I Physiology of bone

- Very important
- Extra information
- Terms

{وَانْظُر إِلَى الْعِظَامِ كَيْفَ نُنْشِزُهَا ثُمَّ نَكْسُوهَا لَحماً} [سورة البقرة: ٢٥٩]

* We recommended you to study CARTILAGE & BONE histology lecture first.

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Objectives

- Define bone & differentiate between types of bone (cortical & trabecular).
- State Ca^{++} concentration and its forms in the ECF and its relation to PO_4.
- Differentiate between the types of bone cells & appreciate their functions.
- Differentiate bone cells &function of each
- Describe bone formation & remodelling.
- Understand what is osteoporosis.
- Appreciate the effects of different hormones on bone.
- Define osteoporosis.

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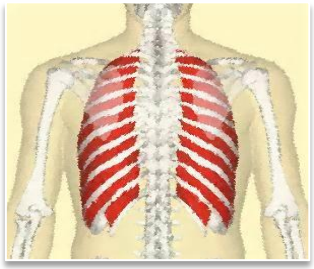
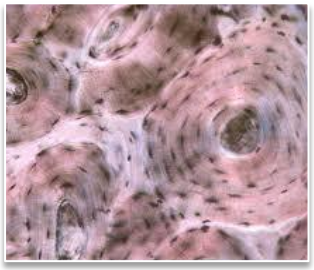
Functions of bones

Bone is a living growing tissue which has several functions :

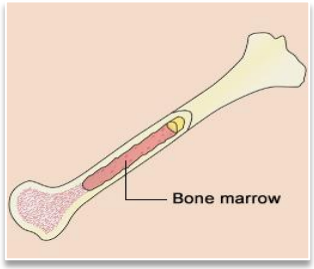


Protects vital organs (cranium, thoracic cavity)

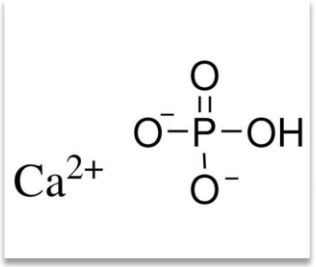


Support soft tissues

Allows & facilitates movement



Contains bone marrow for blood cells synthesis



Reservoir for calcium&phosphate

maintain constant concentrations of them in body fluids

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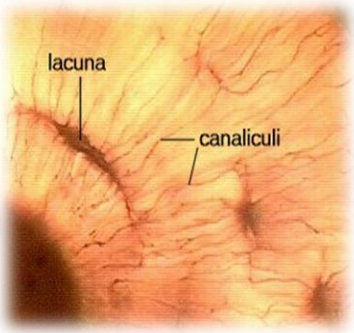
Structure of bone

Porous mineralized structure formed of :

- **Cells**
- **Bone Matrix**
  - **Calcified material** "mainly deposits of calcium and phosphate salts, magnesium ,potassium and carbonate".
  - Called **osteoid**, makes **30%** of a bone.
  - Made of **collagen fibers**.
  - **Lacunae** " Unfilled space"
  - **Canaliculi** " Micro-canals"
- **Red or yellow bone marrow**
  " In the **center** of bone"
- **Periosteum**
  "covers the outer surface of all bones except at the joints of long bones"
- **Endosteum**
  "lines the inner surface of all bones"



lacunae & canaliculi عبارة عن فتحات صغيرة تشبه القنوات موجودة داخل العظم لتنقل السوائل ومنها نستنتج أن العظام ليست مصمتة.

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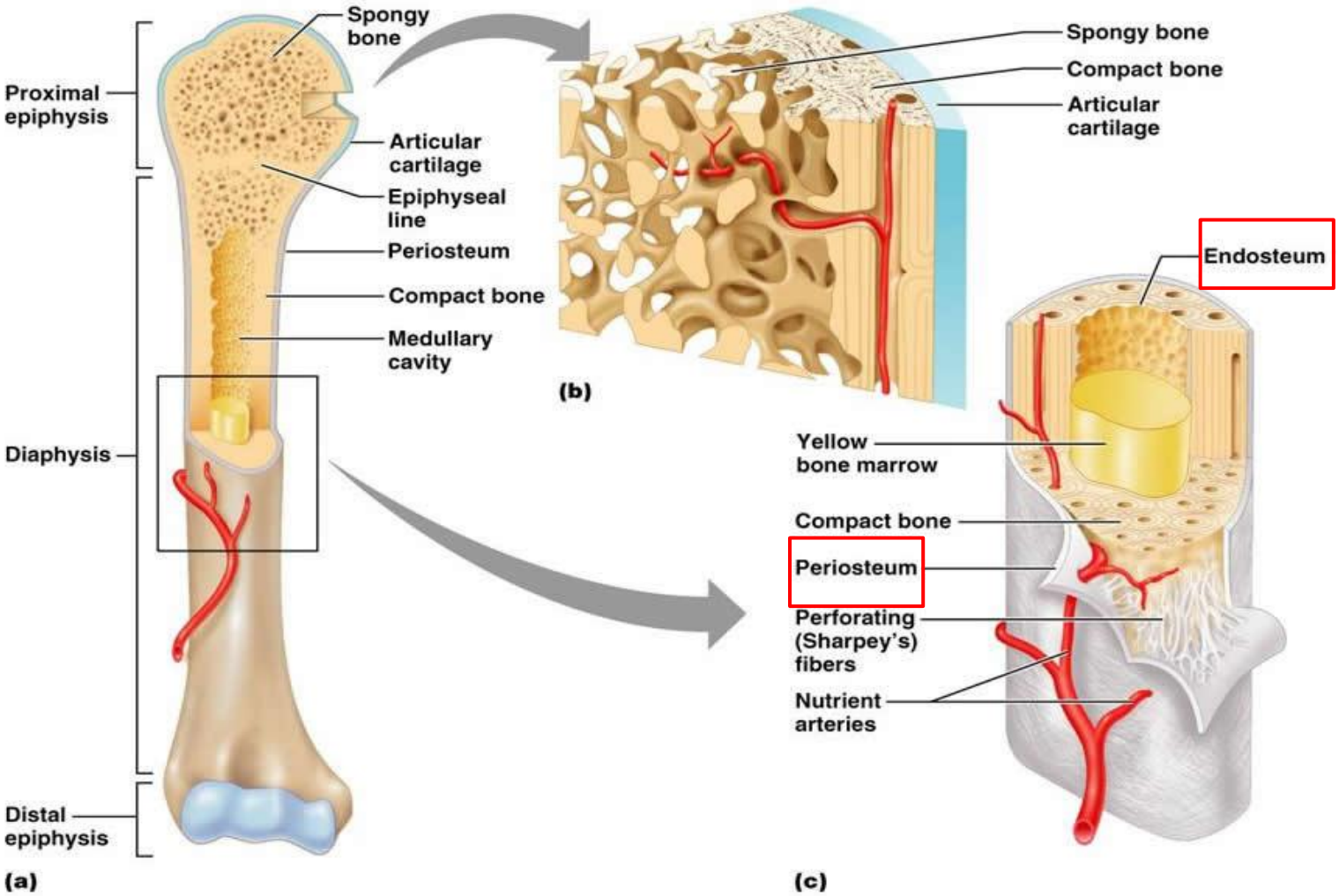
Structure of bone



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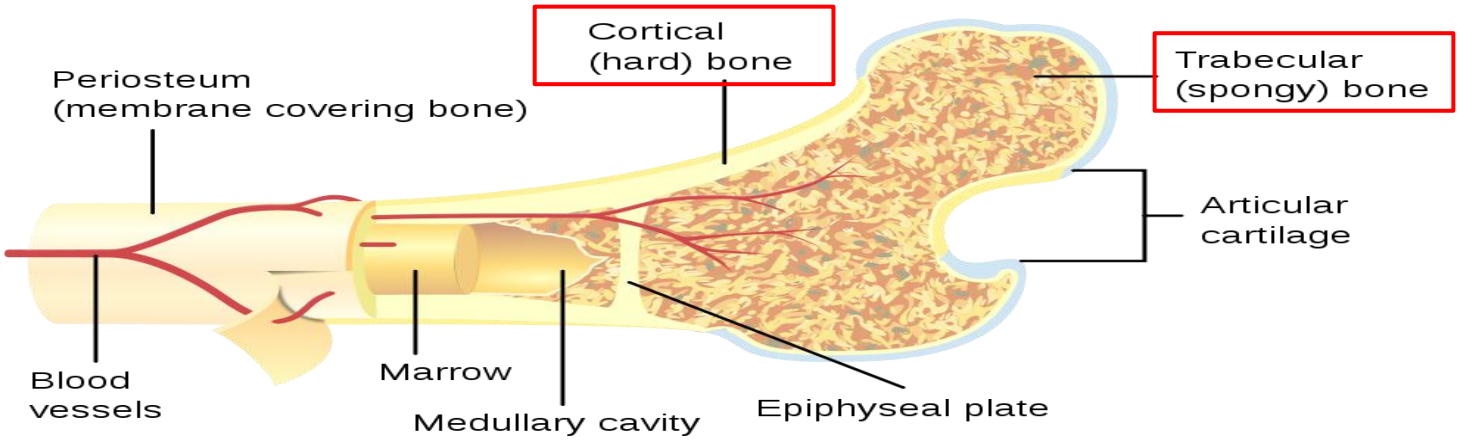
Types of bones

- **Trabecular bone** "spongy bone"
- **Cortical bone** "compact bone"



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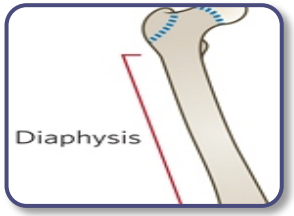
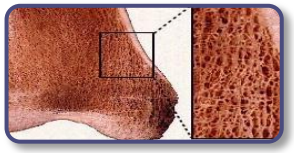
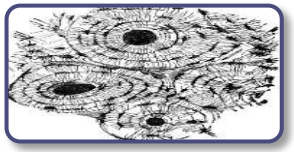
cortical (compact) bone



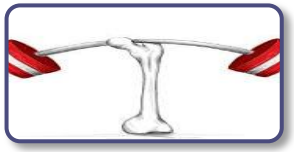
It forms a protective outer shell around spongy bone in the body" outer layer surround trabecular bone at ends of long bones" & Constitutes the dense concentric layers of long bones (diaphysis) (Diaphysis = shaft)



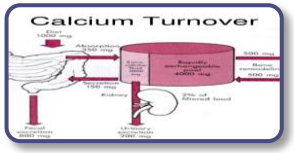
Comprises 80% of total body bone mass.



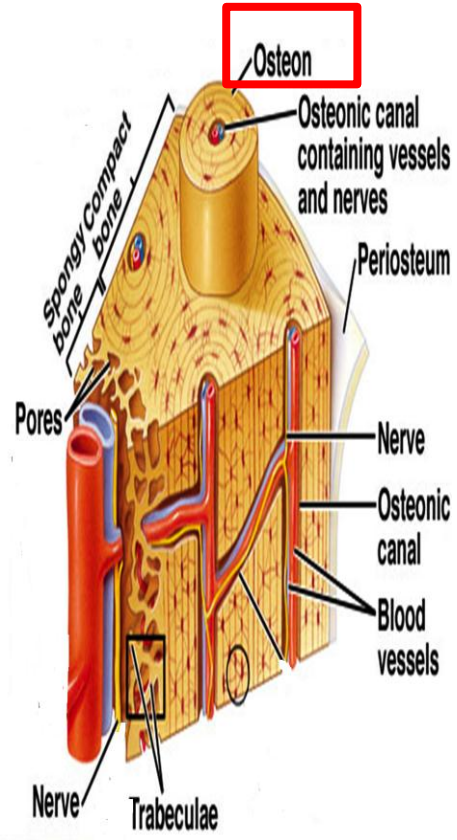
Contain a series of adjacent bull's eye called osteons or Harvesian systems.



Has high resistance to bending & torsion, so presents where bending would be undesirable as in the middle of long bones.



Has a slower calcium turnover rate



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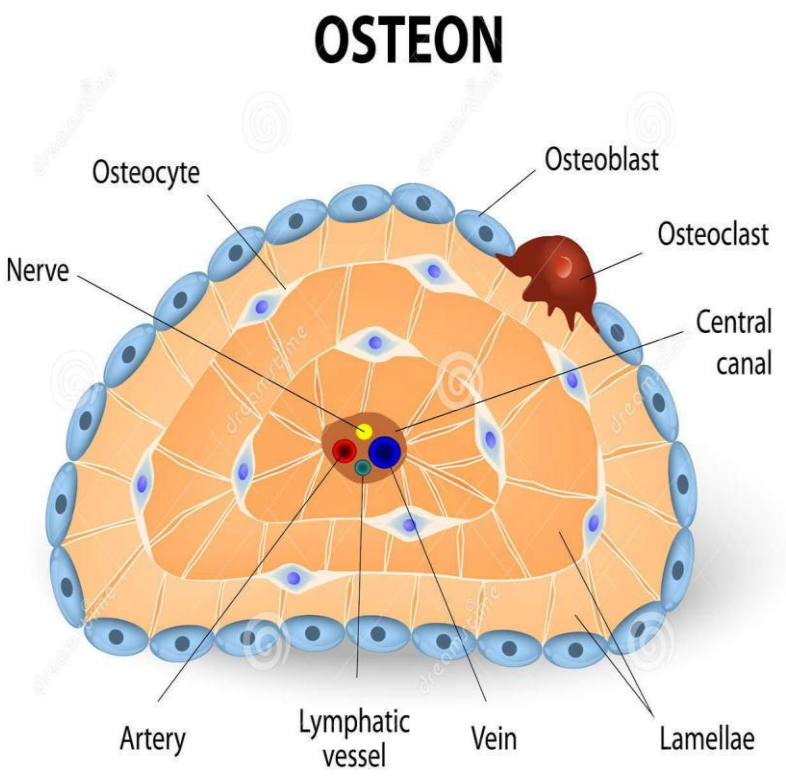
Osteon system

Compact bone is composed of overlapping circular structures called **haversian system** or **osteons**.

Each osteon has a central vascular canal called **osteonic canal** or **haversian canal**.

Osteonic canal contain blood vessels (capillaries, venules, arterioles), nerves, lymphatics.

Between haversian systems are concentric layers of mineralized bone called **interstitial lamellae**.



Osteon systems are found only in compact bone.

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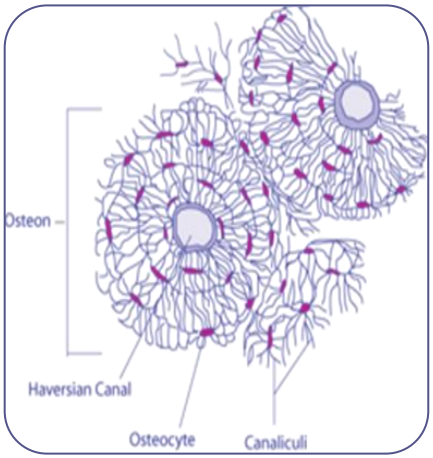
Extra Notes

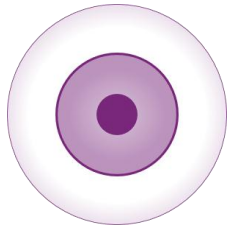
"compact bone"



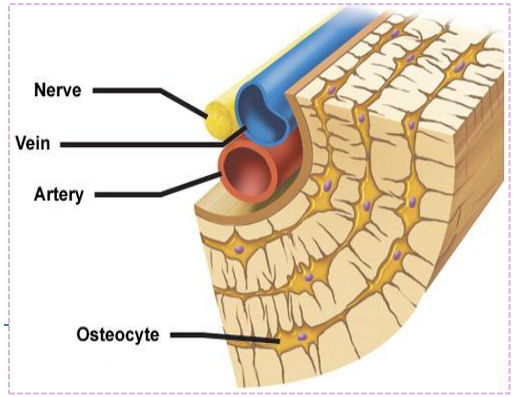
Osteons

onion

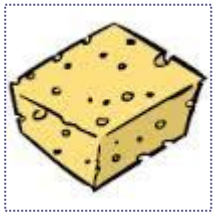
bull's eye



- Cortical = cortex = قشرة خارجية
- Osteons resemble : cow's eye .
- Concentric lamellae "onion-like" = صفائح متحدة المركز
- Hervesian system has central canal " hervesian canal" that consist of blood vessels, nerves, venules and arteries.



Trabecular (spongy-Cancellous) bone



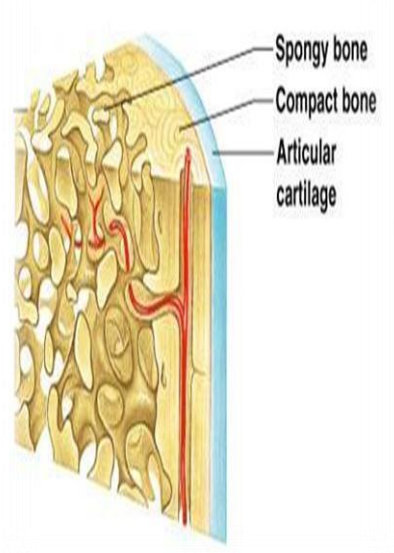
Rigid but appears spongy

Comprises 20% of total bone mass

Cancellous = porous = مسامي

The center of the bone contains red and yellow marrow, bone cells and other tissues.

Present in the interior of bones



Compared to cortical bone, it is :

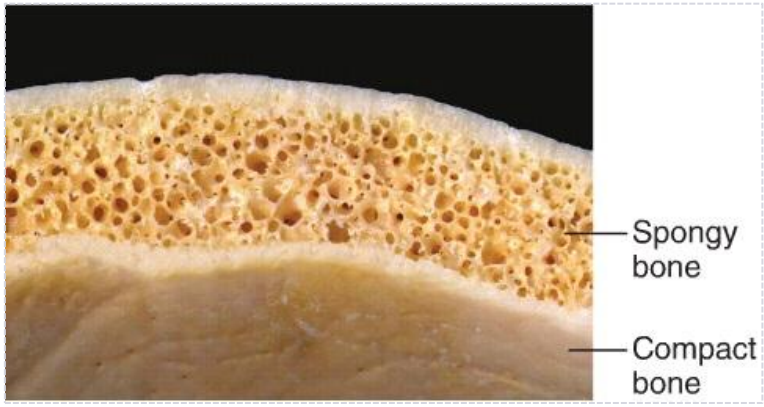
- Less dense.
- More elastic.
- it has high calcium turnover rate because of the greater surface area.

(It has 5 times greater surface area than cortical bone. Due to its large surface " 80% of the bone surface area").

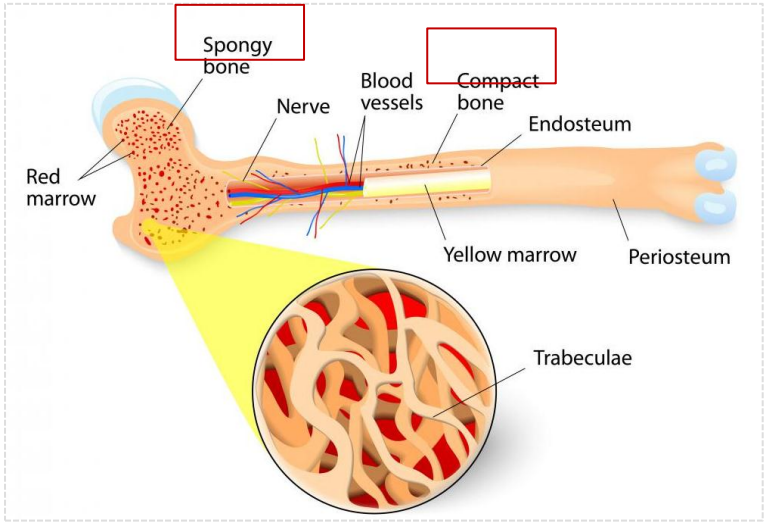
مفارقة بسيطة : الـ compact boneتشكل ٨٠% من عظام الجسم ولكن الـ spongy bone
تشكل ٨٠% من مساحة العظم المتواجدة به لأنه غالباً يكون في الـ flat bones مما يعطيها مساحة سطح كبيرة

Comparison

Compact bone	Trabecular bone
▪ Comprises **80%** of total body bone mass.	▪ Comprises **20%** of total body bone mass.
▪ Exist in **diaphysis of long bones (shaft)** and surround spongy bone.	▪ Exist only **interior of bones.** (skull, ribs, vertebrae, pelvis) in long bones present only in **epipheseal** and **metaphysal** regions.
▪ Small surface area	▪ **Large** surface area.
▪ Has a **slower** calcium turnover rate	▪ it has **high** calcium turnover rate.
▪ Contain **osteons or Harvesian systems.**	▪ **NO** osteons.



Compact bone surrounds spongy bone



Calcium homeostasis

1. Extracellular fluid Calcium :

Normal range

Normal Ca^{2+} level in plasma ranges from 8.5-10 mg/dl (mean 9.4 mg/dl).

Albumin & globulin are plasma proteins
ECF calcium : الكالسيوم المتواجد في الدم وحول الخلايا

It exists in 3 fractions:

1- Ionized calcium 50%	2- Protein bound 40%	3- Bound to serum constituents 10%
• Diffusible through capillary membrane. • Only biologically active , produce all Ca++ functions on heart & nervous system .	• 90% bound to albumin. • Remainder 10% bound to globulins. • Non- diffusible through capillary membrane	• Diffusible • Non- ionized • Bound to citrate & phosphate

Calcium homeostasis

- **Alkalosis increases calcium binding to protein and decreases ionized calcium.**

شرح إضافي : يعتمد على الـ PHلو كان "Alkalosis" Alkaline بالتالي سيزداد ارتباط الكالسيوم مع البروتين ويقلل الـ Ionized form، أي أنه كلما مال الـ PH للقلوية كلما قل الـ Ionized form >يقل الكالسيوم المسموح له بالدخول إلى الخلايا مما قد يسبب : spasm of muscles

What are Ca++ functions?

1) Contraction of muscles.
2) Formation of bones.
3) Blood coagulation.

"No calcium = No blood coagulation"

4) Transmission of nerve impulses.

What is effect of hypo and hypercalcemia on central nervous system?

Hypocalcemia : cause the nervous system to become more excited.

Hypercalcemia : cause progressive depression of the nervous system.

سؤال نبهت عليه د.فاتن

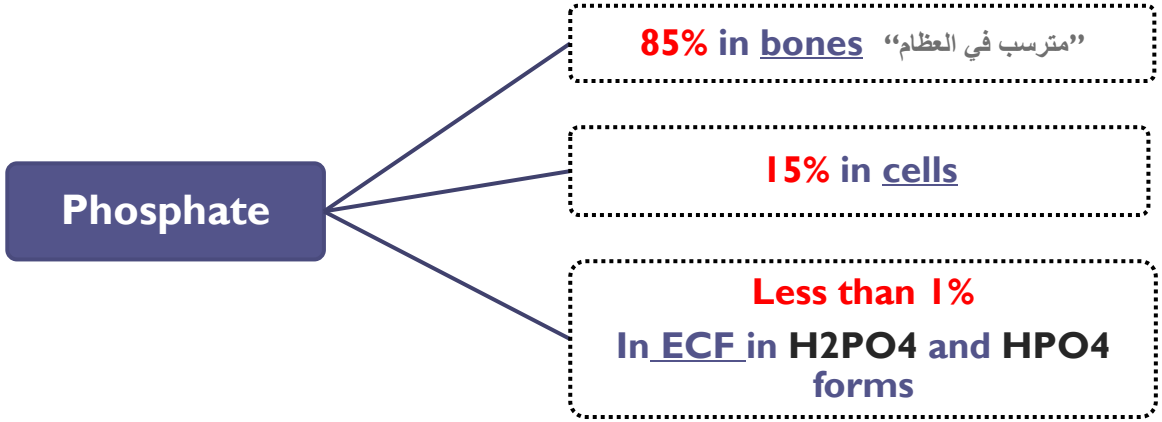
Calcium homeostasis

2. Phosphate (PO4):

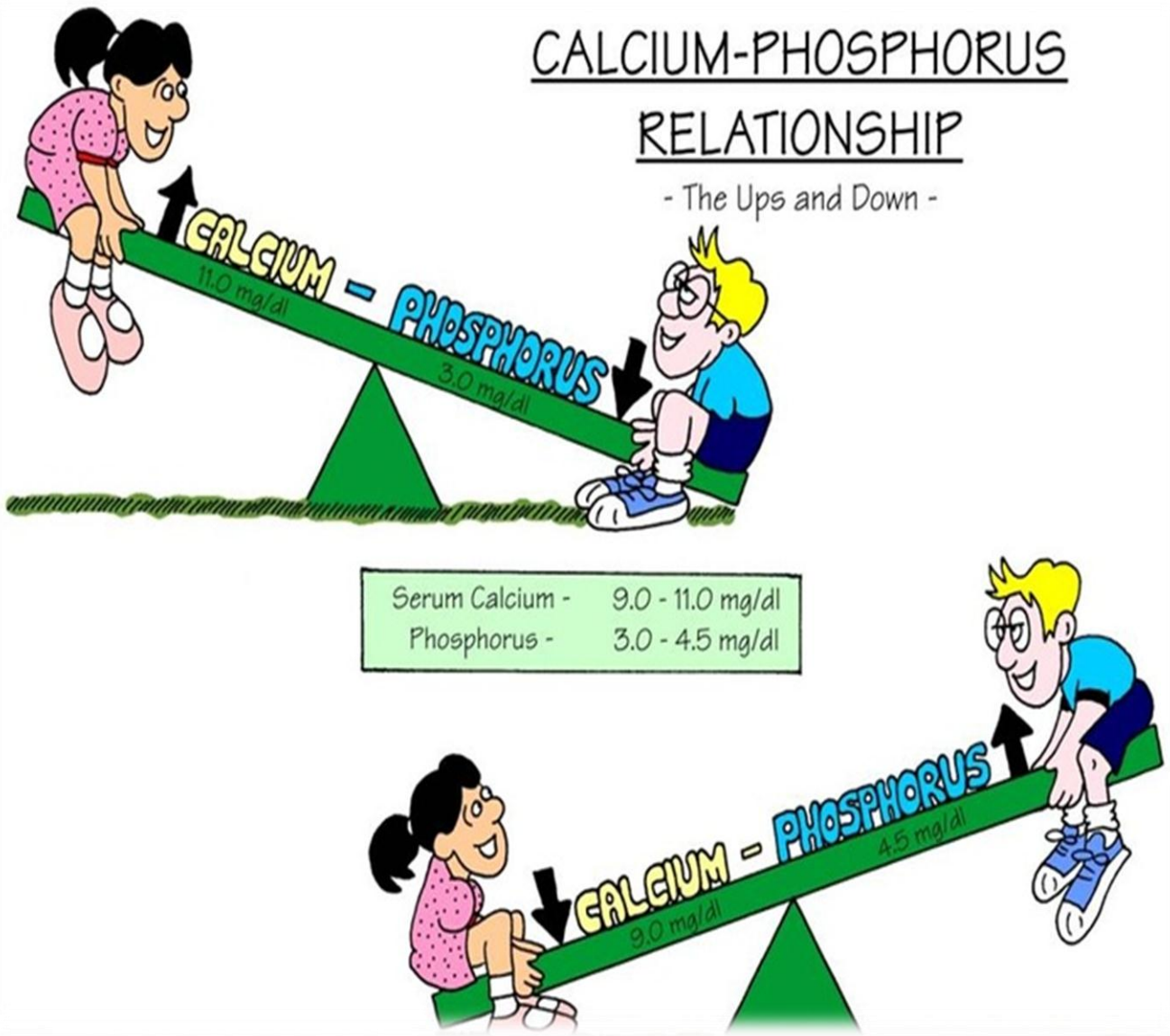
- Calcium is tightly regulated with Phosphorous in the body."العلاقة بين الكالسيوم والفوسفات علاقة عكسية"

Ca++ x PO4 = constant (solubility product)

- If any one increase it should participate in bone.
- Normal plasma concentration is **3-4.5 mg/dl.**



H2PO4 : Di-hydroxy-phosphate / HPO4: mono-hydroxy-phosphate.



Calcium and phosphate in the body react in opposite ways : as blood calcium levels rise, phosphate levels fall and vice versa.

Bone and calcium

- About 99% of Ca of our body is in bone.
- 70% of Bone is formed of calcium in the form of :

  1)Hydroxyapatite crystal.
  2) phosphate salts ($CaP0_4$ and hydroxide).

- Calcium salts in bone provide structural integrity of the skeleton.
- Exchangeable calcium of bone :

- Only (0.4 – 1% of total bone Ca++).

"النسبة ضئيلة لأن صلابة العظم ستقل لو حدث العكس وأصبحت النسبة كبيرة"

- Has rapid buffering mechanisms, to keep ECF Ca++ levels constant if ECF Ca++ falls below normal, this Ca++ will move from bone into ECF.

في حالة نقص الكالسيوم، الجسم يمتص كالسيوم من العظام وينقله إلى الـECF للموازنة والتعويض.
وفي حال أن الكالسيوم ارتفع في الـECF يتوجه إلى العظام ويترسب بها .

Hydroxyapatite:
A major component and an essential ingredient of normal bone and teeth. Hydroxyapatite makes up bone mineral and the matrix of teeth. It is hydroxyapatite that gives bones and teeth their rigidity.

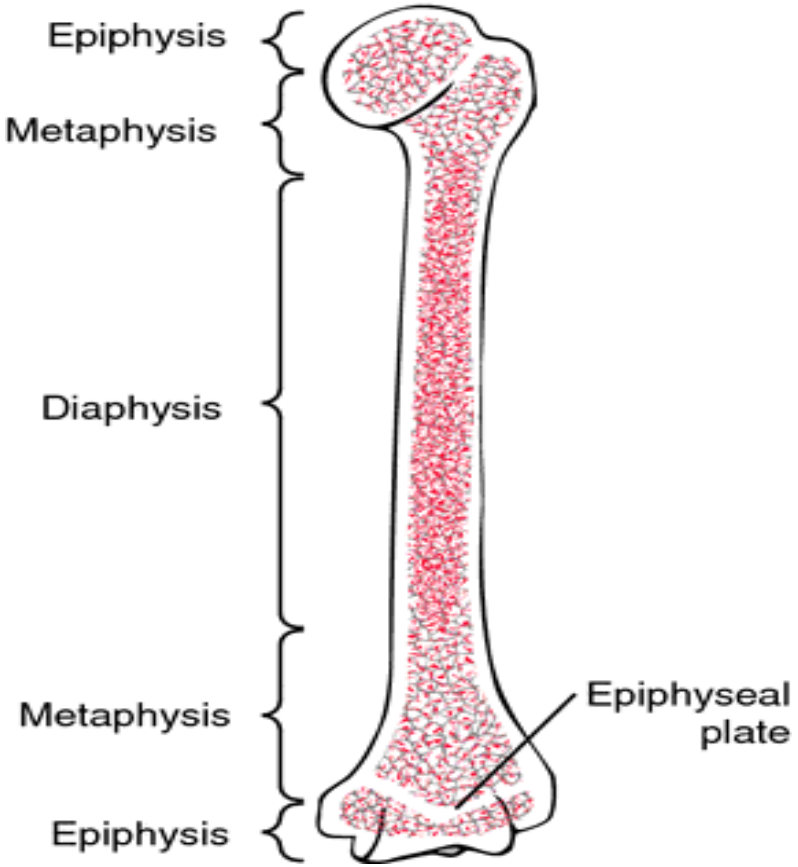
Bone Growth

Linear Growth

" Epiphyseal plates"

Increase in width

"periosteum"



Video

Bone Growth

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

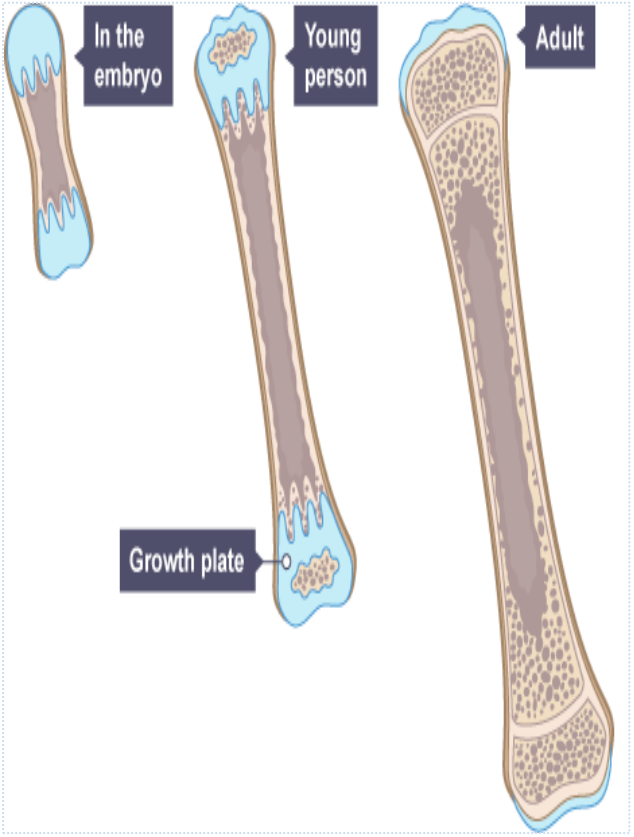
  "Bone formation increases, bone resorption decreases"

- **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 resorption increases, bone formation decreases"

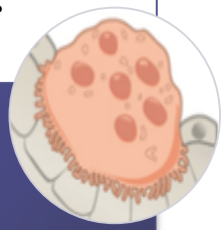


Bone resorption : امتصاص أو إزالة الكالسيوم من العظام
Bone remodeling : استبدال العظم القديم بعظم جديد (إعادة تشكيل العظم)

Bone cells

There are three types of bone cells :

- **Bone-resorbing (removing)cell**
- large phagocytic multinucleated cell derived from monocytes
- its activity controlled by Parathormone hormone
- Stimulated by **PTH**
- Function is to resorb the formed bone.

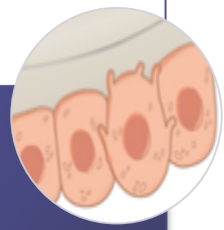


osteoclast

- Mature bone cell derived from osteoblasts
- enclosed in bone matrix.
- Its function is transfer of calcium from bone canaliculi to the ECF.

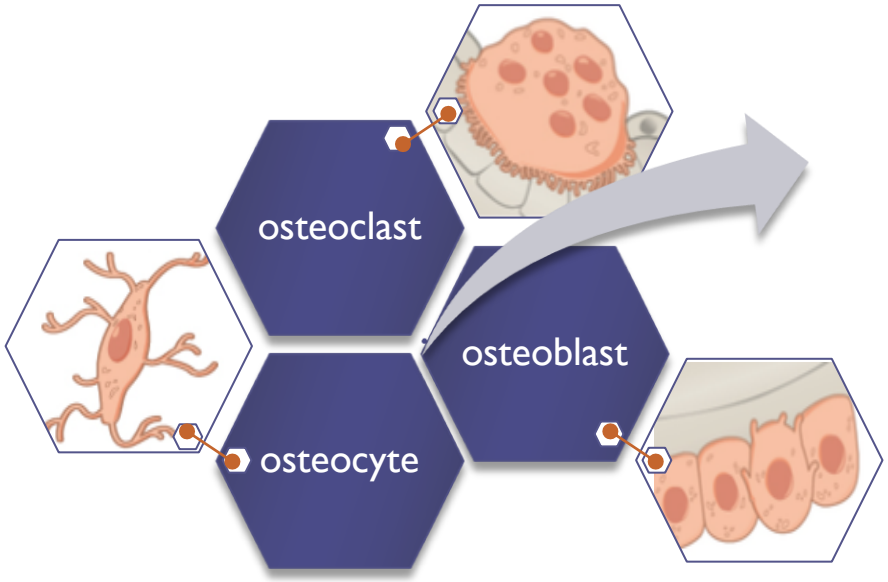
osteocyte

- **Bone-forming cell,** present on outer surface of bone and bone cavities (periosteum & endosteum)
- Stimulated by anabolic steroids.
- Secretes collagen forming bone matrix around themselves then they calcified (on which $Ca^{++}$and PO_4 precipitate).



osteoblast

Bone cells



Functions of Osteoblast :

secrets unclassified collagen (which forms matrix called osteoid) around themself becoming trapped , quiescent → now called osteocytes

Functions of Osteocyte :

Transfer of calcium from bone canaliculi to the ECF

Functions of Osteoclast :

Osteoclasts secrete enzymes that dissolve the matrix of old bone tissue and acids that dissolve bone salts

They secrete :

1. Proteolytic enzymes as proteases digest collagen and dissolve the matrix of old bone
2. HCL, citric and lactic acids to acidify area of bone to dissolve bone salts as hydroxyapatites acid.

Canaliculi

2

Canaliculi traverse the mineralized bone

3

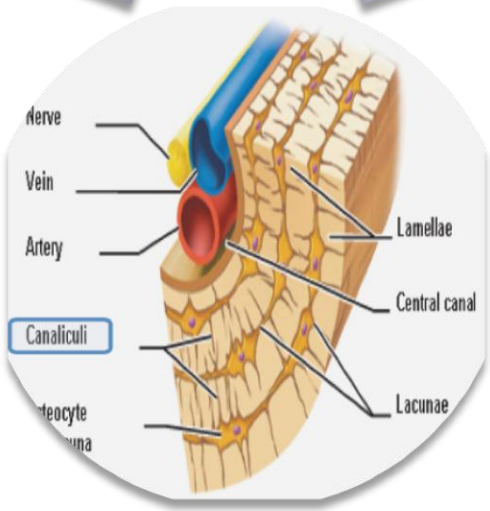
Interior osteocytes remain connected to surface cells (osteoblasts) via syncytial cell processes

1

Inside mineralized bone are fluid-containing channels called the canaliculi

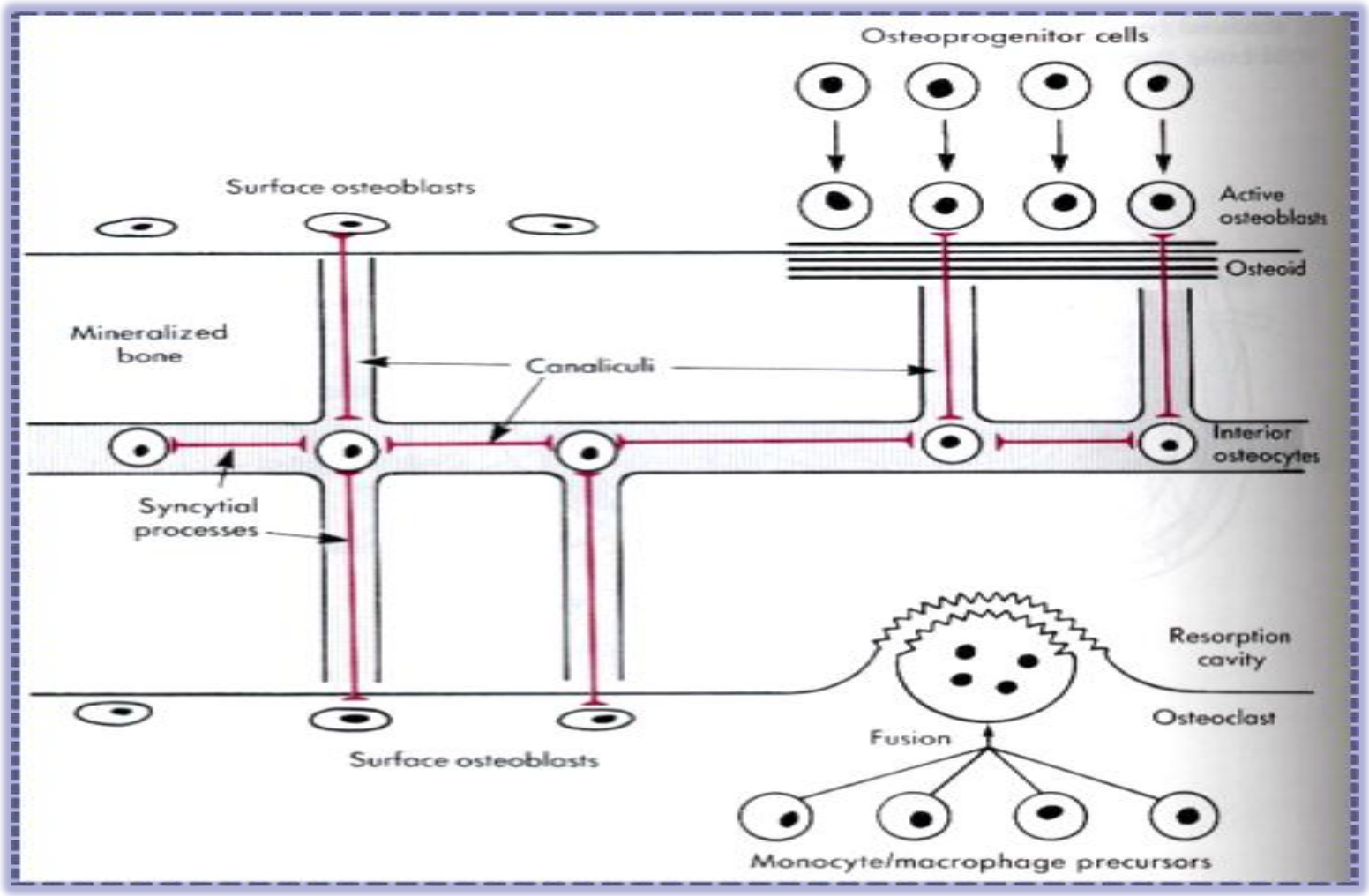
4

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



Video

Canaliculi



Osteocytes هي عبارة عن قنوات داخل الـ **matrix** تحتوي على Processes or branches تنقل الكالسيوم إلى سطح العظم لـ **osteoblasts** لها

Bone Formation

Bone formation begins when active osteoblasts synthesize uncalcified Collagen fibrils to form (rows) of an organic matrix called Osteoid

some of osteoblasts become entrapped in it and become quiescent now are called **osteocytes.**

Then Mineralization occurs
(Deposition & precipitation of Calcium & Phosphate on the Osteoid collagen fibers forming hydroxyapatite crystals over a period of weeks or months)

عن طريق إدخال الكالسيوم إلى الكولاجين المترسب، "mineralization"
ثم يصبح الكالسيوم في صورة : **hydroxyapatite crystals**

- **Osteoid :** the organic matrix of bone; young bone that has not undergone calcification. (Osteoid =كولاجين طري لا يحتوي على كالسيوم)
- **Mineralization = calcification**(لتحويل الكولاجين الطري إلى عظم صلب)

Bone Formation

- Mineralization is dependent on Vitamin D
- Alkaline phosphatase and osteocalcin play roles in bone formation.

Their plasma levels are indicators of osteoblast activity

Further information

* يستخدم هذا الاختبار للتأكد من مدى نشاط تكوين العظام وللتأكد من وجود هشاشة عظام (Osteoporosis)لدى المريض من عدمه.
كما أنه يستخدم لتحديد سرعة تكوين العظام بالإضافة إلى أنه يستخدم لمرضى السرطان للكشف عن انتشاره في العظام (metastasize of cancer).

- Acidic environment is necessary to remove calcium
- Alkaline environment is necessary to add calcium.

Video "min 2:45"

Bone Resorption

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

- **Osteoclastic resorption**
- **Osteocytic osteolysis**

*** Both are stimulated by Parathyroid Hormone (PTH) and vitamin D "they stimulate production of mature osteoclasts".**

*** Estrogen inhibit bone resorption , it stimulates OPG factor(Osteoprotegrin) that inhibit formation of mature osteoclasts.**

Females after menopause :
low estrogen which may lead to osteoporosis.

- Vit D is needed for BOTH :
  (Bone formation & Bone resorption).

Osteocytic = osteocyte
Osteoclastic = osteoclast
Osteolysis = resorption

Bone Resorption

By **osteoclasts**

Acidify area of bone to **dissolve hydroxyapatite** by Hcl then lysosomes & acid proteases digest collagen

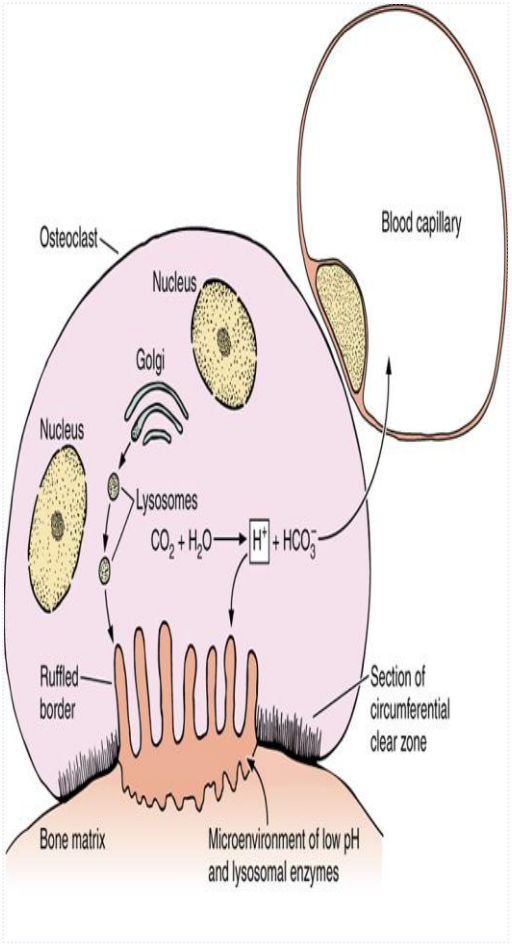
Slow and **Sustained** mechanism.

"needs several days or weeks "

Osteoclastic osteolysis

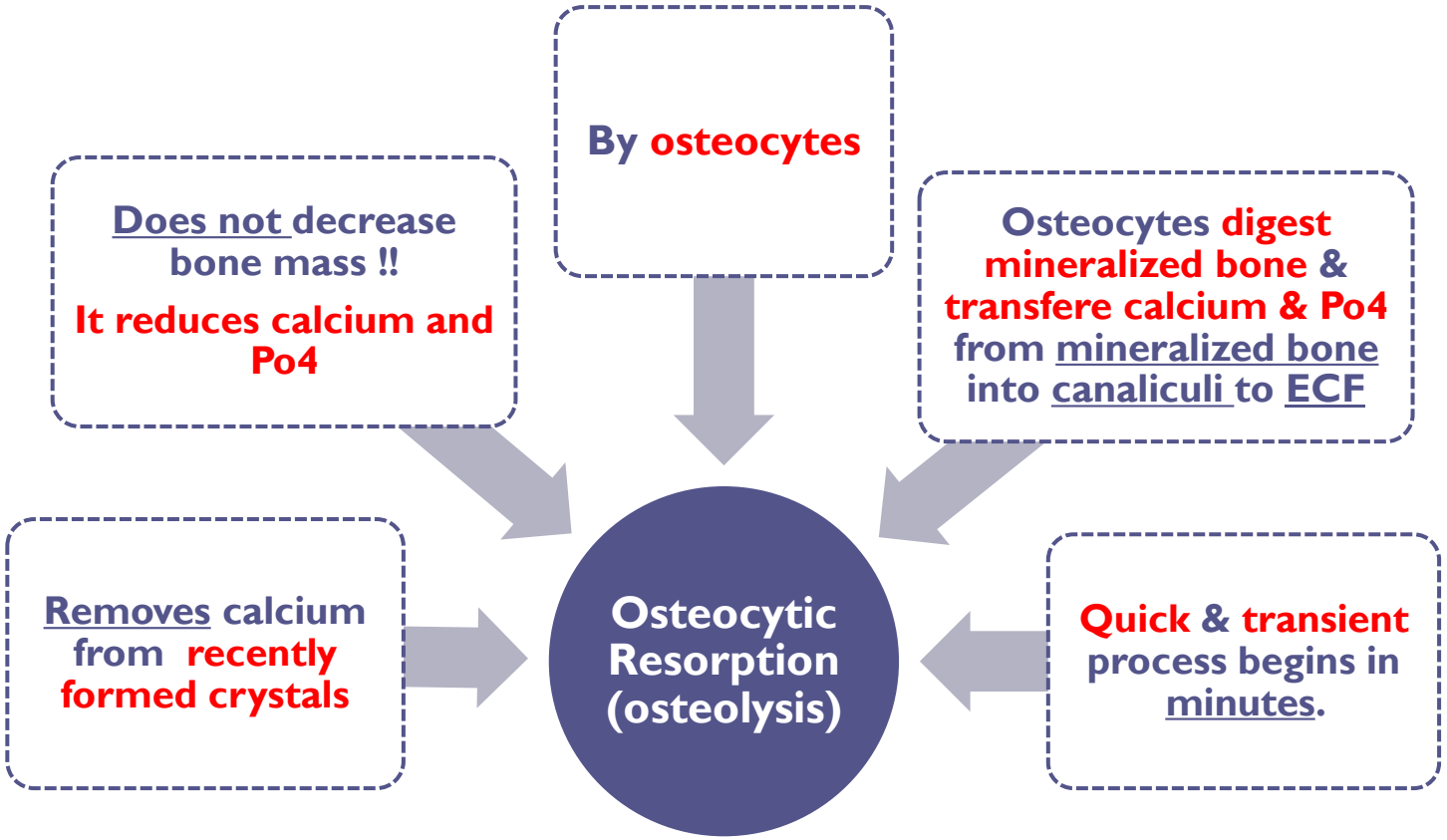
Diminishes **bone mass** but NOT calcium and Po4 !!

Destroys matrix of **old** bone



يقلل كثافة العظم ولكنه لا يؤثر بتاتاً على الكالسيوم أو الفوسفات نظراً لأن الكالسيوم هنا مُستهلك "old bone".

Bone Resorption



تقلل نسبة الكالسيوم والفوسفات داخل العظم ولكن لا تؤثر بتاتاً على كثافة العظم

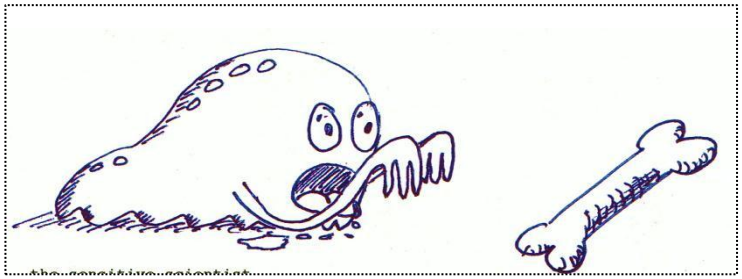
Bone remodeling

Bone remodeling :

Refers to the continuous processes of bone absorption (by Osteoclasts) and then its deposition (by Osteoblasts).

{ Means continuous deposition of new bone by osteoblasts and absorption of old bone by osteoclasts }

- **This results in a 10% turnover of the adult bone mass per year.**
- **It maintain normal toughness of bone.**



Video

Mechanism of Bone remodeling

1

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

2

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

3

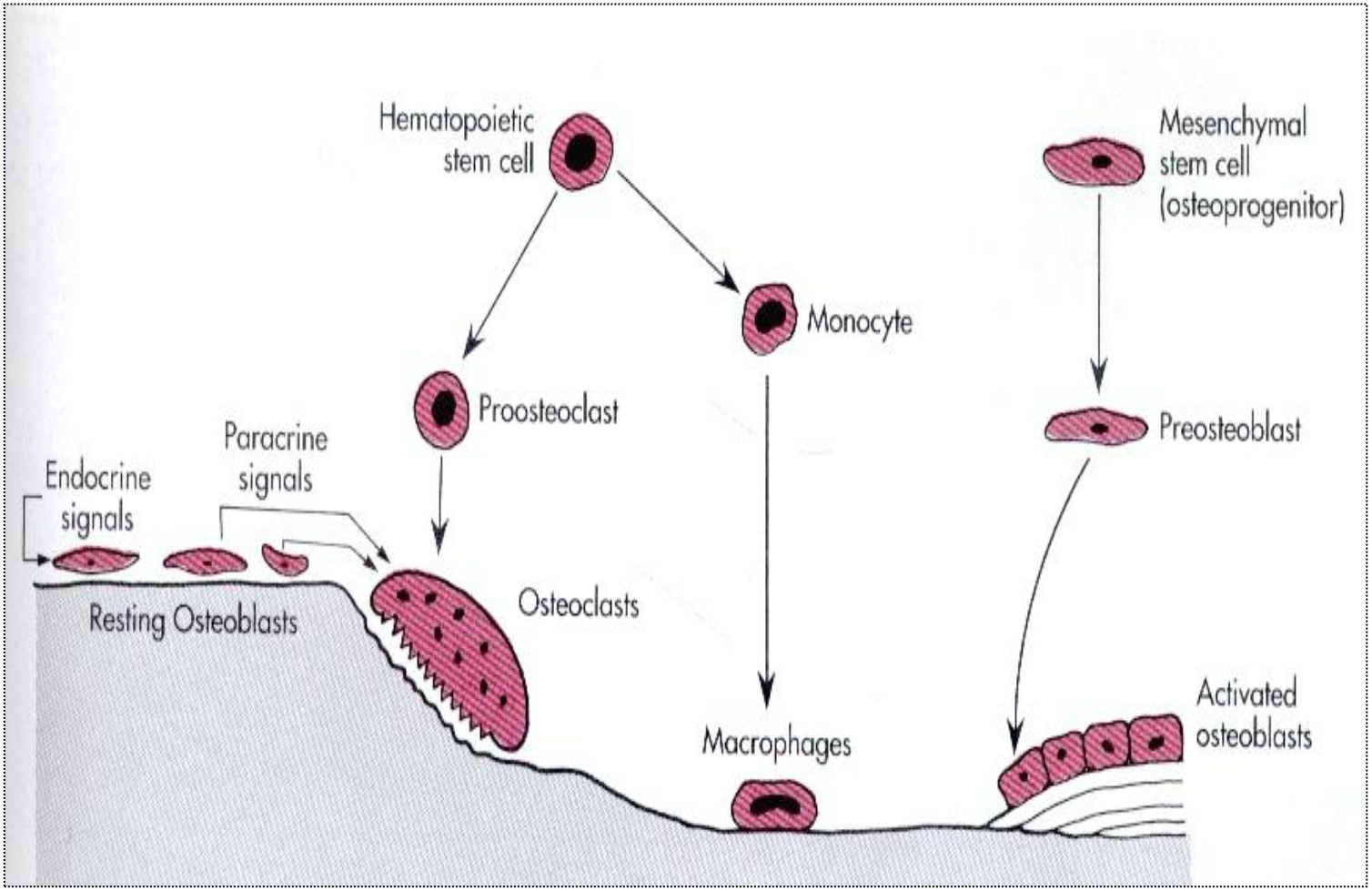
Local macrophages clean up debris

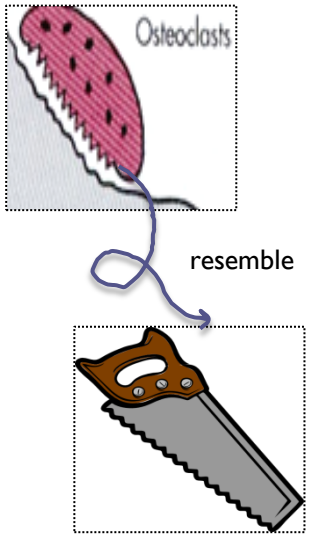
4

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)

5

New bone replaces previously reabsorbed one.



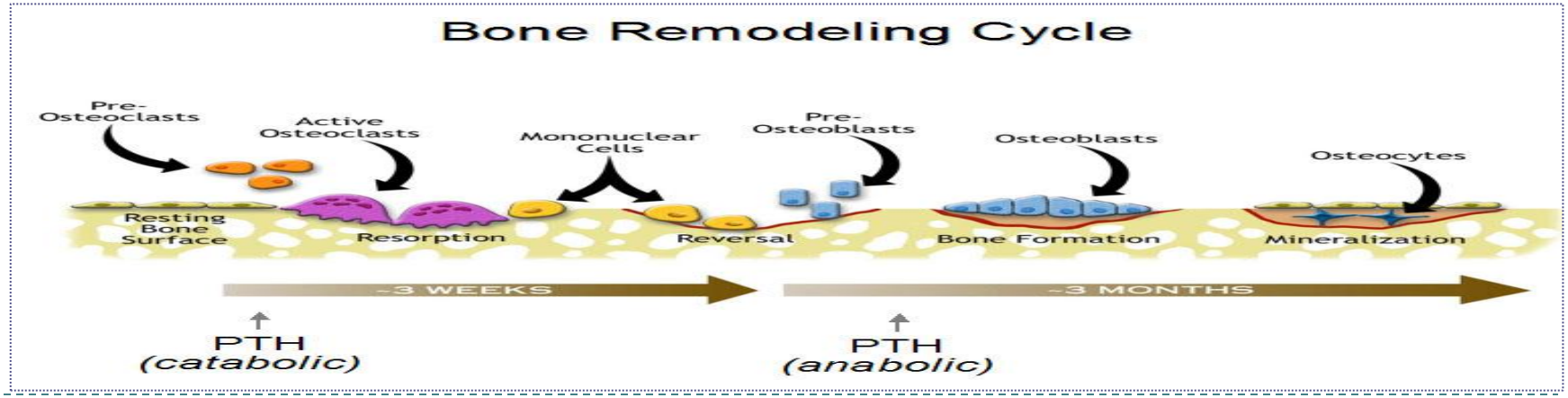


The resting osteoblasts receive endocrine signal which says :"we need a new bone!"
then they will release factors that stimulate the maturation and differentiation of osteoclasts
Now the mature osteoclasts start to "eat" the bone by HCl, lactic acid, citric acid and proteolytic enzymes. In addition, they will digest collagen and calcium which produce "debris" that must be cleaned by macrophages. Now the area is clean, so we can build a new bone!

Bone remodeling

Bone remodeling affected by :

- Mechanical stress on bone stimulates formation of stronger bone, athletes bone is stronger & heavier than non athletes.
- Parathyroid hormone **(PTH)** and **1,25 dihydroxycholecalciferol** stimulates osteoclastic activity & formation of osteoclasts
- Calcitonin (inhibits activity& formation of osteoclasts)

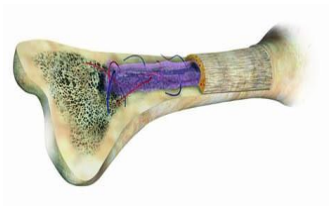


Hormonal control of calcium

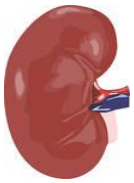
Hormonal control of calcium

- Parathyroid hormone **(PTH)**
- 1,25 dihydroxycholecalciferol **(active form of Vitamin D3)** "cholicalcefirol = Vitamin D3"
- Calcitonin

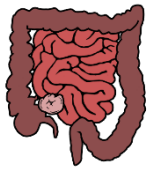
They regulate Ca^{++} resorption, absorption and excretion from the **three organs** that function in Ca^{++}homeostasis.



Bone



Kidney



Intestine

Hormonal control of calcium

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

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 deficiency }

2) ingested in the diet.

In liver	Vit D3(cholicalcefirol) ⟶ 25 hydroxycholecalciferol
In Kidney	25 hydroxycholecalciferol { By Parathormone (PTH) } ⟶ 1,25 dihydroxycholecalciferol { Active form }

* If plasma Ca++ level is high formation of 1,25 dihydroxycholecalciferol (active form) is inhibited, so calcium absorption from intestine,bone,kidney is reduced.

how vitamin D become 1,25 ? **VitD3(cholecalciferol)** "from diet" goes to liver and become **25 hydroxycholecalciferol**
Then it goes to kidney to be converted by PTH into **1,25 dihydroxycholecalciferol (note that we add a hydroxyl group)**

Vitamin D

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

1- Stimulates **absorption of Ca^{2+} & PO4** from the intestine (calbindin protein).

2- Stimulates **Calcium reabsorption** in kidneys.

3- Helps in bone **formation & absorption.**

Vit D-dependent-calcium-binding proteins in the intestine.

- **In bone resorption:-**

large amounts of vit D cause **bone absorption**, 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).**

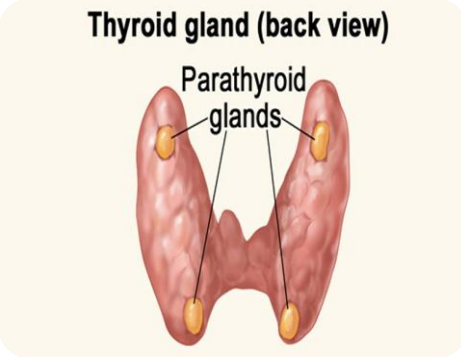
In small amounts stimulates bone calcification as it increase calcium absorption from intestine & kidney also increases calcium transport to inside bone to through osteoblast & osteocyte membranes.

لو زاد فيتامين د عن المعدل الطبيعي سيسبب امتصاص الكالسيوم من العظام ونقله إلى الـECF

Parathyroid Hormone (PTH)

- It is a 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 and bone resorption by activating osteoclasts.

2- On kidney to stimulate Ca++ reabsorption in the distal tubule and prevents its excretion & inhibit re-absorption 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).

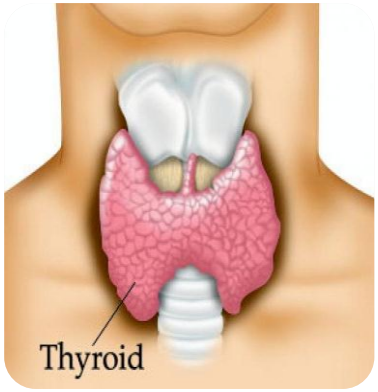
4- On intestine to stimulate Ca++ re-absorption .

how does parathyroid effect remodeling ?
1) Increase absorption of ca++ in intestine.
2) Increase absorption of ca++ in kidney.
3) Stop phosphate absorption
4) Stimulate the kidney to produce 1,25 dihydroxycholecalciferol
5) In bone increase formation&activation of osteoclast which resorption to the bone and release ca++ to blood.

Video

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



How does Calcitonin work ?

1) Inhibit absorption of ca++ in intestine.
2)Inhibit absorption of ca++ in kidney.
3) Activate osteoblast to increase the ca++ inside the bone.

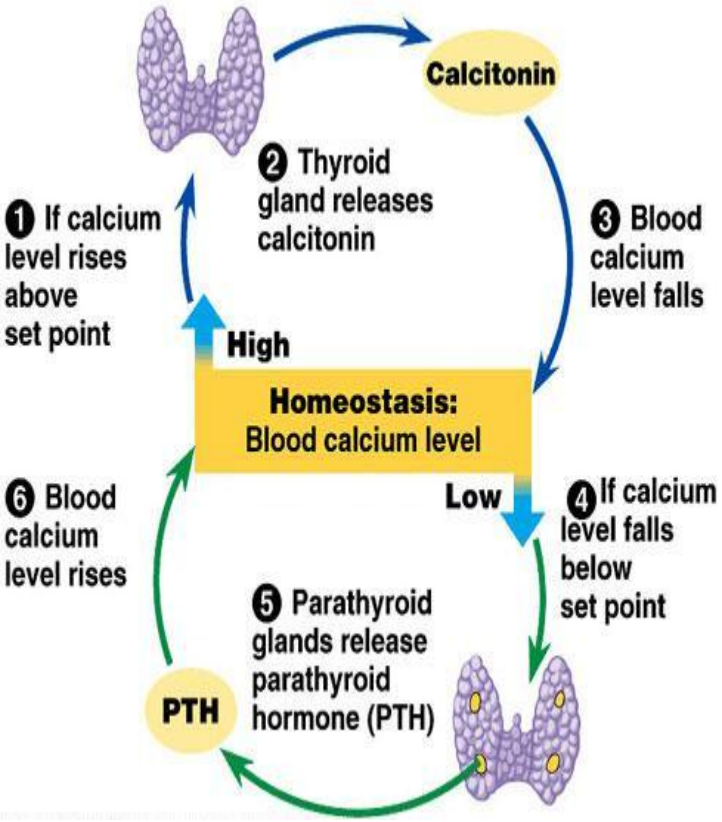
EXTRA

PTH Function :

دائماً يرفع نسبة الكالسيوم في الدم عن طريق زيادة امتصاص الكالسيوم من الأمعاء ومنع امتصاص الفوسفات (العلاقة بين الكالسيوم والفوسفات علاقة والكليتين عكسية) بالإضافة إلى زيادة نشاط الـ osteoclasts
لزيادة امتصاص الكالسيوم من العظام ونقله إلى الدم .تحدث هذه العملية عند نقص الكالسيوم في الجسم ، بالتالي عند أخذ كمية من الكالسيوم ولو كانت بسيطة سيمتصها الجسم بسرعة ويمنع إخراجها من الكلية.
استمرار هذه العملية قد يؤدي إلى Osteomalacia

Calcitonin Function :

يقلل مستوى الكالسيوم في الدم عن طريق منع امتصاص الكالسيوم من الأمعاء والكليتين كما أنه يرفع معدل الكالسيوم في العظام.
كذلك ينشط الـOsteoblasts



Video

Osteoporosis

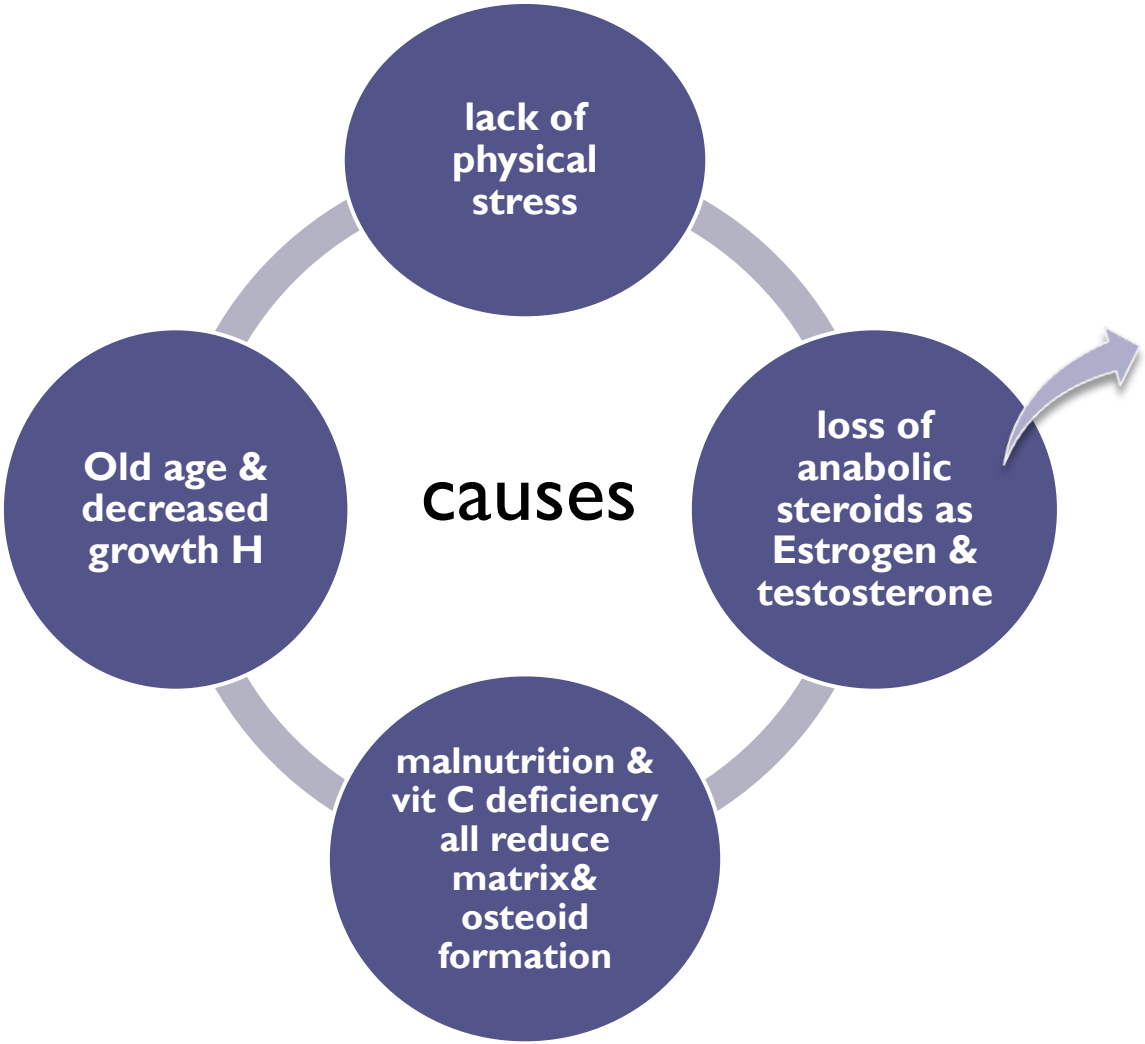
Osteoporosis : Reduced bone density and mass

- **Diminished bone matrix**
  (Not from poor calcification as in rickets or osteomalasia)
- **Bone becomes weak and ca++ is lost from skeleton.**
- **Susceptibility to fracture.**
- **Earlier in life for women than men due to increased resorption during pre-menopause .**
- **The rate of osteoclastic resorption exceeds deposition of new bone by osteoblastic activity**

Further information

سبب هذا المرض لا يكون بنقص الكالسيوم فقط وإنما يرافقه خلل بالهرمونات.
during pre-menopause تبدأ العظام بالتآكل بسبب الانخفاض الشديد في مستويات الأستروجين.

Osteoporosis



They stimulate **osteoblastic** activity& decrease **osteoclastsic** activity

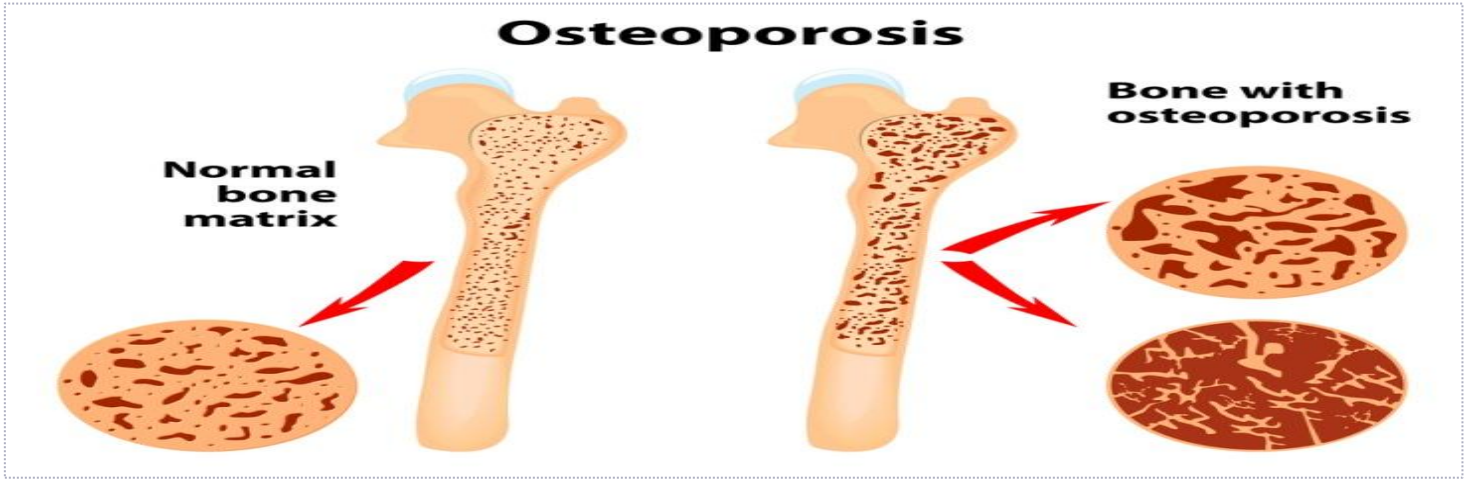
Video

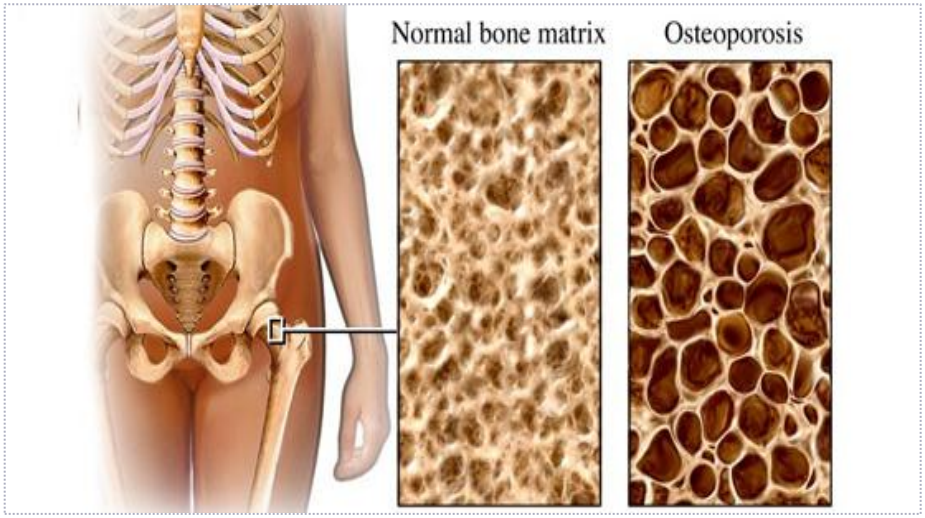
Osteoporosis

Reduced risk by :

- **High Calcium in the diet**
- **Habitual exercise**
- **Avoidance of smoking & alcohol intake & drinking carbonated soft drinks.**

Osteoporosis

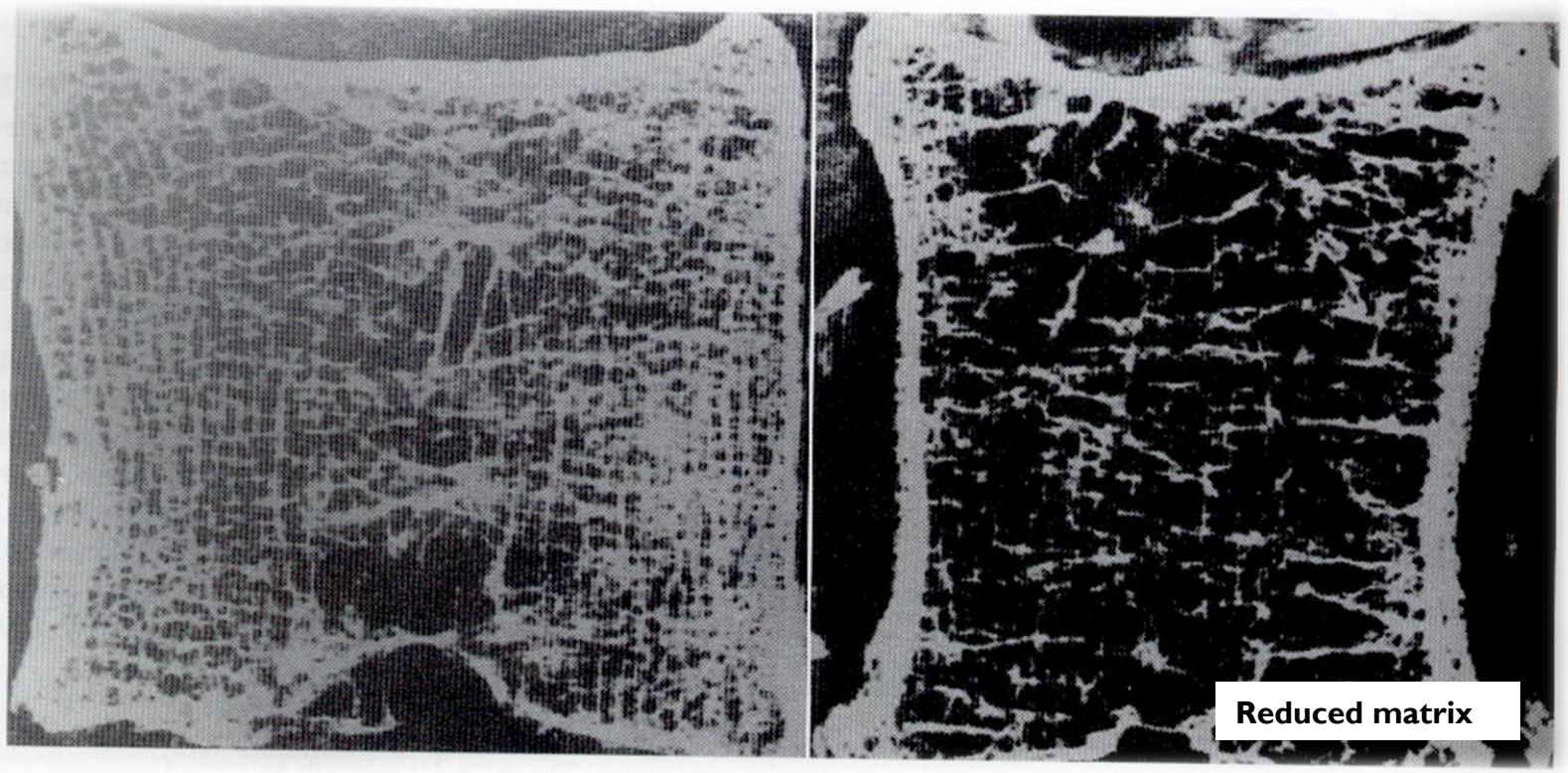




Osteoporosis

Vertebrae of 40 vs. 92 -year-old women

Note the marked loss of trabeculae with preservation of cortex.



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