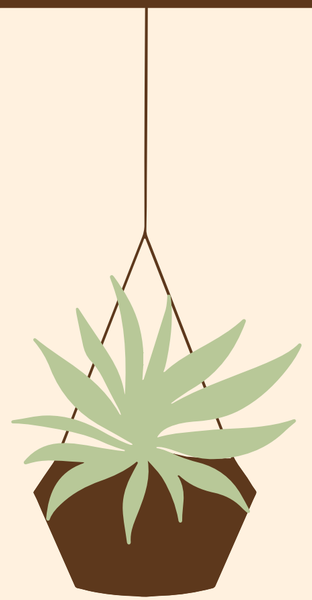
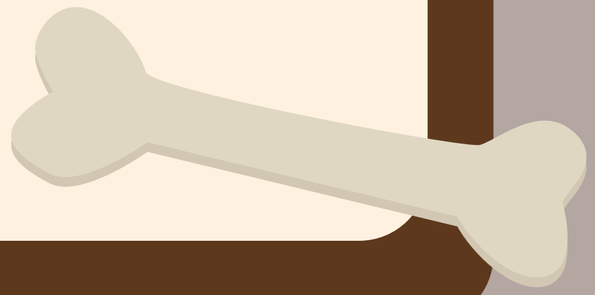


BONE BIOLOGY



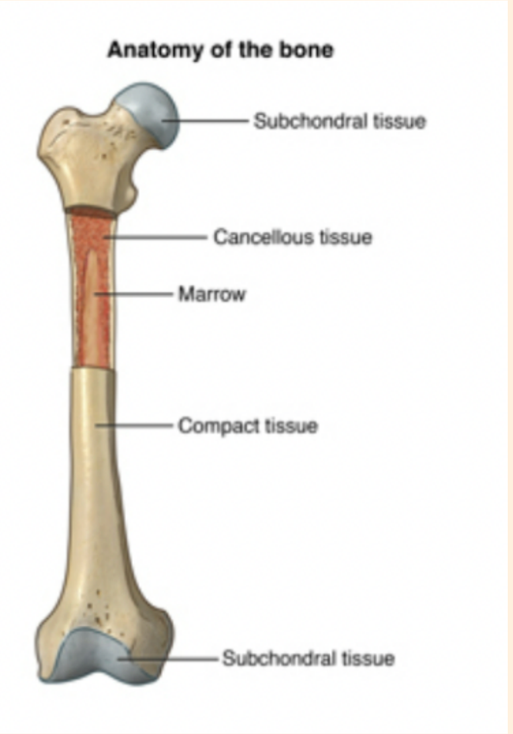
FUNCTIONS

Bone Consists of 3 types of tissue:

1. Compact: harder outer tissue of bones
2. Cancellous: spongey like tissue inside bones
3. Subchondral: smooth tissue at the ends of bones covered in cartilage

Functions of bones:

1. Support of the body
2. Protection of organs
3. Site for Haematopoiesis
4. Regulation of mineral homeostasis



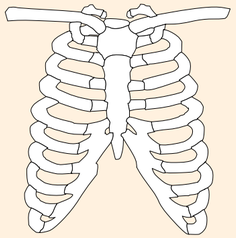
Classifications of Bones

Long Bones

- Longer than it is wider
- Mostly located in the appendicular skeleton
- Lower limb: Tibia, Fibula, Femur etc
- Upper limbs: Humerus, Radius, Ulna

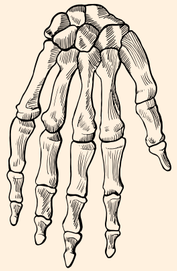
Flat Bones

- Enclose and protect soft organs
- Skull bones, Ribs, Sternum, Scapula
- Formed from Intramembranous ossification



Short Bones

- Length = Width (approx)
- IE carpal and tarsal bones
- Contain mainly spongey bone

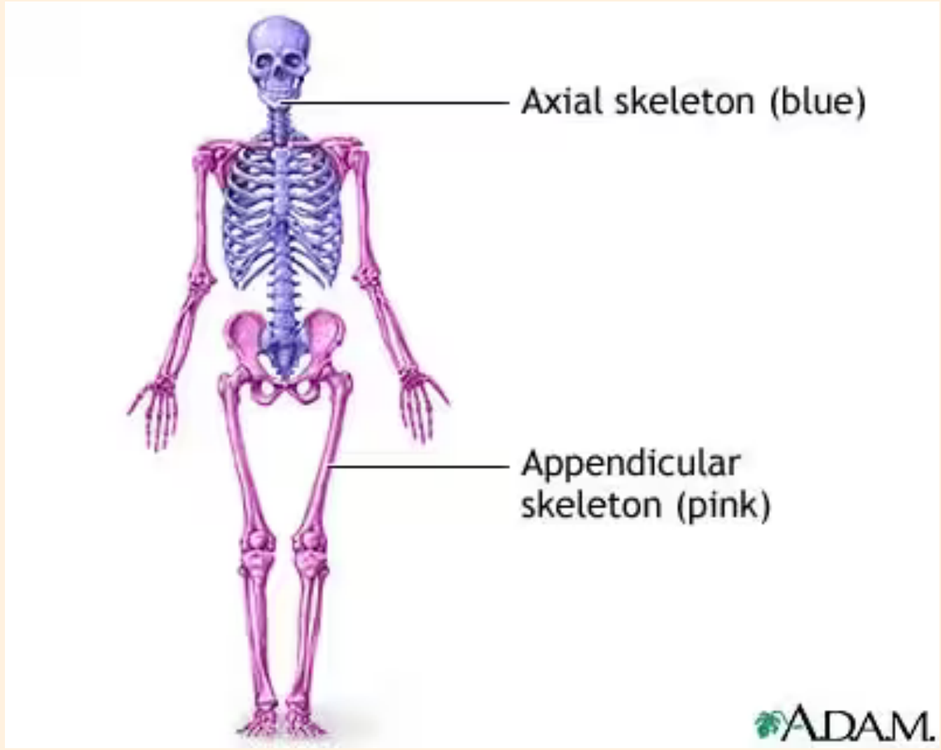


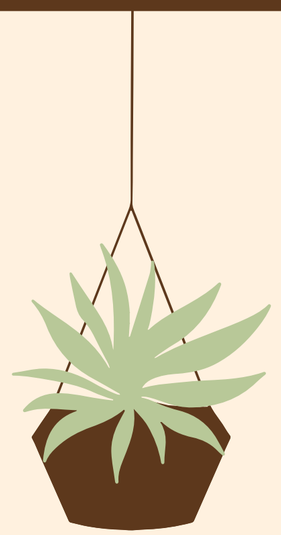
Irregular Bones

- Vary in shape and structure and so do not fit into any other category
- Vertebrae
- Some skull bones: sphenoid, facial

Axial: skull, vertebral column, rib cage and sternum

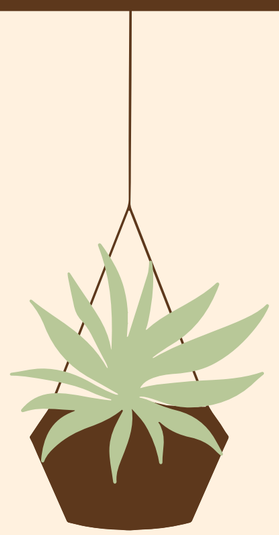
Appendicular: clavicle, scapula, arms, legs etc





WHAT IS DISTINCT ABOUT INTRAMEMBRANOUS OSSIFICATION?

1. The main kind of ossification
2. There is no cartilage intermediary
3. Forms the acetabulum
4. Bone develops by replacing hyaline cartilage
5. Forms the Sternum

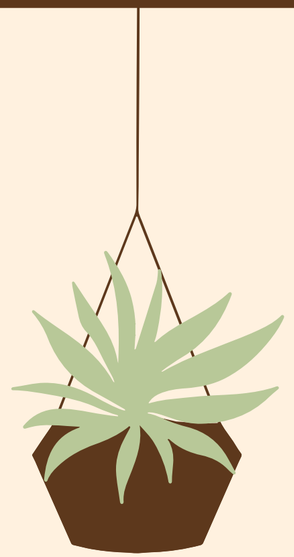


1. No, that is Endochondral Ossification
2. **There is no cartilage intermediary ->**
3. Forms the acetabulum? This is a socket
4. No, that is Endochondral Ossification
5. Despite being a flat bone, the sternum is formed from Endochondral Ossification

WHAT IS DISTINCT ABOUT INTRAMEMBRANOUS OSSIFICATION?

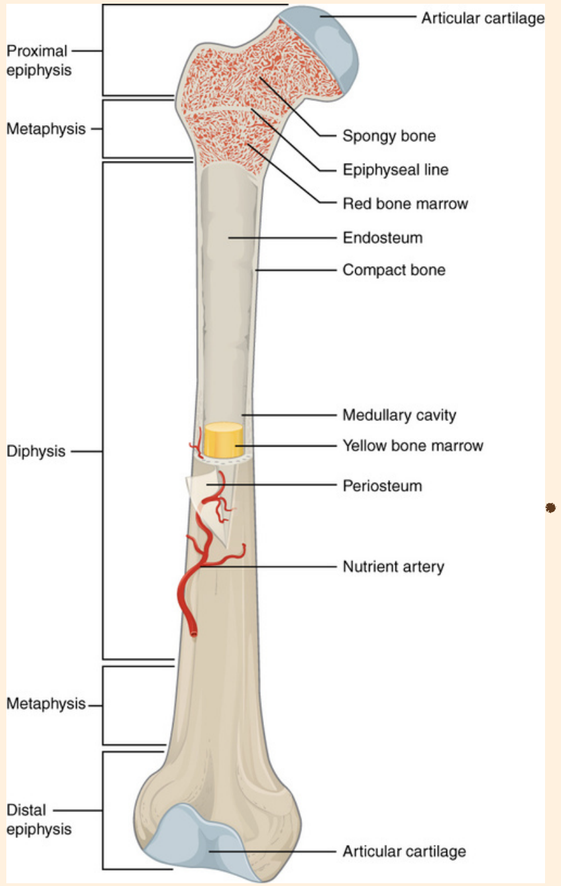
!!! Intramembranous ossification is dependent on mesenchymal condensation where there is no cartilage intermediary.
This is because the bone develops STRAIGHT from clustered mesenchyme !!!

STRUCTURE



Diaphysis

- The shaft, forms the long axis, main weight bearing portion of the bone
- Consists of thick layer of compact bone surrounding a central medullary cavity
- Containing bone marrow



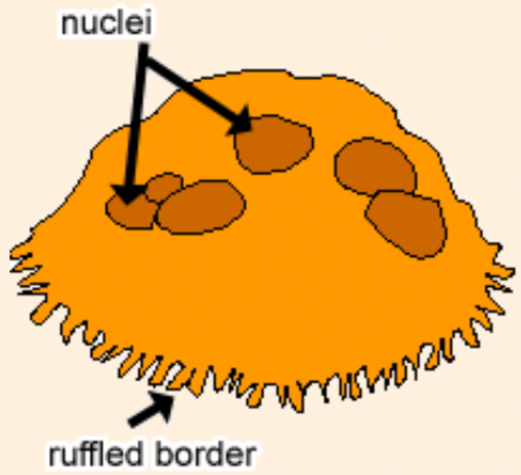
Epiphysis

- Ends of the bones (at joints)
- ↑ SA for tendon and ligament attachment
- Primarily trabecular bone (spongy), outside layer compact bone
- Covered in articular cartilage (hyaline cartilage)
- Lubricating fluid: decreases friction for easier joint movements.

Metaphysis

- In between the epiphysis and diaphysis
- Remnant of the epiphyseal plate or line
- Hyaline cartilage allowed for bone elongation in childhood

OSTEOCLASTS

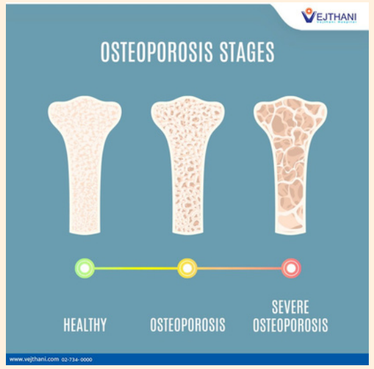


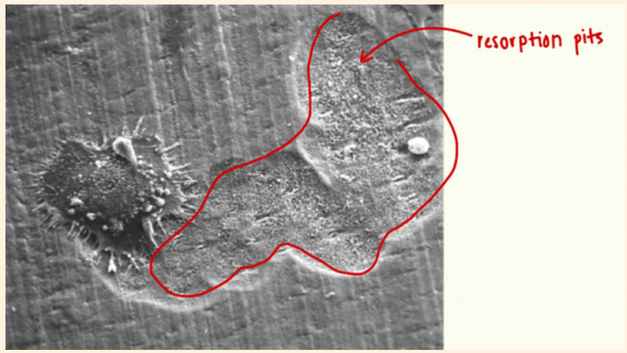
BONE RESORPTION

- Motile, multinucleate cells concentrated in the endosteum, derived from the fusion of pro-monocytic precursors.
- On the side of the cell that faces the bone surface, the osteoclasts plasma membrane is deeply folded into a **“ruffled border”** that produces lysosomal enzymes and acids to catabolise protein and mineral components of bone ECM
- Express high levels of **carbonic anhydrase II**

CLINICAL RELEVANCE

!!! Oestrogen can inhibit osteoclasts, therefore a lack of Oestrogen in women after menopause can lead to increased Osteoporosis (low bone density)





These multi-nucleated cells can slide into the bone matrix and by secreting enzymes can result in bone degradation

ROLE OF RANKL IN OSTEOCLAST BIOLOGY AND FUNCTION

- Osteoclast precursor cells express RANK receptor on its surface
- RANKL is the ligand of RANK
- When these two proteins interact, then we have a cascade which results in the fusion of osteocyte and osteocyte precursor
- This activates osteogenic differentiation and inhibits osteoblast apoptosis
- Final result is a mature osteoclast which are ready to resorb bone

- OPG secreted from mesenchymal stromal cells, osteocytes and osteoblasts
  - Plays role of the decoy receptor for RANKL
  - OPG binds to RANKL
  - Interrupts interaction of RANKL and RANK
  - Leads to non activation of osteoclast precursor
  - Inhibition of bone resorption
  - This happens when theres excessive bone absorption
- RANKL + OPG can determine the development of Osteopetrosis

ROLE OF OSTEOCYTES IN BONE TURNOUER

- Osteocytes are embedded in a bone matrix and respond to mechanical loading
- They produce a wide range of factors that regulate bone cells
- IE: Prostaglandins, NO, RANKL, Sclerostin
- Sclerostin has a major role in bone formation
- Osteocytes are connected by osteocyte processes
- Located in spaces within mineralised matrix called lacunae

- Sclerostin inhibits the activation of pre-osteoblastic cells to become active
- Therefore Sclerostin inhibits bone formation
- Loss of Sclerostin leads to high bone mass disease:
  Sclerosteosis
  van Buchem disease (rare)
- Caused by SOST inactivation mutations
- Anti-sclerostin antibodies recently approved for osteoporosis

BONE MEMBRANES

PERIOSTEUM: EXTERNAL

- Outer layer surrounding bone on the external surface (except at the joints, which are covered in articular cartilage)
- Vascularised and innervated

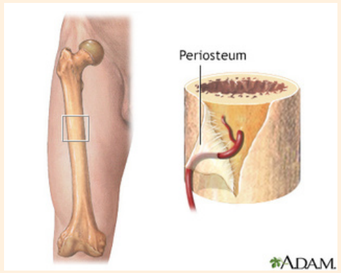
2 Layers:

Fibrous Layer:

- Composed mainly of collagen fibres (Sharpey fibers)
- These provide strength and support to the bone
- Continuous with muscles tendons on top of the bone + penetrate deep into bone matrix to secure periosteum and overlying muscle to the bone.

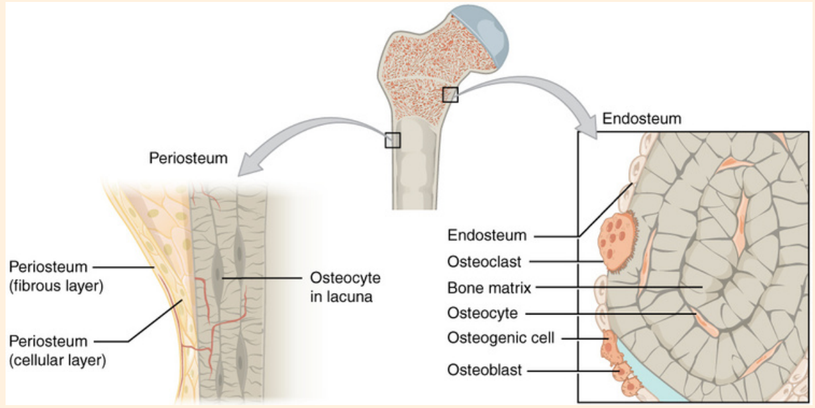
Osteogenic layer:

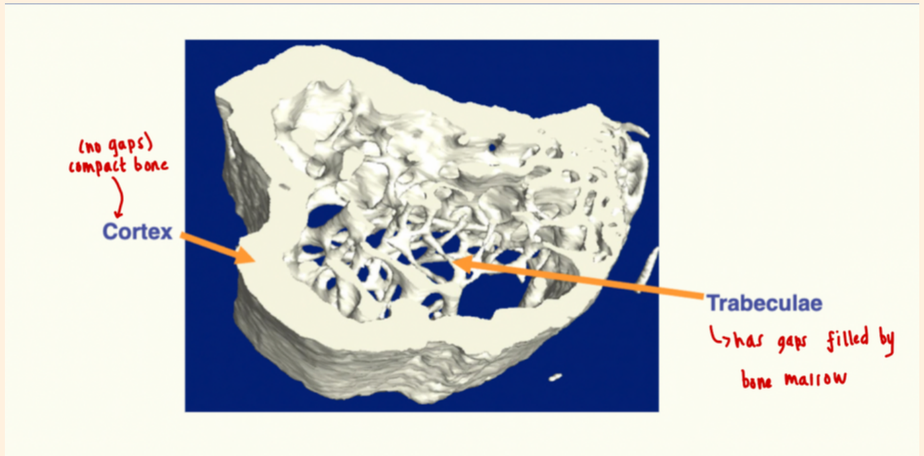
- Inner layer composed of cells such as osteoblasts, osteocytes, and osteoclasts
- important in bone healing and growth

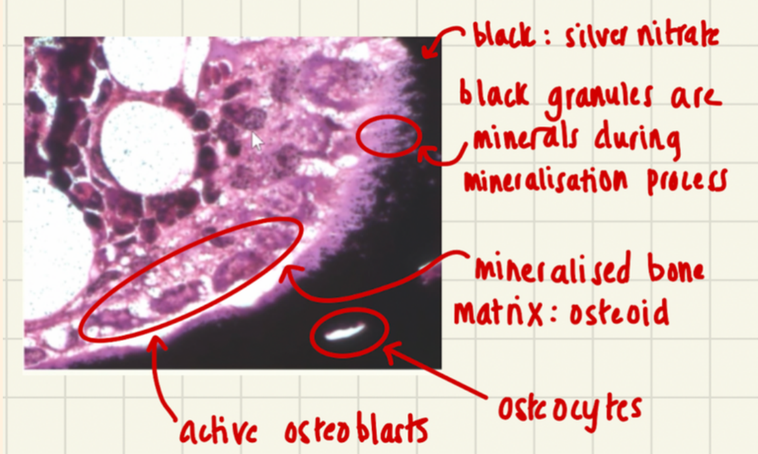


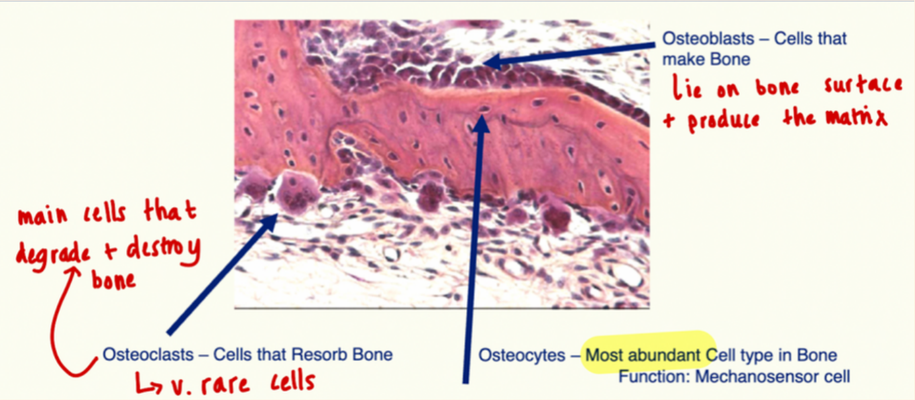
ENDOSTEUM: INTERNAL

- Lines internal surfaces of bone: covers the medullary cavity and trabeculae.
- Contains same bone forming cells as the osteogenic layer of the periosteum
- Short Irregular and Flat bones: Endosteum covered spongy bone









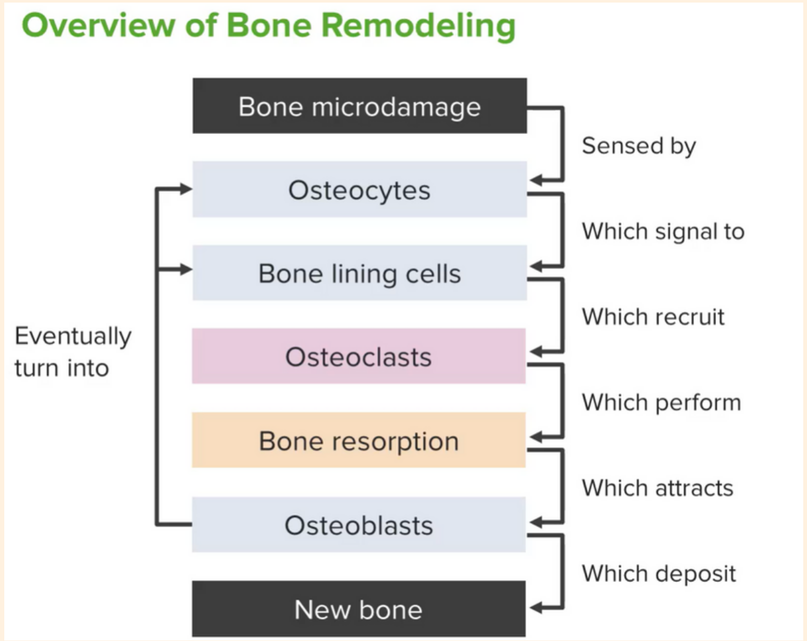
Osteocytes: Mechanoreceptors, connected by osteocyte processes, embedded in bone matrix, maintain bone metabolism

Osteoprogenitor Cells: Pre-cursors of osteoblasts, derived from mesenchymal bone cells (differentiate into osteoblasts -> stimulated by stress)
They are found along the osteogenic periosteum, in the endosteum and in canals.

OSTEOBLASTS

- Bone forming cells of **mesenchymal** origin
- Express high levels of **alkaline phosphatase**
- Secrete and respond to many growth factors and cytokines
- Active or inactive (flattened) osteoblasts cover most bone surfaces
- Osteocytes are incorporated into the matrix
- Unable to divide: must come from osteogenic cells

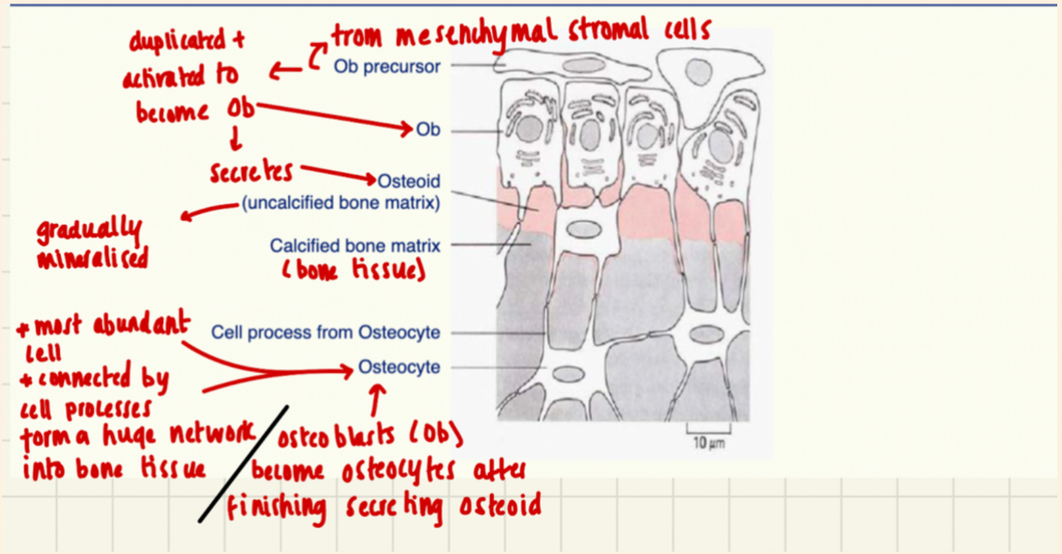
BONE REMODELING

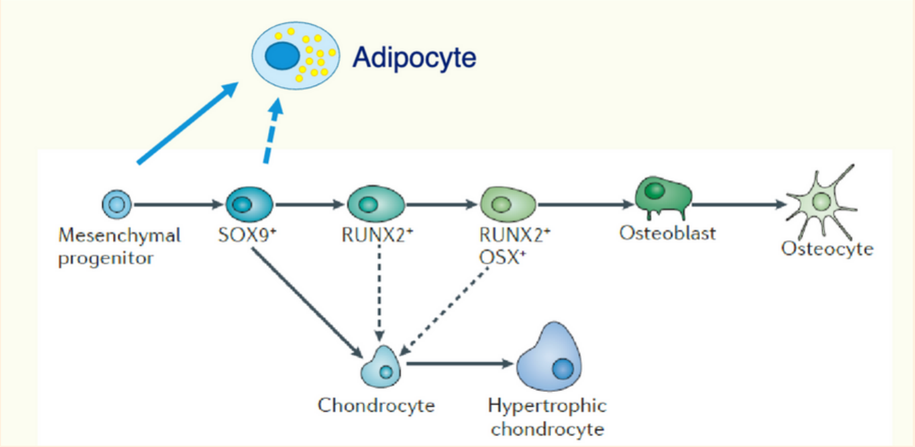


Used to maintain and grow the skeleton (renewal every 7-10 years)
Bone remodelling occurs in response to 3 things:

1. **Bone micro-damage (macro or micro fractures)**
2. **Stress on the bone (Wolff's Law)**
3. **Hormonal Requirements: Calcium deficit**

OSTEOBLASTS

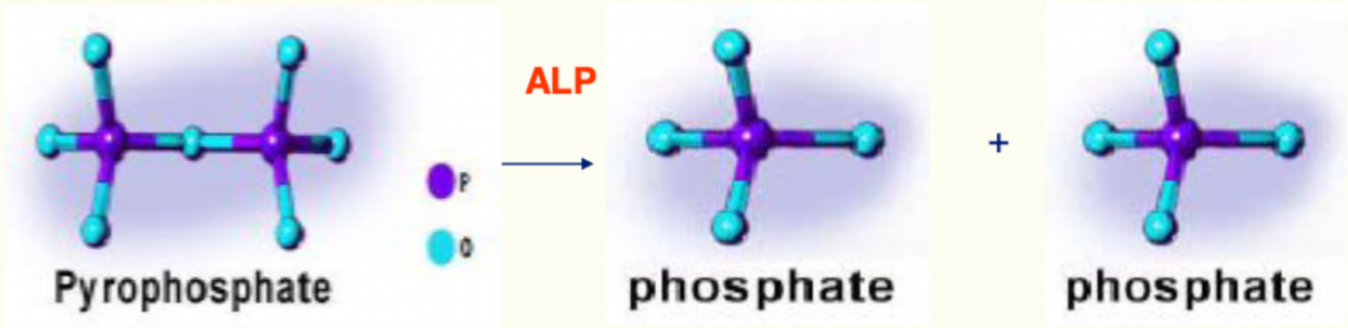




SOX9 is the master regulator!!!

Alkaline phosphatase (ALP) and Mineralisation

- expressed on surface of differentiated osteoblasts; also released into the extracellular fluid and circulation (bone formation marker)
- releases inorganic phosphate ions (PO_4^{3-}) from diverse molecules (hydrolysis)
- ALP promotes mineralisation (ie, precipitation of calcium phosphate/ hydroxyapetite) in 2 ways:
  - by **increasing** the local **concentration** of **inorganic phosphate ions**
  - by hydrolysing **pyrophosphatase**, a key inhibitor of mineralisation



BONE MATRIX

Bone Matrix

- Bone is a composite material (like reinforced concrete)
- **Inorganic Hydroxyapatite Mineral (2/3rd by weight) =** Calcium Phosphate
- **Organic component (1/3rd of weight) is ~90% type I collagen**
  - Structural protein providing strength and flexibility
  - Major structural protein in the body
  - Also present in tendon, ligaments, skin and scar tissue
- Remaining 10% of organic component is a complex mixture
  - Growth factors
  - **Osteocalcin (used as bone formation marker)**
  - **Osteonectin**
  - **Osteopontin: cytokines → attract osteoclasts + osteoblasts**
  - Glycoproteins

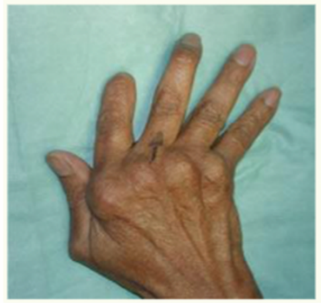
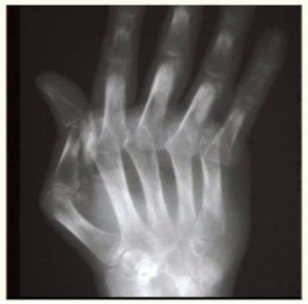
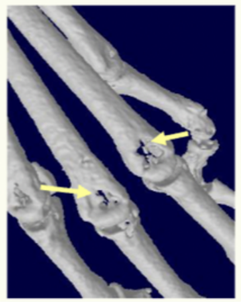
Bone matrix mineralisation

- Skeleton contains **~98% of body calcium**
- Mineral component in **Hydroxyapetite**

  $-Ca_{10}(PO_4)_6(OH)_2$
  - tiny crystals surround collagen fibres
  - provides rigidity, resistance to compression
- Mineralisation of **osteoid** dependent on **hormonally active form of vitamin D3 (1,25-$(OH)_2$D3)**
  - Main source of this is sunlight
  - Deficiency results in failure to mineralise
  - Leads to **rickets** in children: bended bones
  - **Osteomalacia** in adults
- Full mineralisation takes several months

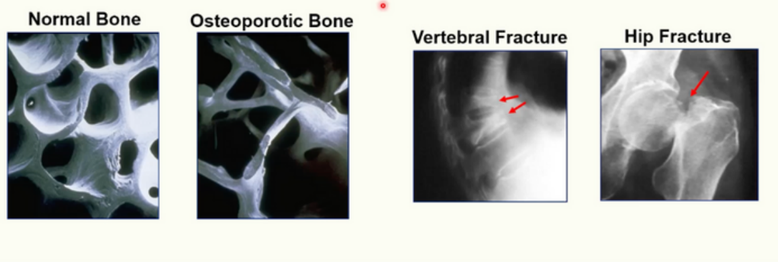
Inflammatory bone loss: Rhematoid Arthiritis

- An inflammatory joint disease with unknown etiology
- Affects about 1% of the population
- Women are affected three times as frequenctly as men
- Onset is usually in the patients 30s/40s
- Features: joint swelling, **cartilage and bone erosions**
- Both local and systemic bone loss

Bone formation and resorption are balanced

- imbalance between formation and resorption leads to disease
- **osteoporosis**
  - most common cause: low E2 (oestrogen) after menopause
  - main cause of bone loss: increased bone resorption

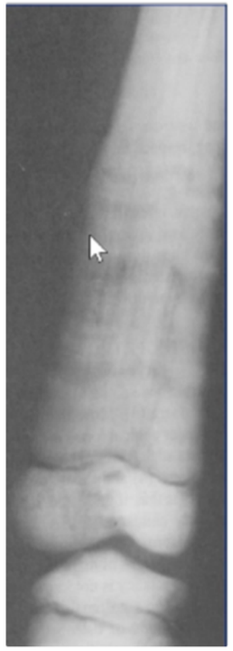


- **Paget's disease**
  - due to overactive osteoclasts

CONDITIONS

Osteopetrosis

- Inherited bone disease
- Increased bone mass
- Caused by dysfunctional osteoclasts
- Also known as ‘marble bone disease’
- On the x-ray can see how it is almost compact bone
- Basically don’t have bone marrow cavity/ only small proportion

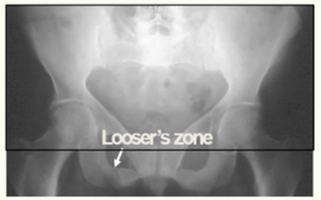


Osteomalacia

Softening of bone due to defective mineralisation of newly formed bone in a mature skeleton

clinical presentation

- Bone pain
- Bone tenderness (sternum, anterior tibia)
- Fractures (spontaneous and pseudo)
- Muscular weakness
- Malaise
- Tetany
- Low bone mineral density



Looser's zones = pseudofractures
• common sites: lateral scapula
ribs
medial femur
pubic rami

MORE CONDITIONS

REGULATION OF BONE METABOLISM

3 primary regulators

Vitamin D
Stimulates Ca2+ absorption in gut
Stimulates bone deposition
Levels controlled by PTH

Calcitonin
Decrease serum calcium
Inhibits bone resorption
Stimulate bone deposition
Opposes PTH action

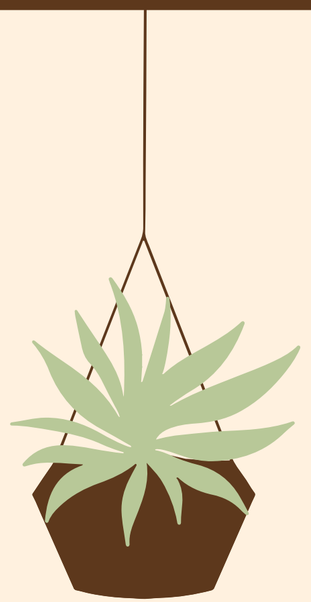
Parathyroid hormone (PTH)
Increase serum calcium
Stimulates bone resorption
Opposes action of calcitonin

Purpose of Bone Metabolism

- Maintains strength and structure of bones
- Storage and regulation of serum calcium (and phosphate)

Calcium levels must be regulated.

Calcium cannot be synthesised in the body so must be obtained via the diet.



VITAMIN D

Summary

- Vitamin D is important for bone mineralisation
- Vitamin D enhances calcium and phosphate absorption from the intestine
- Vitamin D metabolism involves 2 hydroxylation steps
  - **25(OH) Vitamin D reflects vitamin D status**
  - **$1,25(OH)_2$ Vitamin D is metabolically active**
- Vitamin D deficiency causes rickets in children
  - bone disease associated with decreased serum calcium
- Vitamin D deficiency causes osteomalacia in adults
  - softening of bone
- calcitonin lowers serum calcium and phosphate

SYNTHESIS

- 7-dehydrocholesterol in skin exposed to UV which causes it to rearrange into cholecalciferol / Vitamin D3 (found in skin or taken in from diet (fish))
- In the liver: hydroxylated by 25(OH)ase to form 25(OH)D3 (Calcidiol)
- In the kidneys: second hydroxylation by 1-alpha-hydroxylase to form 1,25(OH)2D3 (Calcitriol)- most active from of vitamin D

EFFECTS

- Kidneys: inhibits action of 1-alpha-hydroxylase by negative feedback loop so not too much active vitamin D is produced
- Bone: increased reabsorption (by increasing RANK-L expression which increases osteoclast activity)
- GI tract: increase calcium and phosphate absorption from the intestines
- Upregulating expression of intracellular calcium binding proteins: Calbindin D9k
- Indirectly, it increases bone mineralisation using Ca2+ and PO4

VITAMIN D: DEFICIENCIES

CAUSES

- **Reduced skin synthesis** due to less sunlight or increased melanin (which absorbs UVB)
- **Decreased Bioavailability**: due to malabsorption of fat in the gut
- **Decreased Synthesis of 25(OH)D3:** liver failure
- **Decreased synthesis of 1,25(OH)D3**: kidney diseases ie CKD

CLINICAL CONSEQUENCES

- **Muscle weakness**
- **Osteoporosis: weakness of bone due to lack of balance between bone reabsorption and deposition**
- **Rickets (children) – softening of bone due to lack of mineralisation**
- **Osteomalacia (adults) - softening of bone due to lack of mineralisation**

PARATHYROID HORMONE

PRIMARY FUNCTION: INCREASE CALCIUM LEUELS

- Synthesised by Chief cells of parathyroid glands.
- Primarily regulated by Calcium levels

- Low calcium: stimulates PTH secretion
- High calcium: inhibits PTH secretion

Bones:

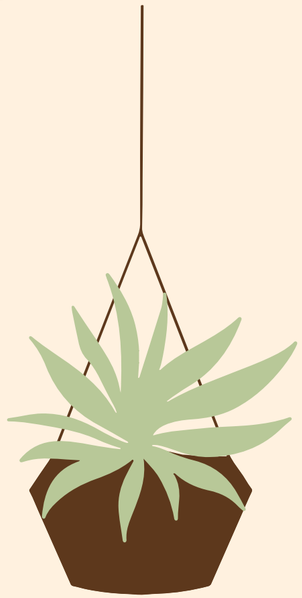
- PTH stimulates osteoclasts: bone resorption
- PTH inhibits osteoblasts: bone deposition
- Results in ↑ serum Ca2+ and Phosphate

Kidneys:

- ↑ Renal Ca2+ reabsorption
- ↑ Renal phosphate excretion (so it does not combine with Ca2+ to form bone)
- ↑ Hydroxylation of calcidiol → calcitriol (activated vitamin D)

GI tract:

Calcitriol promotes intestinal Ca2+ absorption



- **Synthesis:** Produced by C cells in thyroid gland
- **Primary Function:** decrease serum Ca2+ levels
- **Opposes the action of PTH**

Bone:

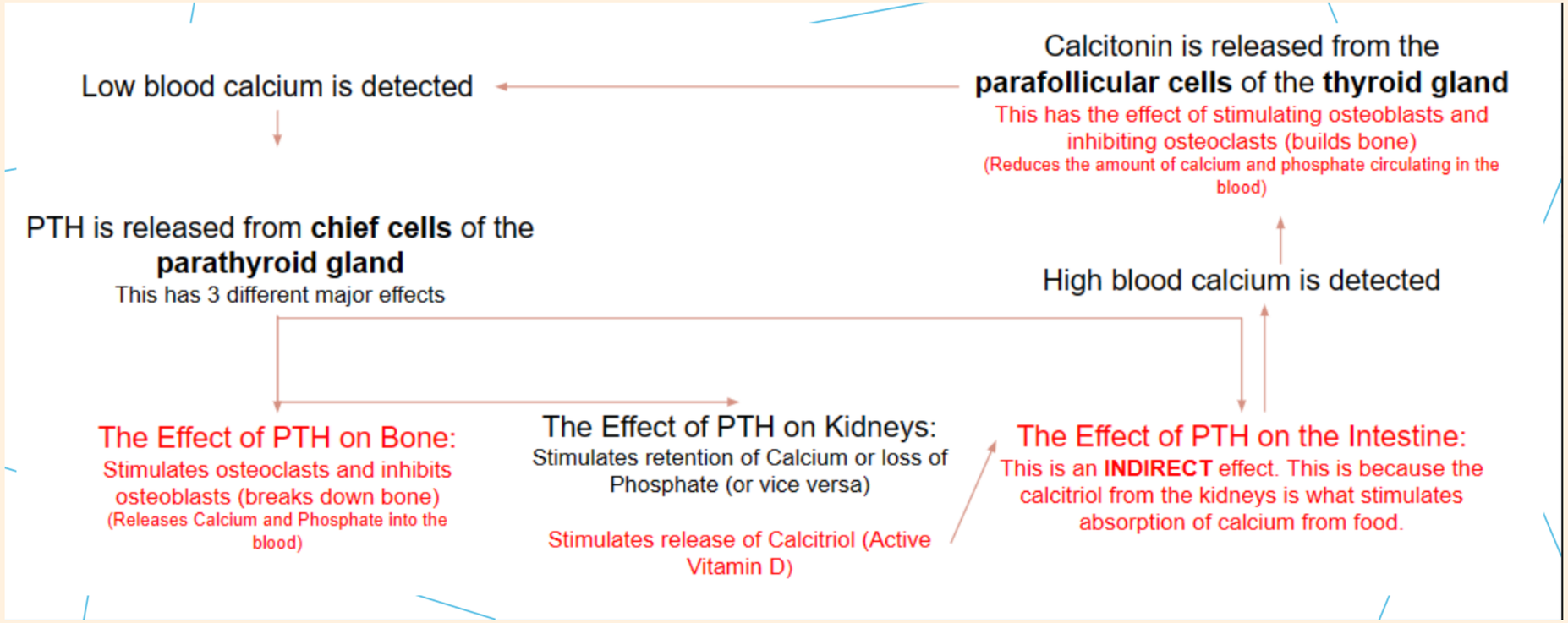
- **Inhibits osteoclasts: inhibit bone breakdown**
- **Stimulates osteoblast: calcium deposition in bone/bone ossification**

Kidneys:

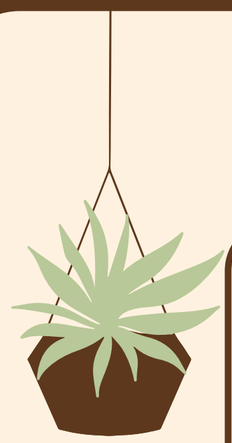
- **↓ Ca2+ reabsorption → ↓ serum Ca2+ level**
- **↓ Phosphate reabsorption → ↓ serum phosphate**

CALCITONIN

HORMONAL REGULATION OF CALCIUM AND PHOSPHATE USING PTH AND CALCITONIN



Creds to Mahad Safdar, Y3



PROSTAGLANDINS

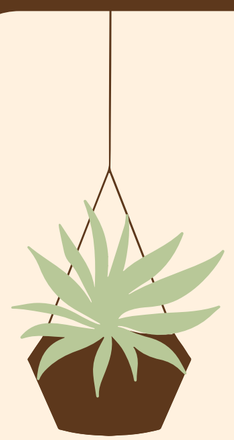
- Fatty Acid Metabolites
- Produced by OsteoBlasts
- Increase and decrease Osteoclast activity, to mediate the actions of growth factors and responses to mechanical loading

CYTOKINES (E.G. INTERLEUKINS)

- Produced by Immune Cells and Bone Cells
- Increase Osteoclast recruitment and activity, increasing bone loss
- Sex steroids can inhibit Interleukin activity

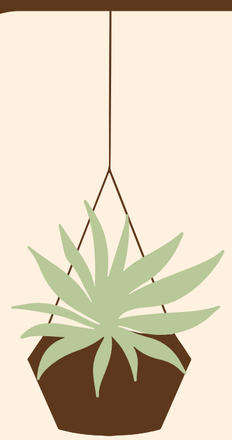
OSTEOCLASTS EXPRESS HIGH LEVELS OF WHAT?

- Carbonic anhydrase II
- Sclerostin
- Calcium
- NO
- PTH



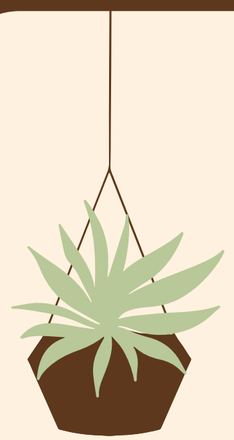
OSTEOCLASTS EXPRESS HIGH LEVELS OF WHAT?

- **Carbonic anhydrase II**
- Sclerostin
- Calcium
- NO
- PTH



OSTEOCYTES ARE WHAT KIND OF CELLS?

- PRODUCE OSTEOPROGENITOR CELLS
- VITAMIN D PRODUCING
- MECHANORECEPTORS
- PTH PRODUCING
- ANASTAMOSING



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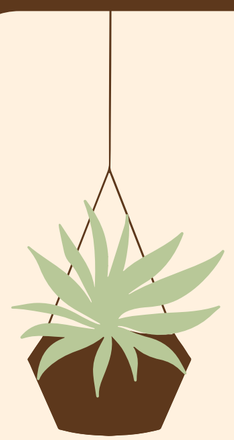
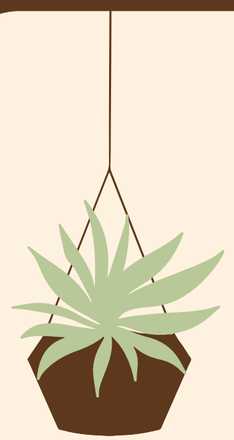


WHICH SKELETON IS THE STERNUM PART OF?



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