Long Bone





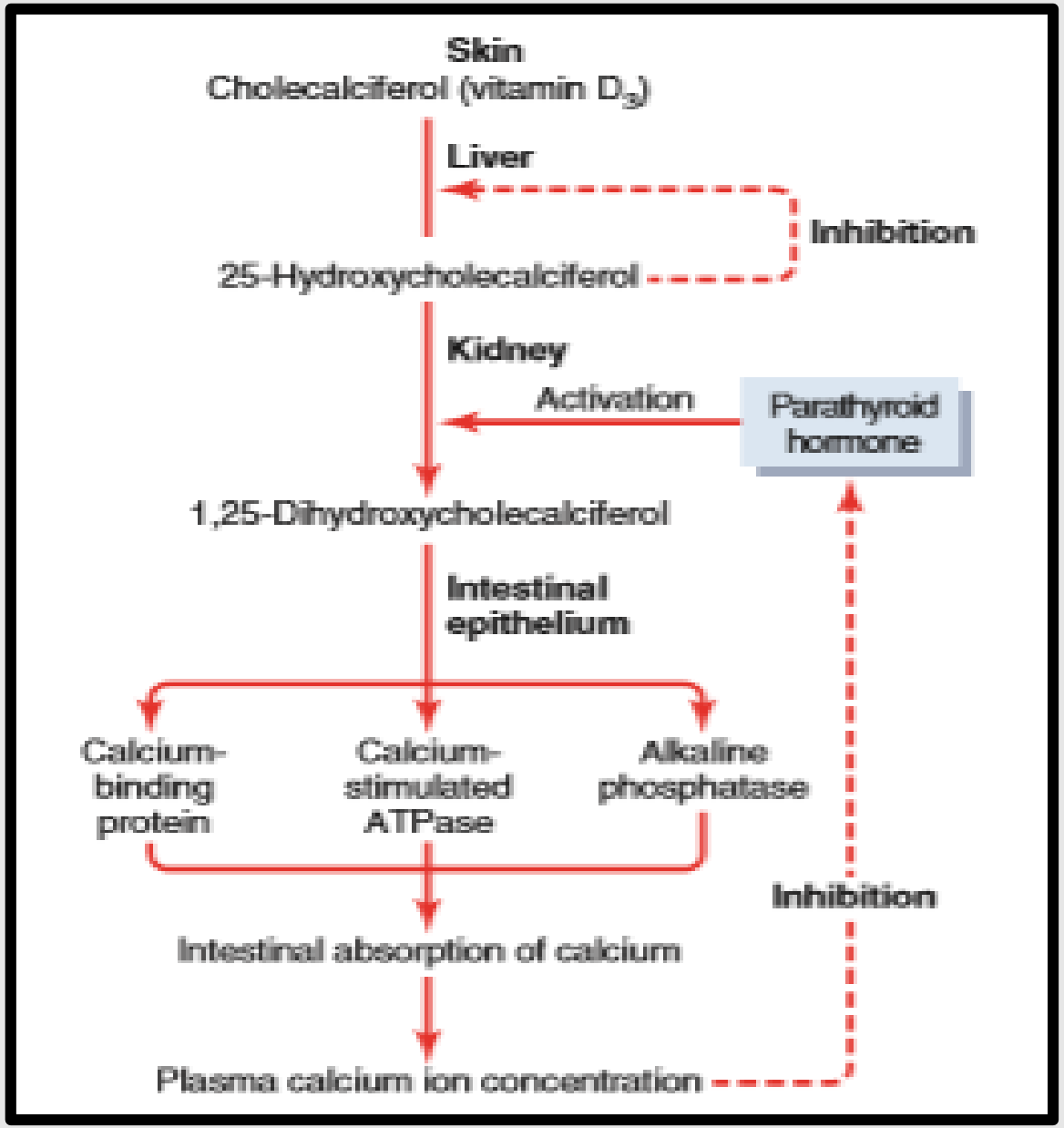
Why does calcium not precipitate in tissues despite high concentrations and what will happen if they precipitate in normal tissues?

Vitamin D

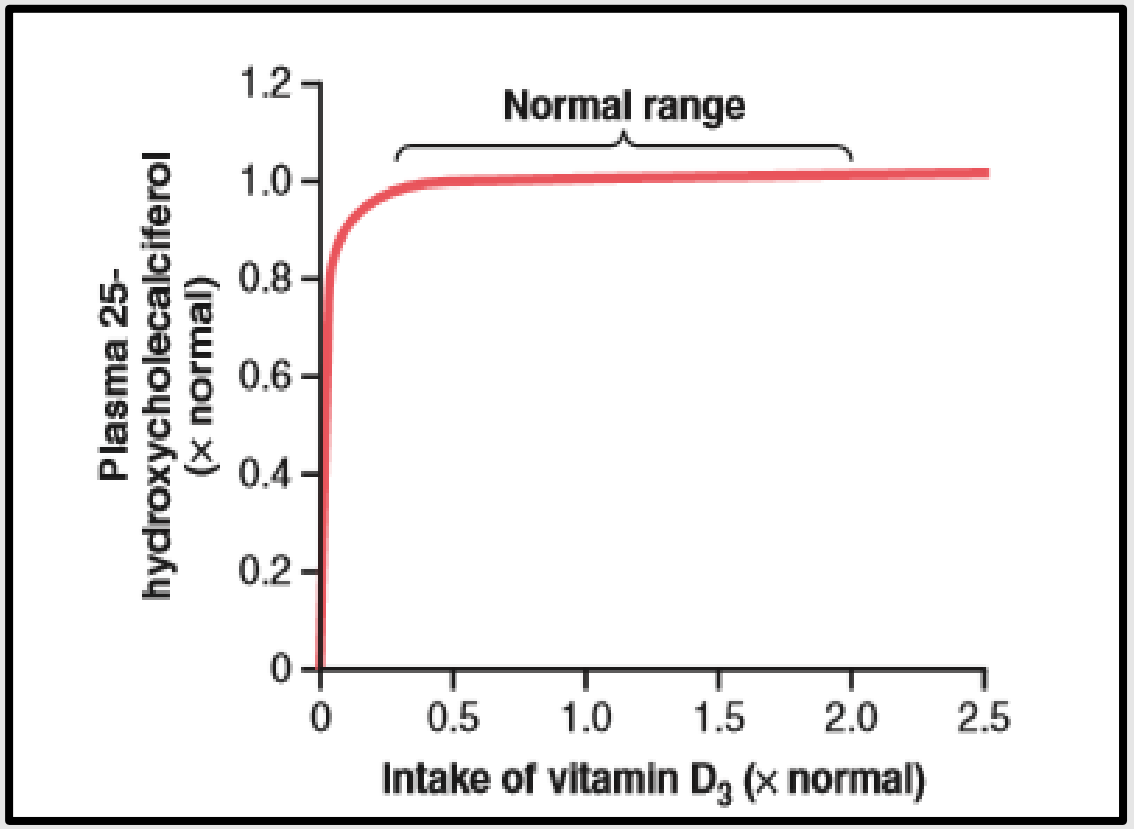
Vitamin D

- ⬆ **calcium absorption** from gut
- bone deposition & resorption
- through a succession of reactions in liver and kidneys to final Active product,

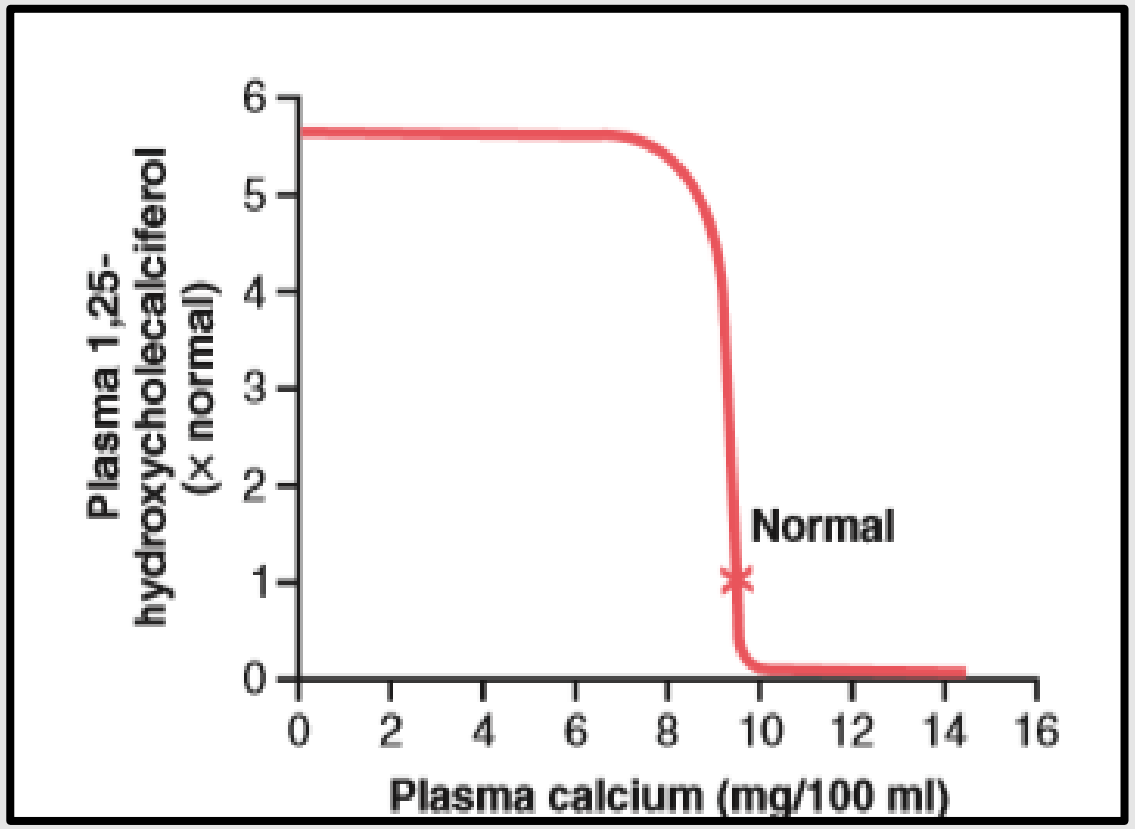
1,25-dihydroxycholecalciferol, (1,25(OH)2D3)

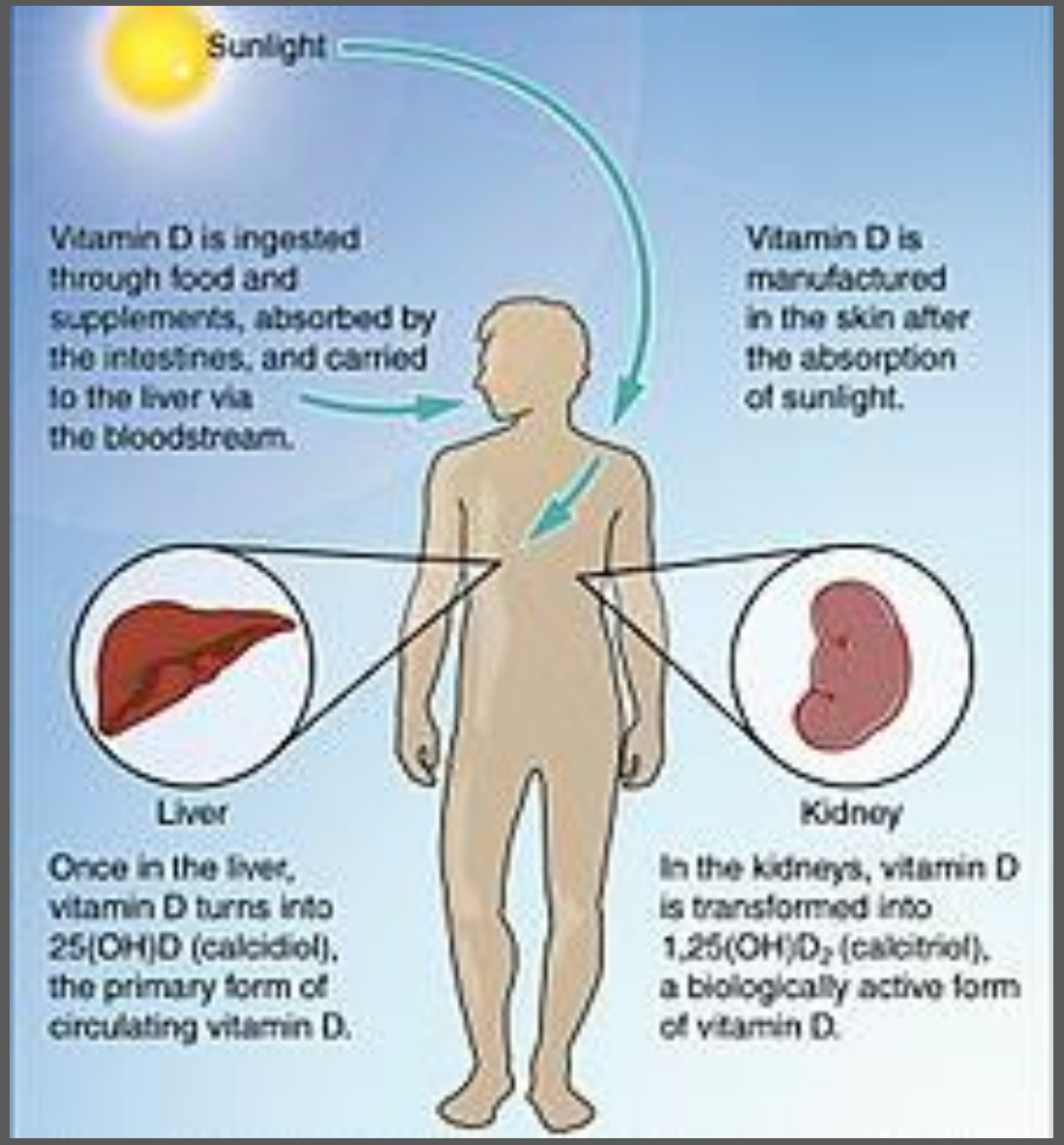


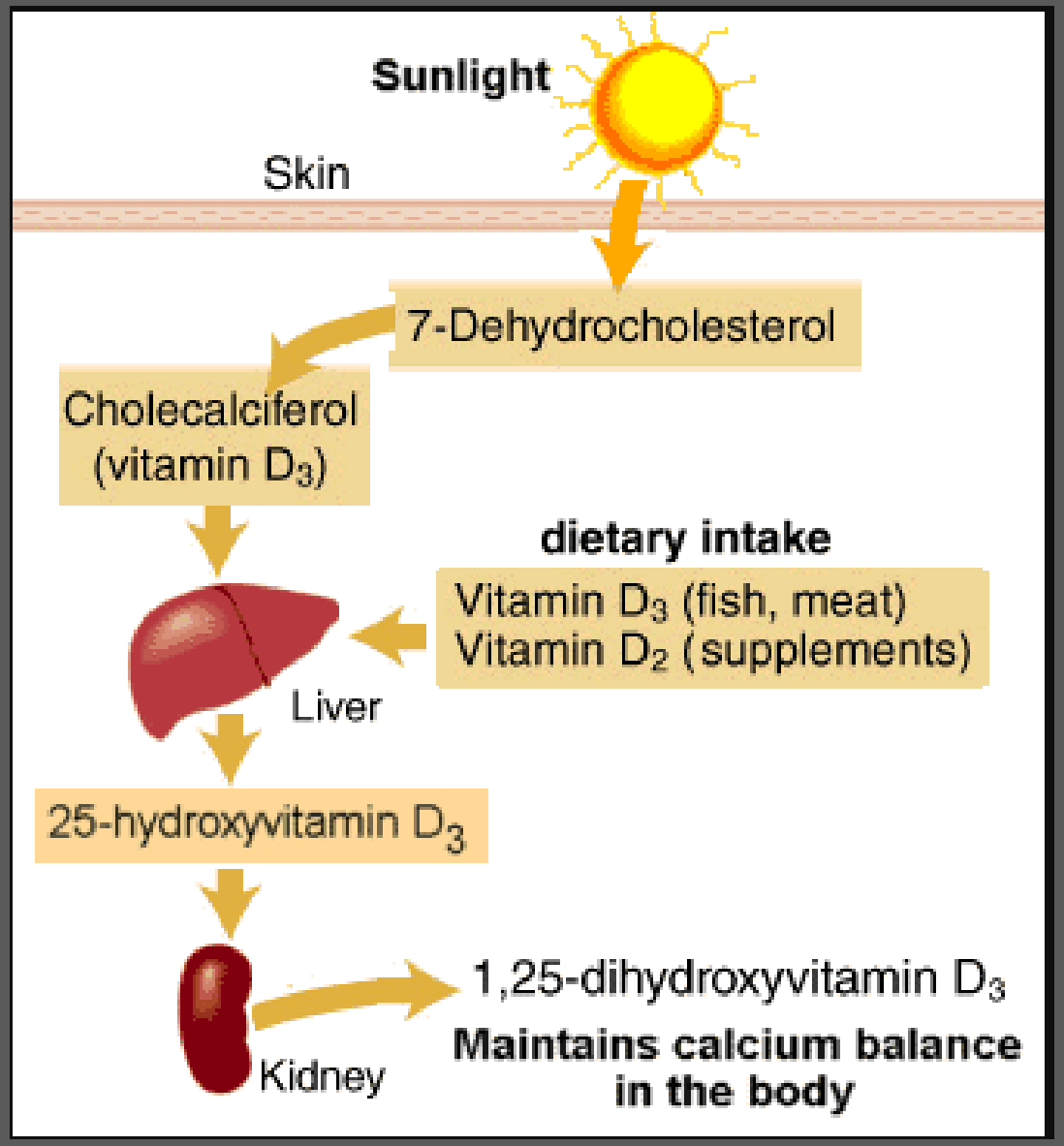
Effect of ↑ Vit D3 intake on plasma concentration of 25-hydroxycholecalciferol



Effect of plasma calcium conc on plasma conc of 1,25-dihydroxycholecalciferol




Sunlight
Vitamin D is ingested through food and supplements, absorbed by the intestines, and carried to the liver via the bloodstream.
Vitamin D is manufactured in the skin after the absorption of sunlight.
Liver
Kidney
Once in the liver, vitamin D turns into 25(OH)D (calcidiol), the primary form of circulating vitamin D.
In the kidneys, vitamin D is transformed into 1,25(OH)D_2 (calcitriol), a biologically active form of vitamin D.

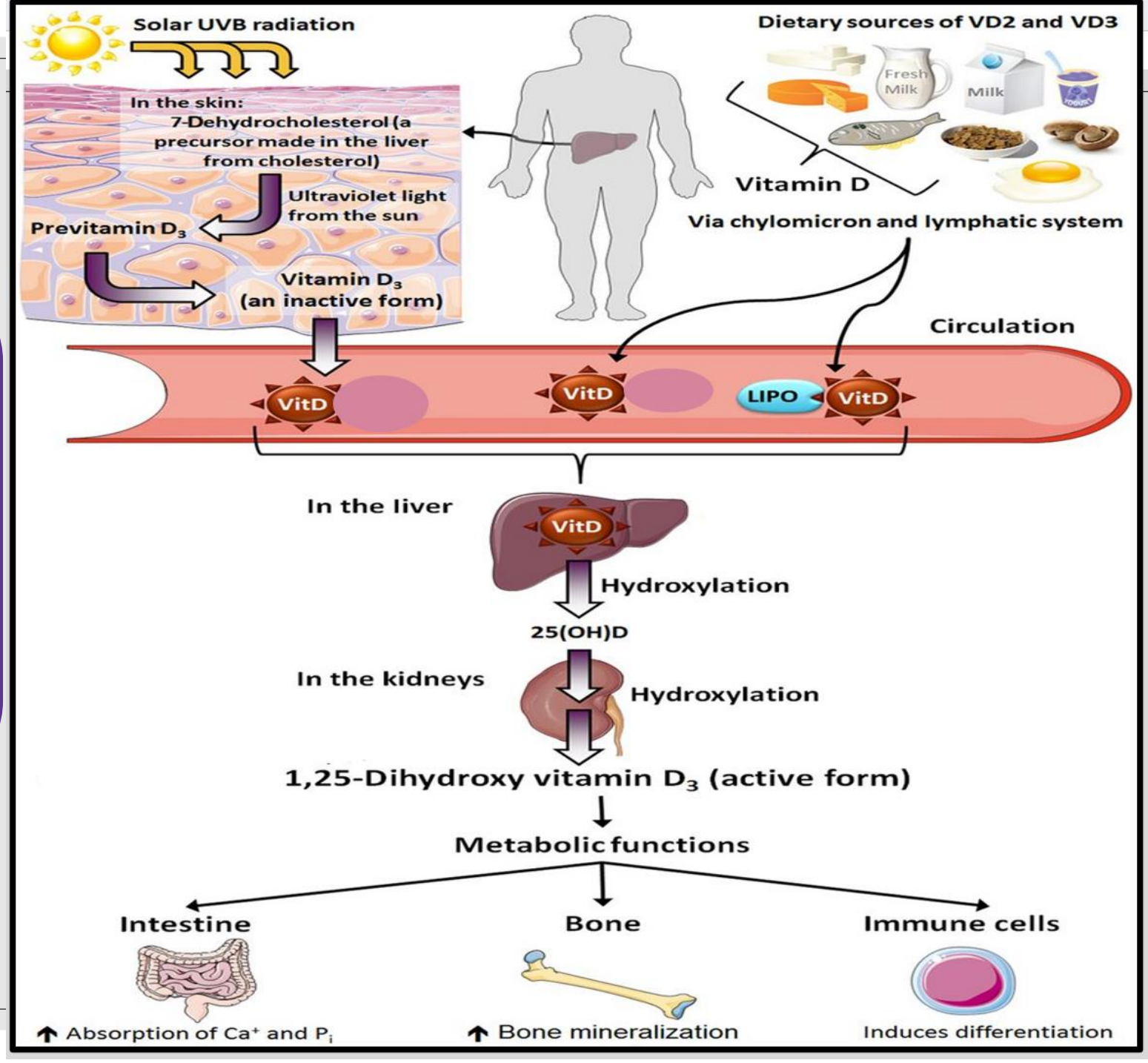

Sunlight
Skin
7-Dehydrocholesterol
Cholecalciferol (vitamin D_3)
dietary intake
Vitamin D_3 (fish, meat)
Vitamin D_2 (supplements)
Liver
25-hydroxyvitamin D_3
Kidney
1,25-dihydroxyvitamin D_3
Maintains calcium balance in the body

Actions of Vitamin D

1. Promotes intestinal calcium absorption
2. Promotes intestinal phosphate absorption
3. Decreases renal calcium & phosphate excretion
4. Effect on bone resorption & deposition
   - Smaller quantities promote bone calcification
   - Large quantities cause bone resorption (↑ Ca++ transport through membranes by 1,25 dihydroxycholecalciferol)

Actions of Vitamin D

(Wjst *et al.* 2010)



Actions of Vitamin D

Promotes Intestinal Calcium Absorption

Promotes Phosphate Absorption by the Intestine

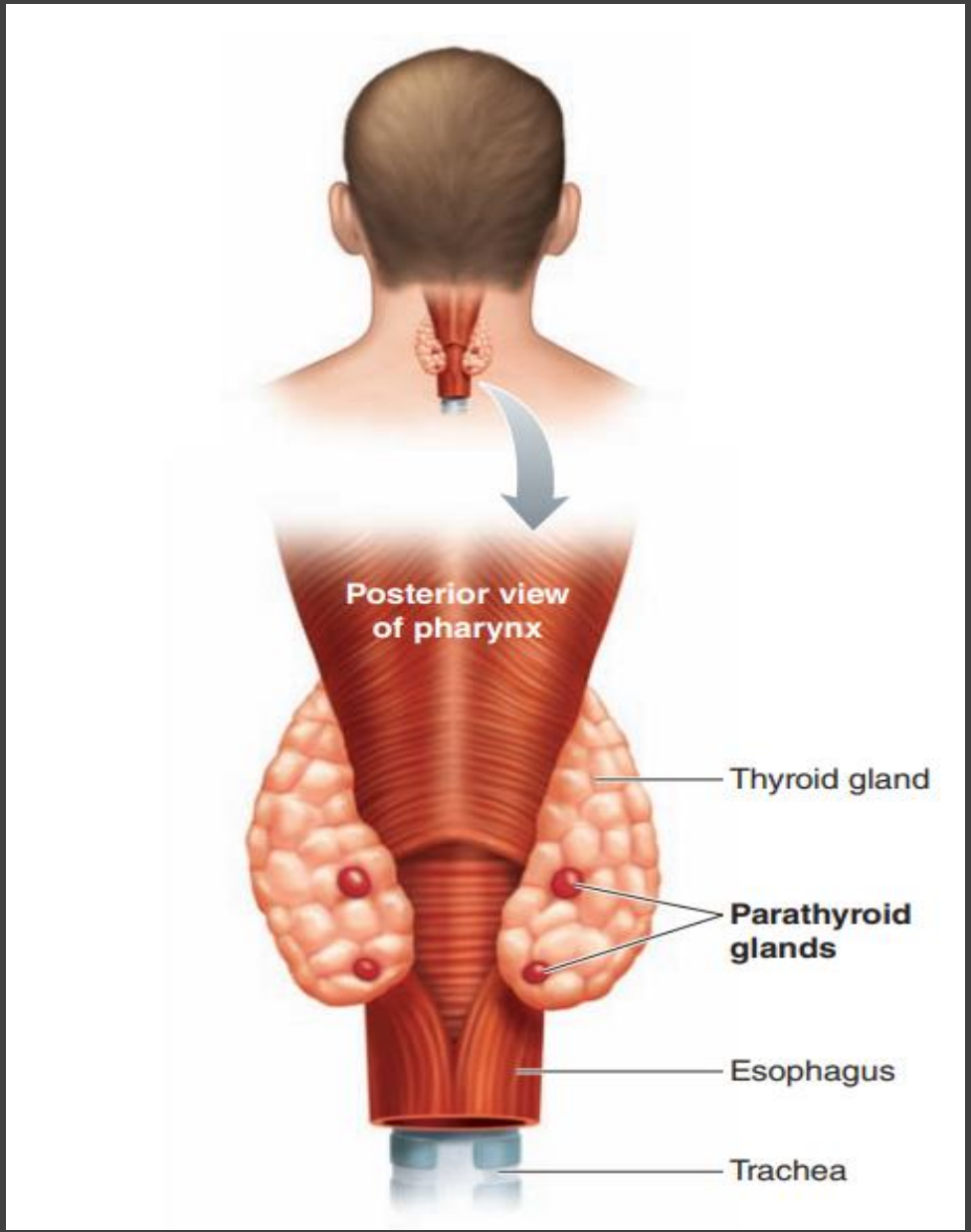
Decreases Renal Calcium and Phosphate Excretion

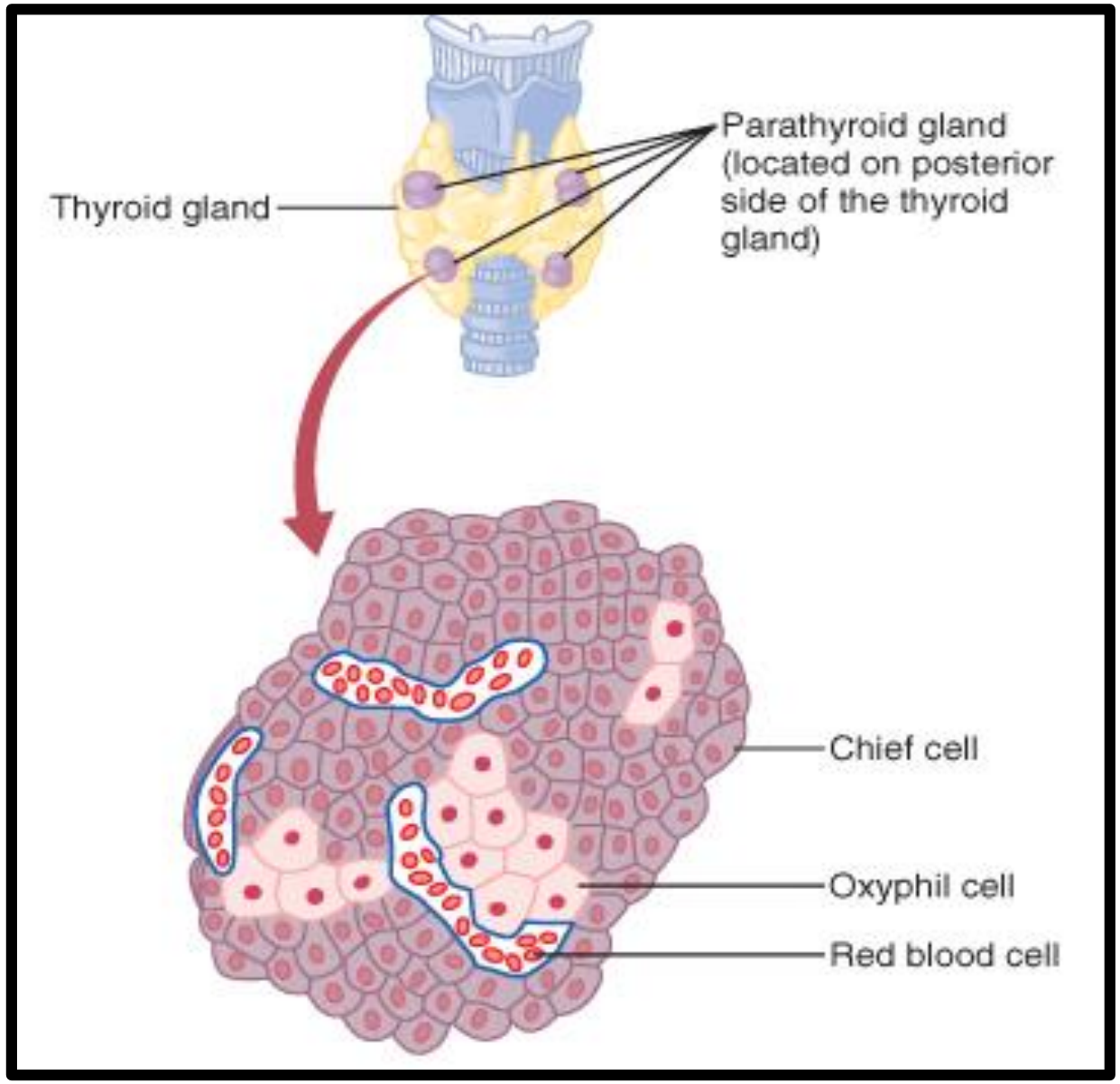
Plays important role in bone resorption, bone deposition & bone calcification

Activates T cells to destroy foreign agents & deficiency leads to increased susceptibility to infection

Parathyroid Gland

Parathyroid Gland





PARATHYROID GLAND

Parathyroid gland

4 glands- one behind each pole of thyroid gland

Size = 6x3x2 mm

Appearance – like dark brown fat

Removal 2-3 gland → transient ↓ parathyroid hormone – later compensated by hypertrophy

Gland consists of

- Chief cells - hormonal production
- Oxyphil cells – no known functions

Parathyroid Hormone

Essential For Life

Parathyroid Hormone

- ↑ Ca^{2+} concentration of plasma
- Complete absence of PTH → asphyxiation caused by hypocalcemic spasm of respiratory muscles → death
- PTH ↑ plasma Ca^{2+} concentration when it falls so prevents hypocalcemia
- lowers plasma $PO4^{3-}$ concentration

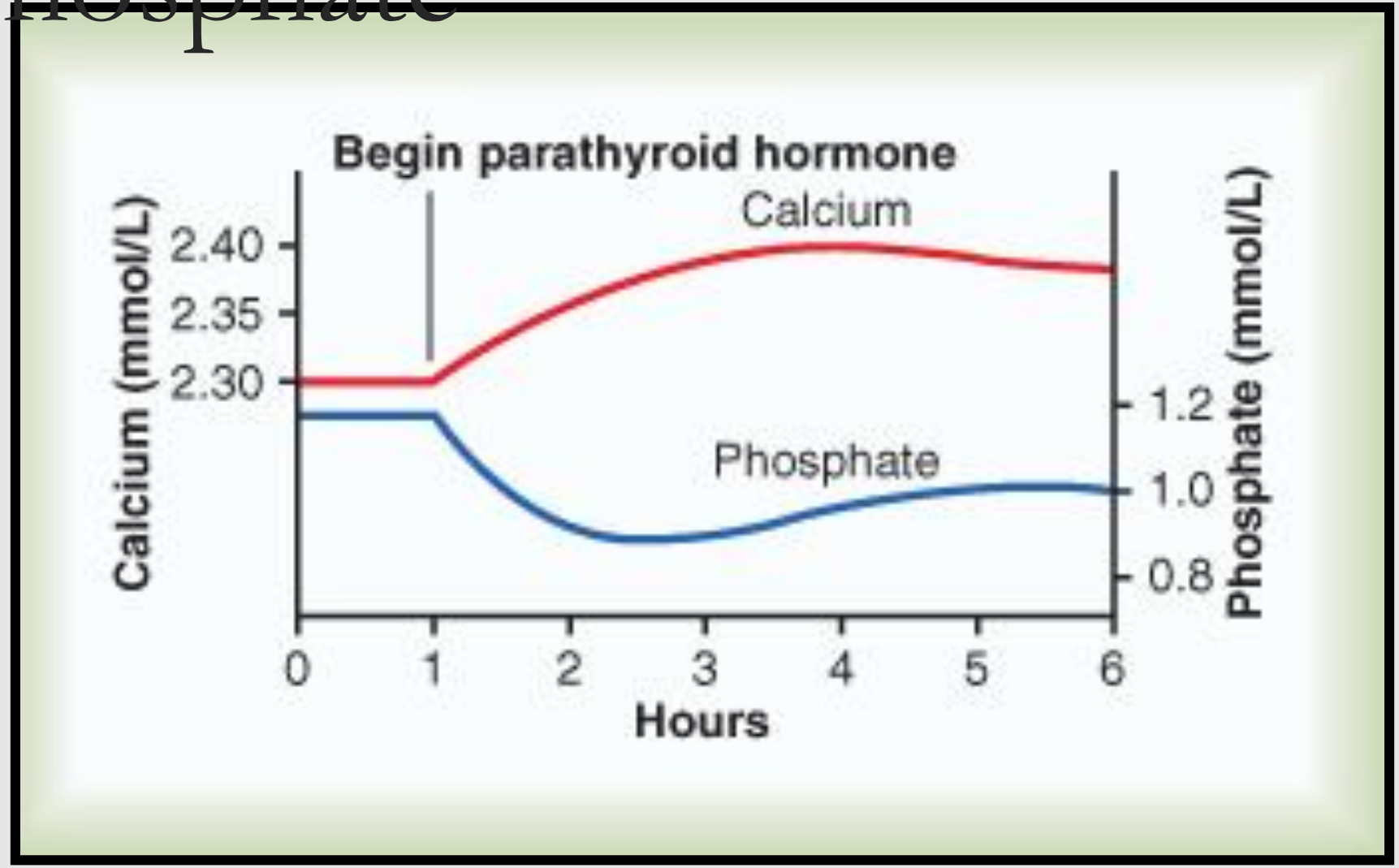
What is Sclerostin?

Sclerostin

- Paracrine that inhibits osteoblast activity to prevent excessive bone growth
- Parathyroid hormone and mechanical stress favour bone formation → inhibit sclerostin
- whereas calcitonin, which favours bone resorption → stimulates sclerostin

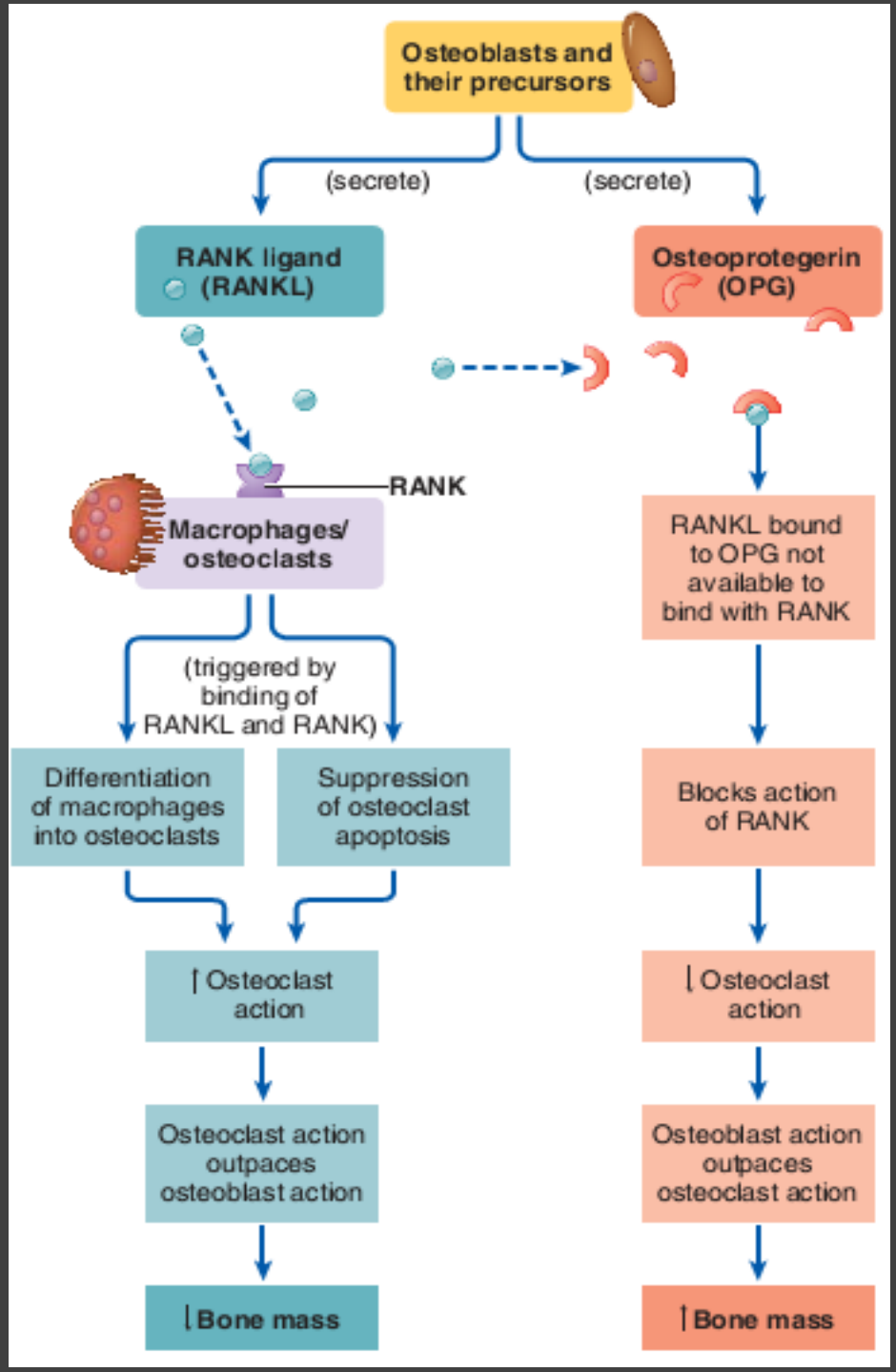
Effect of PTH on Calcium and Phosphate Concentrations in Extracellular Fluid

Effects of PTH on Blood Calcium and Phosphate



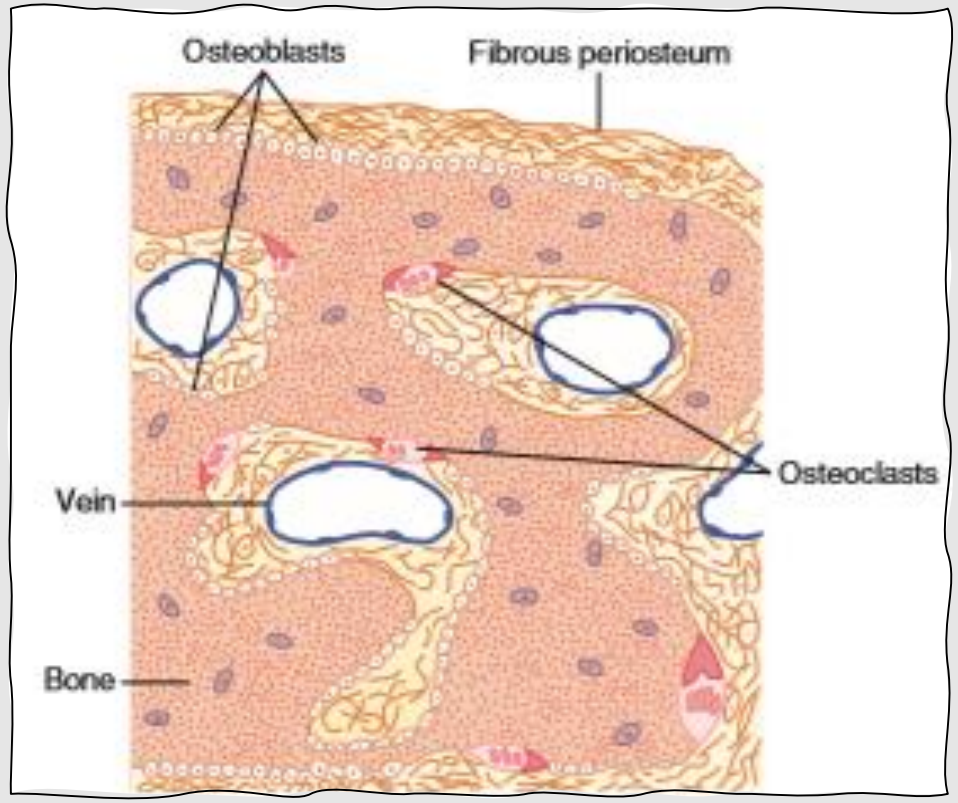
Role of Osteoblasts & Osteoclasts

Role of Osteoblasts & Osteoclasts

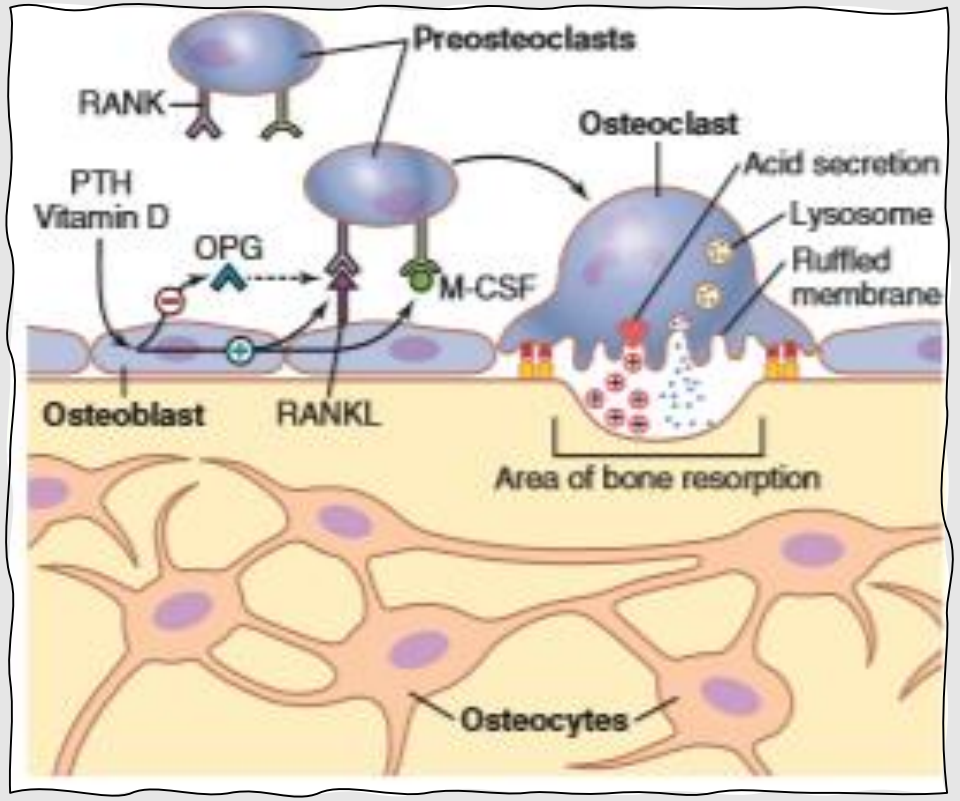


Remodeling Of Bone

Deposition of Bone



Resorption of Bone



Resorption of Calcium and PO_4 from the Bones
Effect of Parathyroid Hormone

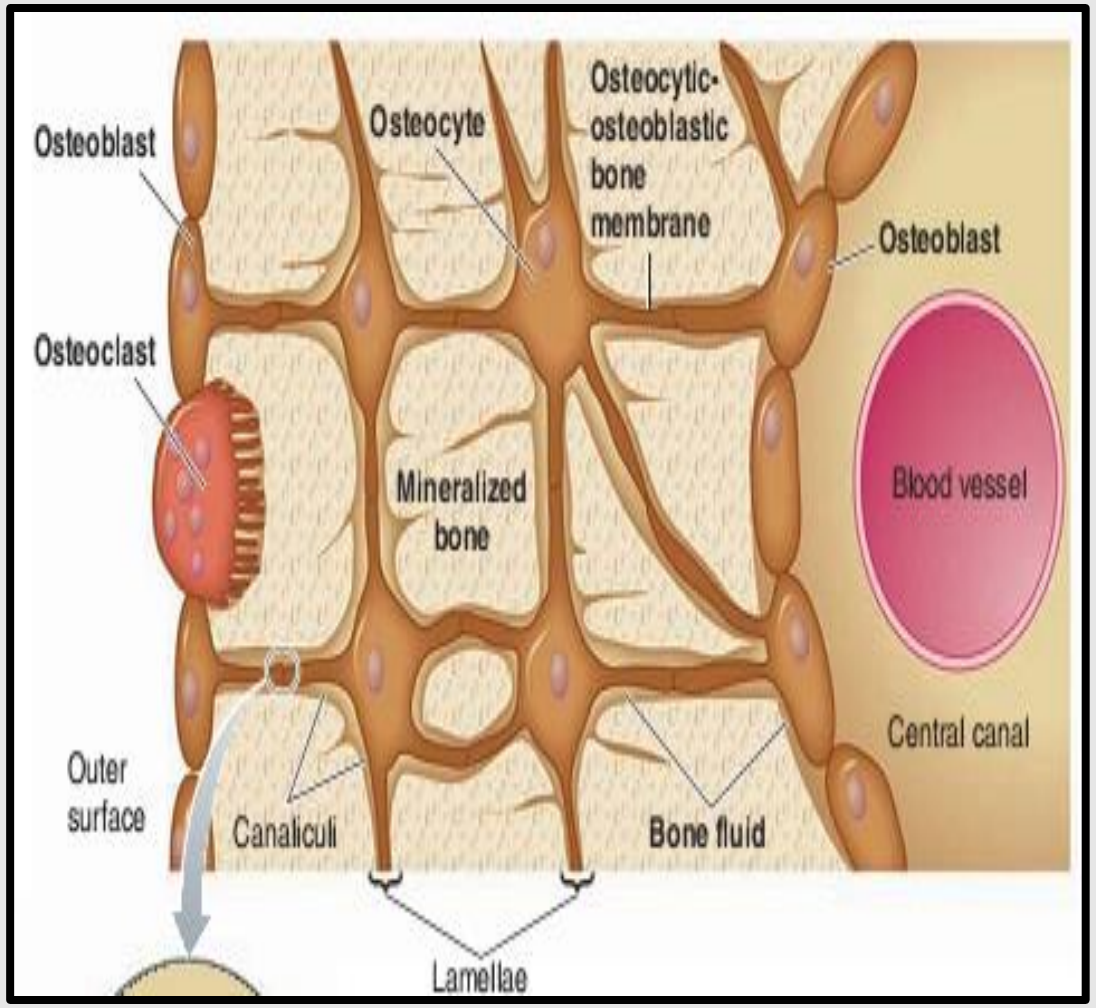
Rapid phase

- **Osteolysis- Begins within minutes**
- **↑activity of osteocytes already present**
- **Release of mostly calcium and PO_4**

Slow phase

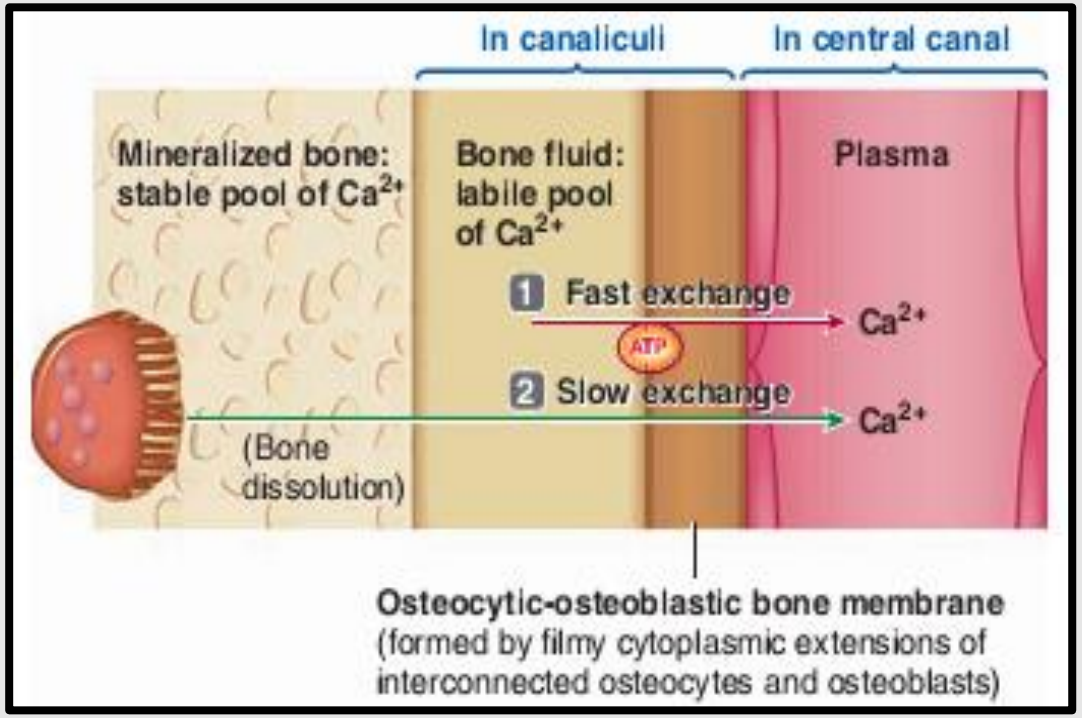
- **Develops fully in days to weeks**
- **Formation of new Osteoclasts**
- **Osteoclastic resorption of bone itself**

Osteocytic-Osteoblastic bone membrane



Fast and slow exchange of Ca++

between bone and plasma



Rapid Phase

- **Osteocytic membrane system**
- **Between Osteocytic membrane and bone is Bone fluid**
- **Active Calcium Pump** in Osteocytic membrane →

  Ca++ level in bone fluid lower than ECF calcium (only 1/3 of ECF Ca++)

PTH ↑ the activity of this pump → ↓ Bone fluid Calcium concentration & release of Ca++ and PO4 from bone - **Osteolysis**

- **Bone Matrix**

Slow Phase

PTH →

- ↑activity of osteoclasts
- ↑No of osteoclasts

→ *RANKL*

- Salts and matrix both are reabsorbed
- May continue for months
- After prolonged osteoclastic activity osteoblastic activity is also ↑
- ↑ PTH activity for years may → osteoporosis

Bones contain 1000 times more Ca++ than ECF

Effects on Kidneys

Effect on Calcium

PTH →↑ reabsorption of calcium in

- Late distal tubules
- Collecting tubules & early collecting ducts
- Ascending loop of Henle (less frequently)

Effect on Phosphate

PTH →↓reabsorption of PO_4→↑excretion of PO_4 → ↓ phosphate level in the blood

PTH →↑ reabsorption of Mg, H^+

PTH→ ↓reabsorption of Na^+, K^+ and amino acids

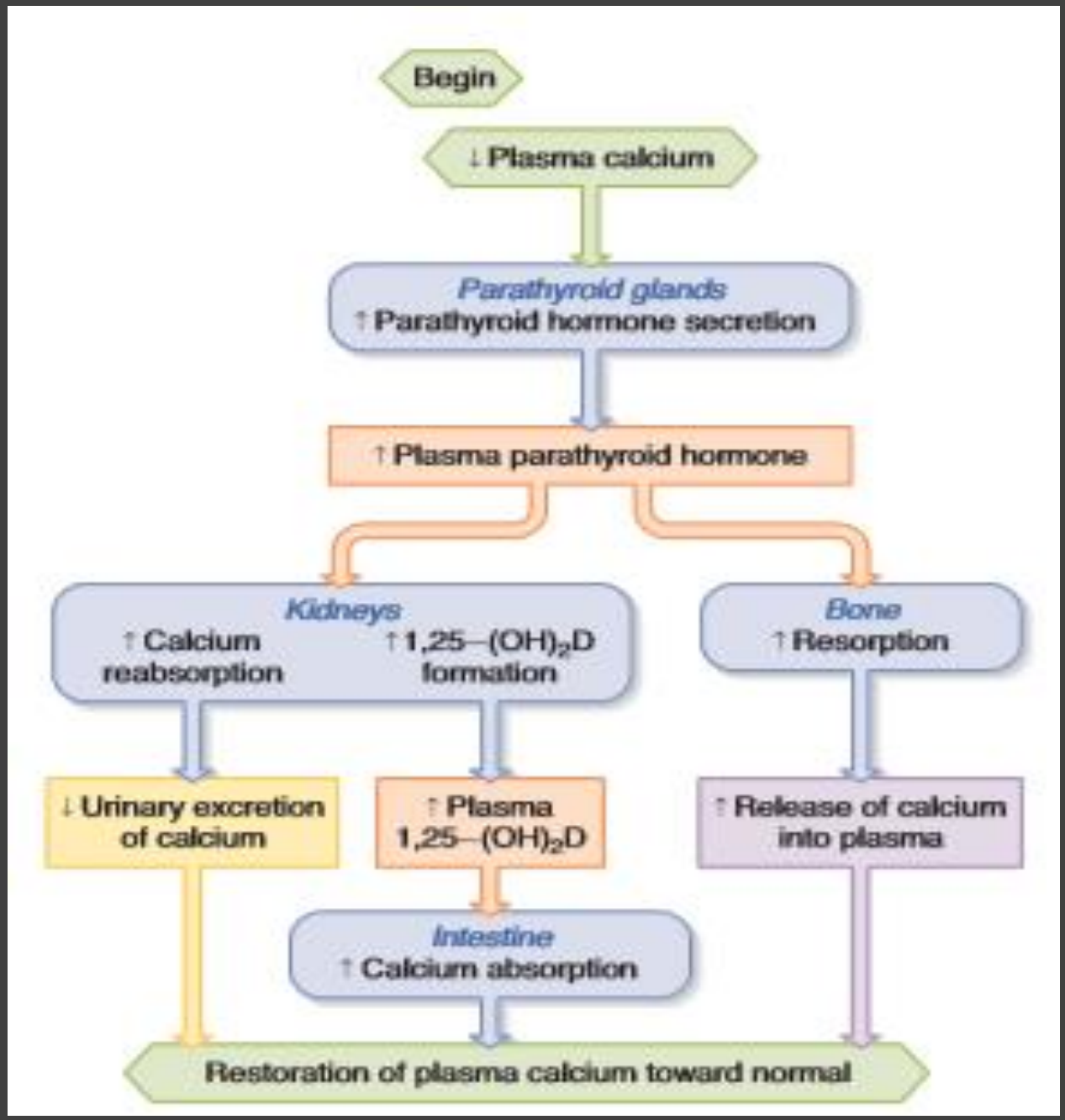
Effects on Intestine

PTH→ ↑ formation of 1,25,dihydroxycholecalciferol from Vitamin D in kidneys → formation of

- Calcium binding protein
- Calcium stimulated ATPase
- Alkaline phosphatase

Increases Calcium & Phosphate Absorption from Intestines

Effect of PTH & 1-25 Dihydroxy-cholecalciferol on body Calcium



Mechanism of Action of PTH

PTH ↑ Cyclic AMP in osteocytes, osteoclasts and target cells

→

Secretion of enzymes and acids by osteoclasts → Bone Resorption &

↑ formation of enzymes to form 1,25, dihydroxycholecalciferol in kidneys

Other direct effects are independent of second messenger mechanism

Control of Parathyroid Secretion by Calcium Ion Concentration

Regulation of secretion of PTH

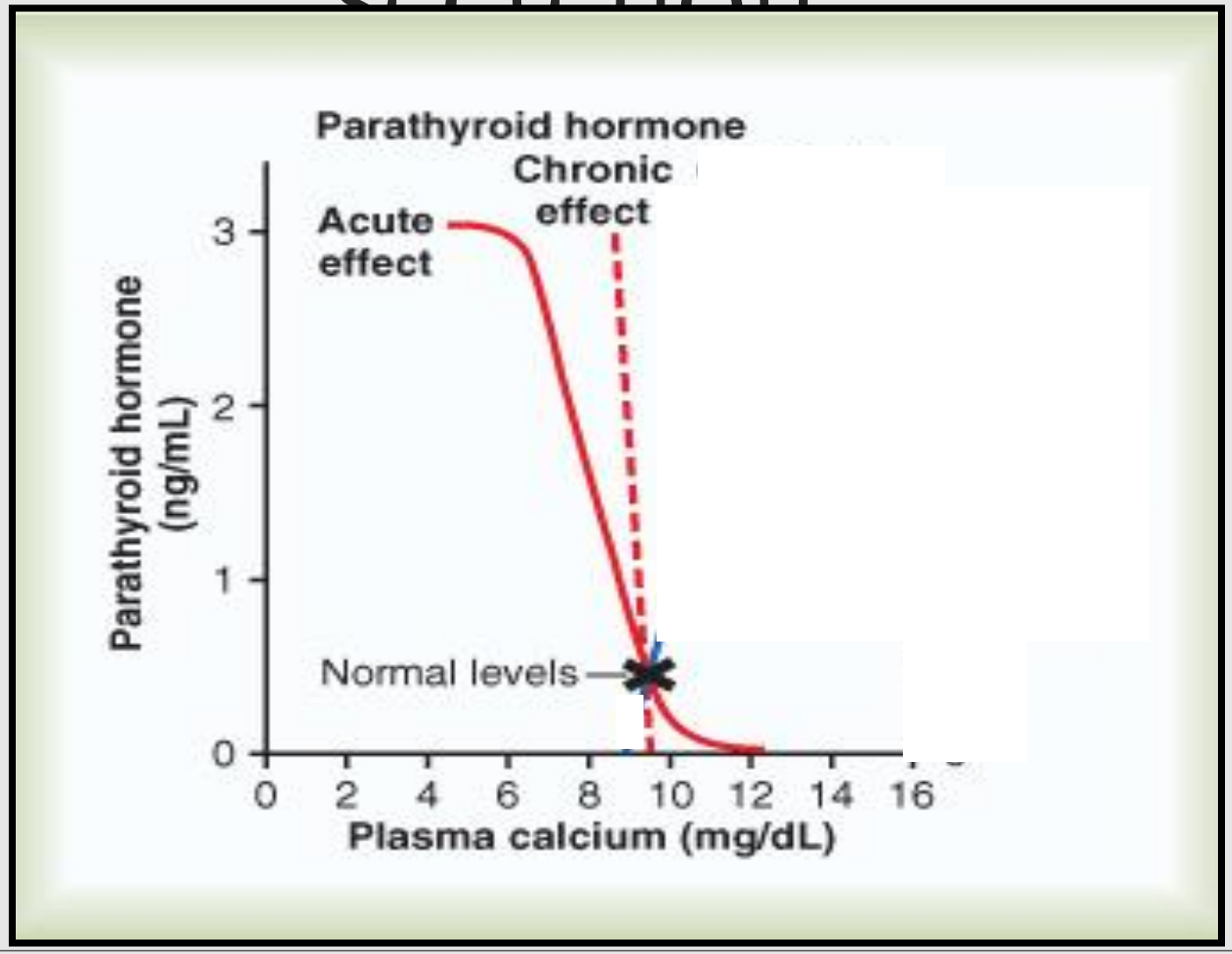
Hypocalcemia is the most important stimulus for PTH production & secretion

Hypocalcemia→ hypertrophy of parathyroid gland in

- **In pregnancy**
- **During lactation**
- **In rickets**

Hypercalcemia →↓activity and size of parathyroid gland

Effect of Ca level on PTH secretion



Control of Parathyroid Secretion By Calcium Ions

Changes in ECF Calcium ions are detected by calcium sensor (G protein) in parathyroid cell membranes

Calcium Ions act on G protein

↓

Activates Phospholipase C and ↑ Intracellular Inositol 1,4,5 triphosphate & Diacyl Glycerol formation

↓

Stimulates Calcium Release and Decreases PTH Secretion

Mrs. X recently had a baby and is breast feeding the baby as well. Her diet is deficient in dairy products and beans and is not taking any supplements as well.

The most likely finding in her will be

A. Decreased parathyroid hormone

B. Increased calcium levels

C. Increased 1-25 dihydroxycholecalciferol

D. Increased parathyroid hormone

E. High calcitonin levels

Summary


Any Questions?

References

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- Sherwood Physiology
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THANK
YOU!