Physiology Team 432

First Lecture: Physiology of Bone

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Lecture Objectives

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

Bone is a living, growing tissue.

The Bone has several functions:

1. **Protects** vital organs : Braine, Heart
2. **Support** the soft tissues
3. **Allows** & facilitates movement by attaching to the muscles
4. **Contains** bone marrow (Blood cell synthesis)
5. **Maintains** the Calcium & Phosphate concentration in the body fluids by acting as **Reservoir** for them.

Blood Calcium is low ⟶ bones are used as a source

Blood Calcium is high ⟶ calcium deposits in bones

Bone Structure

According to the nature of the component the bone is consists of :

(1) Organic matrix made of specialized collagen (osteoid) 30% of bone.

(2) (Inorganic or mineral) bone component calcium & phosphate crystals 70% of bone

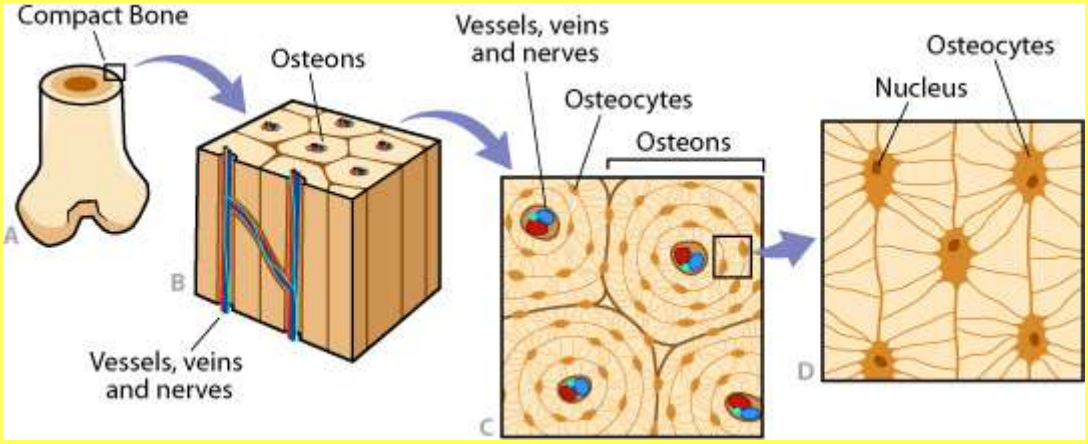
The bone tissues are two types:

1) Compact (Cortical) Bone

is the hard material that makes up the shaft of long bones and the outside surfaces of other bones. Compact bone consists of cylindrical units called **osteons**. 80% of Bone Mass

- Has a slow calcium turnover rate*
- Has high resistance to bending and torsion

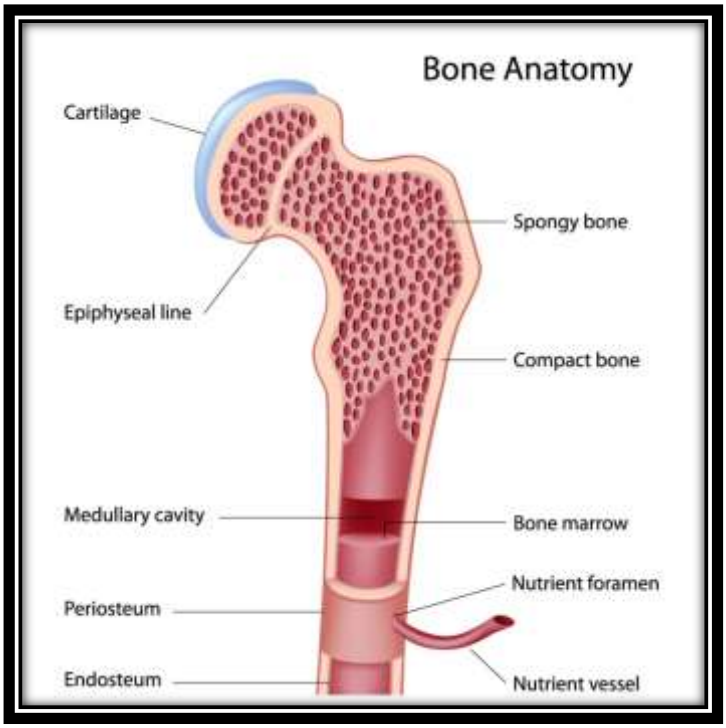
Composition of the osteon:



- Each osteon has a central canal called Osteonic Canal or Haversain Canal
- The Osteonic Canal contain blood vessels (capillaries, arterioles, venules), nerves and lymphatics.
- Between Harvesian systems are concentric layers of mineralized bone called interstitial lamellae

Turnover Rate or Bone Remodeling : It is the process of bone restoration and formation, the bone is constantly being remodeled .

2) Spongy (Trabecular or cancellous) Bone



- Comprises 20% of total bone mass
- Present in the interior of bones & has spongy appearance .
- Though it represents only 20% of the skeletal mass, it has 5 times greater surface area than cortical bone
- Because of its large surfac, it has faster turnover rate than cortical bone ; hence it is more important than cortical bone in terms of calcium turnover
- Compared to cortical bone , it is:

(1) less dense,

(2) more elastic and

Bone tissue	Bone Mass	Composition	Surface area	Calcium turnover
Cortical	80% of bone mass	Osteons	Less surface area	Slow calcium turnover
Trabecular	20% of bone mass	Trabeculae	Great surface area	High Calcium turnover

Extracellular (ECF) Calcium

99% **of total Calcium** is inside the bone in form of hydroxyapatite crystal) & phosphate salts(CaP04 and hydroxide), while 70% **of the bone** is made up of calcium.

- Calcium level in plasma is 8.5-10 mg/dL (1% of total Calcium inside the body)
- If calcium increase in the plasma it will excreted with urine or deposited inside the bone.

If calcium decreased (Hypocalcaemia) Voltage-gate ion channel start opining spontaneously, casing the muscles & nerves to be Hyperactive

- It exists in 3 fractions :

  (1) Ionized calcium → 50% of total ECF calcium

  (2) Protein-bound calcium → 40% of total ECF calcium

  Most of this is bound to albumin,

  And much less is bound to globulins

  (3) The remaining 10% of plasma calcium bound to citrate & phosphate

- Only the free, ionized Ca^{2+} is biologically active.

Biologically active: means play a role in the biological processes in the body. Ex: Muscle contraction, Coagulation.

- Binding of calcium to albumin is pH-dependent :

  Alkalosis increases calcium binding to protein → thereby decreases ionized calcium level

- Calcium is tightly regulated with Phosphorous in the body.
- Calcium salts in bone provide structural integrity of the skeleton

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

- 1-13 % Non-diffusableprotein bound (85-90 % is found in bone.)
- 2-87 %Diffusableform (52% ionized & rest bound to ions)
- small amount in ATP, cAMPand proteins compounds

Bones Cell

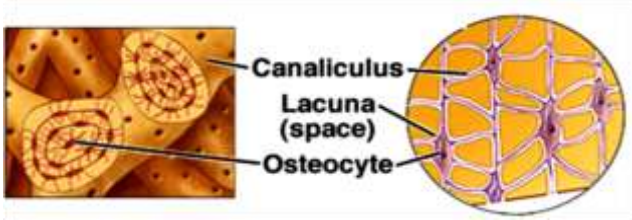
There are three special types of cells that are found only in the bone. These cell names all start with "OSTEO" because that is the Greek word for bone.

OSTEOCLASTS are large cells that dissolve the bone. They come from the bone marrow and are related to white blood cells. They are formed from two or more cells that fuse together, so the osteoclasts usually have more than one nucleus. They are found on the surface of the bone mineral next to the dissolving bone.

OSTEOBLASTS are the cells that form new bone. They also come from the bone marrow and are related to structural cells. They have only one nucleus. Osteoblasts work in teams to build bone. They produce new bone called "osteoid" which is made of bone collagen and other protein. Then they control calcium and mineral deposition. They are found on the surface of the new bone.

When the team of osteoblasts has finished filling in a cavity, the cells become flat and look like pancakes. They line the surface of the bone. These old osteoblasts are also called **LINING CELLS**. They regulate passage of calcium into and out of the bone, and they respond to hormones by making special proteins that activate the osteoclasts.

OSTEOCYTES are cells inside the bone. They also come from osteoblasts. Some of the osteoblasts turn into osteocytes while the new bone is being formed, and the osteocytes then get surrounded by new bone. They are not isolated, because they send out long branches (canaliculi) that connect to the other osteocytes.
Canaliculi are small, fluid-filled channels that are used for exchange of Ca++PO4 ,nutrients and waste products through gap junctions



Many recent studies suggest that Osteocytes :

(1) Have mechanosensory mechanisms → detects degree of mechanical stresses & strain

(2) Act as regulators of osteogenesis & osteolysis → by translating the degree & type of mechanical strain into biochemical signals, osteocytes regulate the amounts of $CaPO_4$ that is transported from (ECF to bone ; or vice versa) and from bone to ECF.

Therefore , osteocytes they can cause :

(A) increased rate of osteogenesis (bone formation) by →

(1) stimulating osteoblasts , &
(2) increasing rate of transfer of calcium & phosphate from ECF to bone.

(B) increased rate of osteolysis (bone resorption) by →

(1) stimulating osteoclasts, &
(2) increasing rate of transfer of calcium & phosphate from bone to ECF
(3) Calcitonin inhibit osteoclast .

Bone Formation & Mineralization

- **Alkaline phosphatase and osteocalcin play roles in bone formation**

Osteoblasts	• osteoblasts synthesize bone matrix (osteoid , mainly collagen) • it will be mineralized by deposition of Calcium & Phosphate
Vitamin D	• this mineralization is dependent on Vitamin D
Phosphatase and Osteocalcin	• Alkaline phosphatase and osteocalcin plasma levels are indicators of osteoblast activity

Bone Resorption

Involves :

(1) calcium exraction (demineralization) , & then

(2) removal of the osteoid matrix

1- Osteocytic Osteolysis

Cell responsible for resorptionis the **osteocyte**.

- Activity of **osteocytes** digest mineralized bone area then calcium transfer from canaliculi to extracellular fluid.
- Does not decrease bone mass.
- Removes calcium **from most recently formed crystals**
  - **Quick process.**

2- Osteoclasitc resorption

is slow and sustained mechanism.

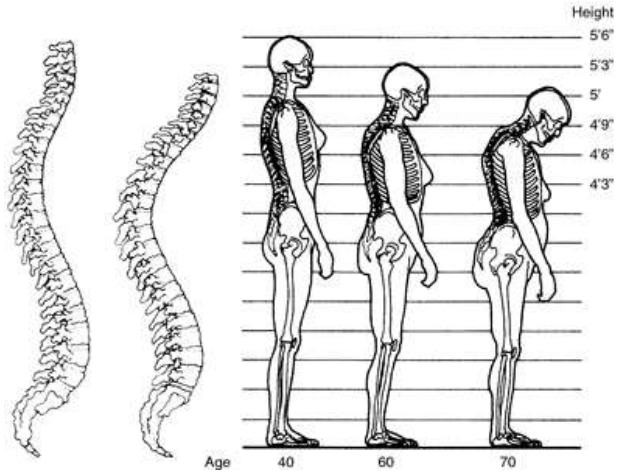
- -destroys matrix of oldbone
- -diminishes bone mass.
- Cell responsible for resorption is the **osteoclast**.
- (acidify area of bone to dissolve hydroxyapatite by Hcl then lysosomes & acid proteases digest collagen)

- Bone resorptopn is stimulated by parathyroid hormonne (PTH) , which stimulates osteoclasts → leads to release of calcium from bone into the ECF

Osteoporosis

- Men have more total bone mass than women .
- During childhood, bone formation exceeds resorption, and the total bone mass peaks at 25-35 years of age .

- ❖ Therefter , because of falling levels of the anabolic steroids (oestrogen & progesterone , which stimulateosteoblasts) , we get osteoporosis , which means reduced bone density and mass
- ❖ This leads to increased susceptibility to fracture.
- ❖ Osteoporosis occurs earlier in life for women than men (especially women around menopause) . But eventually both genders succumb to it



Bone remodeling

•**Remodeling** means continuous deposition of new bone by osteoblasts& absorption of old bone by osteoclasts
•-Endocrine signals to resting osteoblasts generate paracrine signals to osteoclasts
•Osteoclasts digest and resorb an area of mineralized bone.
•Local macrophages clean up debris.
•Then osteoblasts are recruited to site and deposit new matrix which will be mineralized.
•New bone replaces previously resorbed bone.

Bone remolding affected by;-

1- **mechanical stress on bone stimulates formation of stronger bone.**

2- **PTH & 1,25 DIHYDROXYCHOLECALCIFEROL (active vitamin D3) stimulates osteoclastic activity & formation of osteoclasts**

3- **CALCITONIN inhibits activity& formation of osteoclasts.**

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 VitD3
(2) Ingested in the diet

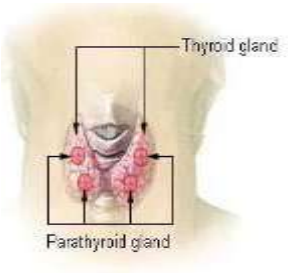
-In liverVitD3 converted to 25 hydroxycholecalciferol,in kidney
-**PTH** convert it to **1,25 dihydroxycholecalciferol (active form)**

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

- stimulate absorption of Ca2+from the intestine
- stimulate Ca reabsorption kidneys
- help in bone formation
- mobilize ca++from bone into plasma by increasing number of **osteoclasts** to increase plasma Ca++levels (**only when it drops**)

2-Parathyroid Hormone (PTH) Action

Parathormone from parathyroid gland



Functions:-

-To increase plasma Ca++levels when it drops and decrease plasma phosphate levels.

- 1- acts **directly** on the **bones** to stimulate **Ca++ resorption** by activating osteoclasts
- 2- on **kidney** to stimulate **Ca++ reabsorption** in the distal tubule & to inhibit reabosorptioin 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)**

3-Calcitonin

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

- Calcitonin acts to decrease plasma Ca++levels.
- The major stimulus of calcitonin secretion is a rise in plasma Ca++levels
- It suppresses osteoclastic activity and number in bone
- It increases osteoblastic activity to mineralize bone

NOTE: parathyroid hormone # calcitonin

- **Parathyroid hormone : increase Ca in plasma and decrease it in bone. And prevent excrete Ca in the urine.**
  - **(parathyroid hormone works when Ca in plasma decreased to make it increased)**
- **Calcitonin hormone: increase Ca in bone and decrease it in plasma.**
  - **(Calcitonin hormone work when Ca in plasma increase to make it decreased)**

GOOD LUCK