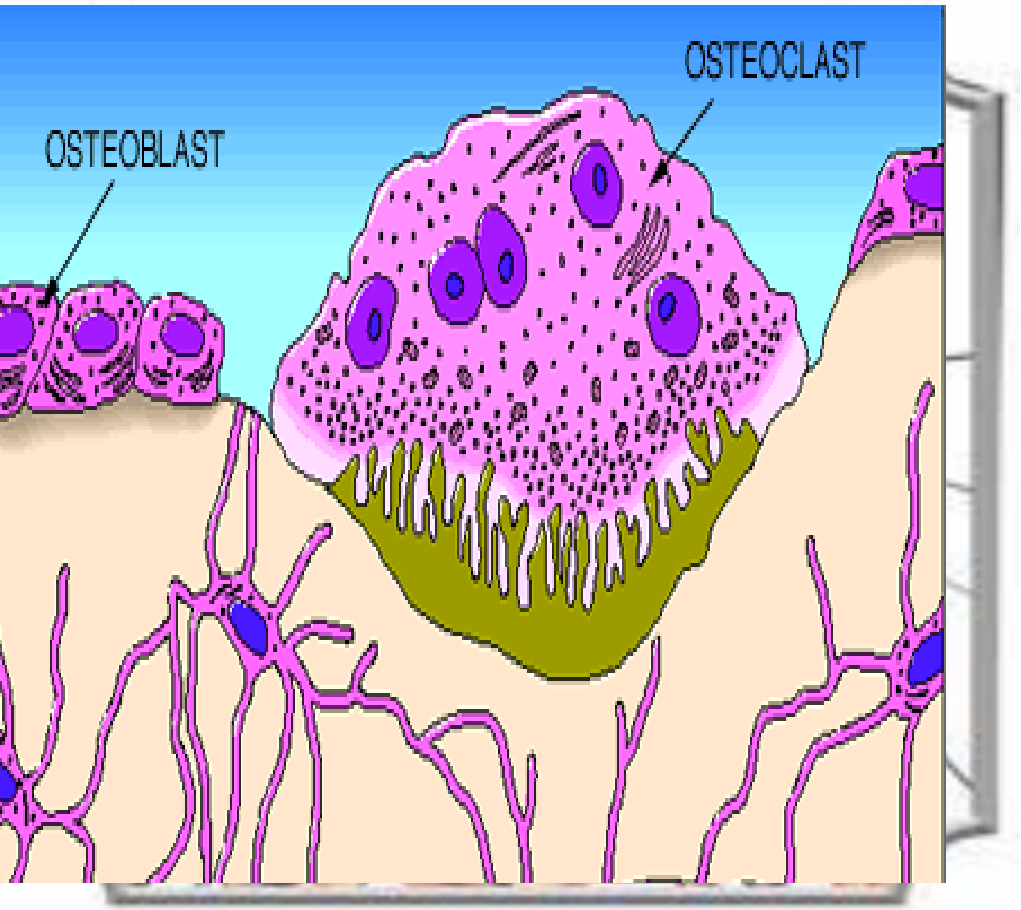
Physiology of Bone



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Lecture1:- Bone physiology (Referece book –Gyton 12 th edition,chapter 79 (p 955-966)

Objectives:-

At the end of this lecture the student should be able to:-

-Define bone and differentiate between types and sites of bone (cortical& trabecular)

-Appreciate differences between both types of bone in function

-know ca++ concentration and forms in the ECF& its relation to PO4

- differentiate bone cells &function of each

- know Bone remodelling & bone formation

- Define osteoporosis

- Appreciate effect of different hormones on bone physiology

Functions of bone:-

1-Supports soft tissue
2-Protects vital organs (cranium, thoracic cavity)
3-Contains bone marrow for blood cells synthesis تخليق
4-Reservoir of Ca++, PO4 to maintain constant concentrations of them in body fluids
5-Allows body movement

Structure of bone:-

Porous mineralized structure

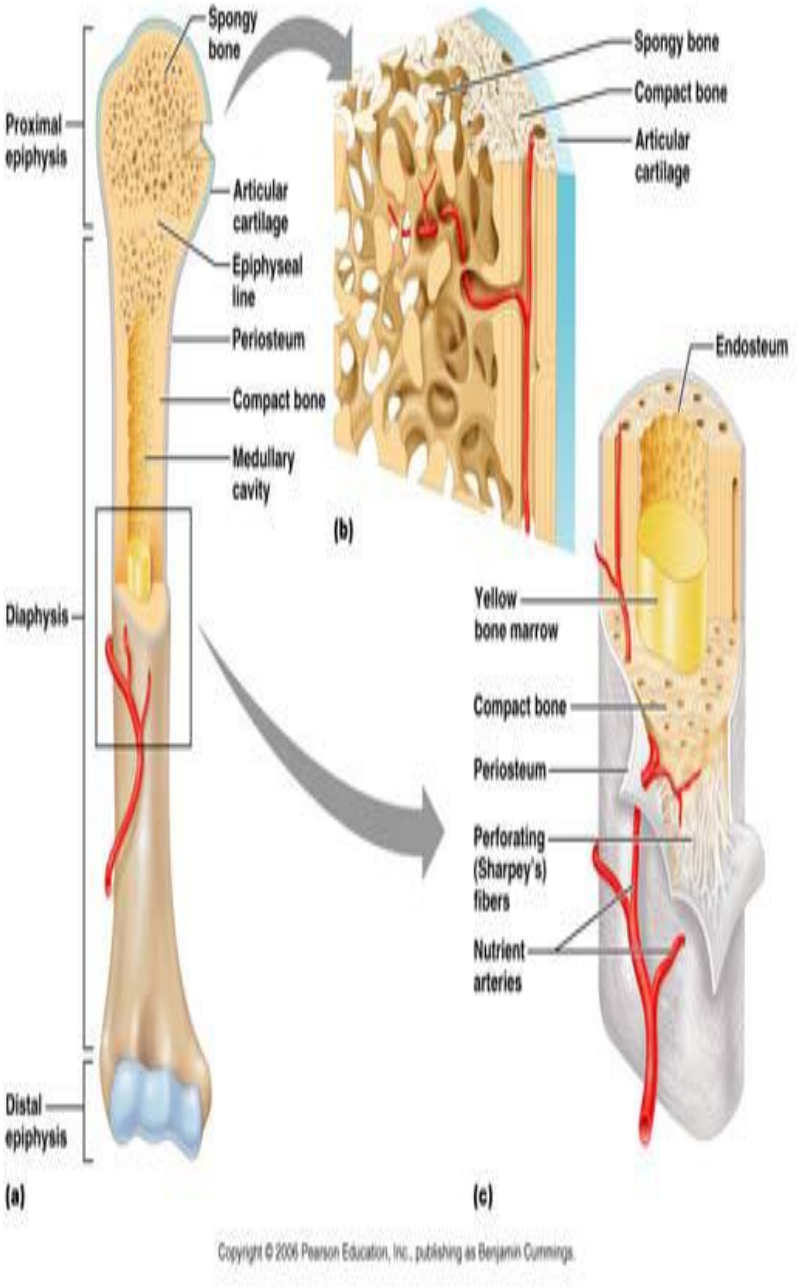
A-Cells ???

B-Bone matrix

Calcified material(**deposits of calcium & phophates salts mainly but there is magnesium ,potassium &carbonate**),collagen fibres lacunae, Canaliculi

c-Periosteum & Endosteum

d- **red or yellow marrow in** the center of the bone



The human skeleton is actually made up of 2 types of bones:

(1) **Cortical bone (compact bone)** → 80 %

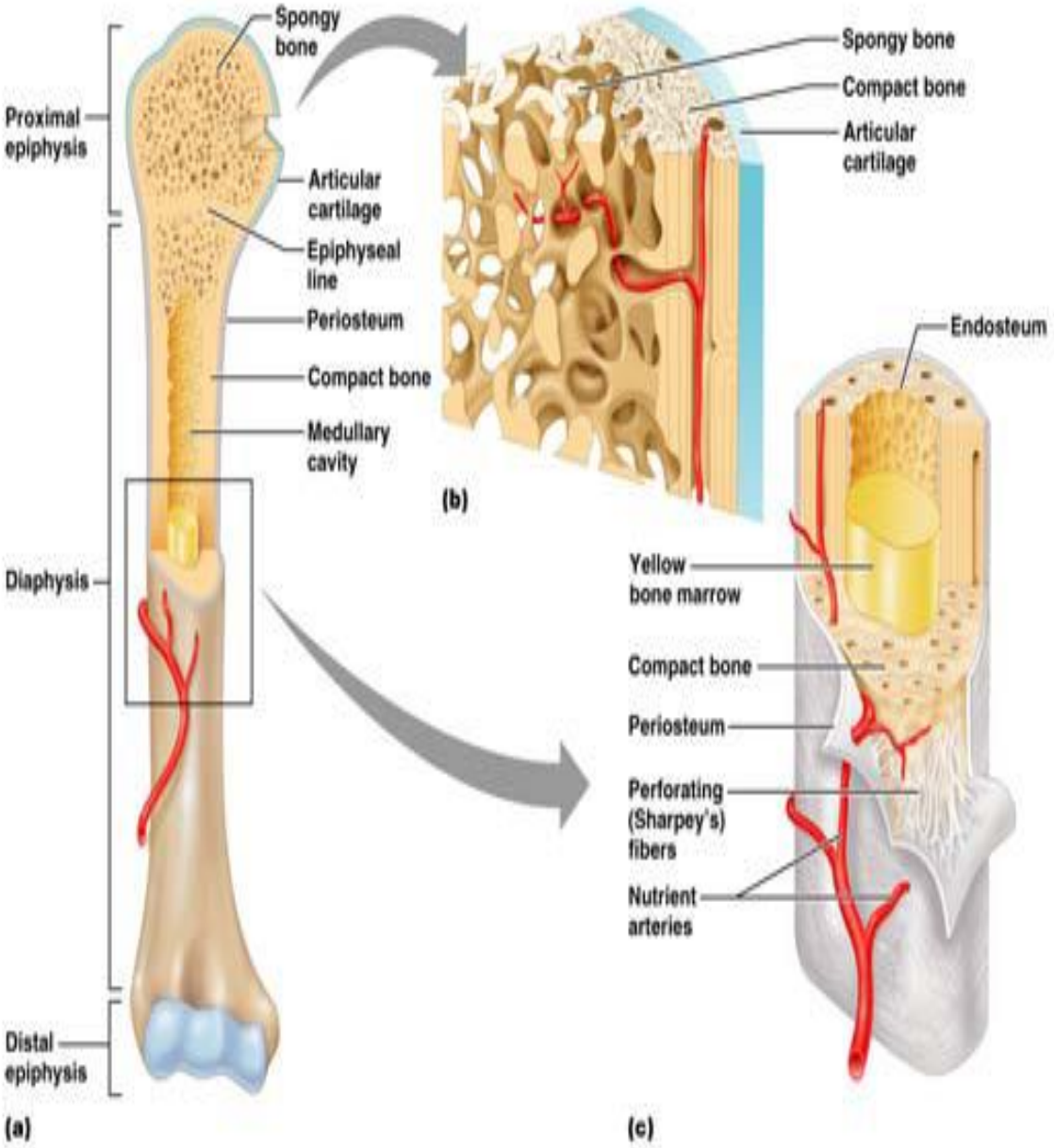
-Constitutes the dense concentric layers of long bones

-Also outer layer surround trabecular bone at ends of long bones

(2) **Trabecular bone (spongy)** → 20%

-Present in the interior of skull, ribs, vertebrae, pelvis and (in long bones present only in epipheseal and metaphysal regions)

It has five times greater surface area than cortical bone (80% of the bone surface area).

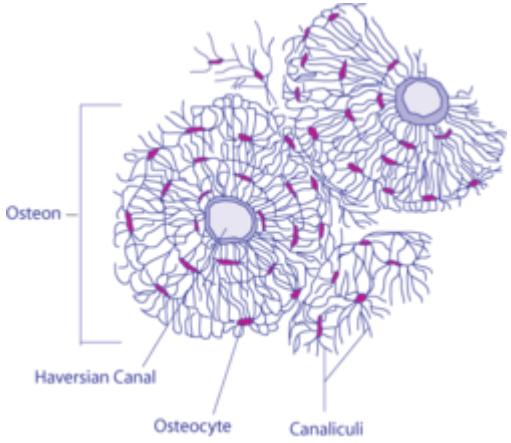


Compact bone

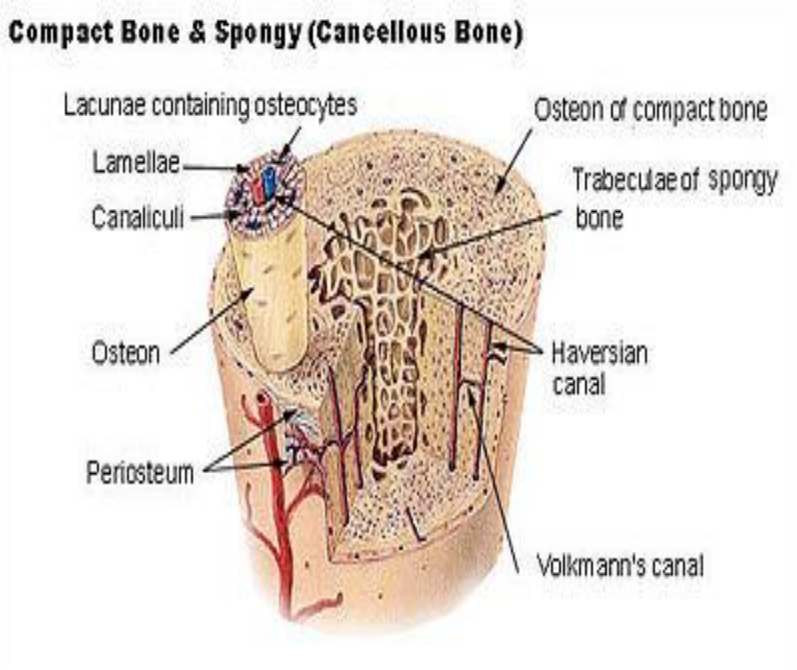
(غلاف)-Forms a protective outer shell around every bone in the body.

دوران معدل-has a slow ca ++ turnover rate

تقويس-Has high resistance to bending present where bending would be (undesirable as in the middle of long bones.)



-There is a series of adjacent bull's eye **osteons or Harvesian** called **systems**.



Osteon is composed of a central vascular channel called the Harvesian canal, surrounded by a kind of tunnel of concentric lamellae of نفق mineralized bone,.

Harvesian canal can contain capillaries, aterioles, venules, nerves and possibly lymphatics.

Trabecular (spongy-Cancellous) Bone

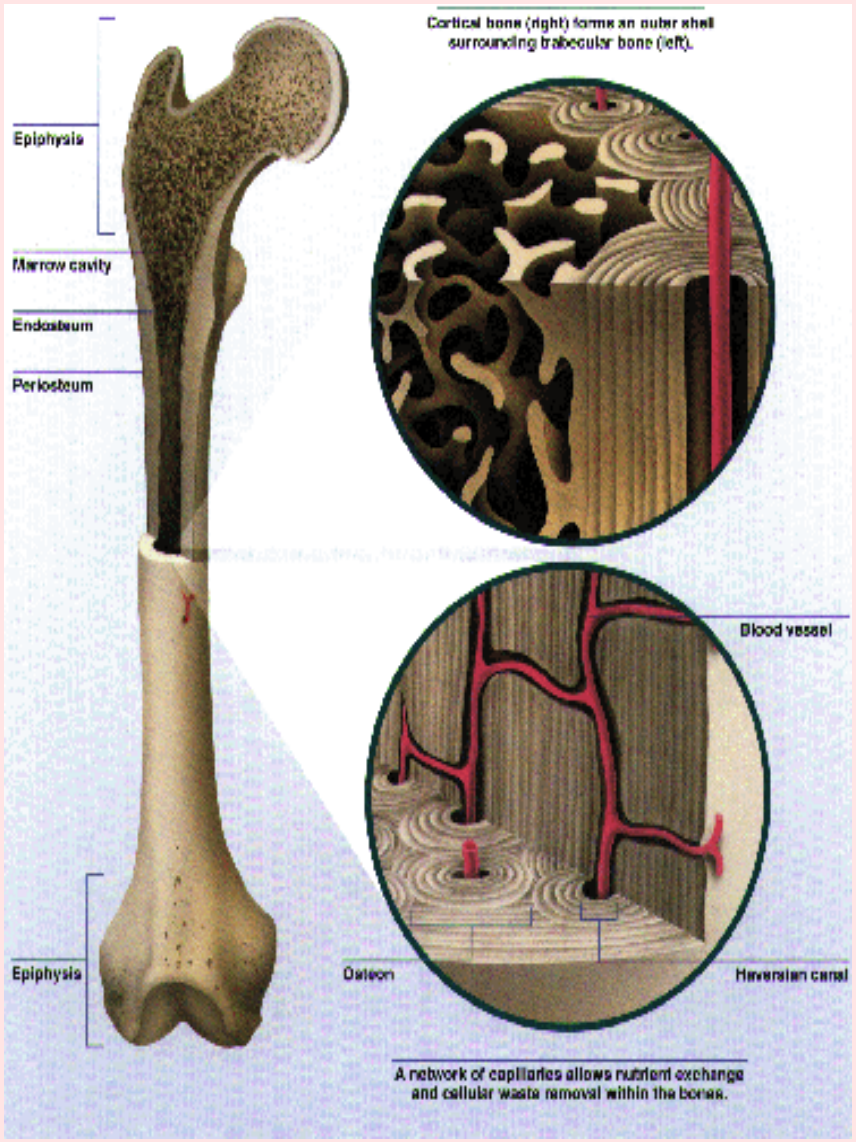
- -Rigid but appears spongy
-)(هيكل)- Forms the interior scaffolding which helps bone to maintain their shape despite compressive forces.
- **Compared to cortical bone it is:**

(1) less dense

(2) more elastic

(3) greater surface area

(4)it has high calcium turnover rate because of the greater surface area



Calcium Homeostasis

Extracellular Fluid (ECF) Calcium

Normal Ca^{2+} level in plasma ranges from **8.5-10 mg/dL**

(mean 9.4 mg/dL) It exists in fractions

:(1) **Free ionized calcium** → **50%** of total ECF calcium, diffusable through capillary membrane

(2) **Protein-bound calcium** → **40**%, (non diffusable through capillary membrane**)**

a-90% bound to albumin

b- Remainder bound to globulins

Alkalosis increases calcium binding to protein and decreases ionized calcium

(3**) Calcium bound to serum constituents** → **10%** (citrate & phosphate) (not ionized- diffusable)

-Only the free, ionized Ca^{2+} is biologically active, produce all Ca++ functions on heart & nervous system .

Q-What are Ca++ functions?

Q-What is effect of hypo and hypercalcaemia on central nervous system?

Phosphate (PO_4):

-

-Calcium is tightly regulated with Phosphorous in the body.

-85% of PO_4 in bone

-’15% in cells

- less than 1% in ECF In forms as H2P04 , HPO4

PO_4 normal plasma concentration is **3.0-4.5 mg/dL**.

Ca++ x PO4 = constant (solubility product)

-if any one increase it should precipitate in bone مترسب

Bone& Ca++

-70% of Bone is formed of calcium (99% of the Calcium of bone in form of hydroxyapatite crystal) & phosphate salts **($CaP0_4$ and hydroxide)**)

- Calcium salts in bone provide structural integrity of the skeleton

-About 99% of Ca of our body is in bone.

- about 0.1% in ECF

- 1% of our body Ca is in cells organells

- Exchangable Ca++ of bone (0.4 – 1% of total bone Ca++) has rapid buffering mechanisms, to keep ECF Ca++ levels constant , if ECF Ca++ falls below normal, this Ca will move from bone into ECF

BONE GROWTH:-

Growth occurs at epiphyseal طولي Linear plates.المشاشي

-Increase in width occurs at periosteum غشاء العظم

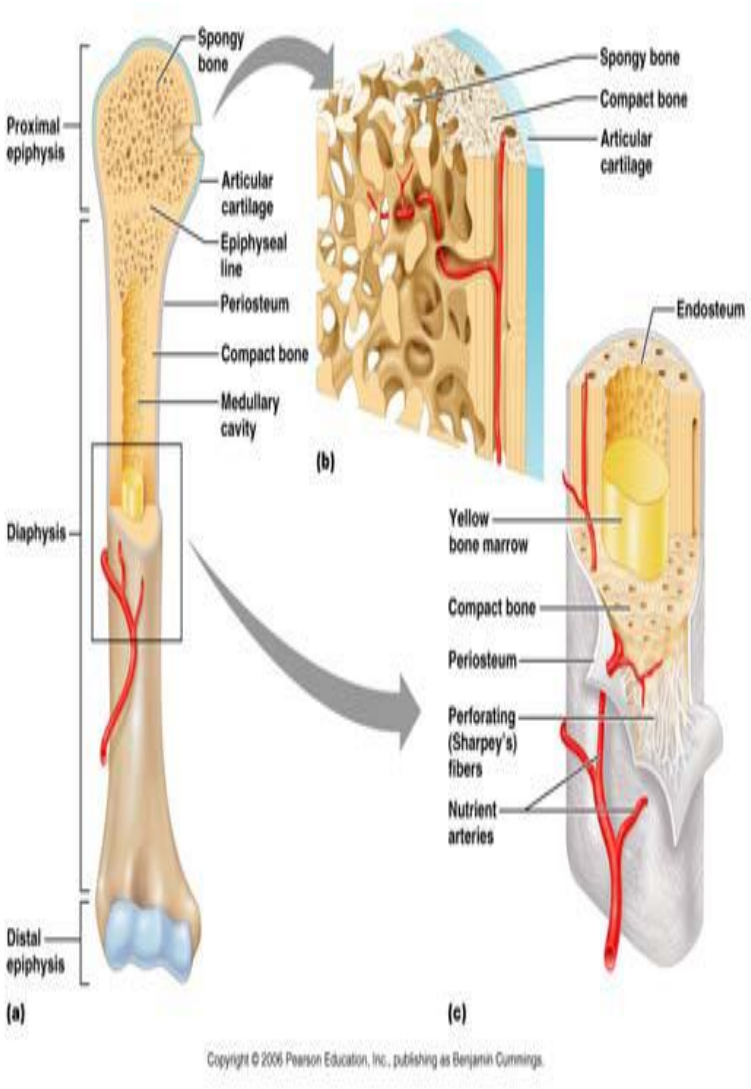
-During growth , bone mass increases and bone formation exceeds امتصاص Resorption

.

- 10% of total adult bone mass turns over each year during remodeling process إعادة تشكيل -

Once adult bone mass is achieved **equal rates of formation and resorption to** maintain bone mass

-At about 30 years old , rate of resorption begins to exceed formation and bone mass slowly decreases.



Bone Cells

There are three types of bone cells:

Osteoblast :

Bone forming cell present on outer surface of bone and in bone cavities
-secretes collagen forming bone matrix around themselves then they calcified (on which Ca^{++} and PO_4 يترسب precipitate)

(2) Osteocytes :

Mature bone cell derived from osteoblasts.
It is enclosed in bone matrix.
Q - What is the function of osteocytes ?
A -Transfer of calcium from bone canaliculi to the ECF

(3) Osteoclast :

large phagocytic multinucleated cell derived from -

monocytes ,its activity controlled by Parathormone hormone
-function is to resorb the formed bone. They secrete:

1- proteolytic enzymes as proteases digest collagen & dissolve organic matrix of bone

2-Hcl also citric and lactic acids to acidify area of bone to dissolve bone salts as hydroxyapatite acid

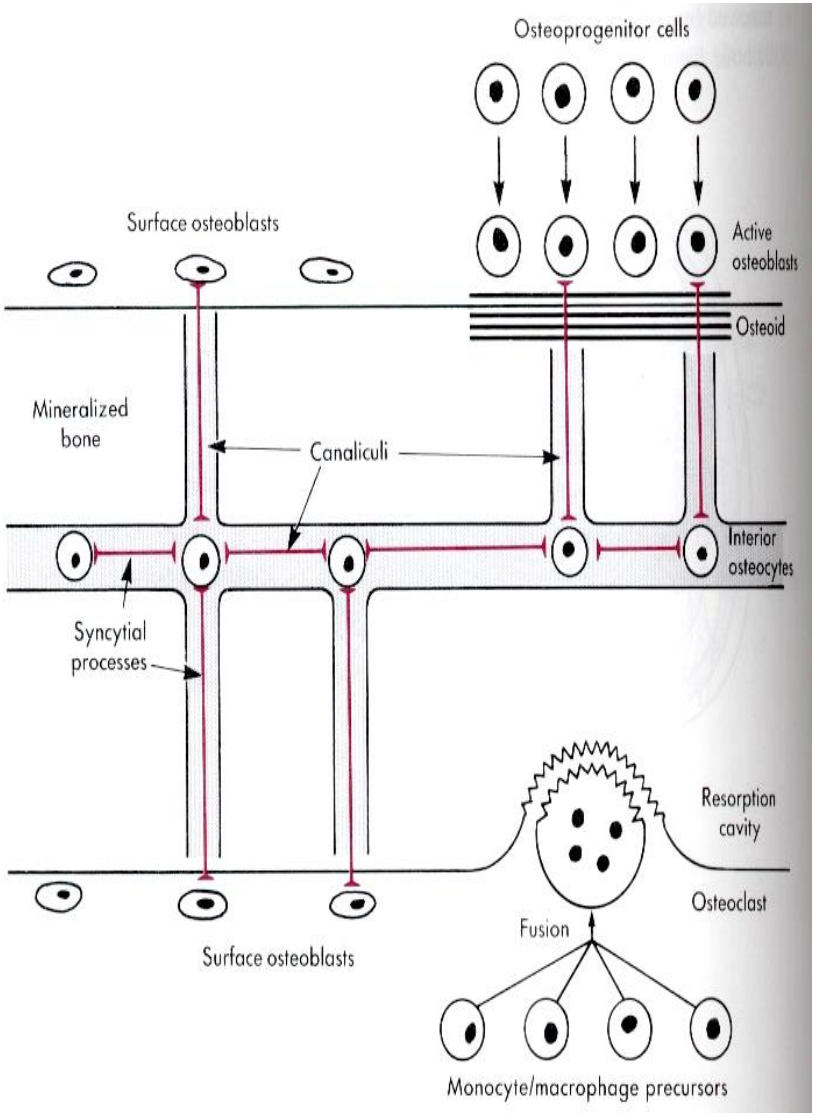
Canaliculi

- fluid-containing channels called the **canaliculi**.

- Canaliculi traverse تعبر خلال the mineralized bone.

-Interior osteocytes remain connected to surface cells (osteoblasts) via syncytial cell processes.

- Osteocytes transfer calcium from large surface area of the interior of canaliculi to the ECF



Bone formation

1-Bone formation begins when Active **osteoblasts** synthesize uncalcified Collagen (raws) of an organic صفائفfibrils to form matrix called Osteoid. (some of **osteoblasts become entrapped in it & become quiescent now are called osteocytes**)

2- Then **Mineralization** (Deposition & precipitation of Calcium & Phosphate on the Osteoid collagen fibers forming hydroxyaptite crystals over a period of weeks or months)

- Requires adequate n Vitamin D
- Alkaline phosphatase and osteocalcin play roles in bone formation(their plasma levels are indicators of osteoblast activity).

ارتشافControl of bone resorption

Bone resorption of Ca^{++} occurs by two mechanims :

(1**) Osteocytic osteolysis** → rapid and transient effect

(2) **Osteoclasitc resorption** → slow and sustained mechanism **.**

-Both are stimulated by Parathyroid Hormone (PTH) & vitamin D they stimulate production of mature osteoclasts. Ostrogen stimulate OPG factor(osteoprotegrin) that inhibit formation of mature osteoclasts

1-Osteocytic Resorption (osteolysis)

- by osteocytes.

-Osteocytes digest mineralized bone & transfere calcium & Po4 from canaliculi to ECF

-Does not decrease bone mass

- reduce calcium & Po4

-Removes calcium from recently formed crystals

- Quick process begins in minutes.

(2) **Osteoclasitc resorption :-**

-

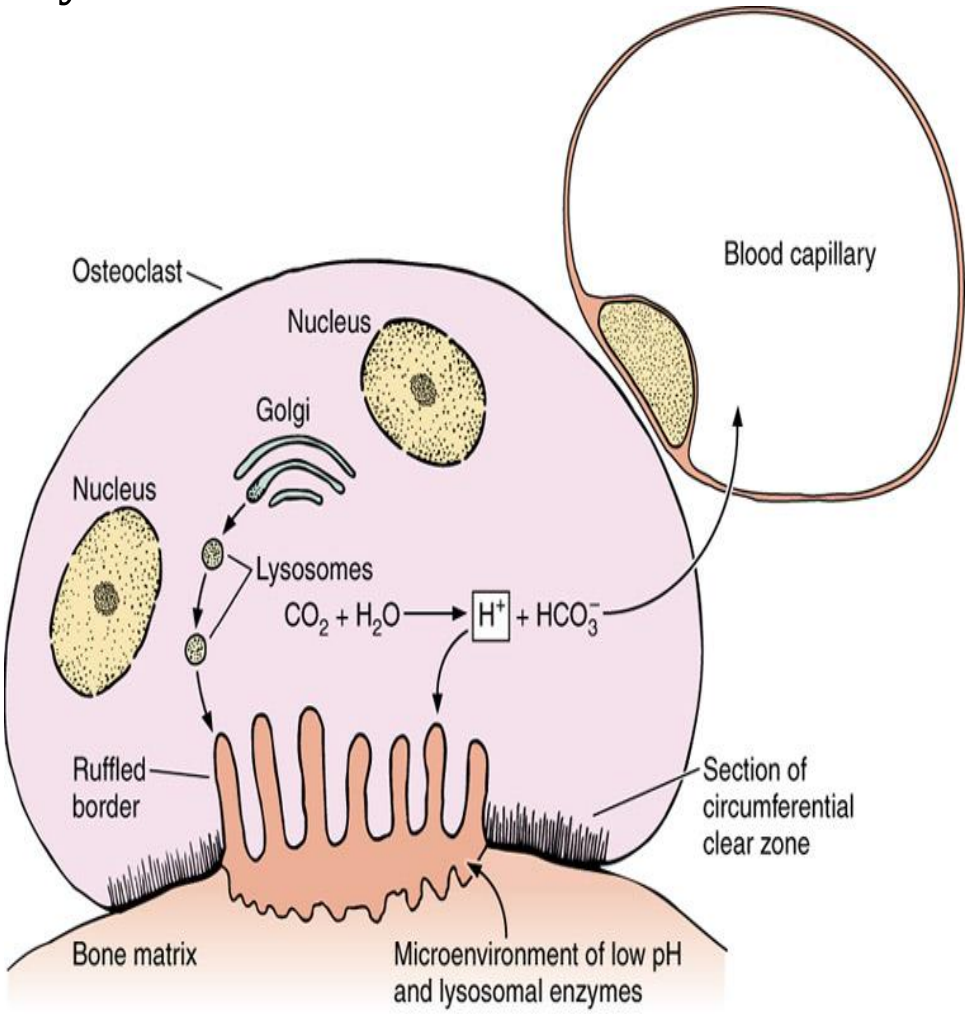
--slow and sustained needs several **days or weeks .**

- destroys matrix of old bone

- diminishes bone mass & not calcium & Po4

- By osteoclasts.

(acidify area of bone to dissolve hydroxyapatite by Hcl then lysosomes & acid proteases digest collagen)



Bone remodeling (اعادة تشكيل)

- Means continuous deposition of newbone by osteoblasts & absorption of old bone by osteoclasts

-it maintain normal toughness of bone.

-Endocrine signals to resting **osteoblasts** generate paracrine signals to osteoclasts (**osteoblasts secrete a factor helps in differentiation and maturation of osteoclasts)**

-Osteoclasts digest and resorb an area of mineralized bone.(by acids& enzymes mentioned before)

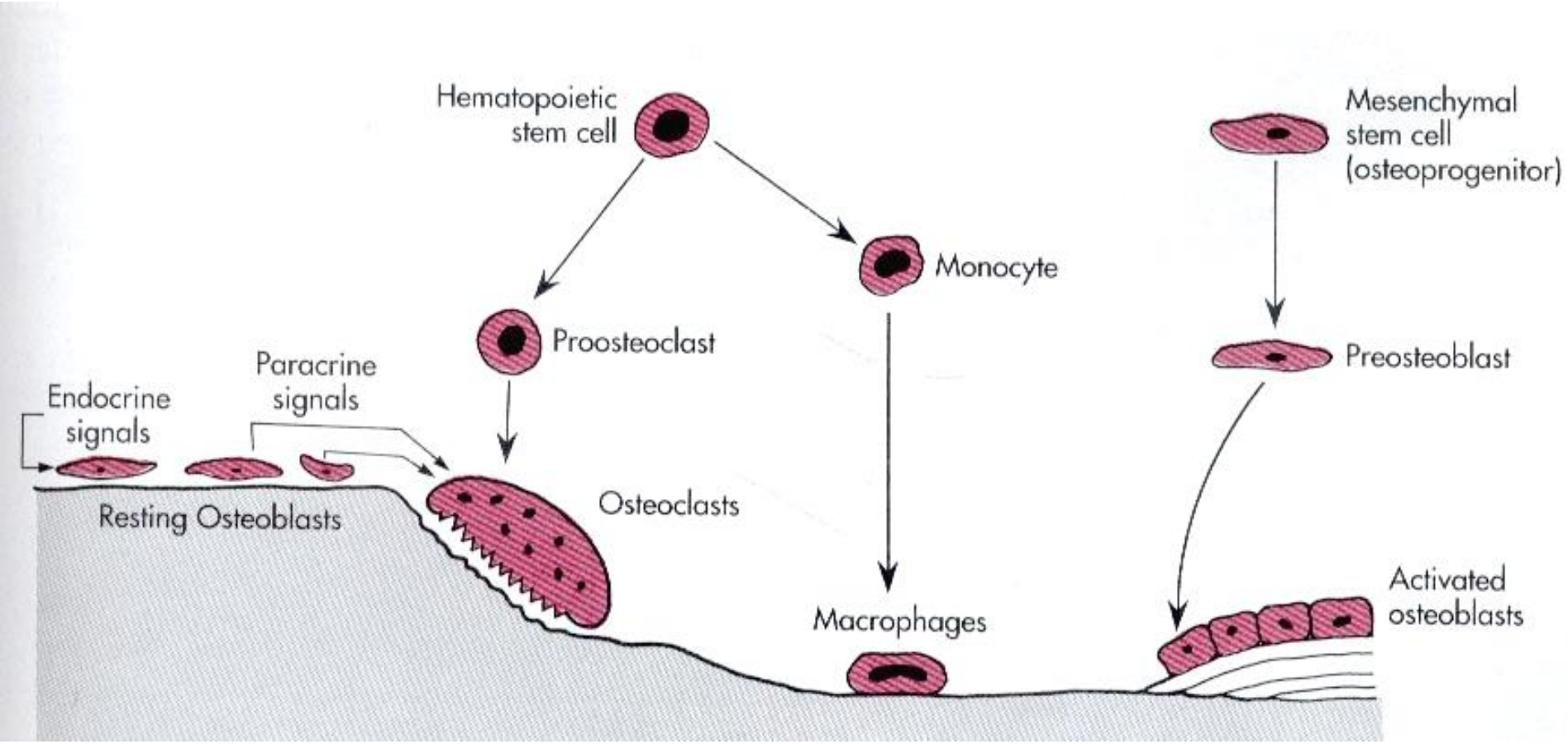
- Local macrophages clean up debris.

-Then **osteoblasts** are recruited to site & deposit new matrix which will be mineralized (Also,osteocytes which are osteoblast entrapped inside in bone matrix form a system of interconnected cells spread all inside bone)

-New bone replaces resorbed bone.

-Figure 79-5 •

Osteoclasts and Ca++ resorption



Bone remodling affected by;-

1-Mechanical stress on bone stimulates formation of stronger bone, athlets bone is stronger & heavier than non athlets

2- Parathyroid hormone (PTH) & 1,25 dihydroxycholecalciferol stimulates osteoclastic activity & formation of osteoclasts

3- Calcitonin inhibits activity& formation of osteoclasts

Osteoporosis :-

-Reduced bone density & mass

- diminished bone matrix (**not from poor calcification as in rickets or osteomalasia**)
-bone becomes weak & ca++ is lost from skeleton

-Susceptibility to fracture.

-Earlier in life for women than men due to increased resorption during pre-menopause .Why ?

-The rate of osteoclastic resorption exceeds deposition of new bone by osteoblastic activity

- Cause/1- loss of anabolic steroids as estrogen & testosterone which stim osteoblastic activity& decrease osteoclasts activity

2- lack of physical stress 3-old age & decreased growth H

4-malnutrition &vit C deficiency all reduce matrix& ostoid formation

Reduced risk by:

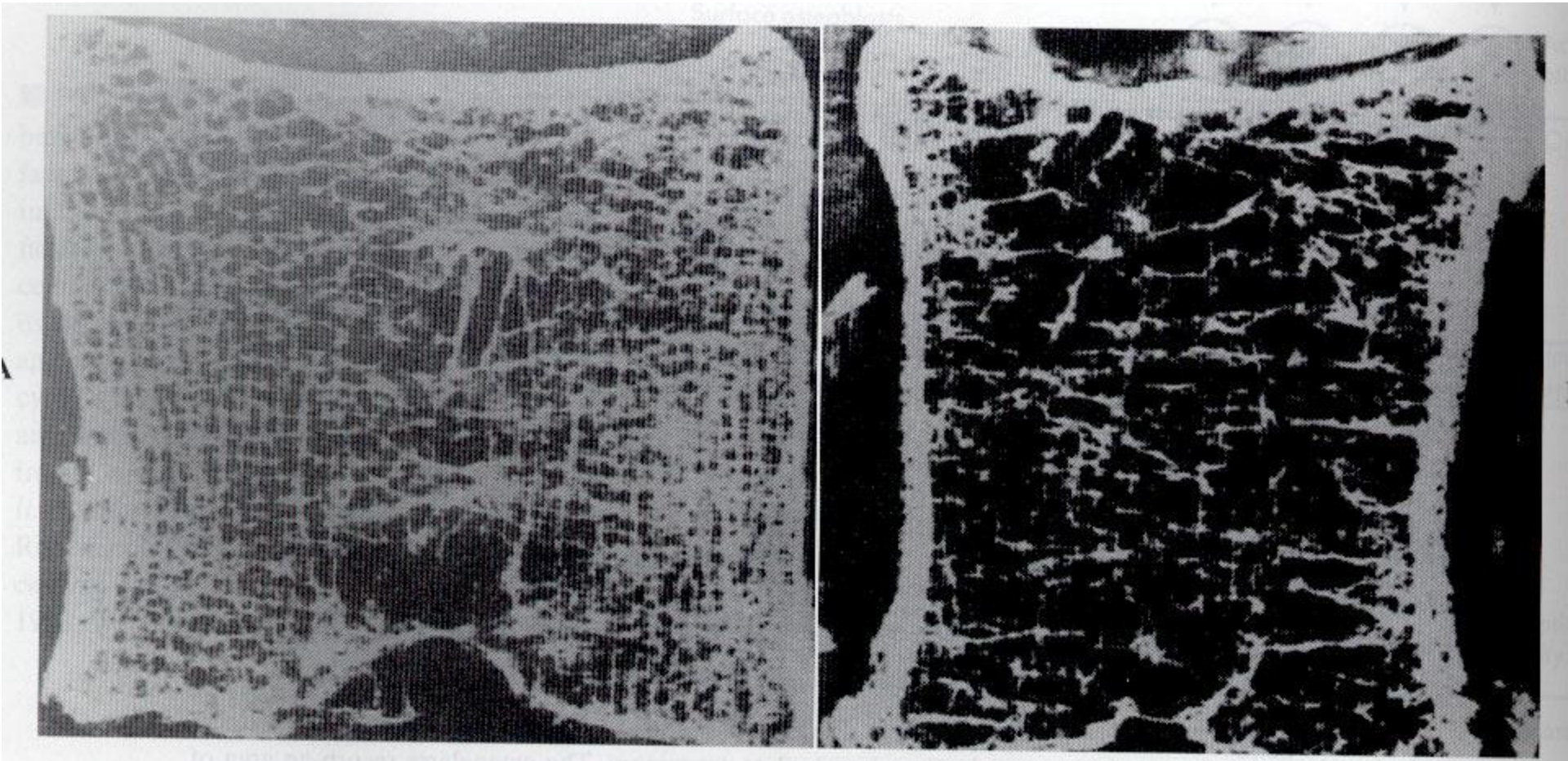
--High Calcium in the diet

--habitual exercise

--avoidance of smoking & alcohol intake & drinking carbonated soft drinks

Vertebrae of 40- vs. 92-year-old women

Note the marked loss of trabeculae with preservation of cortex.



Hormonal control of Calcium

1-Parathyroid hormone (PTH)
2- 1,25-dihydroxycholicalcefirol (active form of Vitamin D3)
(cholicalcefirol = Vitamin D3)
3- Calcitonin
- They regulate Ca^{++} resorption, absorption and excretion from the three organs that function in Ca^{++}homeostasis (bone, kidney and intestine).

Table 48-1 Major effects of various hormones on bone

Bone formation	*Bone resorption*
Stimulated by	**Stimulated by**
Growth hormone (constant)	Parathyroid hormone (constant)
Insulin-like growth factors	Vitamin D
Insulin	Cortisol
Estrogen	Thyroid hormone
Androgen	Prostaglandins
Vitamin D (mineralization)	Interleukin-1
Transforming growth factor-β	Interleukin-6
Skeletal growth factor	Tumor necrosis factor α
Bone-derived growth factor	Tumor necrosis factor β
Platelet-derived growth factor	
Calcitonin	
Parathyroid hormone (intermittent)	
Inhibited by	**Inhibited by**
Cortisol	Estrogen
	Androgen
	Calcitonin
	Transforming growth factor-β
	γ-Interferon
	Nitric oxide

Hormonal control of bones

-1-Vitamin D

-**Humans acquire vitamin D from two sources**.

-1-produced in the skin by ultraviolet radiation on cholesterol to form Vit D3(cholecalciferol) (exposure to sun ultravioletprevents vit D defeciency)

2- ingested in the diet-

-**In liver:**- Vit D3 converted to 25 hydroxycholecalciferol ,

in kidney :- Parathormone (PTH) convert it to **1,25 dihydroxycholecalciferol (active form)**

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--I f plasma Ca++ level is high formation of 1,25 dihydroxycholecalciferol (active form) is inhibited,

-so calcium absorbtion from intestine,bone,kidney is reduced

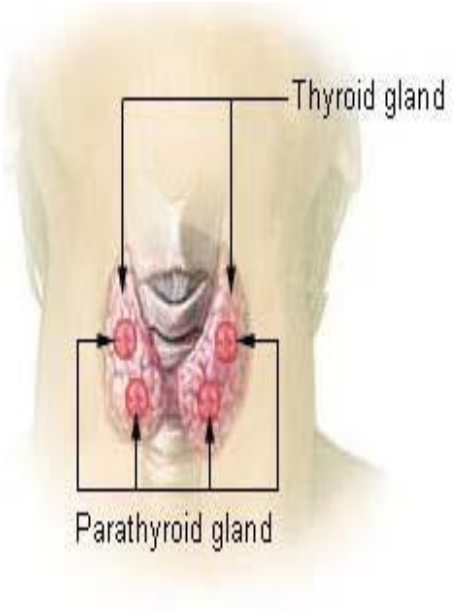
The main action of active Vitamin D (1,25 dihydroxycholecalciferol)

- stimulate absorption of Ca^{2+} & PO4 from the intestine (calbindin protein)
- stimulate Ca reabsorption in kidneys
- help in bone formation & absorption(large amounts of vit D cause bone absorpion, it increases calcium transport through cell membranes to outside bone , but in small amounts stimulates bone calcification as it increase calcium absorption from intestine & kidney also increases calcium transport through cell membranes to inside bone to osteoblast & osteocyte membranes

- Mobilize ca++ from bone into plasma by increasing number of osteoclasts to increase plasma Ca^{++} levels (only when it drops

2-Parathyroid Hormone (PTH)

Parathormone from parathyroid gland



Functions:-

- increase plasma Ca^{++} levels when it drops and decrease plasma phosphate levels by:

1- acts directly on the bones to stimulate Ca^{++} absorption from bone & bone resorption by activating osteoclasts

2- on kidney to stimulate Ca++ reabsorption in the distal tubule & prevents its execretion & inhibit reabosorption of phosphate (thereby stimulating its excretion).

3- acts indirectly on kidney by activation of 25-(OH)-D into $1,25\text{-}(OH)_2\text{-}D$ (active vit D)

4-on intestine to stimulate Ca++ reabsorption

3-Calcitonin

-Calcitonin is synthesized and secreted by the parafollicular cells of the thyroid gland (C cells)

-Calcitonin acts to decrease plasma Ca^{++} levels.

-Stimulated by a rise in plasma Ca^{++} levels

- suppresses osteoclastic activity(osteocytic osteolysis) and number in bone

-decrease formation of new osteoclasts

-it increases osteoblastic activity to mineralize bone

(over long period decreased osteoclasts activity are followed with decreased number of osteoblasts & little effect on bone)