Pharmacology of drugs used in calcium & vitamin D disorders

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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

BONE

- Is a dynamic organ undergoes continuous remodeling process involving resorption of old bone by osteoclast & formation of new bone by osteoblast

- **The principal hormones involved in calcium metabolism & bone remodeling are : Parathyroid hormone (PTH) , calcitonin , vitamin D (D3)** (active form).
- **Other hormones , such as growth hormone, thyroid hormones, androgens , estrogen & glucocorticoides may be also involved .**
- **The target tissues for PTH, calcitonin & vitamin D are bone , kidney & intestine.**
- **PTH, calcitonin & vitamin D & their target tissues maintain serum calcium levels and bone integrity.**

FDA-Approved Therapeutic Options

Prevention Stops bone loss	Treatment Reduces vertebral fractures
Estrogen	**Calcitonin** (*(Miacalcin, Fortical)*) **PTH** *(Forteo)* **Teriparatide** *"syntheses form of* **PTH** *"*
Alendronate *(Fosamax)* **Risedronate** *(Actonel)* **Ibandronate** *(Boniva: oral, injection)* **Raloxifene** *(Evista)*	

1- Parathyroid Hormone

- Human PTH is an 84- amino acid peptide .

- PTH is an important physiological regulator of calcium metabolism , it maintains the plasma calcium concentration.

Synthesis & Secretions

- Plasma calcium concentration is the principal factor regulating PTH synthesis & secretion.

- **Hypocalcemia** increases PTH synthesis through activation of parathyroid gland adenylyl cyclase increasing cAMP

The principle factor to stimulate **PTH is plasma ca concentration " hypoglycemia"**

Physiological role of PTH

- **On BONE**

  In response to severe "acute" Hypocalcemia

PTH stimulates surface osteocytes (osteoclast)to increase the outward flux of calcium ion from bone to rapidly restore serum calcium.

- **This effect is not associated with any significant ↑ In plasma phosphate or bone resorption**

PTH has remolding MOA:

first it activates osteoclasts >> release H+ and protolytic enzyme which make holes in matrix >> stimulate IGF-1 and Gβ1 which increase the activity of the osteoblast >> increase thickening of the bone ! (we can say indirect effect on osteoblast)

Continue

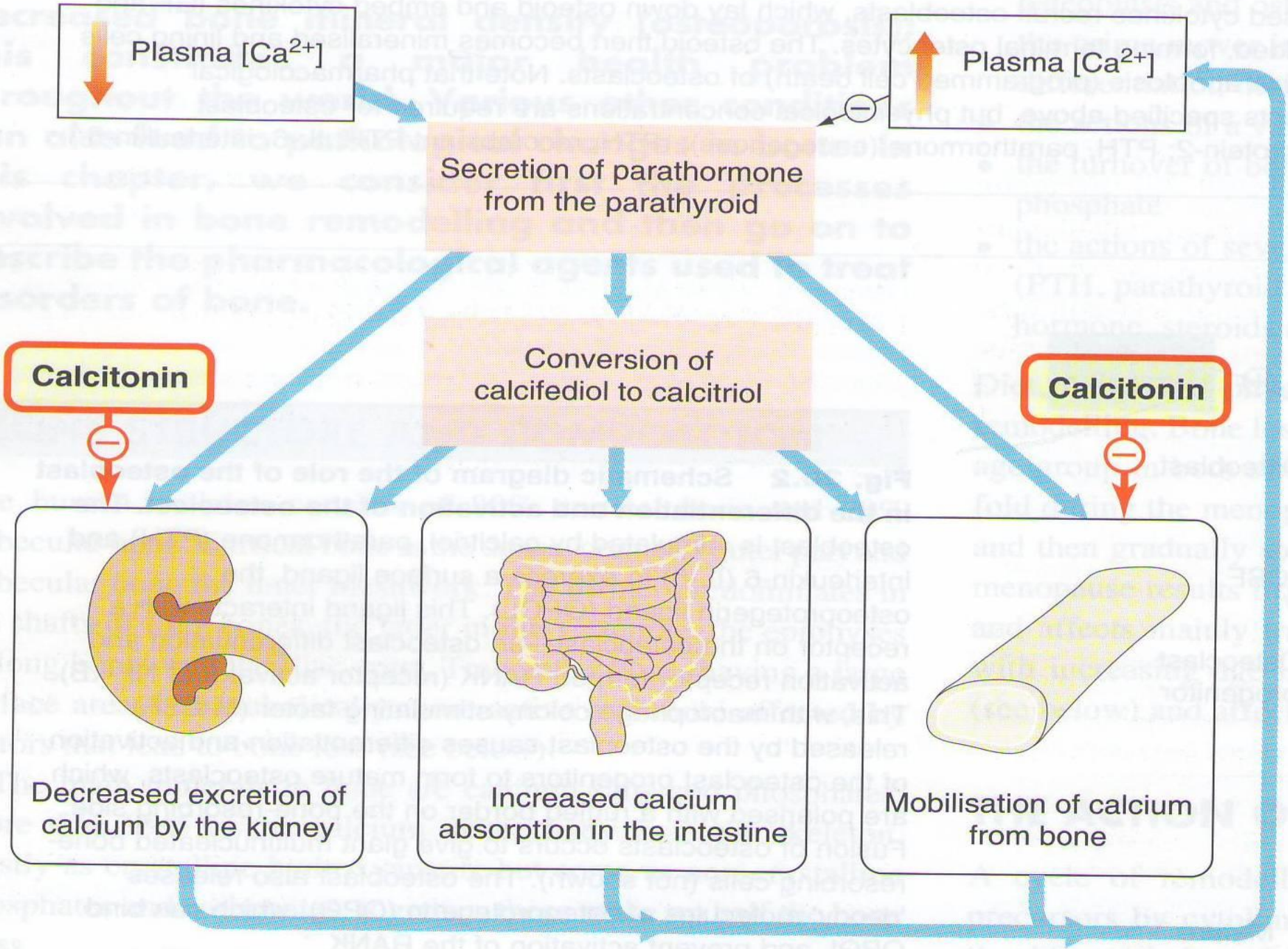
- **On the kidney**

PTH increasing renal calcium reabsorption

“ decrease Ca execration”

- **On the intestine**

Indirect increase in calcium reabsorption through activating form of vitamin D (1,25-(OH)2 D3)


Plasma [Ca2+]
Plasma [Ca2+]
Secretion of parathormone from the parathyroid
Conversion of calcifediol to calcitriol
Calcitonin
Calcitonin
Decreased excretion of calcium by the kidney
Increased calcium absorption in the intestine
Mobilisation of calcium from bone

Clinical uses

- For treatment of severe osteoporosis or in case of failed response to other therapy..

  ** It leads to↑ trabecular bone density

- Given in low & intermittent dose

- It reduces vertebral fracture risk

Disadvantage:

(Expensive & only given by i.v injection)

Notice

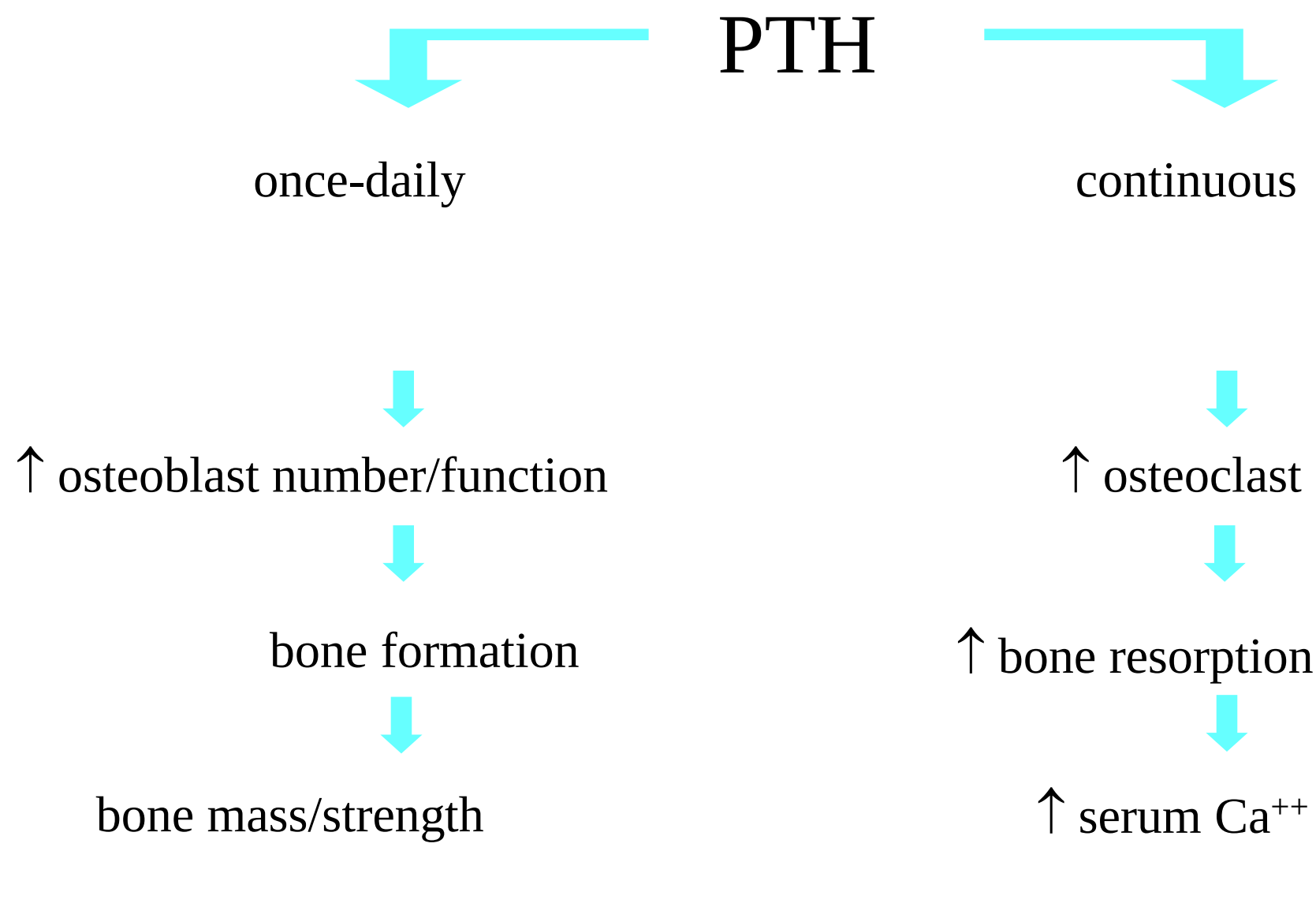
Continuous use or secretion of PTH

- stimulates osteoclast mediated bone resorption (lead to osteoporosis)

- increases production of other inflammatory factors as IL-6 , TNF-α or prostaglandins that increase bone resorption (lead to osteoporosis)

Because of that it is Given in low & intermittent dose

SKELETAL RESPONSE TO PTH



FOR reading :

The skeletal effects of teriparatide depend upon the pattern of systemic exposure. Once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. In monkey studies, teriparatide improved trabecular microarchitecture and increased bone mass and strength by stimulating new bone formation in both cancellous and cortical bone. In humans, the anabolic effects of teriparatide are manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. By contrast, continuous excess of endogenous PTH, as occurs in hyperparathyroidism, may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation.

2- Teriparatide *"syntheses form of* PTH "

- **PTH analog [recombinant human PTH (1-34) amino acids]**
- **Represent a new class of anabolic therapies for treatment of severe osteoporosis**
- **<u>In patients established glucocorticoid –induced osteoporosis</u>**

(osteoporosis caused by glucocorticoids)

Teriparatide : called Anabolic hormons .
b/c the first action is bone formation "on osteoblast" ((direct action))
(becausse of this direct action its mechanism called <u>modeling-based formation.)</u>

Continue

- For management of individuals at high risk for fractures (have low bone mineral density measurements).

- **Teriparatide** therapy is not recommended for more than 2 years ((induction of osteosarcoma ,,cancer,,)) !

Comparison between PTH & Teriparatide

PTH

- Acts through a mechanism named **remodeling- based formation**
- stimulate bone formation through an increase in the bone remodeling rate- ongoing gains in the amount of bone tissue, including trabecular thickness)

Teriparatide

- Acts through a mechanism named **modeling-based formation .**
- stimulating formation **directly** without a need for prior resorption
- Increase trabecular bone in thickness & connectivity

3- Vitamin D (Cholecalciferol)

- Is a hormone that requires further metabolic conversion to exert biological activity in its target organs (liver & kidney).

- The initial transformation of D3 occurs in liver to

25-(OH)D3 (**calcifediol**)

- In the kidney converted to active form of D3 (1,25-$(OH)_2$ D_3) **calcitriol**

Sources of Vitamin D

- **Dietary ergocalciferol (D2) , derived from ergosterol in plants , milk, egg yolk & fish oils**

- **Cholecalciferol (D3) : Generated in the skin from 7-dehydrocholesterol by the action of ultraviolet radiation (sunshine). 7- dehydrocholesterol having been formed from cholesterol in the wall of the intestine .**

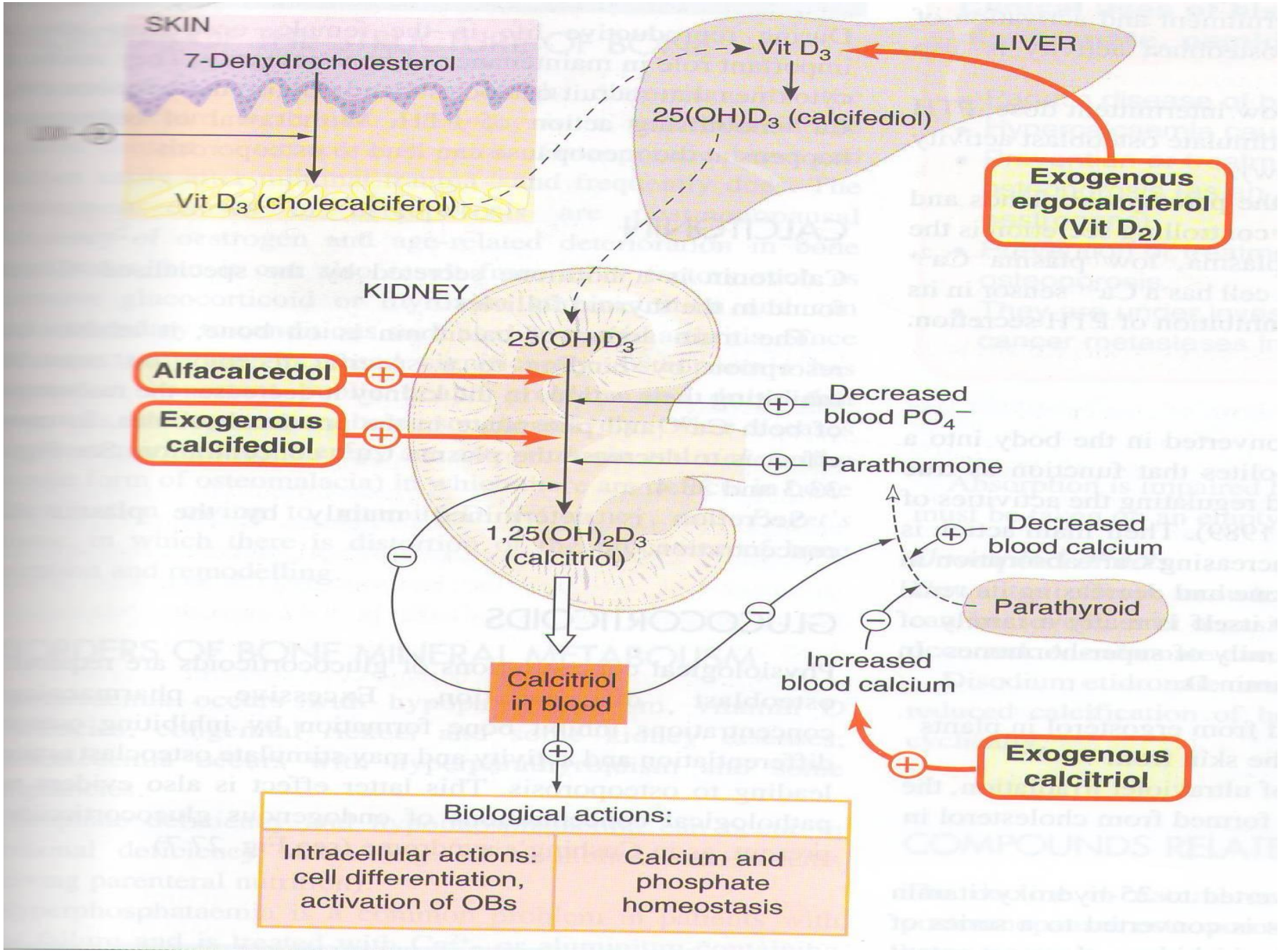
- **A deficiency of Vitamin D (1,25 dihydroxy vitamin D3) in adults causes Osteomalacia. " لين عظام " In children it is called Rickets. In this condition the bones weaken due to decalcification. This can also occur with a severe shortage of sun exposure.**

ACTIONS OF VITAMIN D3

Through its active metabolite 1,25-(OH)2 D_3

Enhances :

- intestinal calcium absorption
- PTH induced mobilization of calcium from bone
- calcium reabsorption in the kidney


SKIN
7-Dehydrocholesterol
Vit D_3 (cholecalciferol)
Vit D_3
LIVER
25(OH)D_3 (calcifediol)
Exogenous ergocalciferol (Vit D_2)
KIDNEY
25(OH)D_3
Alfacalcedol
Exogenous calcifediol
Decreased blood PO_4^-
Parathormone
1,25(OH)$_2D_3$ (calcitriol)
Decreased blood calcium
Parathyroid
Calcitriol in blood
Increased blood calcium
Exogenous calcitriol
Biological actions:
Intracellular actions: cell differentiation, activation of OBs
Calcium and phosphate homeostasis

Ergocalciferol (vitamin D2)

- Exogenous sterols is derived from plant
- Act as substrate for both’ the 25-hydroxylase and 1-hydroxylase enzyme system in the liver & kidney to form the active vit. D3
- Used in commercial vitamins and supplemented dairy products.

Remember : D2 converted into D3 in the body (active form)

Why are elderly individuals more likely to be vitamin D deficient than young ?

- They spend less time outdoors exposed to the sun which is important in the synthesis of vitamin D.

- Their appetite & intake of essential nutrients is diminished with aging

- **The formation of the active form of vitamin D is diminished by chronic liver & renal conditions associated with aging**

- **Vitamin D nuclear receptors “ inside the cell” have less affinity for vitamin D3 with aging**

4- Calcitonin

- **Synthesis / Release**

  Regulation of calcitonin synthesis & release from parafollicular cells of the thyroid gland is calcium dependent.

- **Hypercalcemia is the principal stimulus for calcitonin synthesis & release. !!! imp**

Continue

- **Other hormones such as glucagon, gastrin stimulate calcitonin release**

- **Gastrin –induced calcitonin release following meals regulate postprandial calcium deposition in bone.**

Principal mechanism of action Of calcitonin in treatment of osteoporosis

- **Decreases serum calcium and phosphate !!!**

(deposition of post absorptive calcium into bone following a meal to prevent postprandial -after meal- hypercalcemia) **(considered as a main action)**

- **Inhibiting bone resorption by binding to a specific receptor on osteoclasts inhibiting their actions**

Metabolic degradation of calcitonin

- **Occur in liver & kidney**

- **Increase blood levels of calcitonin have been found in carcinoma of the thyroid gland**

((pathological condition))

- **Serum calcitonin levels are used to screen & monitor patients who have or are suspected of carcinoma of thyroid**

Clinical uses of Calcitonin

- Disorders of calcium and bone metabolism
- ↓lumbar fracture risk ,but not hip
- ↓bone turnover
- ↓bone pain of osteoporotic compression

Preparation : S.C. or nasal spray (called salmon)

1- used mainly with young age cuz with aging the calcitonin receptors are down regulated.
2- used when osteoporosis associated with **Hypercalcemia** .

Adverse effects

- Nausea , local inflammation (injection)
- Nasal irritation " with nasal form "
- Flush of face & hands

Thank You.