

Pharmacology of drugs used in calcium & vitamin D disorders



Objectives

By the end of lecture, the students will be able to:

- **Recognize** the common drugs used in calcium & vitamin D disorders
- **Classify** them according to sources & pharmacological effects
- **Detail** the pharmacology of each drug regarding; mechanism, clinical utility in affecting calcium & vitamin D



Calcium Metabolism

- Calcium plays an essential role in many cellular processes, including muscle contraction, hormone secretion, cell proliferation, and gene expression.
- Calcium balance is a dynamic process that reflects a balance between calcium absorption by the **intestinal tract**, calcium excretion by the **kidney**, and release and uptake of calcium by **bone** during bone formation and resorption.

Three principal hormones regulate Ca^{2+} homeostasis

- **Parathyroid hormone (PTH)**
- **Vitamin D**
- **Calcitonin**

Three target tissues regulate calcium homeostasis

-  **Bone**
-  **kidney**
-  **Intestine**



Bone

- The dominant site of calcium storage in the body is bone, which contains nearly 99.9% of body calcium.
- Most body calcium is stored in bone (~1000 g), which is a very dynamic site as bone is remodeled continuously by resorption of old bone by **osteoclasts** & formation of new bone by **osteoblasts**
- Although only a small fraction of total body calcium is located in the plasma, **it is the plasma concentration of ionized calcium** that is tightly regulated, primarily under the control of **PTH** and **vitamin D**.

The following are involved in calcium metabolism & bone remodeling:

-  **Parathyroid hormone (PTH)**
-  **Teriparatide**
-  **Vitamin D**
-  **Calcitonin**

PTH and vitamin D play central roles in the regulation of bone metabolism.



Parathyroid Hormone

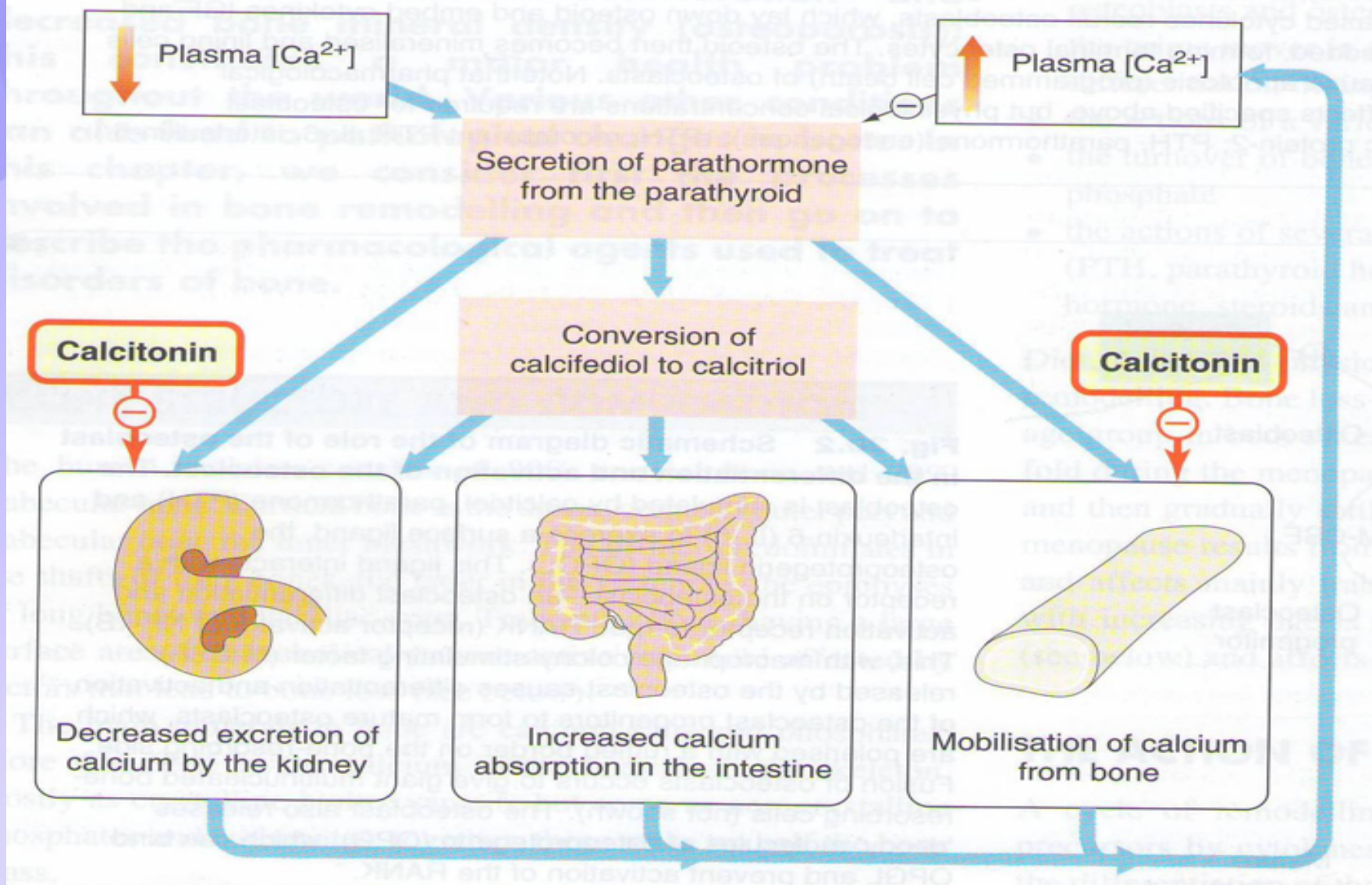
- PTH: A hormone that plays a critical role in controlling calcium and phosphate balance.
- PTH is released from the **parathyroid gland** in response to low plasma Ca^{2+} level
- Secretion of PTH is inversely related to **$[\text{Ca}^{2+}]$** .



PTH action

The overall action of PTH is to increase plasma Ca^{2+} levels in response to hypocalcemia:

- First, PTH enhances **intestinal calcium** absorption in the presence of permissive amounts of **vitamin D**.
- Second, PTH stimulates **bone resorption** by stimulating **osteoclasts** to increase the outward flux of calcium.
- Third, PTH stimulates the active reabsorption of calcium from the **kidney**.



Calcitonin is a physiological antagonist to PTH with regard to Ca^{2+} homeostasis

Response to PTH

PTH

Intermittent

Continuous

↑ **Osteoblast** number/function

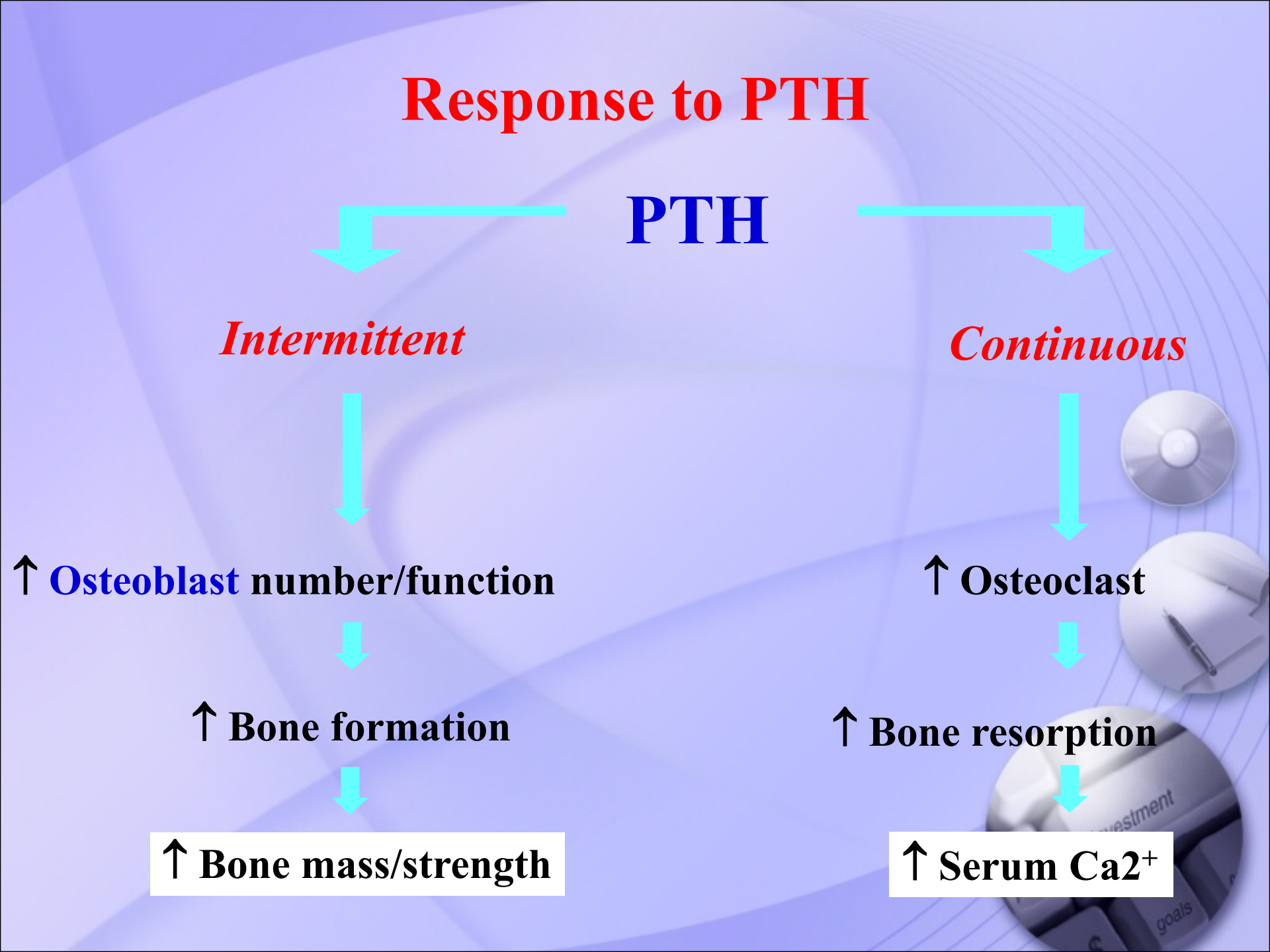
↑ **Osteoclast**

↑ **Bone formation**


↑ **Bone resorption**


↑ **Bone mass/strength**

↑ **Serum Ca²⁺**



Response to PTH

 Daily, **intermittent** administration of recombinant human PTH, **SC** in the thigh (alternate thigh every day) leads to a net stimulation of bone formation.

 **Continuous** or **chronic** exposure to high serum PTH concentrations (as seen with primary or secondary hyperparathyroidism) results in bone resorption.

Clinical uses of PTH

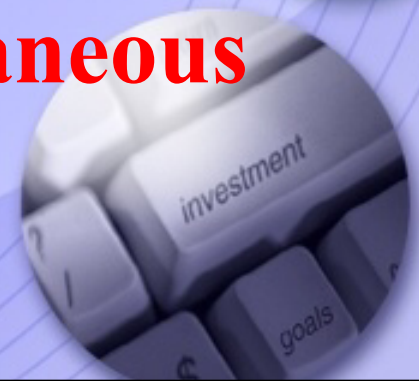
 **Treatment of severe osteoporosis**

 **Resistant cases failed to respond to other medications**





Teriparatide

- Synthetic polypeptide form of PTH (**PTH analogue**).
- It belongs to a class of anti-osteoporosis drugs, the so-called **“anabolic” agents**.
- Given, once / daily by **subcutaneous injection**



Therapeutic effects of teriparatide depend upon the pattern of systemic exposure.

 Once-daily administration of teriparatide stimulates **new bone formation** by preferential stimulation of **osteoblastic** activity over osteoclastic activity.

 By contrast, **continuous** administration of teriparatide , may be detrimental to the skeleton because **bone resorption** may be stimulated more than bone formation.



Therapeutic uses of Teriparatide

- Good for postmenopausal osteoporosis.
- For treatment of osteoporosis in people who have a risk of getting fracture (**increased bone mass & strength**)
- Used in severe osteoporosis or patients not responding to other drugs.
- Should not be used routinely due to **carcinogenic effects.**



Adverse effects of Teriparatide

- **Carcinogenic effect (osteosarcoma)**
- **Diarrhea, heart burn, nausea**
- **Headache, leg cramps**
- **Hypotension when standing
(orthostatic hypotension)**
- **Elevated serum calcium which may occur in some cases can lead to kidney stones**





Contraindications

Teriparatide should not be used by people with increased risk for bone tumors (**osteosarcoma**) including:

- People with **Paget's disease** of bone
- People who had **radiation treatment** involving bones
- **Not recommended** in children

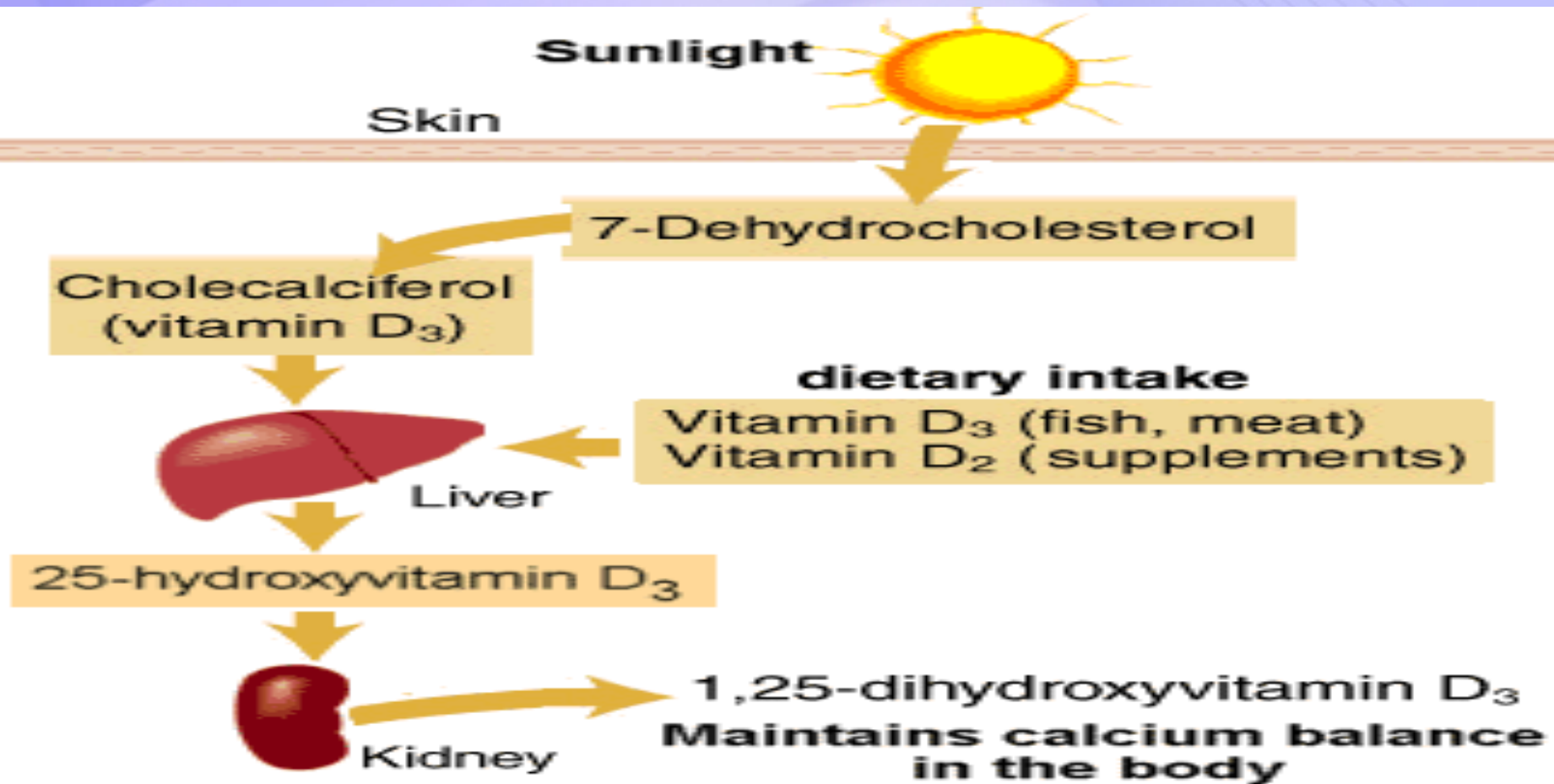


Vitamin D

-  Vitamin D is a steroid hormone that is intimately involved in the regulation of plasma calcium levels.
-  Its role in calcium metabolism first was recognized in the childhood disease rickets, which is characterized by **hypocalcemia** and various skeletal abnormalities.

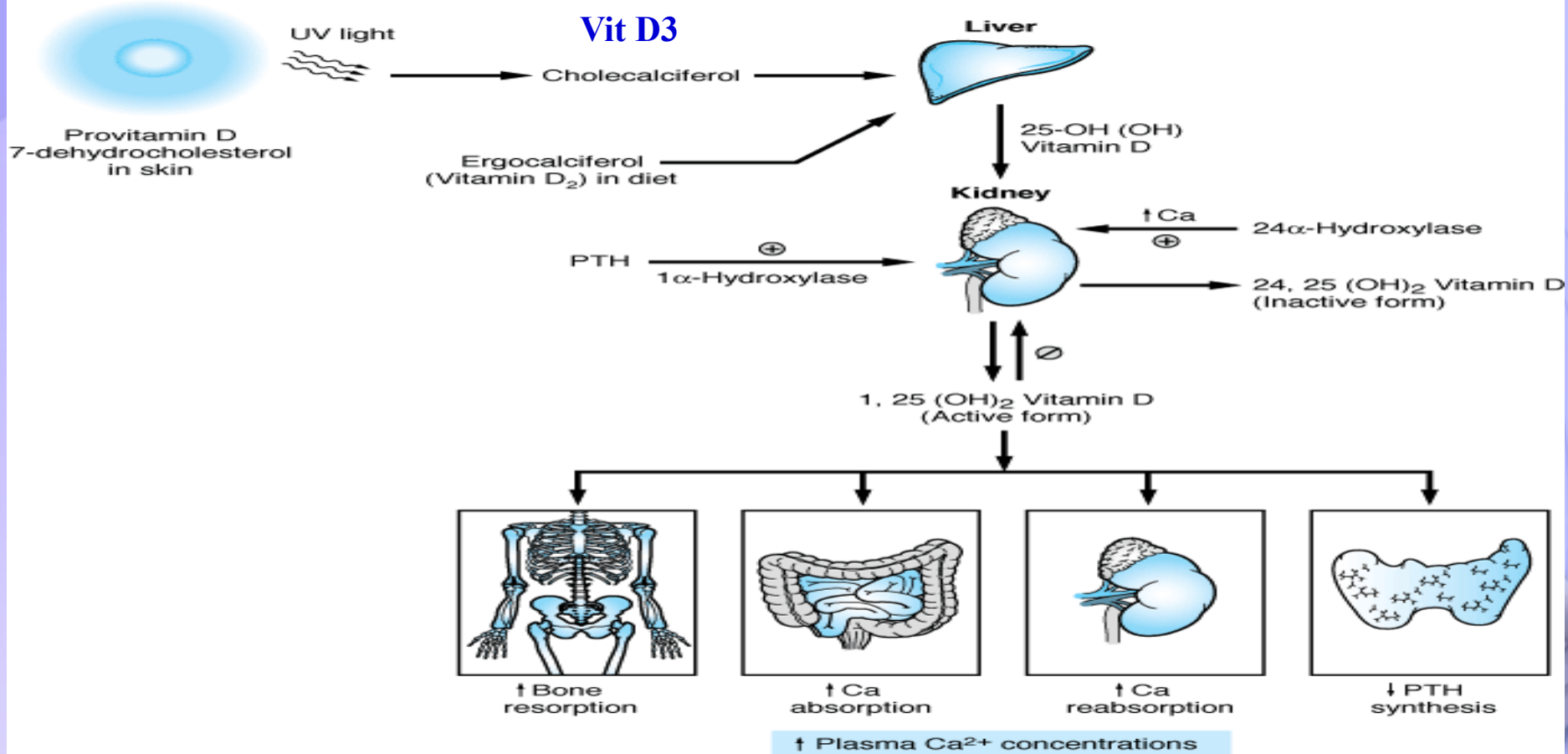


Vitamin D Metabolism



Exposure to the ultraviolet rays in the sunlight convert 7DC to cholecalciferol. Vitamin D₃ is metabolically inactive until it is hydroxylated in the liver then the kidney (by **α hydroxylase**) to the **active form** 1,25 Dihydroxycholecalciferol.

Calcium and Vitamin D



Source: Molina PE: *Endocrine Physiology, 3rd Edition*:
<http://www.accessmedicine.com>

Vitamin D increases bone resorption, increases Ca^{2+} absorption from intestine, increases renal Ca^{2+} reabsorption, and decreases the production of PTH by the parathyroid glands. The overall effect of vitamin D is to increase plasma Ca^{2+} concentrations.

Deficiency of vitamin D leads to:

- Rickets in small children**
- Osteomalacia**
- Osteoporosis**

Therapeutic uses of vitamin:

- Rickets & Osteomalacia**
- Osteoporosis**
- Psoriasis**
- Cancer prevention (prostate & colorectal)**



Remember that

- **1,25-dihydroxyvitamin D (calcitriol)** is The most active form of vitamin D.
- **25-hydroxyvitamin D (calcidiol, 25-hydroxycholecalciferol):** an inactive form of vitamin D.
- **1alpha-hydroxylase:** The enzyme that converts the inactive form of vitamin D.



Vitamin D

- Cholecalciferol (**Vitamin D3**) in skin
- Ergocalciferol (**Vitamin D2**) in plants
- Vit D2 and Vit D3 have equal biological activities.
- **Vitamin D2** is the prescription form of **vitamin D** & is also used as food additive (milk).
- **Vitamin D3** is usually for vitamin D-fortified milk & foods & also available in drug combination products.



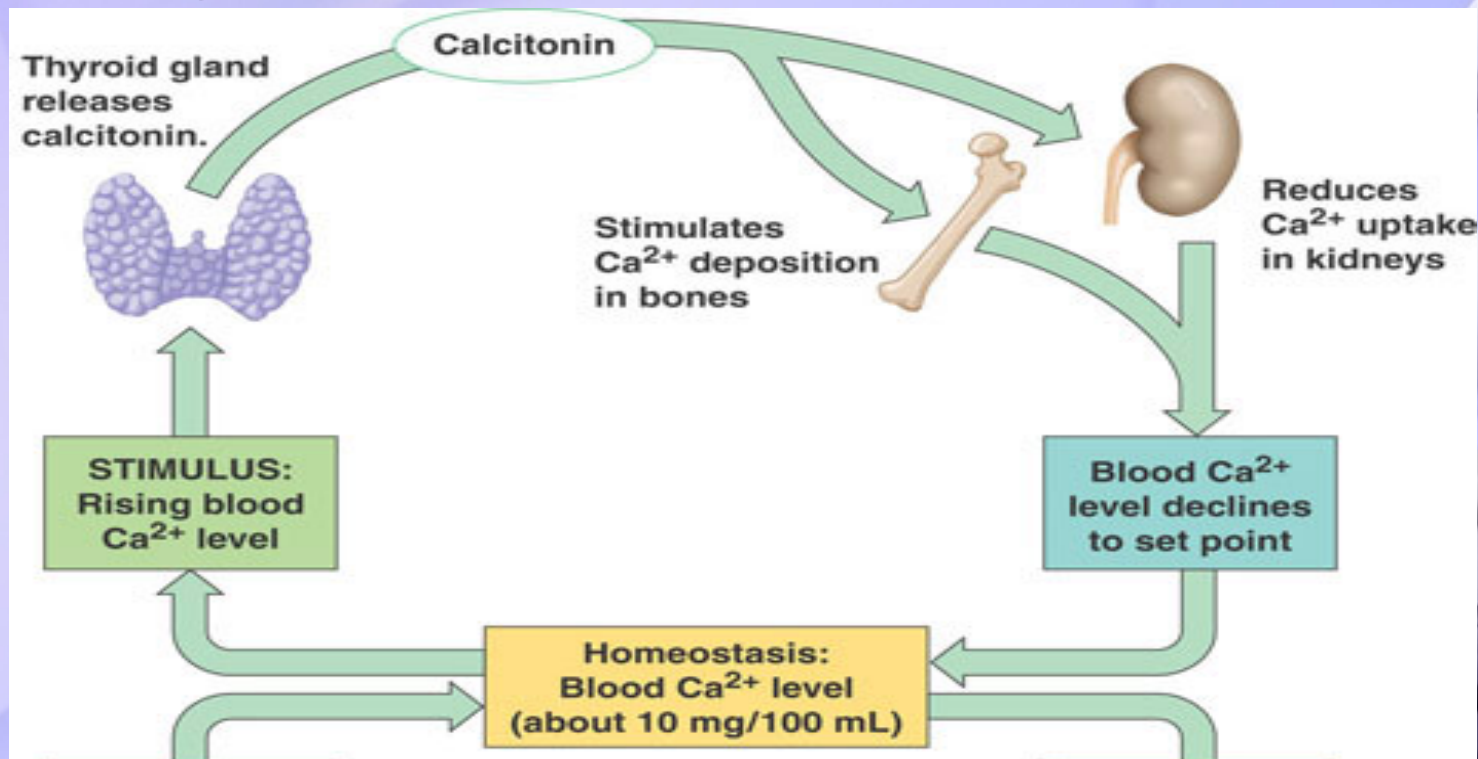
Calcitonin

- Calcitonin is synthesized and secreted by the parafollicular cells (C cells) of the thyroid gland. It is released when there is a rise in plasma Ca^{2+} levels
- While PTH and vitamin D act to increase plasma Ca^{2+} , only calcitonin causes a decrease in plasma Ca^{2+}
- Calcitonin protects against development of **hypercalcemia** caused by a variety of conditions, including increased calcium absorption (milk-alkali syndrome) and decreased calcium excretion (thiazide use).





Calcitonin

- Calcitonin does not appear to be critical for the regulation of calcium homeostasis even if thyroid gland is removed.



Effects of calcitonin

The major effect of calcitonin administration is a rapid fall in Ca^{2+} caused by:

-  Inhibiting bone resorption by **inhibiting osteoclast** activity. The osteoclast bone cells appear to be a particular target of calcitonin
-  Decreasing reabsorption of Ca^{2+} & PO_4 by the kidney, thus **increasing their excretion**



Clinical uses of Calcitonin

Used clinically in treatment of **hypercalcemia** and in certain bone diseases in which sustained reduction of osteoclastic resorption is therapeutically advantageous

- **Osteoporosis** (major indication; alternative to other drugs).
- **Hypercalcemia** (short-term treatment of hypercalcemia of malignancy), Paget's disease.
- It has lower efficacy compared to other drugs.



Routes of administration

S.C., Nasal spray or solution
(**Calcitonin Salmon**) has more affinity towards human calcitonin receptors

Adverse effects

- Nausea
- Local inflammation at site of injection
- Flushing of face & hands
- Nasal irritation



Thank You.



Treasure
your
BONES!