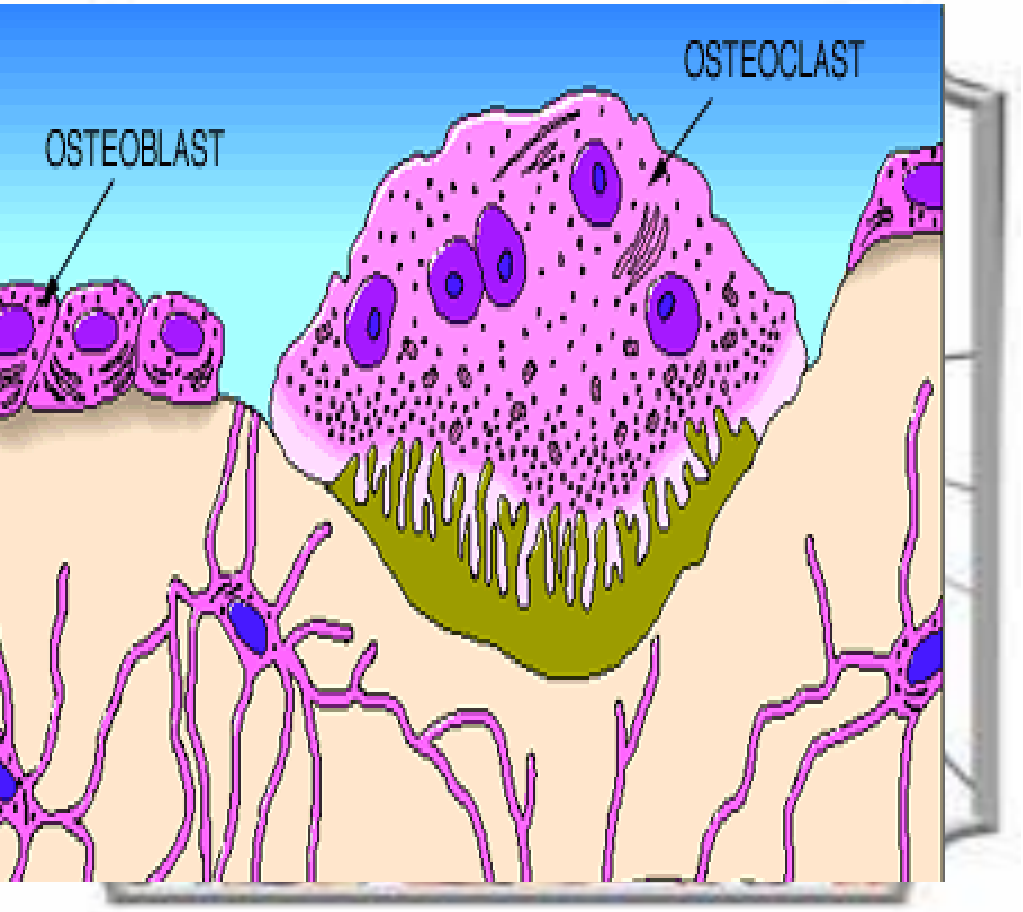
Physiology of Bone



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Lecture1:- Bone physiology (Referece book –Gyton &Hall 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

- Appreciate effect of different hormones on bone physiology

- Define osteoporosis

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 formed of:-

A-Cells

B-Bone matrix

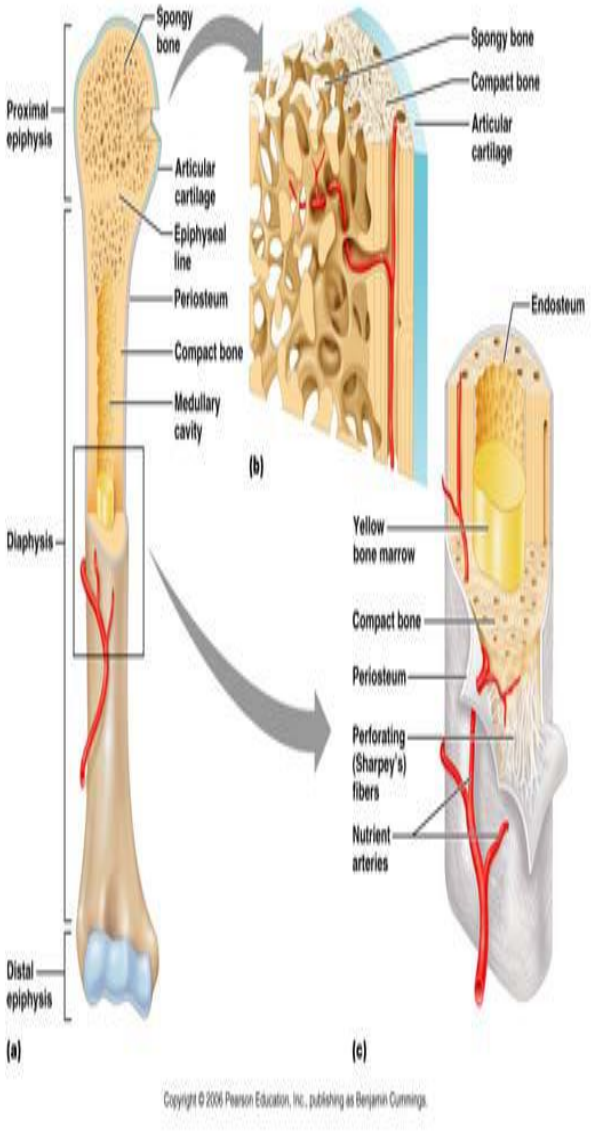
-Calcified material (**mainly deposits of calcium & phophates salts, also magnesium ,potassium &carbonate**)

- 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:

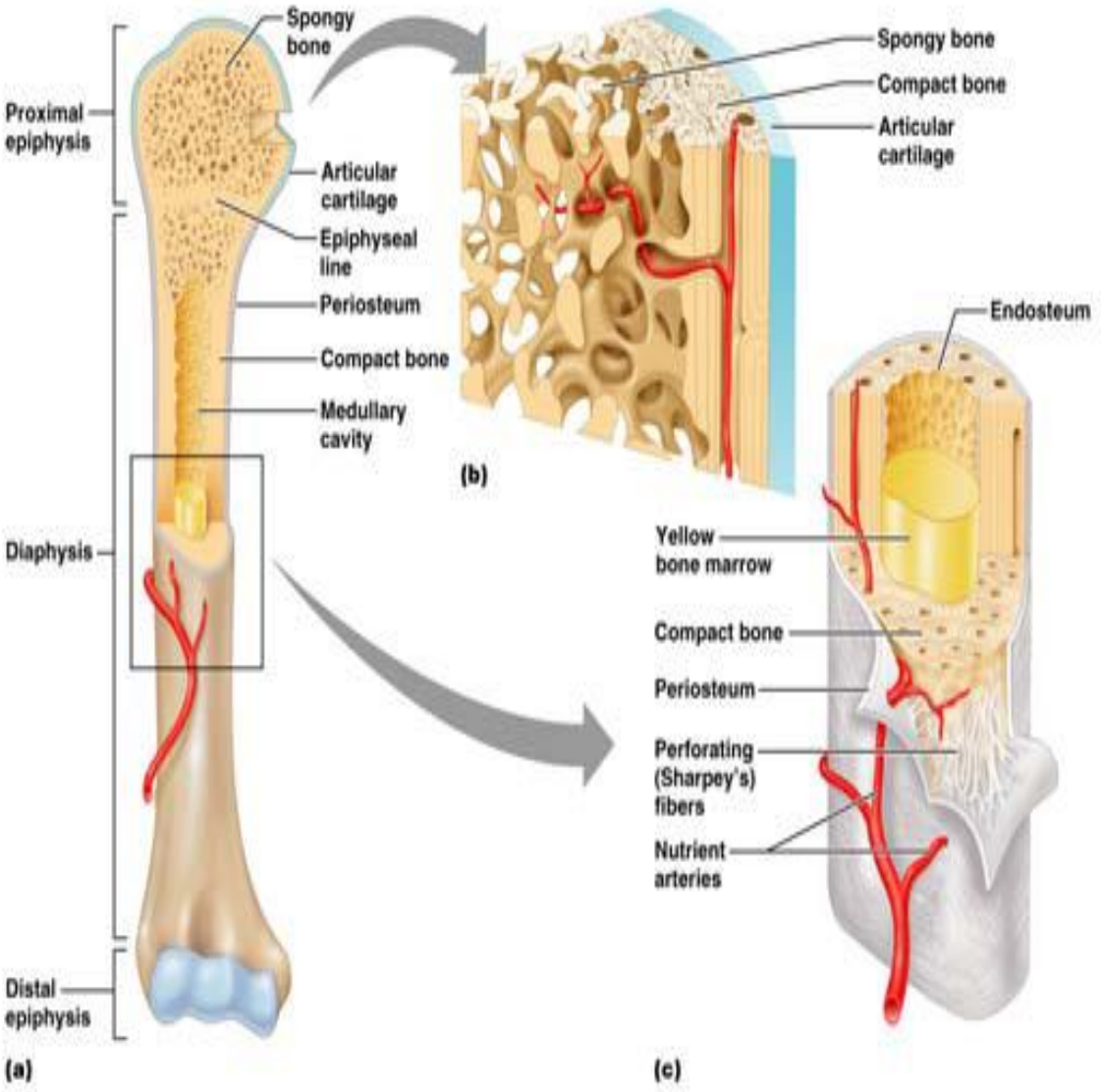
(1) **Cortical bone (compact bone)** → 80 %

- Constitutes the dense concentric layers of long bones (diaphysis)
- Also outer layer surround trabecular bone at ends of long bones

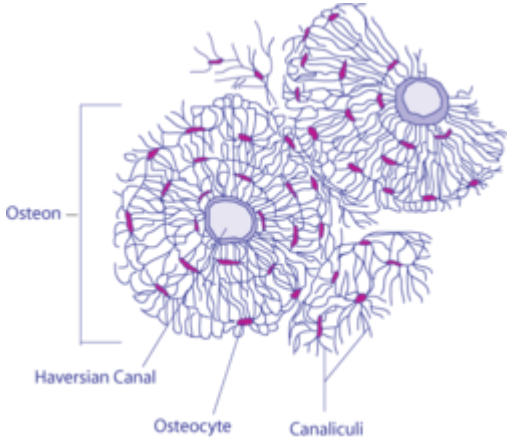
(2) **Trabecular bone (Cancellous = spongy)** → 20%

-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

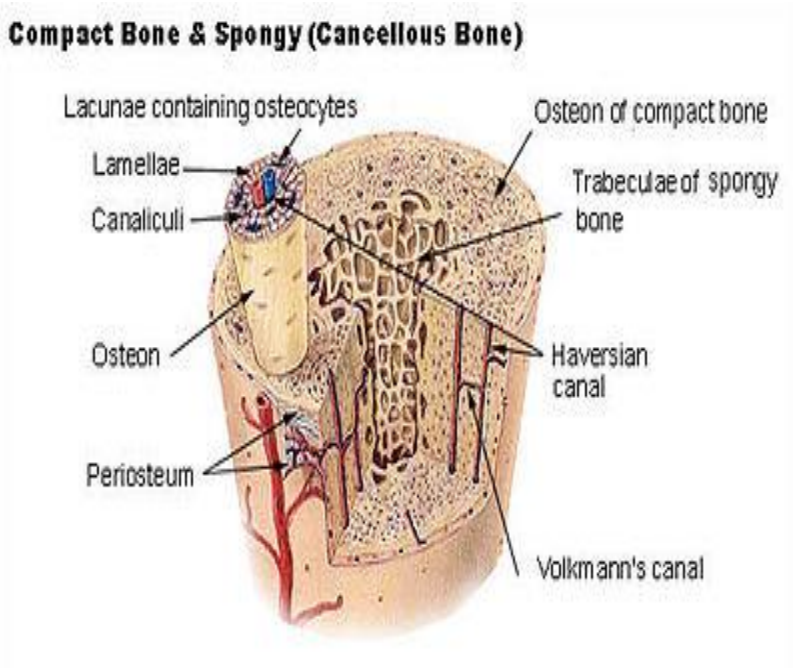


-Forms a protective outer shell of bone around spongy bone in the body & diaphysis of long bones

-has a slow ca ++ turnover rate

-Has high resistance to bending so presents where bending would be undesirable as in the middle of long bones.)

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



Osteon is composed of a central vascular channel called the Harvesian canal, surrounded by concentri lamellae of mineralized bone

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

Trabecular (spongy-Cancellous) Bone

-Rigid but appears spongy.

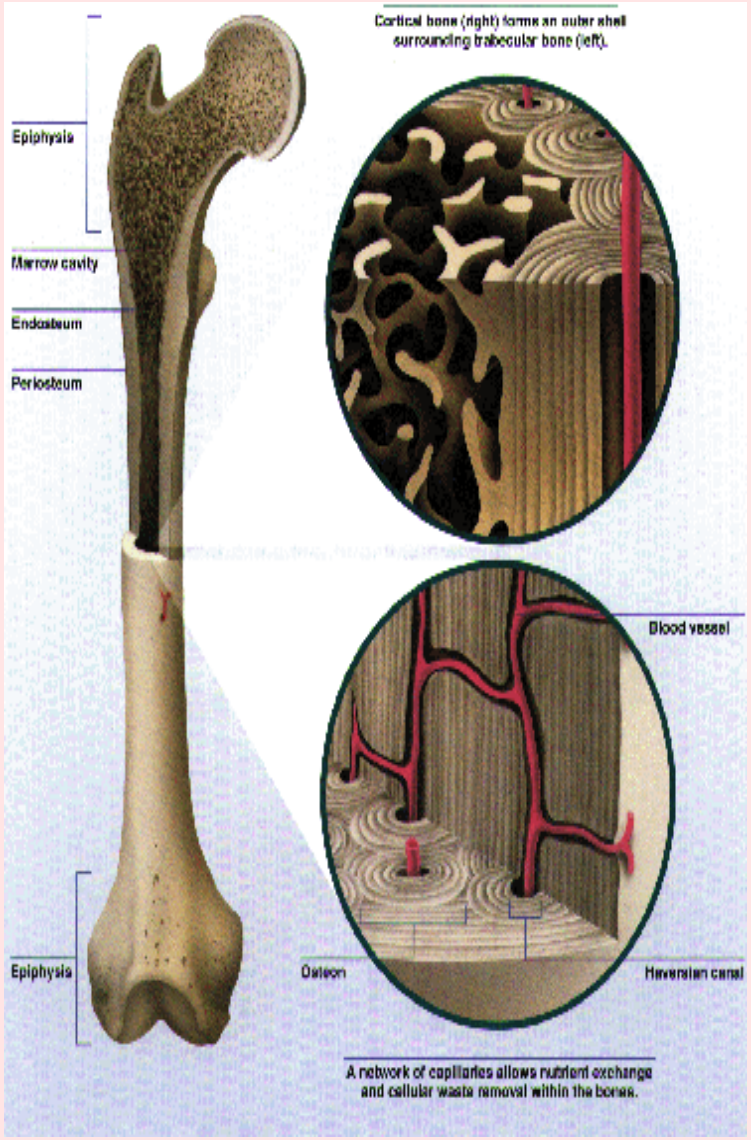
Compared to cortical bone it is:

(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 the following 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 10% 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.

Ca++ x PO4 = constant (solubility product)

-if any one increase it should precipitate in bone مترسب

-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**.

Bone & Ca++

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

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

- Calcium salts in bone provide structural integrity of the skeleton

- 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:-

–Linear Growth occurs at epiphyseal plates.المشاشي

-Increase in width occurs at periosteum
غشاء العظم

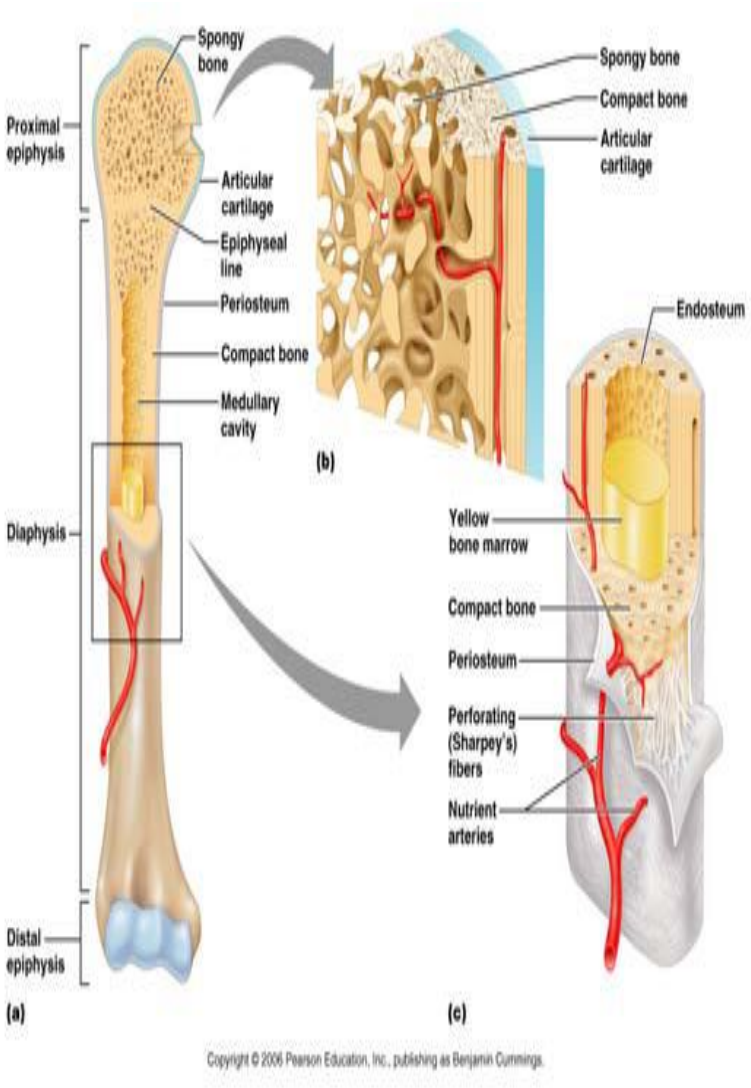
-During growth , bone mass increases and bone formation exceeds Resorption
امتصاص

.

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

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:

1- 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 precipitate) يترسب

(2) Osteocytes :

Mature bone cell derived from osteoblasts enclosed in bone matrix.

- Its function is transfer of calcium from bone canaliculi to the ECF

(3) Osteoclast :

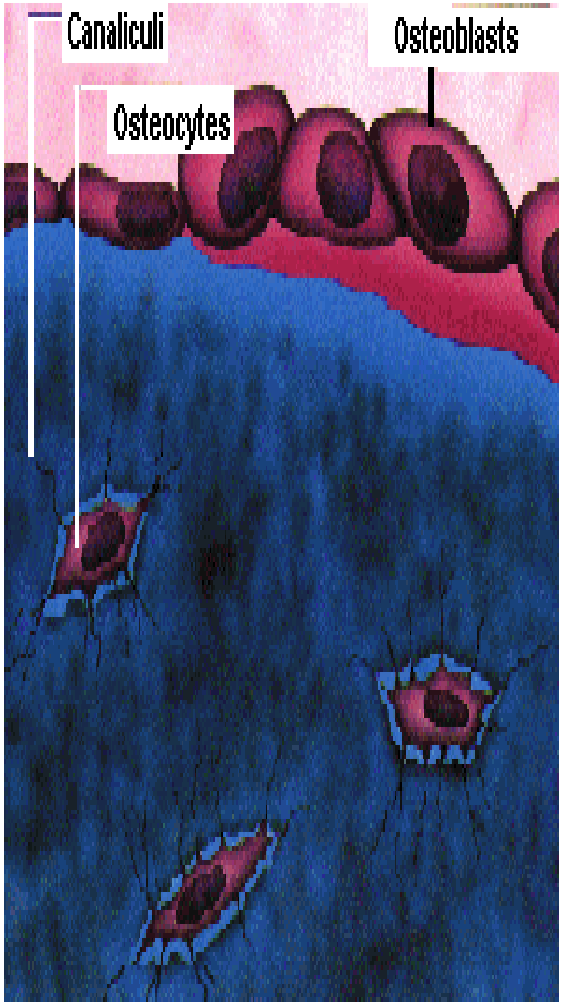
large phagocytic multinucleated cell derived from monocytes ,its activity controlled by Parathormone hormone

-function is to resorb the formed bone.

They secrete:_

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

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



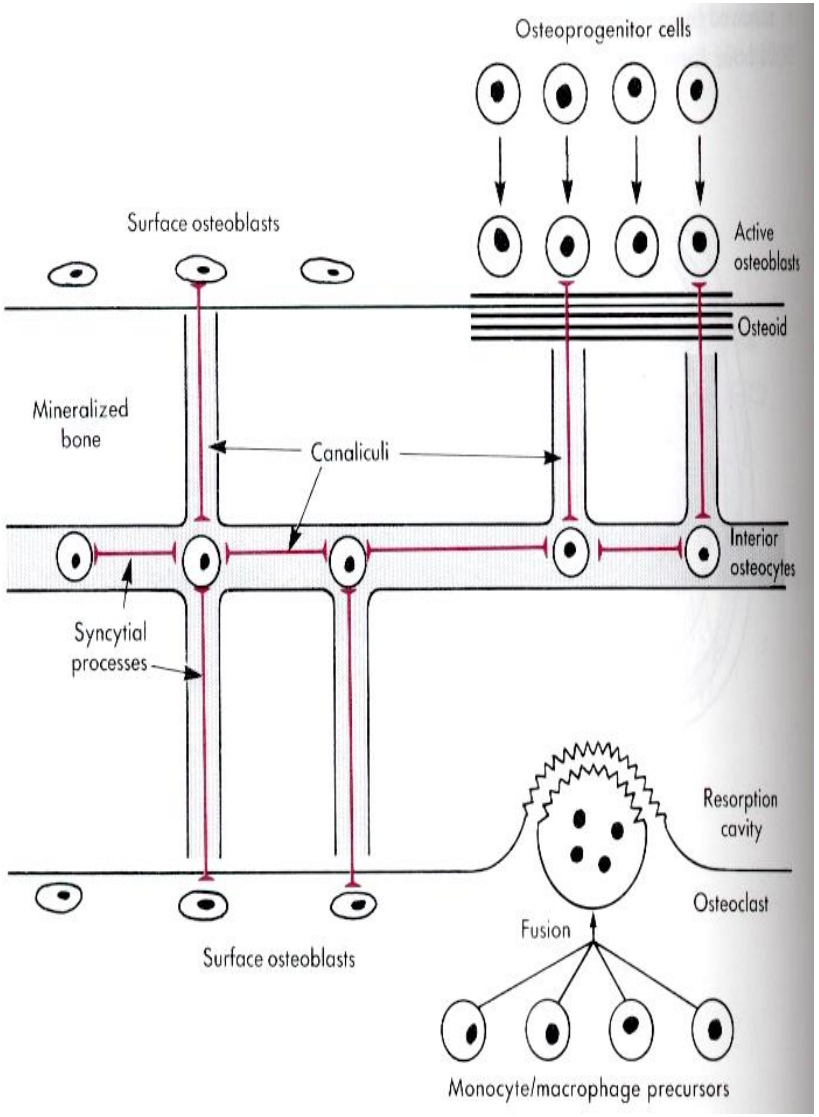
Canaliculi

- Inside mineralized bone are 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 fibrils to form (raws) of an organic matrix called **Osteoid**.صفائف

(some of **osteoblasts become entrapped in it & become quiescent now are called osteocytes**)

2- Then **Mineralization** occurs (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 inhibit bone resorption , it stimulates OPG factor(osteoprotegrin) that inhibit formation of mature osteoclasts

1-Osteocytic Resorption (osteolysis)

- by osteocytes.

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

-Does not decrease bone mass

- reduce calcium & Po4

-Removes calcium from recently formed crystals

- Quick & transient process begins in minutes.

(2) **Osteoclasitc resorption :-**

-

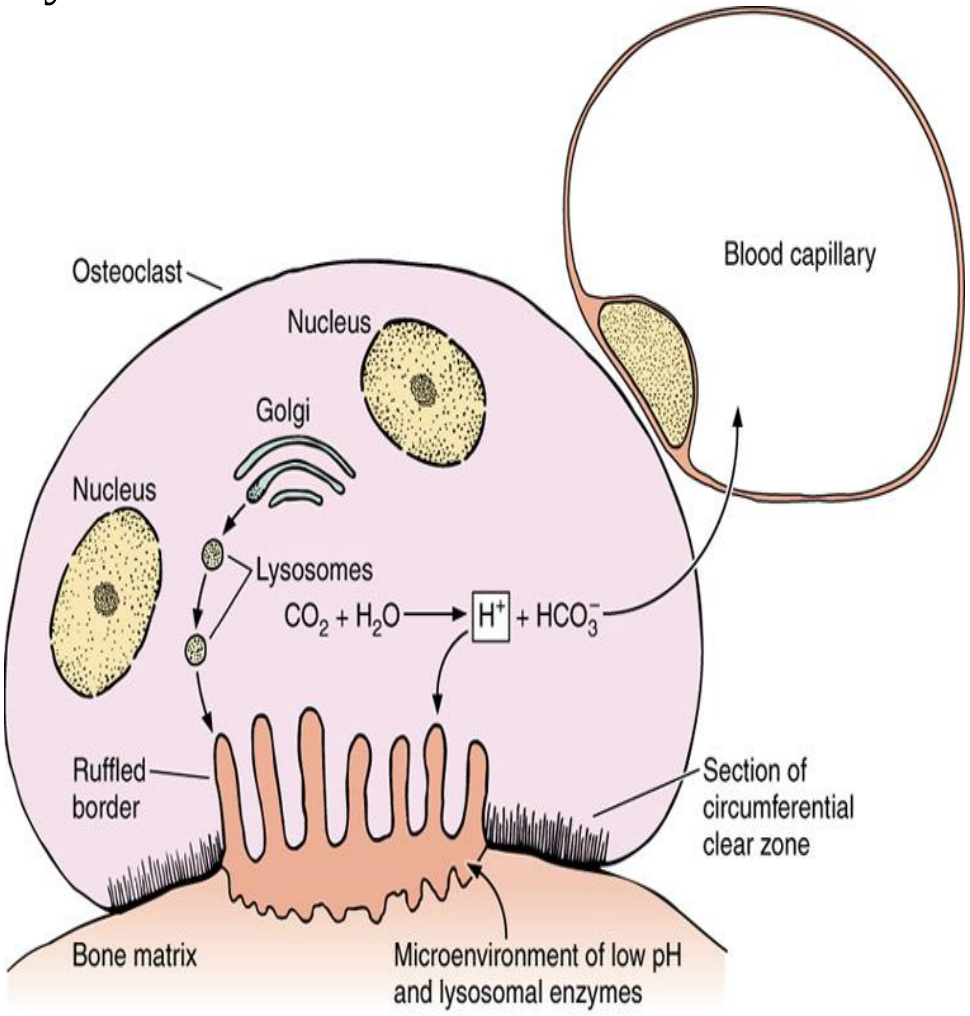
-Slow and sustained needs several days or weeks .

- destroys matrix of old bone

- diminishes bone mass & but 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 new bone by osteoblasts & absorption of old bone by osteoclasts

-it maintain normal toughness of bone.

Mechanism:- -

-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)

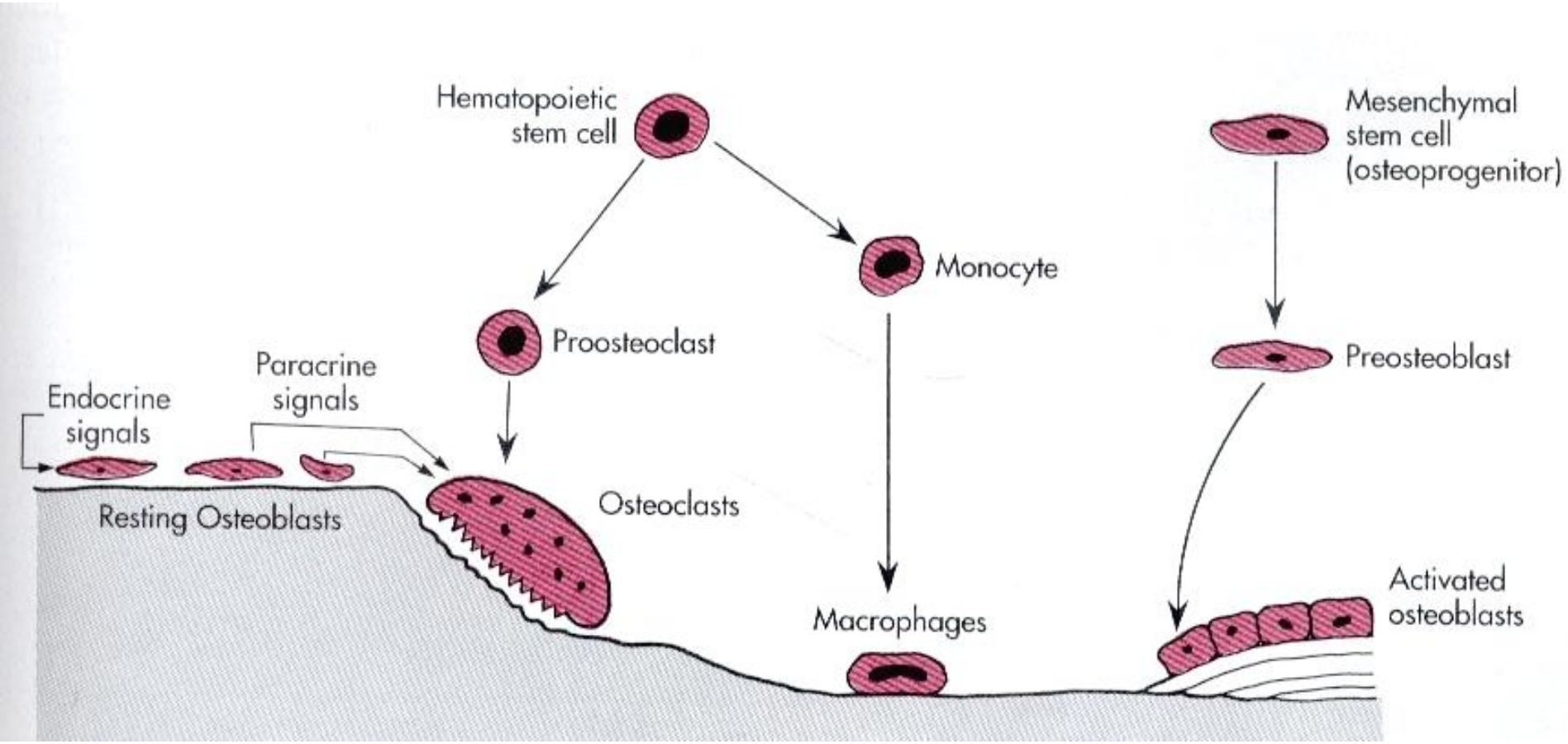
- Local macrophages clean up debris.

-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)

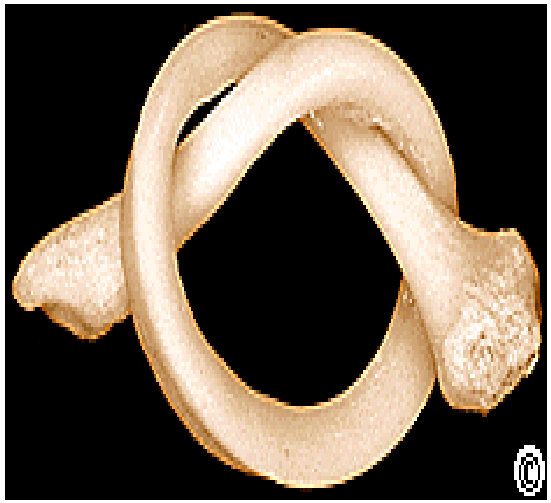
-New bone replaces resorbed bone.

-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

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 ultraviolet prevents 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)

-If 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)

- stimulates absorption of Ca^{2+} & PO4 from the intestine (calbindin protein)
- stimulates Ca reabsorption in kidneys
-Helps in bone formation & absorption

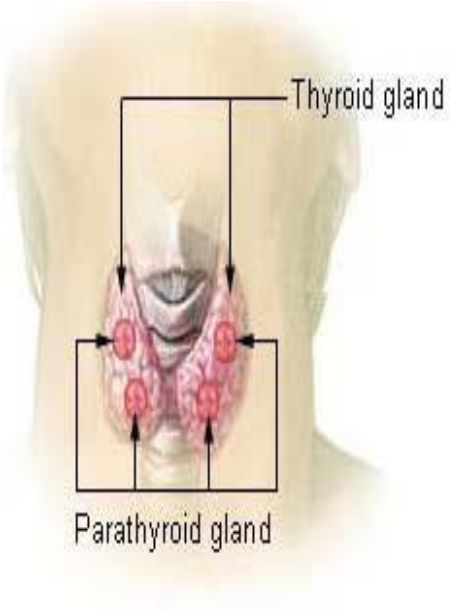
In bone resorption:-

- large amounts of vit D cause bone absorpion, it increases calcium transport to outside bone .
- -Mobilize ca++ from bone into plasma by increasing number of osteoclasts to increase plasma Ca^{++} levels (only when it drops)

- - In small amounts stimulates bone calcification as it increase calcium absorption from intestine & kidney also increases calcium transport to inside bone to through osteoblast & osteocyte membranes

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-$(OH)_2$-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

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.