Pharmacology of drugs used in calcium & vitamin D disorders

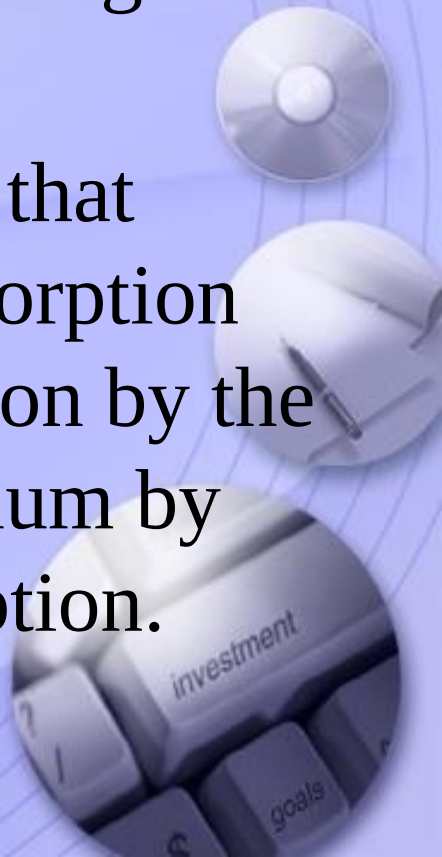
Objectives

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

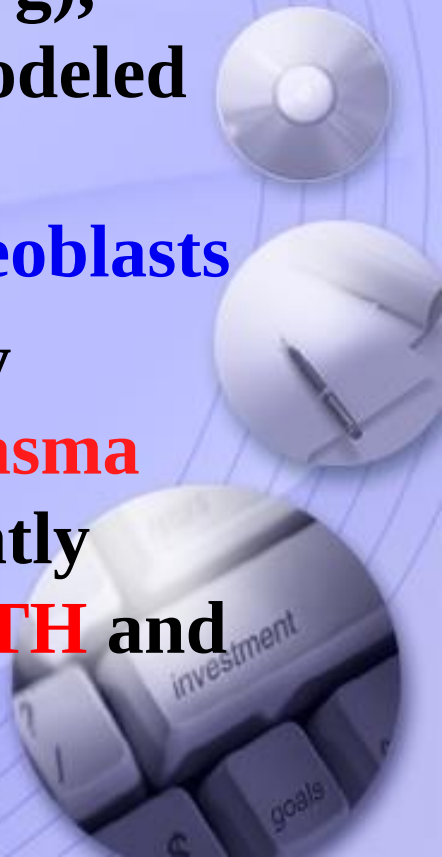
- **Parathyroid hormone (PTH)**
- **Vitamin D**
- **Calcitonin**

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.

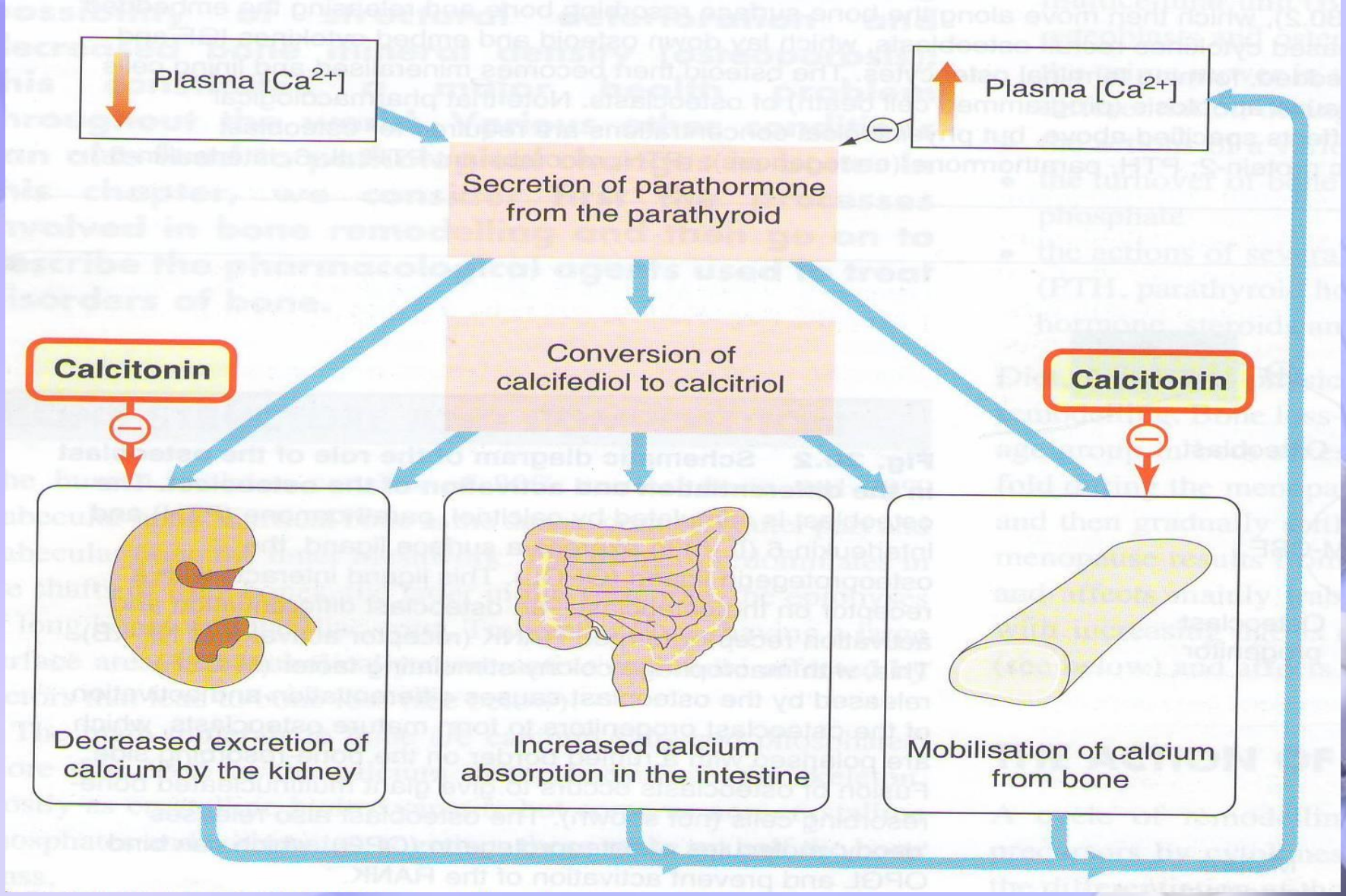
Parathyroid Hormone

- **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 [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

↑ **Osteoblast number/function**

↑ **Bone formation**

↑ **Bone mass/strength**

Continuous

↑ **Osteoclast**

↑ **Bone resorption**

↑ **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.

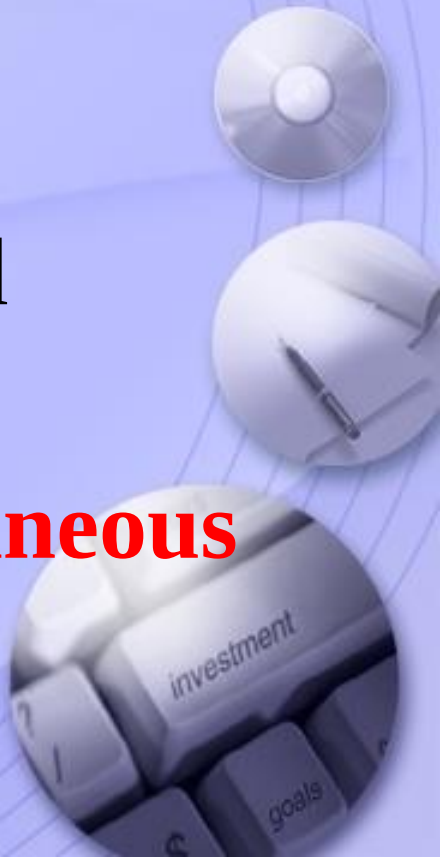
Clinical uses of PTH

- 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

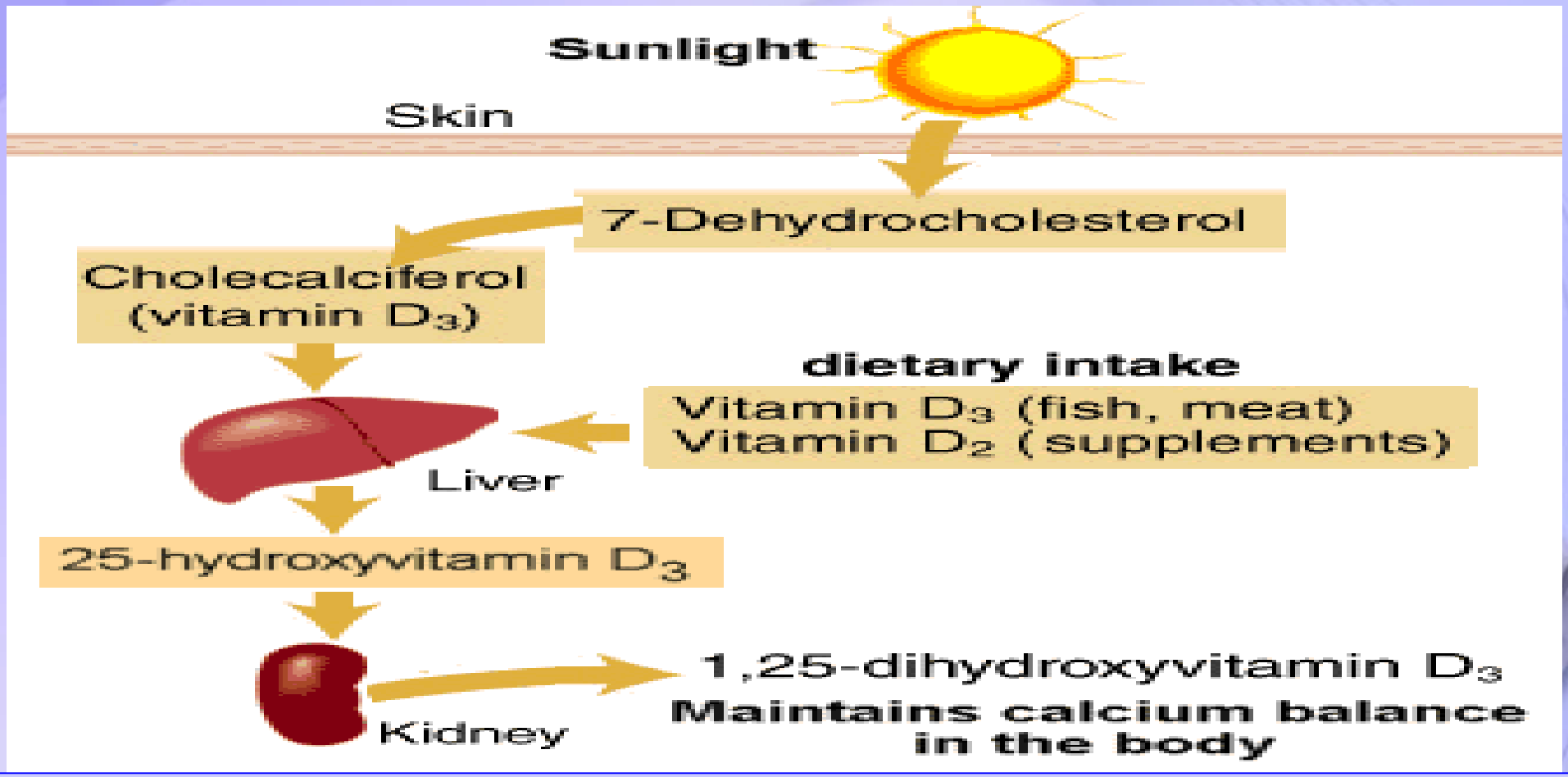
Teriparatide should not be used by people with increased risk for bone tumors (osteosarcoma) including:

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

Vitamin D

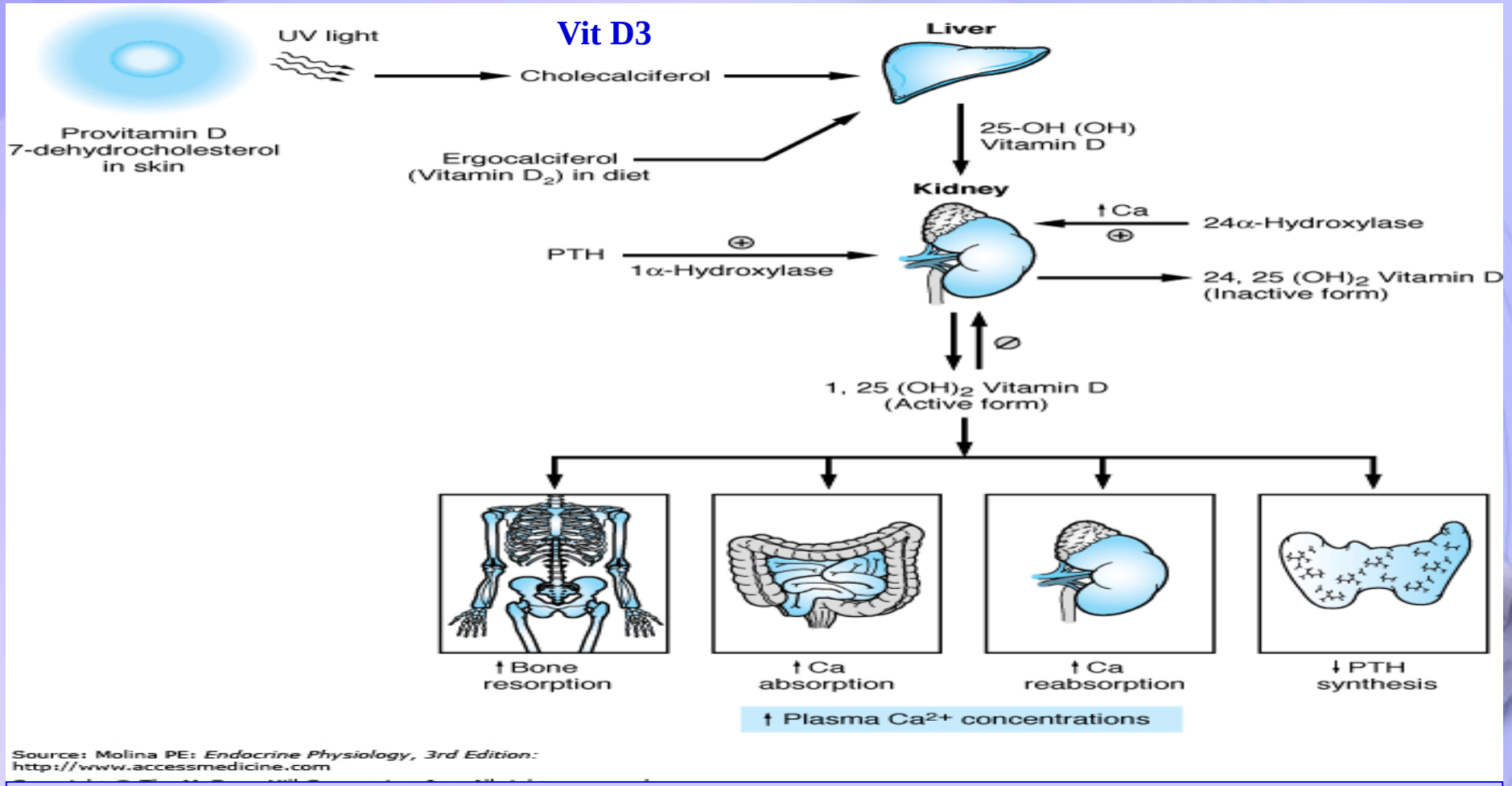
- Vitamin D is a steroid hormone that is intimately involved in the regulation of plasma calcium levels.
- Its role in calcium metabolism first was recognized in the childhood disease rickets, which is characterized by hypocalcemia and various skeletal abnormalities.

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

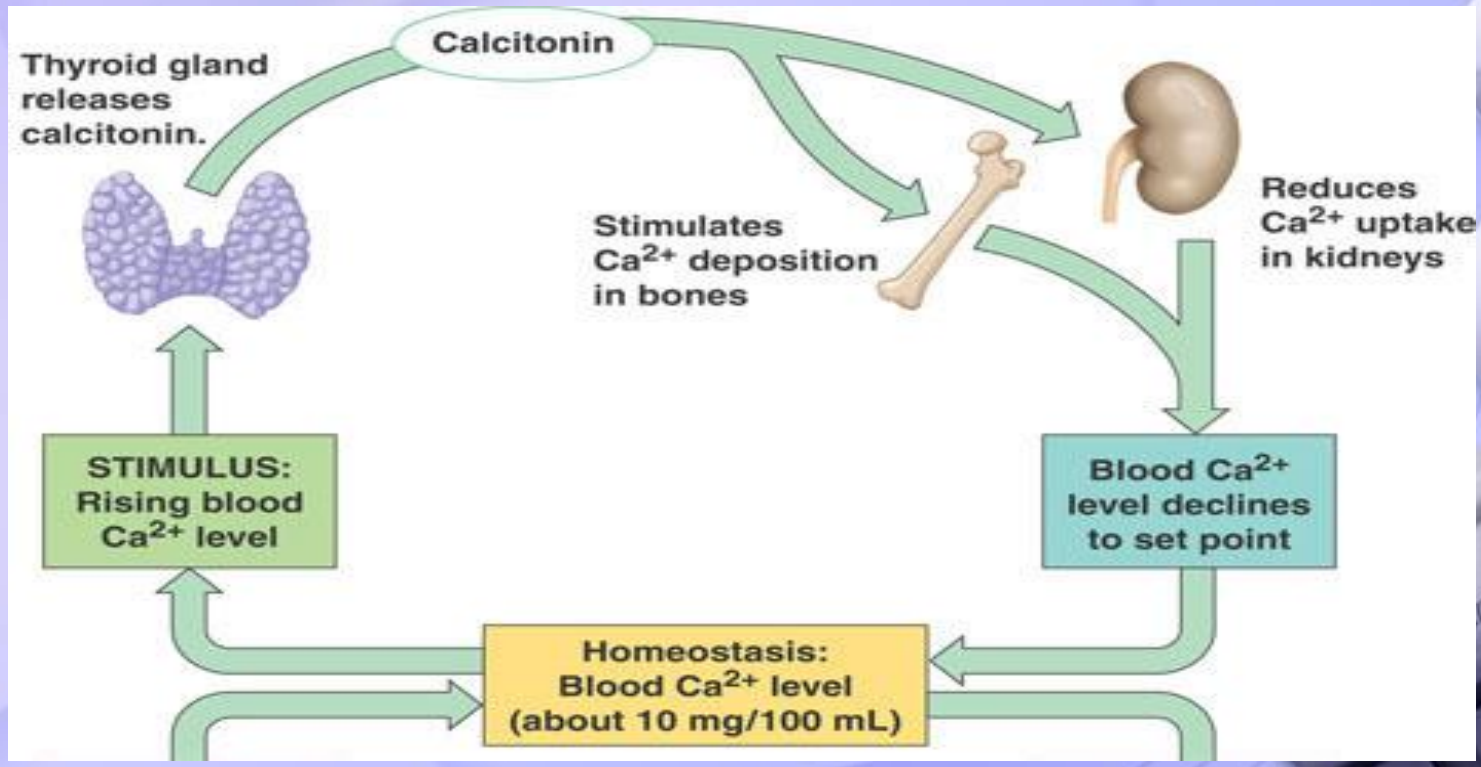
- Cholecalciferol (Vitamin D3) in skin
- Ergocalciferol (Vitamin D2) in plants
- Vitamin D2 is the prescription form of vitamin D & is also used as food additive (milk).
- Vitamin D3 is usually for vitamin D-fortified milk & foods & also available in drug combination products.
- Vit D2 and Vit D3 have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

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

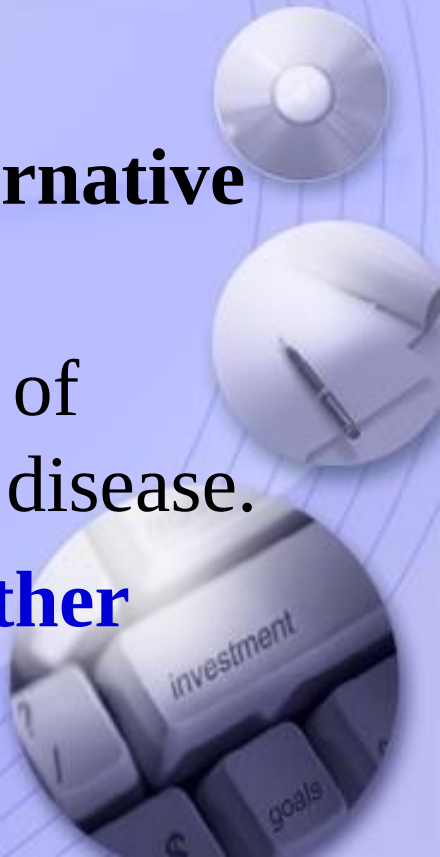
The major effect of calcitonin administration is a rapid fall in Ca^{2+} caused by:

- **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.