Pharmacology of parathyroid hormone, calcitonin, vitamin D and calcium

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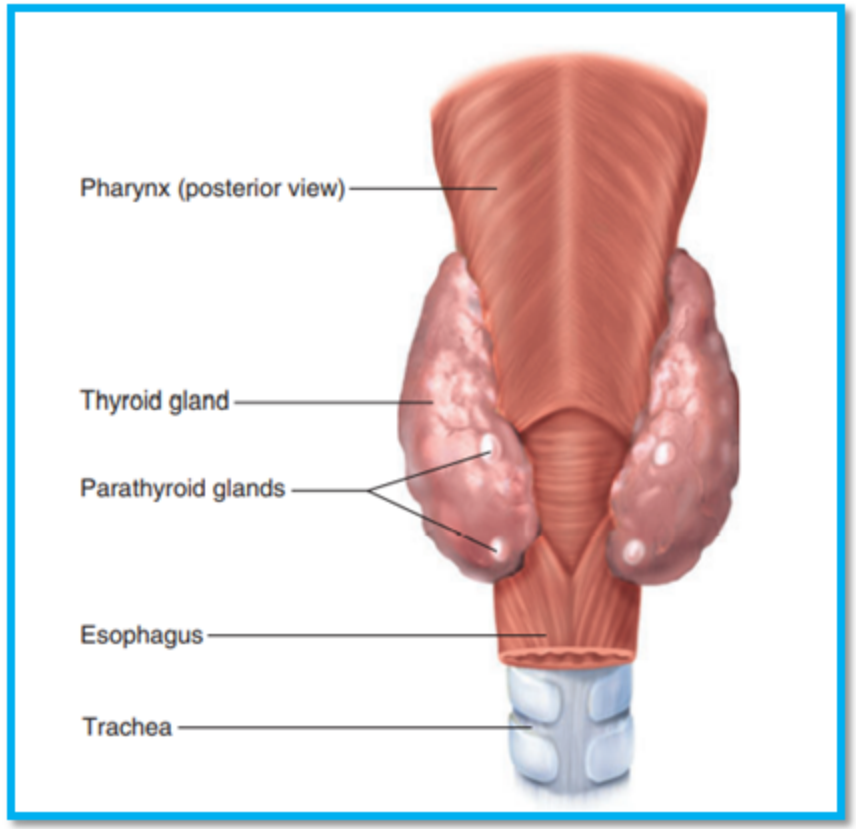
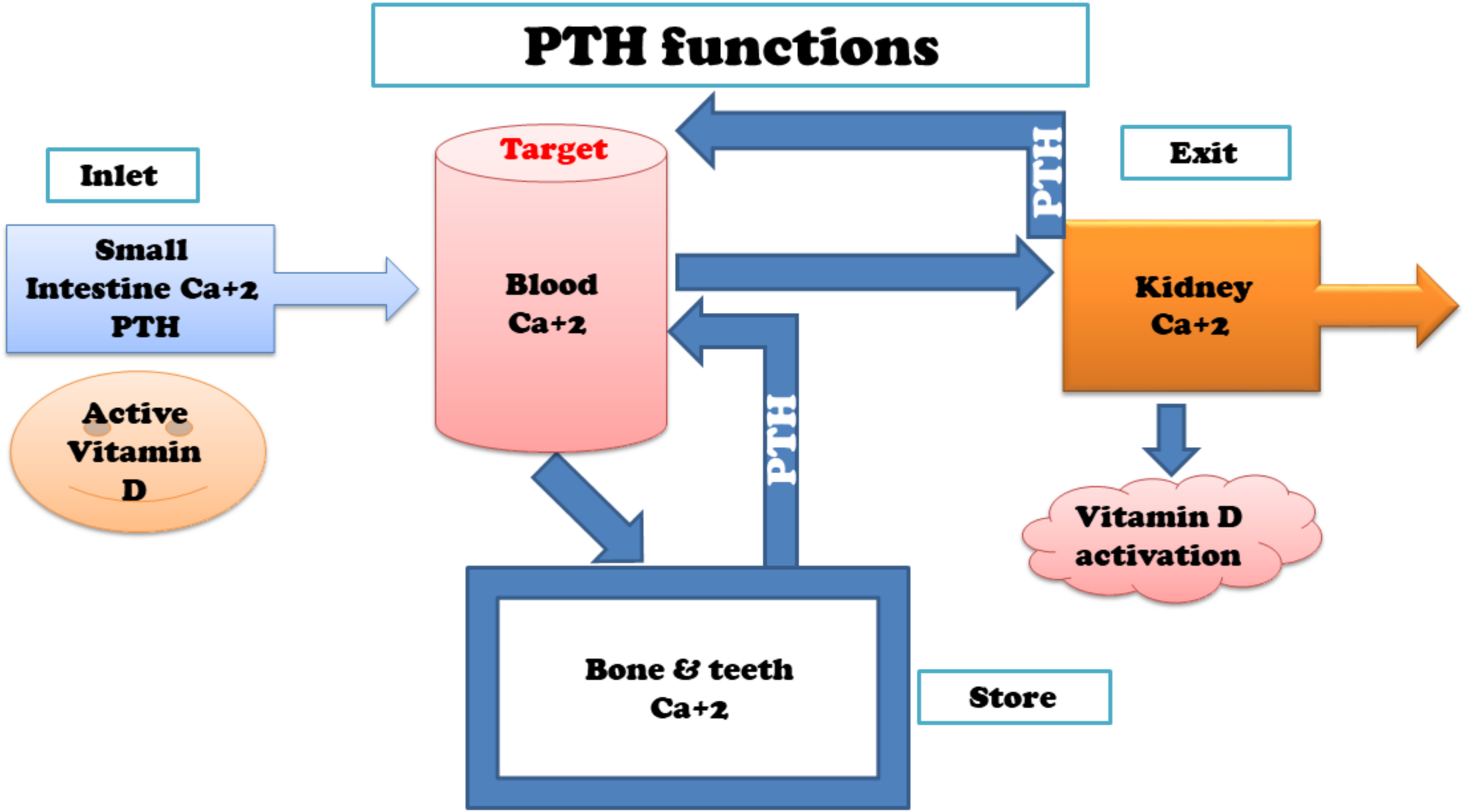
Objectives

1- Parathyroid hormone: secretion, target organs, function and regulation
2- Body calcium contents
3- Calcium homeostasis
4- Role of calcitonin in calcium homeostasis
5- Vitamin D: forms, sources, role in calcium hmeostsis, preparations and indications
6- Hyperparathyroidism
7- Hypoparathyroidism
8- PTH test
9- Parathyroid hormone analogues
10- Calcimimetics
11- Bisphosphonates

Parathyroid gland & PTH

- The parathyroid glands are partially embedded in the posterior surface of the thyroid gland.
- There are four parathyroid glands, two on the back of each lobe of the thyroid gland.
- The hormone they produce is called **parathyroid hormone (PTH) (Parathormon).**
- The **major function of the parathyroid glands** is to maintain the body's calcium level within a normal range, so that the nervous and muscular systems, blood coagulation and hormone secretion can function properly.
- PTH is important for the maintenance of normal blood levels of calcium and phosphate.
- **The target organs of PTH** are the bones, kidneys and small intestine.




PTH functions
Inlet
Small Intestine Ca+2 PTH
Active Vitamin D
Target
Blood Ca+2
PTH
Exit
Kidney Ca+2
Vitamin D activation
PTH
Bone & teeth Ca+2
Store

PTH

Hormone	Function	Regulation of secretion
Parathyroid hormone PTH	• **Increase** resorption of calcium and phosphate from bone to blood • **Increase** reabsorption of calcium and excretion (inhibition of reabsorption) of phosphate by kidney • Increase absorption of calcium and phosphate from small intestine to blood (requires vitamin D): indirect effect • **Activation** of vitamin D (in kidney)	• **Stimulators of PTH secretion:** • 1- Decreased serum [Ca2+]. • 2- Mild decreases in serum [Mg2+]. • 3- An increase in serum phosphate: • increased phosphate causes it to complex with serum calcium, forming calcium phosphate, which reduces stimulation of Ca-sensitive receptors that are **NOT** sensitive to calcium phosphate, triggering an increase in PTH. • **Inhibitors of PTH secretion:** • 1- Increased serum [Ca2+]. • 2- Sever or chronic decreases in serum (Mg2) paradoxical block, leading to suppressed PTH secretion and sever, refractory hypocalcemia

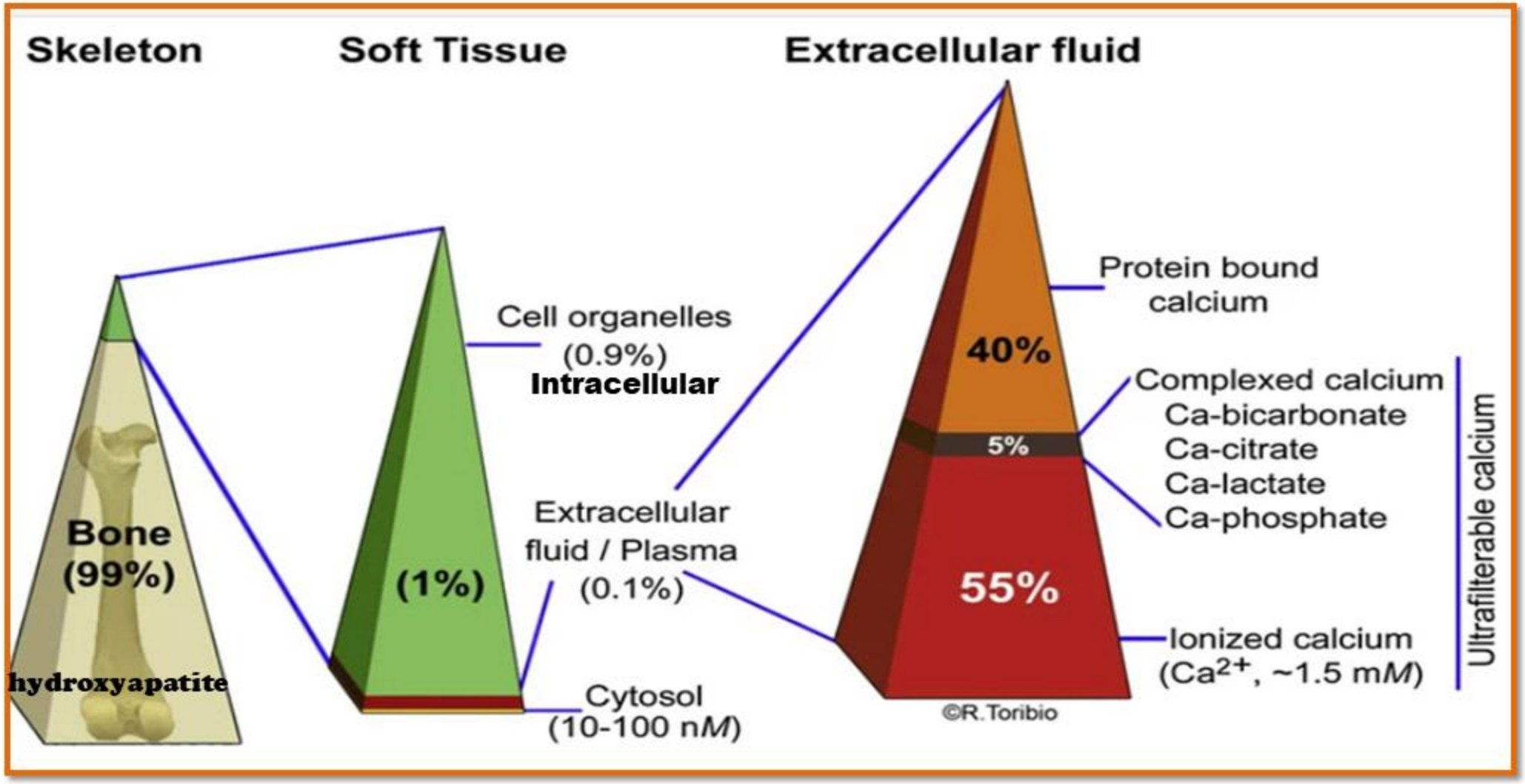
PTH Effects on Bone

- PTH has a rapid effect (occurring within minutes)
- PTH stimulates osteoclasts to pump Ca++ ions out of the fluid surrounding the bone (which has a higher Ca++ concentration) into the ECF.
- Over a longer time course (continuous exposure), PTH stimulates bone resorption: depletion of bone stores of calcium (**catabolic**).
- PTH stimulation of osteoblasts causes them to express a signaling molecule: RANKL (Receptor Activator of Nuclear factor Kappa-B Ligand) that activates osteoclasts.
- **N.B.** Intermittent exposure to PTH (pulsatile mode): single daily injection: activation of osteoblasts and increasing bone mass (used in osteoporosis): anabolic

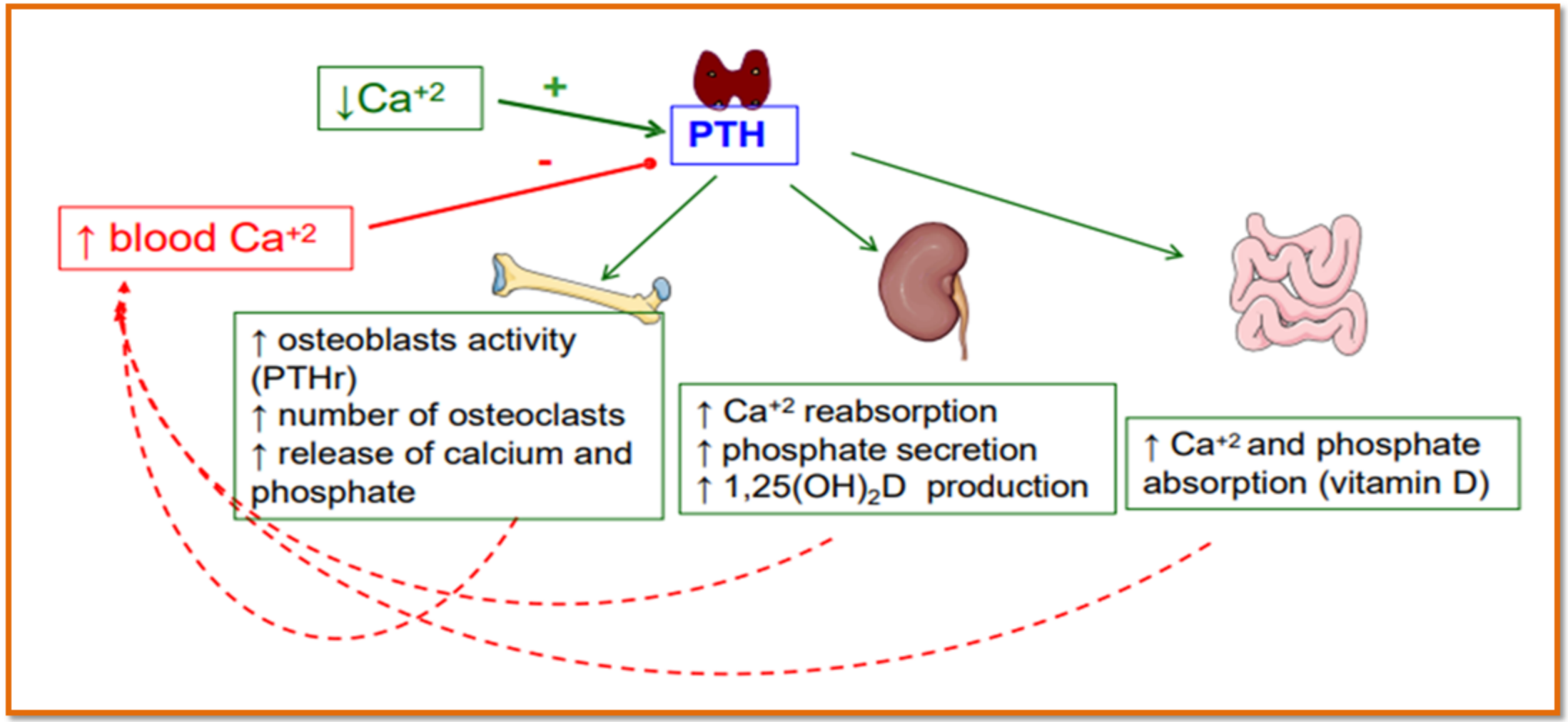
PTH versus calcitonin

- **Calcitonin** (a polypeptide hormone produced by the parafollicular cells (C cells) of the thyroid gland) acts to decrease blood calcium (and phosphate) concentrations by:
- Inhibiting bone-resorbing osteoclasts and increasing renal excretion of both minerals (decreasing renal reabsorption)
- **Net result**: Parathyroid hormone (PTH) increases serum calcium levels and decreases serum phosphate levels to maintain mineral homeostasis
- By the **antagonistic effects of PTH and calcitonin (with vitamin D):**
- Together, these hormones maintain blood calcium within a normal range (8.5-10 mg/dl).

Calcium distribution in body compartments



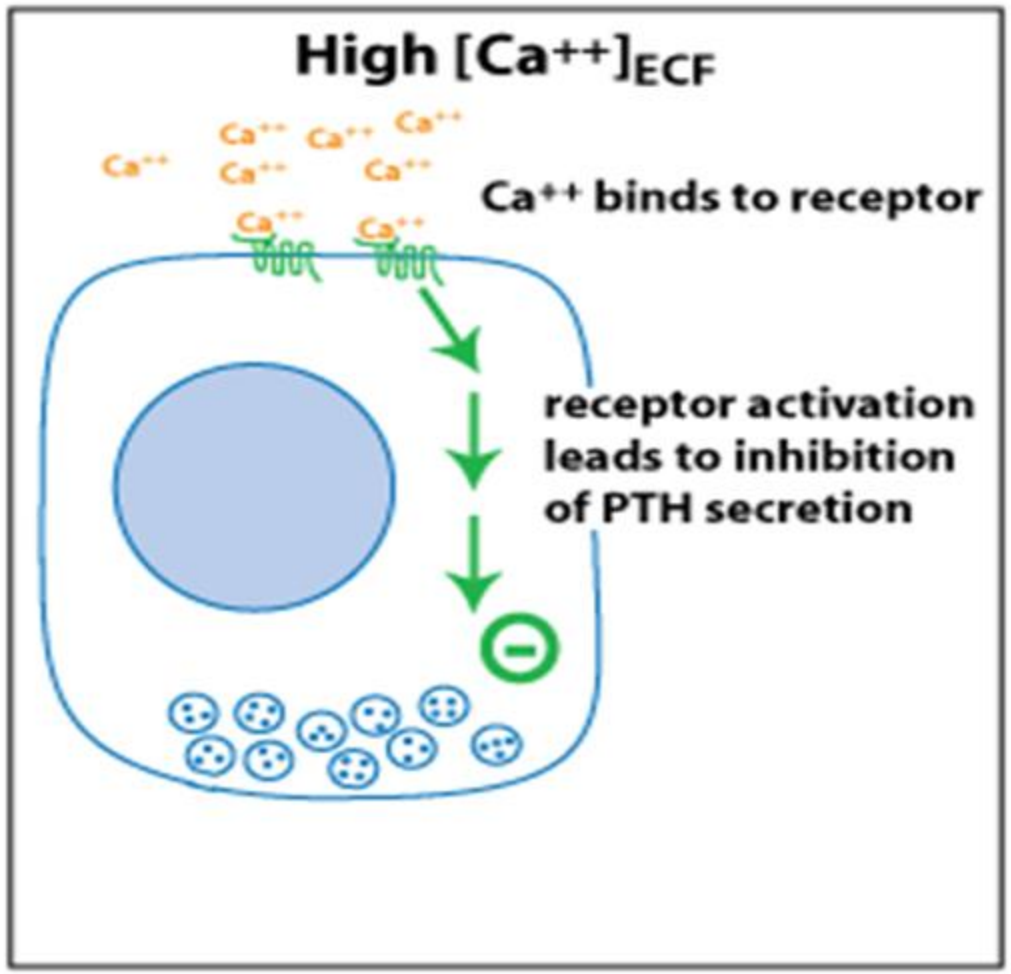
Regulation of blood calcium levels by PTH

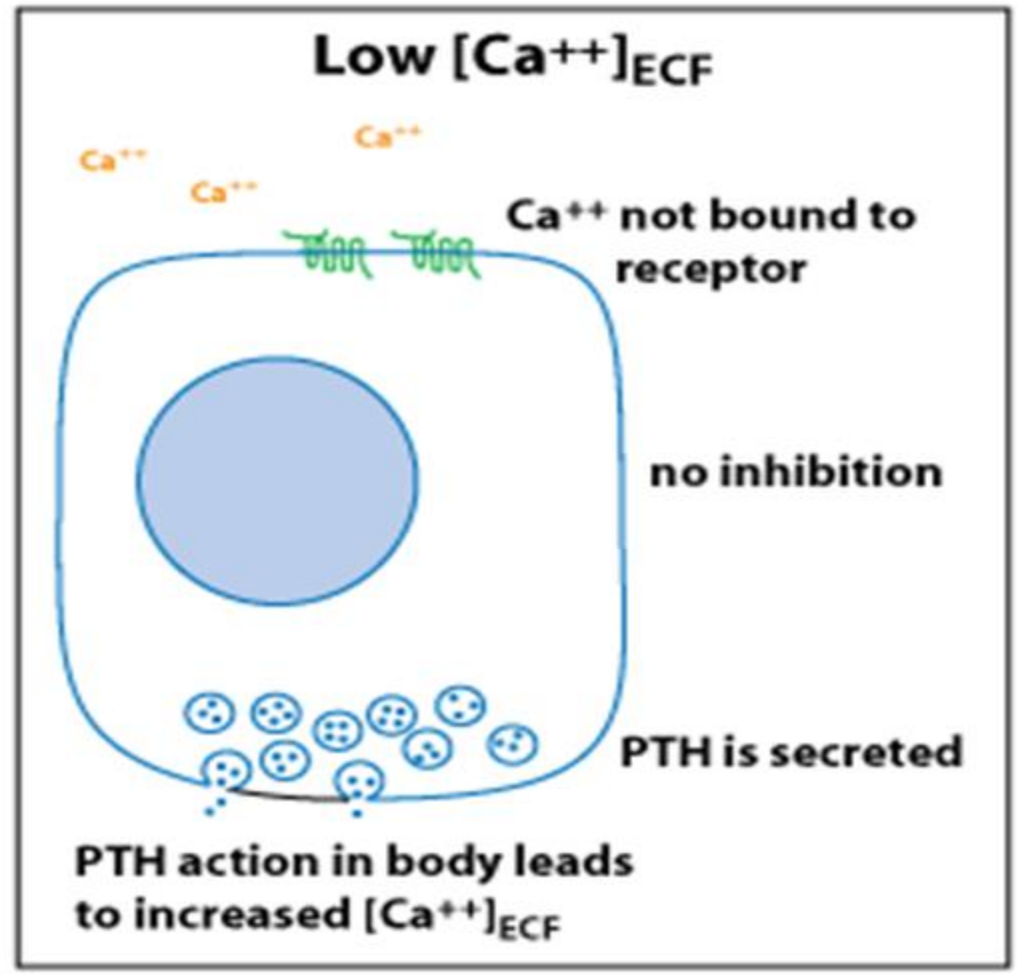


Regulation of PTH secretion: a negative feed back mechanism

- The sensor on the parathyroid gland cells that detects changes in the ECF calcium concentration is a **G-protein coupled calcium receptor (Calcium-Sensing Receptor (CaSR)** magnesium acts on this receptor in a similar, but less potent, manner as calcium).
- When ECF calcium is **high**, calcium binds to the receptor and this inhibits PTH secretion.
- When ECF calcium is **low,** the receptor is unbound and so there is no inhibition, and PTH secretion occurs.

Regulation of PTH secretion

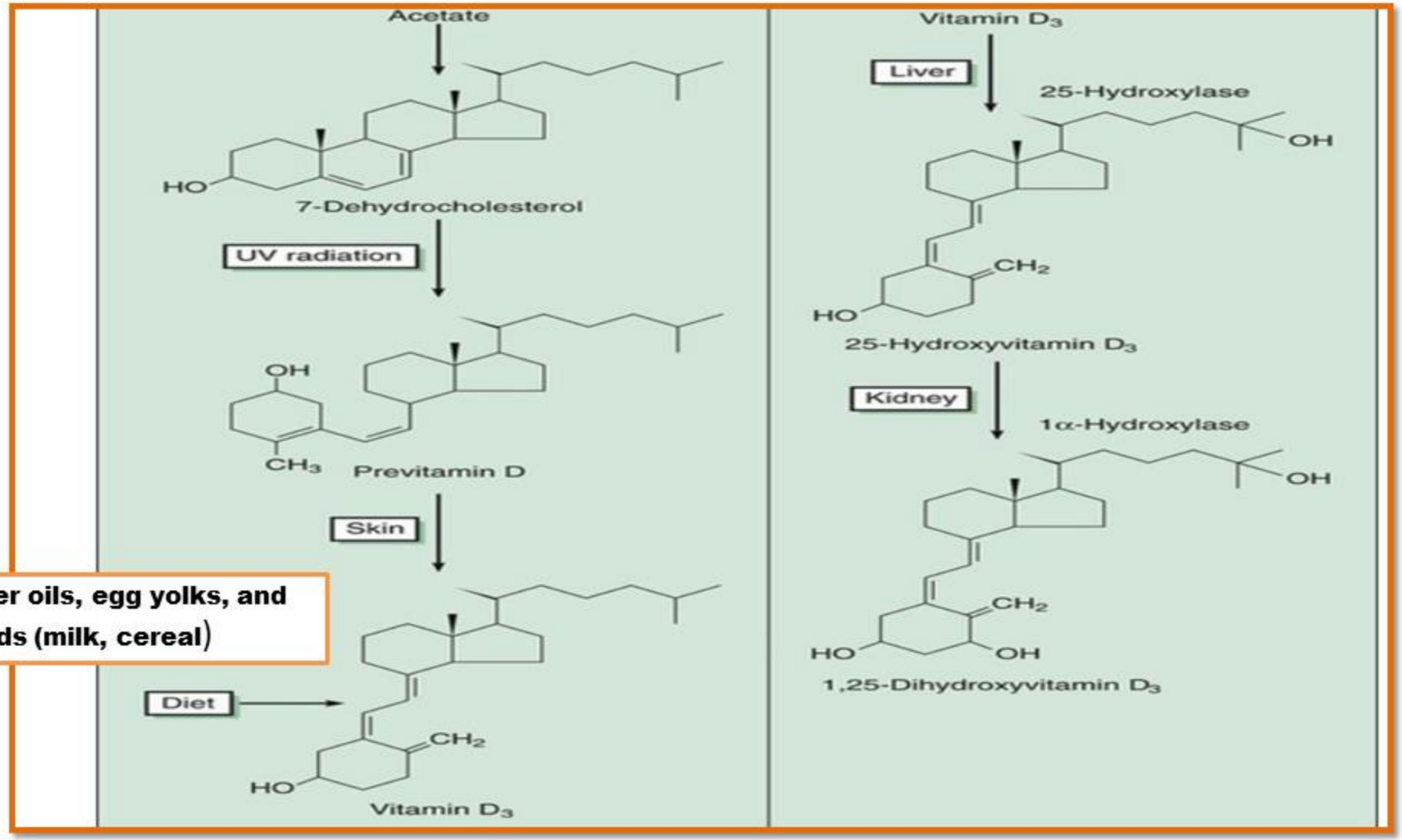




Vitamin D

- **Forms**:
- **Vitamin D3 (Cholecalciferol) (animal form)**
- Steroid hormone
- It is generally more effective at raising blood calcium levels than D2.
- **Vitamin D2 (Ergocalciferol): (Plant form)**
- Produced by UV irradiation of ergosterol in yeast and fungi.
- Commonly used for food fortification and in vegan supplements.

Sources of Vitamin D



Fatty fish, fish liver oils, egg yolks, and fortified foods (milk, cereal)

Pharmacological effects of vitamin D on bone minerals

- **Mechanism of action:** binding to intracellular Vitamin D Receptors (VDR), modulating gene transcription to maintain serum calcium/phosphate homeostasis and promoting bone mineralization.
- **Effects:**
- **1- Mineralization (Bone Formation):** Vitamin D stimulates osteoblasts (bone-forming cells) to produce essential matrix proteins and enzymes, such as alkaline phosphatase, which deposit calcium and phosphate into the bone matrix, strengthening it.
- **2- Calcium Absorption**: It acts on the intestinal cells to stimulate the expression of **calbindin** (calcium binding protein) and **calcium channels**, increasing the uptake of dietary calcium.
- **3- Bone Remodeling (Resorption):** Vitamin D stimulates osteoblasts to express RANKL, a molecule that promotes the differentiation of pre-osteoclasts into mature osteoclasts.
- **4- Increasing renal calcium and phosphate (to a lesser extent) reabsorption**

Vitamin D

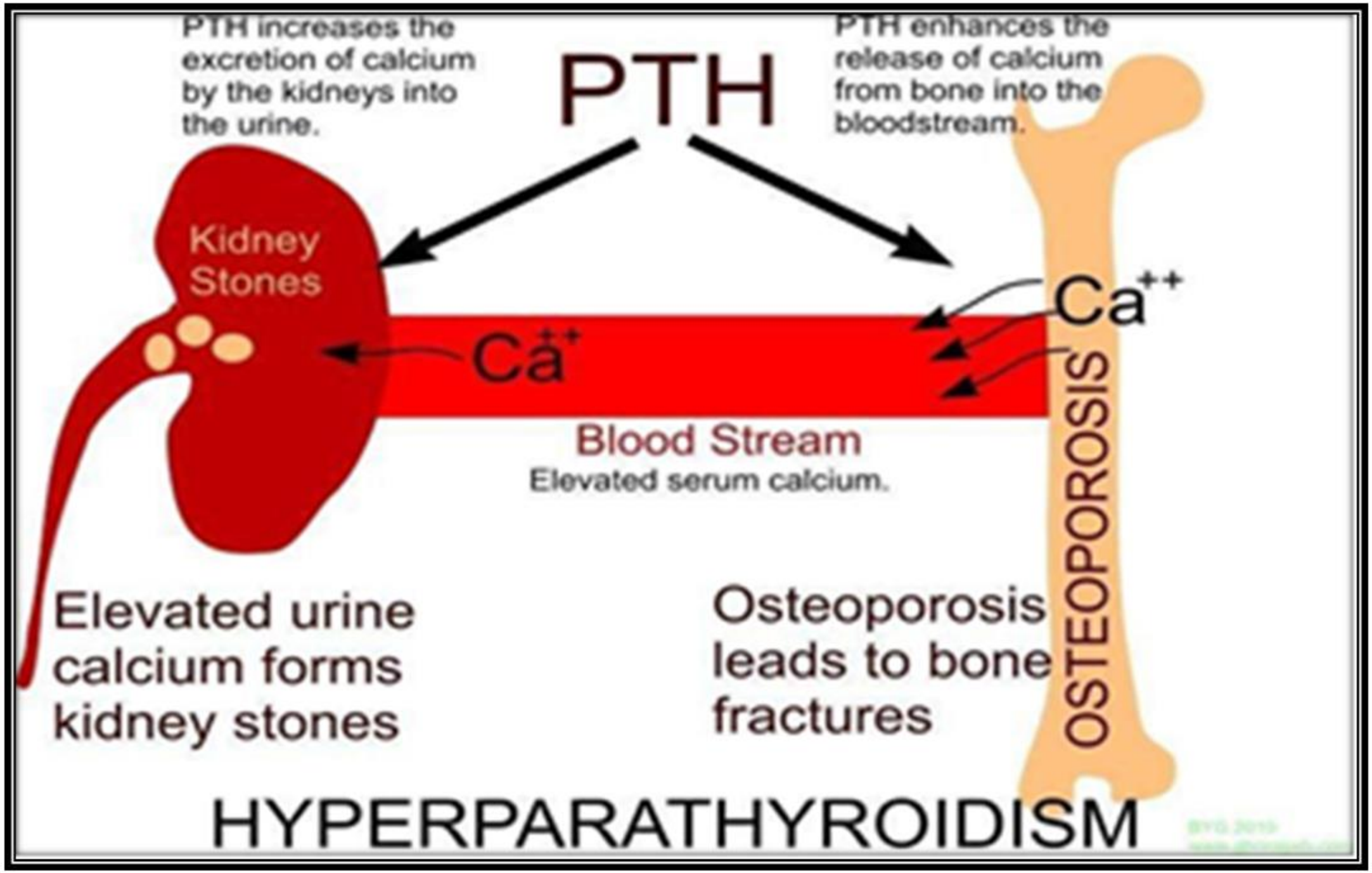
- **In kidney disease**: Inadequate amounts of 1,25(OH)2D are made thus[Ca++](ECF) drops because of a lack of Ca++ absorption from the diet.
- Hypocalcemia stimulates high levels of PTH secretion; this is termed **secondary hyperparathyroidism** because the problem that causes the hyperparathyroidism is in the kidney, **NOT** at the parathyroid gland.
- **Treatment of secondary hyperparathyroidism**: vitamin D: synthetic analogue of vitamin D3 (1 α-hydroxyl D3) (one-alpha) and Ca++ supplements.

Vitamin D

- **Vitamin D preparations:**
- **Calcitriol:** 1, 25 dihydroxycalciferol
- **Alphacalcidiol (one-alpha)**: needs hepatic activation, used in secondry hyperparathyroidism
- **Monitoring of serum vitamin D**: 25-hydroxyvitamin D test
- **Indications:**
- **1- Vitamin D Deficiency**: Serum levels below (<12–20 ng/mL)
- **2- Bone Disorders:** Treatment of rickets (children), osteomalacia (adults), osteoporosis,
- **3- Hypoparathyroidism**
- **4- Psoriasis:** Topical vitamin D analogues are used to treat mild-to-moderate plaque psoriasis by inhibiting rapid skin cell turnover.

Hyperparathyroidism

- **Primary hyperparathyroidism**
- Due to parathyroid gland disease, most commonly due to a parathyroid tumor (adenoma) which secretes the hormone without proper regulation.
- **Secondary hyperparathyroidism**
- Due to disease outside of the parathyroid gland leads to excessive secretion of parathyroid hormone.
- **A common cause**: **kidney disease**: kidneys are unable to reabsorb calcium, blood calcium levels will fall, stimulating **continuous secretion** of parathyroid hormone to maintain normal calcium levels in blood.


PTH increases the excretion of calcium by the kidneys into the urine.
PTH
PTH enhances the release of calcium from bone into the bloodstream.
Kidney Stones
Ca++
Ca++
OSTEOPOROSIS
Blood Stream
Elevated serum calcium.
Elevated urine calcium forms kidney stones
Osteoporosis leads to bone fractures
HYPERPARATHYROIDISM

Hypoparathyroidism

- **Inadequate production of parathyroid hormone** typically results in decreased concentrations of calcium and increased concentrations of phosphate in blood.
- **Causes:**
- **1- Surgical removal of the parathyroid glands**
- **2- Autoimmune hypoparathyroidism:** rare condition where the immune system destroys parathyroid glands, low (PTH) and hypocalcemia, often linked to Autoimmune Poly-endocrine Syndrome Type 1 (APS-1).
- **3- Pseudo-hypoparathyroidism:** A genetic condition where the body resists PTH, leading to symptoms of hypoparathyroidism despite having normal or high PTH levels.
- **Manifestations:** hypocalcemia often leads to tetany, and can be life-threatening.
- **Treatment** focuses on restoring normal blood calcium concentrations by calcium infusions, oral calcium supplements and vitamin D therapy.

Parathyroid hormone (PTH) test

- **A parathyroid hormone (PTH) test measures** the amount of PTH in the blood.
- **Indications:**
- To monitor calcium levels
- To check for bone diseases
- To evaluate kidney function.
- It is used to diagnose hyperparathyroidism or hypoparathyroidism.
- **Method**: A blood sample is taken, often requiring 10-12 hours of fasting (allowing only water).

Parathyroid drugs

- Parathyroid drugs either mimic or regulate parathyroid hormone (PTH) to treat bone diseases or calcium imbalances.
- **1- Parathyroid Hormone Analogs:**
- for Hypoparathyroidism/Osteoporosis: Teriparatide, abaloparatide
- **2- Calcimimetics**: for hyperparathyroidism: Cinacalcet
- **3- Other agents:**
- **Vitamin D Supplements**: Essential for managing hypoparathyroidism.
- **Bisphosphonate:** in hyperparathyroidism-induced osteoporosis.

1- Parathyroid Hormone Analogs

- **Indicated for hypoparathyroidism /Osteoporosis.**
- **Teriparatide**: Recombinant human PTH.
- **Abaloparatide**: A synthetic parathyroid hormone-related protein (PTHrP) analog
- **Administration:**
- Are typically administered via daily injection.
- **Adverse Effects**: dizziness, joint pain, and high calcium levels.
- These drugs are typically available by prescription only

Teriparatide : Parathyroid Hormone Analogs

- **Indications:**
- **Osteoporosis:** It reduces the risk of vertebral and non-vertebral fractures or for patients who cannot tolerate other osteoporosis treatments.
- **Mechanism:** As a recombinant form of parathyroid hormone, it stimulates osteoblast activity, increasing bone formation (**intermittent exposure**).
- **Administration**: daily injection pen, SC, requiring refrigeration.
- **Duration of Therapy** is typically limited to a maximum of 2 years, with subsequent transition to a bisphosphonate or other anti-resorptive agent to maintain bone density gains.
- **Precautions:** It has a potential risk of bone cancer (osteosarcoma), and should not be used by individuals with high risk for this type of cancer

Abaloparatide: Parathyroid Hormone Analogs

- **Indications: potent anabolic (bone-building) agent for osteoporosis**
- **1- Postmenopausal Osteoporosis**: in women at high risk for fracture.
- **2- Male Osteoporosis**: at high risk of fracture.
- **Treatment Limitations**: Used when patients cannot tolerate other osteoporosis treatments or for those who have failed other therapies

Abaloparatide

- **Mechanism:** It acts as an agonist at the parathyroid hormone type 1 (PTH1) receptor.
- **Bone Growth**: It stimulates bone formation more than bone resorption, leading to increased bone density, particularly in the spine and hip.
- **Difference from Teriparatide**: While it shares a receptor with Teriparatide, it is a derivative of PTHrP, which may offer a greater reduction in fracture risk.
- **Administration:** daily SC injection, usually self-administered into the abdominal area
- Typically used for a duration of up to 18 months: due to the potential risk of osteosarcoma.

Abaloparatide

- **Adverse effects**:
- Hypercalcemia
- Hypercalciuria: Increased urine calcium: risk of renal stones
- Orthostatic hypotension, palpitation
- Injection Site Reactions: Bruising, redness, pain, or swelling.
- **Warnings and Restrictions:**
- **Osteosarcoma Risk**: Abaloparatide is **not recommended** for individuals at a high risk of bone cancer, including those with Paget's disease, unexplained high alkaline phosphatase levels, or prior bone radiation therapy.

2- Calcimimetics: Cinacalcet

- A calcimimetic medication that treats **hyper**parathyroidism by reducing parathyroid hormone (PTH) levels, which in turn lowers serum calcium and phosphate.
- Acts by mimicking serum calcium: It increases the sensitivity of the calcium-sensing receptor (CaSR) in the parathyroid gland
- **Indications:**
- **Secondary Hyperparathyroidism**: Treats high PTH levels in patients with chronic kidney disease (CKD) on dialysis.
- **Parathyroid Carcinoma**: Manages high calcium levels (hypercalcemia).
- **Primary Hyperparathyroidism**: sever hypercalcemia is present but surgery is not an option.

2- Calcimimetics: Cinacalcet

- **Adverse effects:**
- **Hypocalcemia**: The most common significant adverse effect, which can cause muscle spasms and cardiac disturbances.
- **Gastrointestinal upset**: Nausea, vomiting, and diarrhea are common.
- **Reduced testosterone levels.**
- **Administration**: orally, a tablet once daily with food.

3- Other agents: Bisphosphonates

- Bisphosphonates are divided into three generations based on potency and chemical structure (nitrogen presence)
- **Mechanism of action: inhibit osteoclast-mediated bone resorption** by binding to hydroxyapatite in bone, inducing osteoclast apoptosis (cell death), and disrupting essential metabolic pathways
- High affinity for calcium hydroxyapatite crystals, allowing them to be specific to sites of active bone remodeling.
- **1. First Generation (Non-nitrogenous)**
- Least potency: less used
- **Examples**: Aledronate.
- **2. Second Generation (Amino-bisphosphonates)**
- Contains a nitrogen atom.
- 10–100 times more potent than first-generation drugs
- **Examples**: Pamidronate
- **3. Third Generation (Nitrogenous-Heterocyclic)**
- Contains a nitrogen atom within a heterocyclic ring
- 10,000 times more potent than the first generation.
- **Examples**: Risedronate, **zoledronic acid**

3- Other agents: Bisphosphonates

- **Indications:** conditions characterized by low bone density and high fracture risk.
- **1- Osteoporosis** (Postmenopausal & Male): Treatment and prevention.
- **2- Glucocorticoid-Induced Osteoporosis**: Prevention and treatment in patients on long-term steroid therapy.
- **3- Paget's Disease of Bone**: Treatment for abnormal bone remodeling.
- **4- Hypercalcemia of Malignancy**: Treatment for high calcium levels caused by cancer.
- **5- Bone Metastases/Multiple Myeloma**: Treatment for skeletal-related events (fractures, pain).
- **Other/Off-Label Indications:**
- **Osteogenesis Imperfecta**: Used in both children and adults.
- **Fibrous Dysplasia**: A condition where normal bone is replaced by fibrous tissue.
- **Giant Cell Tumors of the Jaw**: Sometimes used as an adjunct

3- Other agents: Bisphosphonates

- **Administration:** Oral (alendronate) or intravenous (zoledronic acid).
- **Contraindications:**
- Severe renal impairment
- Hypocalcemia
- Inability to sit upright for 30–60 minutes (for oral forms): increased risk of esophageal irritation
- **Adverse Effects:**
- Esophageal irritation (oral)
- Flu-like symptoms
- Rare: risks of osteonecrosis of the jaw (ONJ) or atypical femur fractures

References

Lippincott's Illustrated Review

Pharmacology, 8th edition

Lippincott Williams & Wilkins

Katzung *by Anthony Trevor, Bertram Katzung, and Susan Masters . 16th edition McGraw Hill,*

Rang & Dale's Pharmacology: *by Humphrey P. Rang ; James M. Ritter ; Rod Flower Churchill Livingstone; 10th edition*

Thank you