Physiological Mechanisms

Bone

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Contents

External link

Animation link for ageing bone:

http://www.argosymedical.com/flash/aging_bone/landing.html

Bone is an organ that forms the endoskeleton. It is a specialized type of connective tissue which also has blood vessels, adipose tissue, cartilage, epithelium, nervous tissue and blood forming cells.

Functions of bone

- ***Support***. Bone supports the body by forming the endoskeleton. Bones also provide attachment to the skeletal muscles.
- ***Movement***. Movement in the body is produced by contraction of muscles that pull at bones.
- ***Protection of internal organs***. Bones provide a rigid covering for protecting the internal organs, e.g. cranial bones protect the brain, vertebral column protects the spinal cord and the rib cage protects the heart and lungs.
- ***Mineral balance***. Minerals, such as calcium and phosphorous, are stored in bones and released into circulation when needed.
- ***Haemopoeisis***. The cavities of bones are lined by red bone marrow that produces blood cells, a process known as haemopoeisis.
- ***Fat storage***. In infants all bones have a red bone marrow engaged in haemopoeisis but with age the red bone marrow is replaced by yellow bone marrow that serves to store fats in the form of triglycerides which are released when needed.

Structure of bones

On the basis of shape, bones can be classified into four types:

humerus

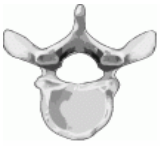
1. **Long bones**. Their length is more than their width, e.g., bones of the upper and lower limbs.

carpal

2. **Short bones**: Their length and width are almost equal and they seem cuboid or round e.g. bones of the wrist and ankles.

sternum

3. **Flat bones**: These are thin, flat, and usually curved, e.g. bones of the skull and the ribs and the breast bone.



vertebra

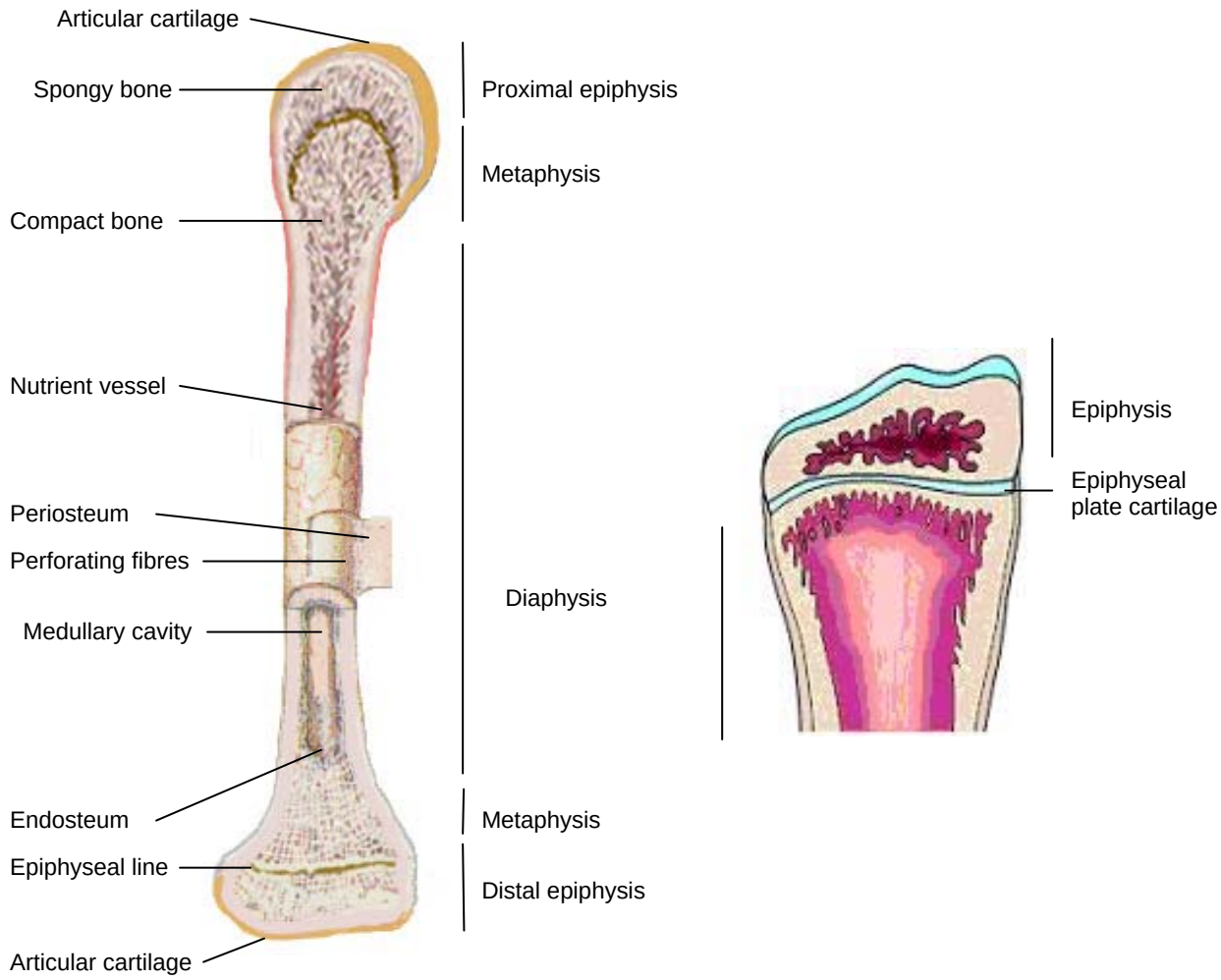
4. **Irregular bones**. These have no definite shape, e.g. the sphenoid bone of the skull and vertebrae.

Long bone

A typical long bone, e.g. the humerus (the bone of the upper arm), is divisible into the following parts (Fig. 1):

- **Diaphysis.** This is the middle, main portion of the bone along its length.
- **Epiphyses**. These are the terminal portions of the bone; the proximal and the distal epiphysis.
- **Metaphyses**. These are the regions between the diaphysis and the epiphysis on each end. Growing bone contains cartilaginous tissue (hyaline cartilage) that forms the *epiphyseal plate*, the region where the bone grows in length. When the bone stops growing this cartilaginous tissue becomes ossified and is known as the *epiphyseal line*.

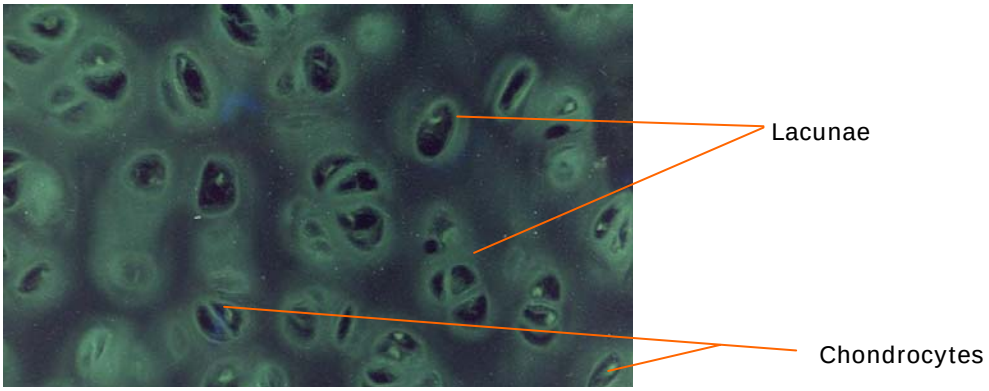
Fig 1: Structure of long bone



Hyaline cartilage

It is made up of cartilage cells, the *chondrocytes*, enclosed in spaces called *lacunae*. The matrix around the cells contains collagen fibres (that are evenly distributed) and proteoglycans. Water is retained by proteoglycans providing flexibility to the cartilage. Collagen fibres provide strength.

Fig 2: Hyaline cartilage



- **Articular cartilage**. It is a thin layer of hyaline cartilage found at the two ends of a bone where it forms a movable joint with another bone. It reduces the friction between bones when they move and also acts as a shock absorber.
- **Periosteum**. It is the tough, outermost covering of the major part of the bone along its length (where the bone is not covered by the articular cartilage). It is made up of dense connective tissue and serves the following functions:
  - It helps nourish the bone tissue.
  - It causes the bone to grow in thickness as it contains bone forming cells.
  - It protects the bone.
  - It helps in fracture repair.
  - It provides the surface for attachment of ligaments and tendons. The collagen fibres of ligaments and tendons are continuous with those of the periosteum. Some collagen fibres of the tendons and ligaments penetrate the periosteum to reach the outer part of the bone. These are known as perforating or ***Sharpey's fibres***.
- **Medullary or marrow cavity**. It is the space in the diaphysis that is occupied by the bone marrow.
- **Endosteum**. It is the inner lining of the medullary cavity that contains the bone forming cells and bone resorbing cells. It is usually one-cell thick (Fig. 1).

Depending on the spaces present in the bone it can be classified as **compact** or **spongy** bone. Compact bone has fewer spaces while the spongy bone has many spaces with a network of mineralized tissue called trabeculae. Both compact and spongy tissues are present in different regions of the same bone. Usually the outer parts of a bone are compact while the inner parts are spongy.

In **long bones**, the shaft is made of compact tissue while the medullary cavity has a layer of spongy bone around it. At the ends (epiphyses) there is an outer thin layer of compact bone while most of the inner region consists of spongy bone. Covering the compact bone of the epiphysis is a layer of hyaline cartilage—the articular cartilage.

Short bones have an outer covering of compact bone and an inner region of spongy bone. The articular surfaces are covered with hyaline cartilage and at other places the perisoteum.

Flat bones have a layer of spongy bone between two thick layers of compact bone.

Irregular bones have air spaces called sinuses (so also called pneumatic bones). Irregular bones can be a combination of any of the other types of bones. The projections in these bones have epiphyseal growth plates.

Histology of bone

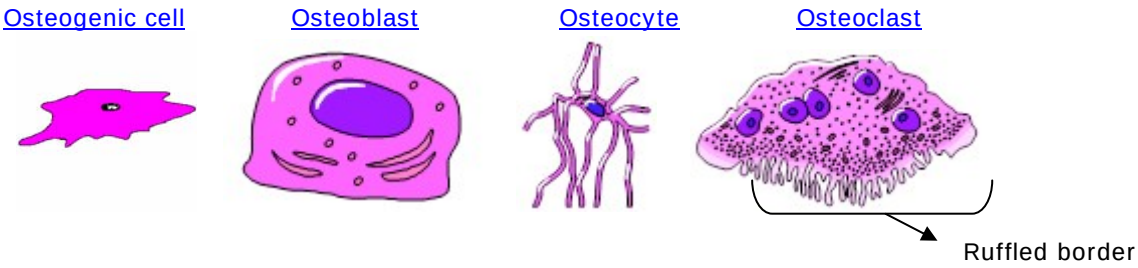
Since bone is a connective tissue it consists of cells and an intercellular matrix. The matrix is made up of 25% water, 25% protein fibres and 50% minerals. The matrix has a framework of collagen fibres and proteoglycans (organic matrix) around which mineral salts, such as calcium phosphate (hydroxyapatite, the major constituent), calcium carbonate and small amounts of magnesium hydroxide, fluoride and sulphate (the inorganic matrix), are deposited. The process of deposition of these mineral salts is known as *calcification or mineralization* and is initiated by a type of bone cell, the osteoblast. Before mineralization, the bone is known as an osteoid.

The collagen fibres and proteoglycans provide flexibility and the mineral salts provide hardness to the bone. Without collagen fibres and proteoglycans bones become brittle and without mineral salts bones become rubbery.

Four different types of cells are present in the bone matrix.

1. **Osteogenic cells**. These are undifferentiated cells of the mesenchyme (also known as the osteochondral progenitor cells) which divide to form osteoblasts. These are the only dividing bone cells. These are present in the inner lining of the periosteum, the endosteum and the blood vessel-carrying channels of the bone.
2. **Osteoblasts**. These cells are responsible for the formation of bone. They synthesize collagen and secrete it by exocytosis. They also secrete minerals like Ca^{2+} and PO_4^{2-} which cause calcification of the bone.
3. **Osteocytes**. Once the matrix is secreted around the osteoblasts they become fully formed cells called osteocytes which are trapped in the matrix. The spaces around the osteocytes are called lacunae. Adjacent osteocytes are connected to each other through projections that run through channels called canaliculi. Nutrients, gases and wastes are carried though the fluid in the canaliculi. Osteocytes do not secrete the matrix but they maintain bone tissue.
4. **Osteoclasts**. These are bone-resorbing cells derived from fusion of many monocytes (a type of white blood cell). Thus, osteoclasts are multinucleated. The surface in contact with the bone matrix has microvilli-like structures forming a ruffled border. Acids, lysozymes, and other enzymes, such as collagenase are secreted by the osteoclasts which dissolve the minerals and proteins in the bone matrix. Some of the digested products are taken in by the osteoclasts by means of endocytosis.

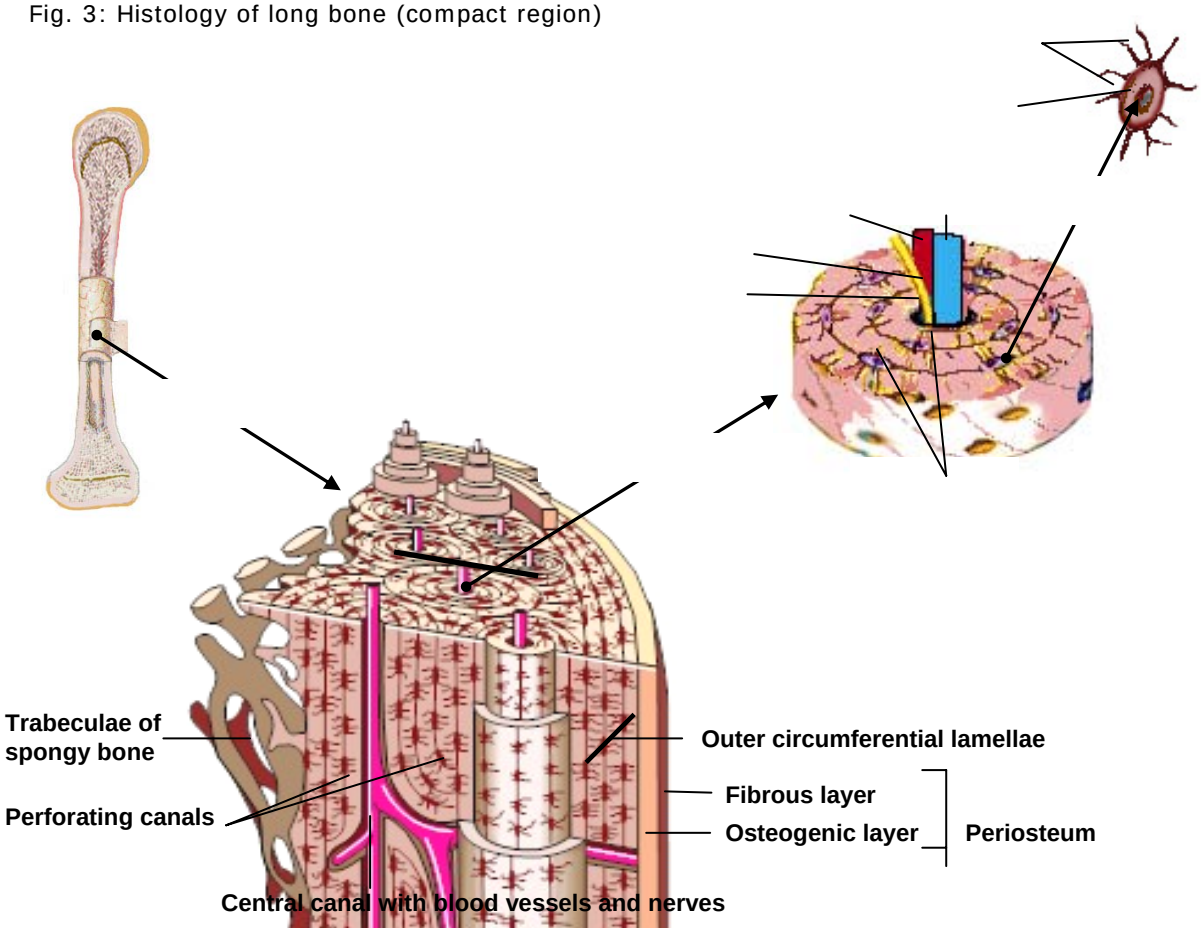
Fig. 2: Types of bone cells



Histology of compact bone tissue

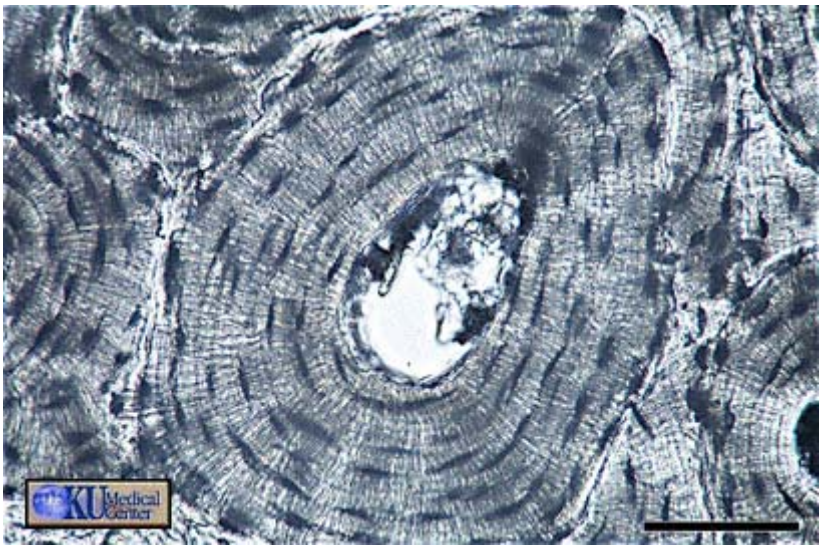
- The bone tissue consists of units called *osteons* or *Haversian systems*. Each osteon consists of a vertical central canal that contains blood vessels, lymphatics and nerves (Fig. 3).
- Around the central canal there are concentric rings of bone matrix—*the concentric lamellae* (Fig. 4).
- Between the lamellae are present the *lacunae*—spaces containing osteocytes which are connected to each other by *canaliculi*.

Fig. 3: Histology of long bone (compact region)



- Osteons in compact bone are lined along the line of stress on the bone, e.g. in the diaphysis of the long bones, the osteons are arranged longitudinally.
- Organization of osteons keeps changing with change in the lines of stress applied to the bone
- In addition to the complete circular osteons there are incomplete osteons, which are remnants of older osteons that have undergone remodeling or are added during growth in thickness of the bone (especially the outer circumferential lamellae; see below). These incomplete units are called *interstitial lamellae*. They also have lacunae with osteocytes and canaliculi.
- Interstitial lamellae towards the periosteum are called *outer circumferential lamellae* and those towards the medullary cavity are called *inner circumferential lamellae*.
- The blood vessels, lymphatics and nerves in the periosteum connect with those in the central canals and the medullary cavity through horizontal channels, called *perforating* or *Volkmann's channels*, running across the bone tissue.
- The periosteum consists of two layers: an outer layer of fibrous connective tissue and an inner layer of osteogenic cells.
- Towards the medullary cavity in long bones there is a layer of spongy bone.

Fig. 4: Micrograph showing histology of compact bone



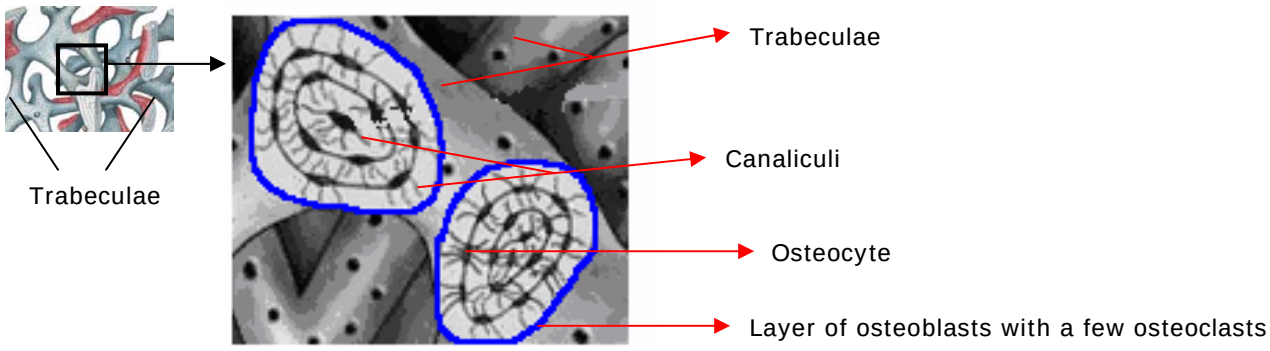
An osteon showing lamellae arranged in concentric circles.
Source: http://www.kumc.edu/instruction/medicine/anatomy/histoweb/bone/bone.htm

Histology of spongy (or cancellous) bone tissue

Spongy bone is present at the ends of long bones and along the medullary cavity. It makes up most of the short, flat and irregular bones (where the compact bone surrounds a central spongy bone). Spongy bone tissue is organized into a network of rod-shaped structures called *trabeculae* with spaces between them. These spaces are occupied by the red bone marrow, blood vessels, lymphatics and nerves. The *trabeculae* are arranged along the lines of stress. Spongy bone is present in regions where stress is applied from many directions. Spongy bone reduces the overall weight of the bone making its movement easier.

The trabeculae of the spongy bone also have concentric rings of matrix forming the lamellae with lacunae containing osteocytes connected to each other through canaliculi. The trabeculae are covered on their surface by osteoblasts with some osteoclasts (Fig. 5).

Fig. 5: Histology of spongy bone



Formation of bone: osteogenesis

Osteogenesis or ossification occurs during fetal life. Bones can be formed by two processes—intramembranous ossification and endochordal ossification—though the end-result of both the processes is the same. Some bones form by one process and some form by the other process.

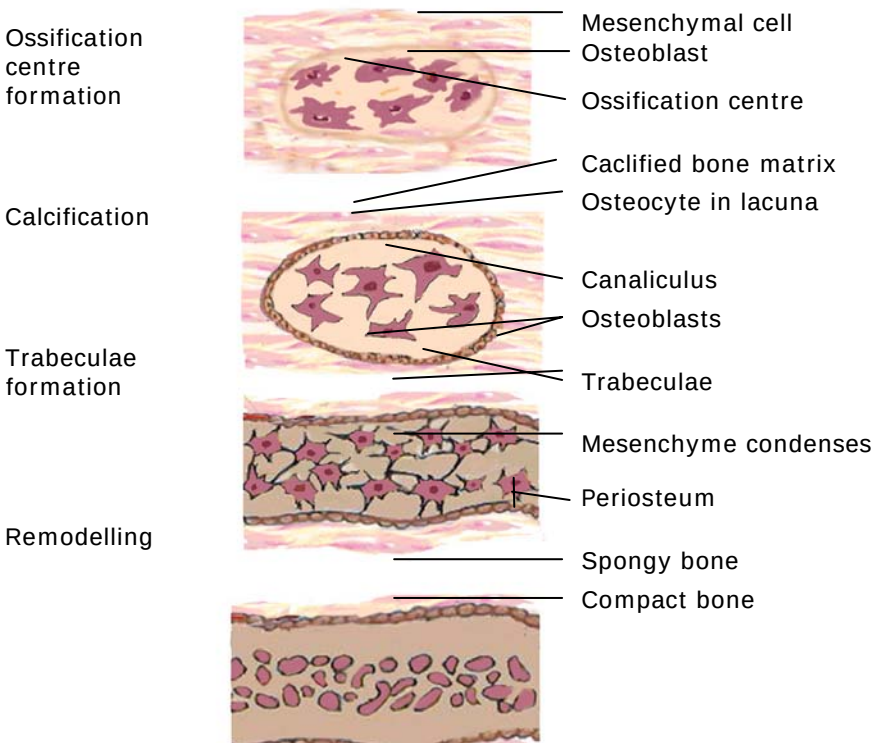
Intramembranous ossification

In this process there is direct calcification in the mesenchymal cells (connective tissue). The sequence of events is as follows—

- The mesenchymal (embryonic connective tissue) cells aggregate to form fibrous connective tissue membranes. Such a cluster is known as the **centre of ossification**.
- The cells then form osteogenic cells that differentiate into osteoblasts.
- Osteoblasts secrete collagenous matrix around them and mineralization takes place.
- Osteoblasts become osteocytes which are surrounded by the matrix. Osteocytes are present in the lacunae which are connected to the adjacent osteocytes by canaliculi (Fig. 6).
- The matrix with the osteocytes gets arranged into trabeculae with spaces in between them to form a spongy bone. The spaces are invaded by blood vessels with the connective tissue around them giving rise to the red bone marrow.
- The blood vessels also invade the mesenchyme surrounding the spongy bone.
- On the outer surface the mesenchyme forms the periosteum.
- Most of the spongy bone is converted into compact bone by a process of remodeling leaving spongy bone in the centre.

Usually flat bones, e.g. the skull bones, are formed by this process resulting in the formation of compact bones on the sides with spongy bone in between.

Fig. 6: Intramembranous ossification

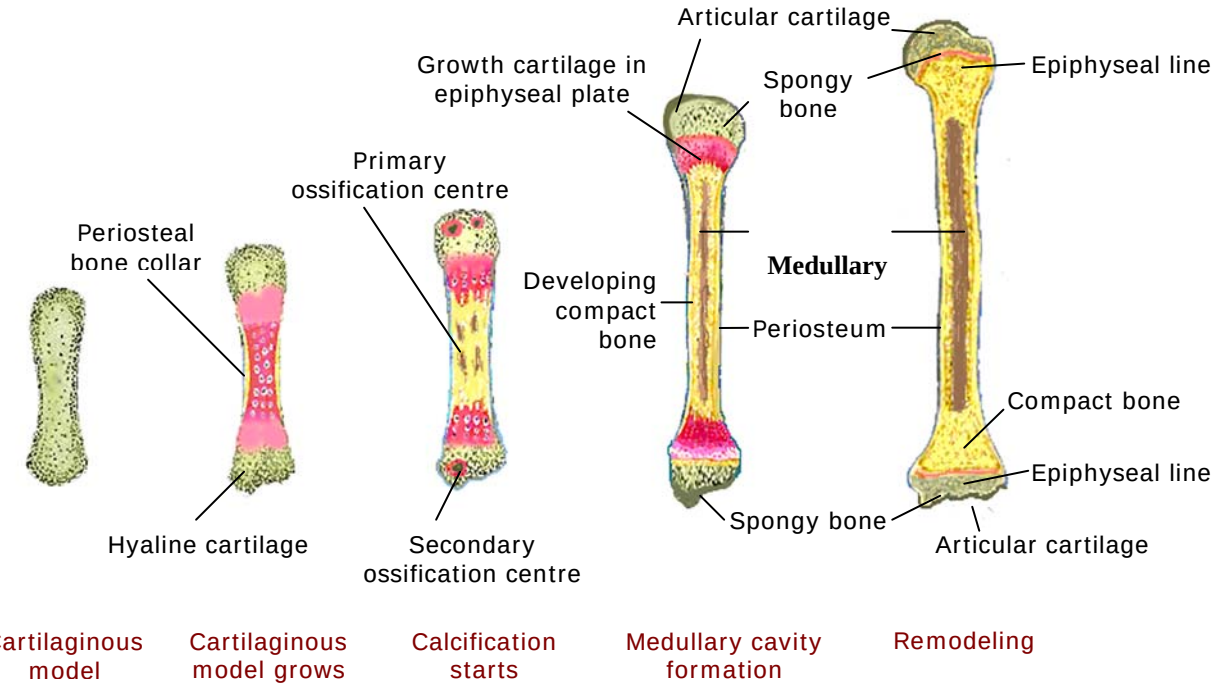


In this process, wherever a bone has to form, first a cartilaginous template is formed which then gets ossified to form a bone (Fig. 7). Most of the bones, especially the long bones, are formed by this process and includes the following steps:

- The mesenchymal cells aggregate in the region of bone formation and get differentiated into chondroblasts.
- The chondroblasts form a cartilaginous matrix and get differentiated into chondrocytes.
- Except at the ends (the future articular surfaces of the bone), the cartilage forms the perichondrium.
- Blood vessels invade the perichondrium and the osteochondral progenitor cells form the osteoblasts.
- The osteoblasts in the perichondrium start secreting the bone matrix and cause calcification forming a layer of compact bone over the cartilaginous tissue. This layer of compact bone is called a *bone collar*.
- Simultaneosly, the cartilaginous tissue grows in length (interstitial growth) because of cell division of chondrocytes which secrete more matrix around them. There is an increase in the thickness of the cartilaginous tissue also (appositional growth) by addition of new matrix secreted by chondroblasts derived from the perichondrium.
- Some chondrocytes located in the center, hypertrophy and burst. This initiates calcification of the matrix in the centre. More chondrocytes in the centre die as nutrients cannot diffuse through the calcified matrix. Spaces formed after the degeneration of these chondrocytes in the centre merge to form cavities.

- The perichondrium surrounding the cartilage forms the periosteum.
- Blood vessels from the periosteum reach the spaces in the region of the calcified cartilage in the centre.
- Osteoblasts and osteoclasts form bone on the surface of the calcified cartilage. This bony tissue gets arranged into trabeculae that forms the spongy bone next to the medullary cavity in a long bone. This region of ossification is known as ***primary ossification centre***.

Fig 7: Endochondral ossification



- Osteoclasts remove calcified regions from the centre to form the medullary cavity and the connective tissue here forms the red bone marrow.
- More cartilaginous tissue along the centre forms bone to give rise to the trabeculae of the spongy bone.
- The bone collar thickens which forms the compact bone of the diaphysis.
- While ossification starts at the centre in the diaphysis which is the primary ossification centre, ossification occurring in other regions, e.g. the epiphyses of the long bones form the ***secondary ossification centres***.
- The process of ossification in the secondary centres is the same as in the primary ossification centre but the spaces here do not form the medullary cavity.
- All the cartilage except those at the articular surfaces and at the epiphyseal plates is converted into bone.
- The original embryonic hyaline cartilage persists as the articular cartilage and epiphyseal plates (which in an adult form the epiphyseal lines when the epiphyseal plates close).
- Final shape of the bone is achieved by remodeling.

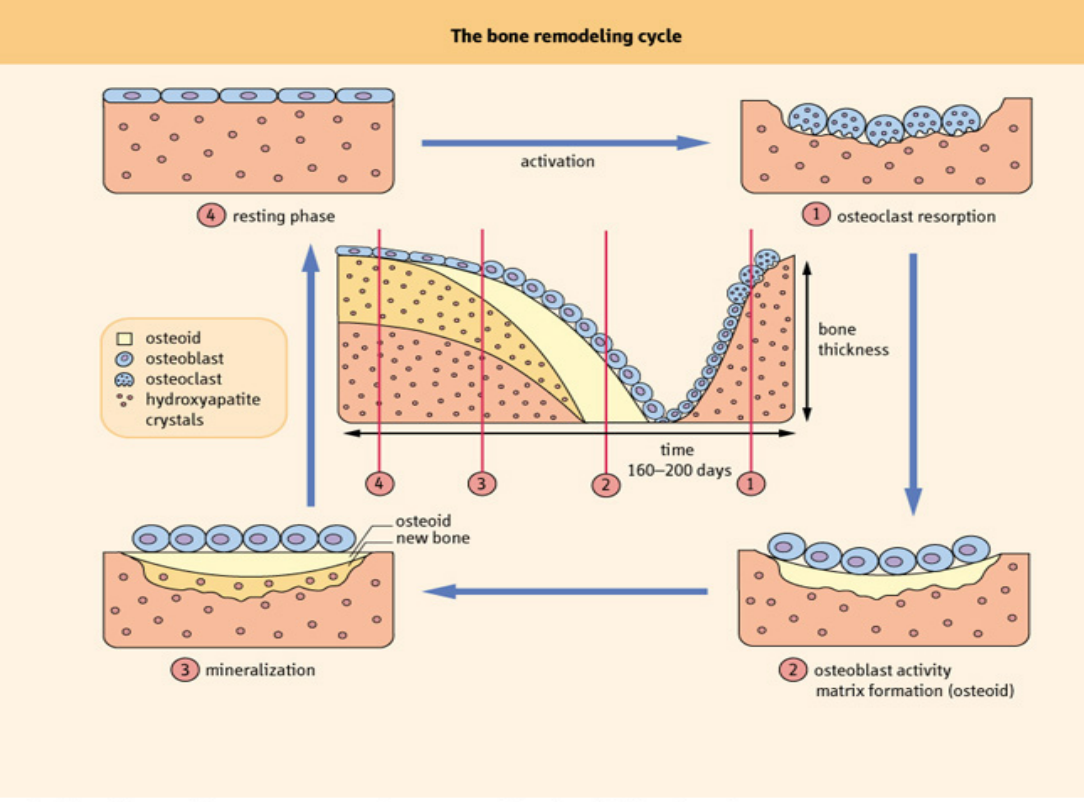
Bone remodeling

Even when bones are not growing in size in an adult there is a renewal or remodeling of the bone. In this process old bone is resorbed by osteoclasts and new bone is formed by osteoblasts (Fig. 8). Remodeling serves three functions:

1. It replaces old bone tissue with new before degeneration starts.
2. It forms new bone tissue along the lines of mechanical stress enabling the bone to meet the demands of the body.
3. Fractures are also repaired by this process (see later).

The osteoclasts brought in by the blood vessels in the periosteum or endosteum arrive at the site of bone resorption. The ruffled border of osteoclasts is in contact with the bone surface. Enzymes and acids are secreted by the osteoclasts that digest the collagen fibres and mineral salts to form a groove on the bone surface. The products of digestion are absorbed by the osteoclasts by endocytosis and released on the other side of the osteoclasts into the interstitial fluid from where they are absorbed into the capillaries. Osteoclasts then leave that site which is then occupied by osteoblasts which secrete new matrix to form the bone tissue.

Fig 8: Bone remodeling



In humans, bones keep growing in both length and thickness till the age of 25 years, after which lengthening of bone stops. However, they keep growing in thickness throughout life.

Bone growth

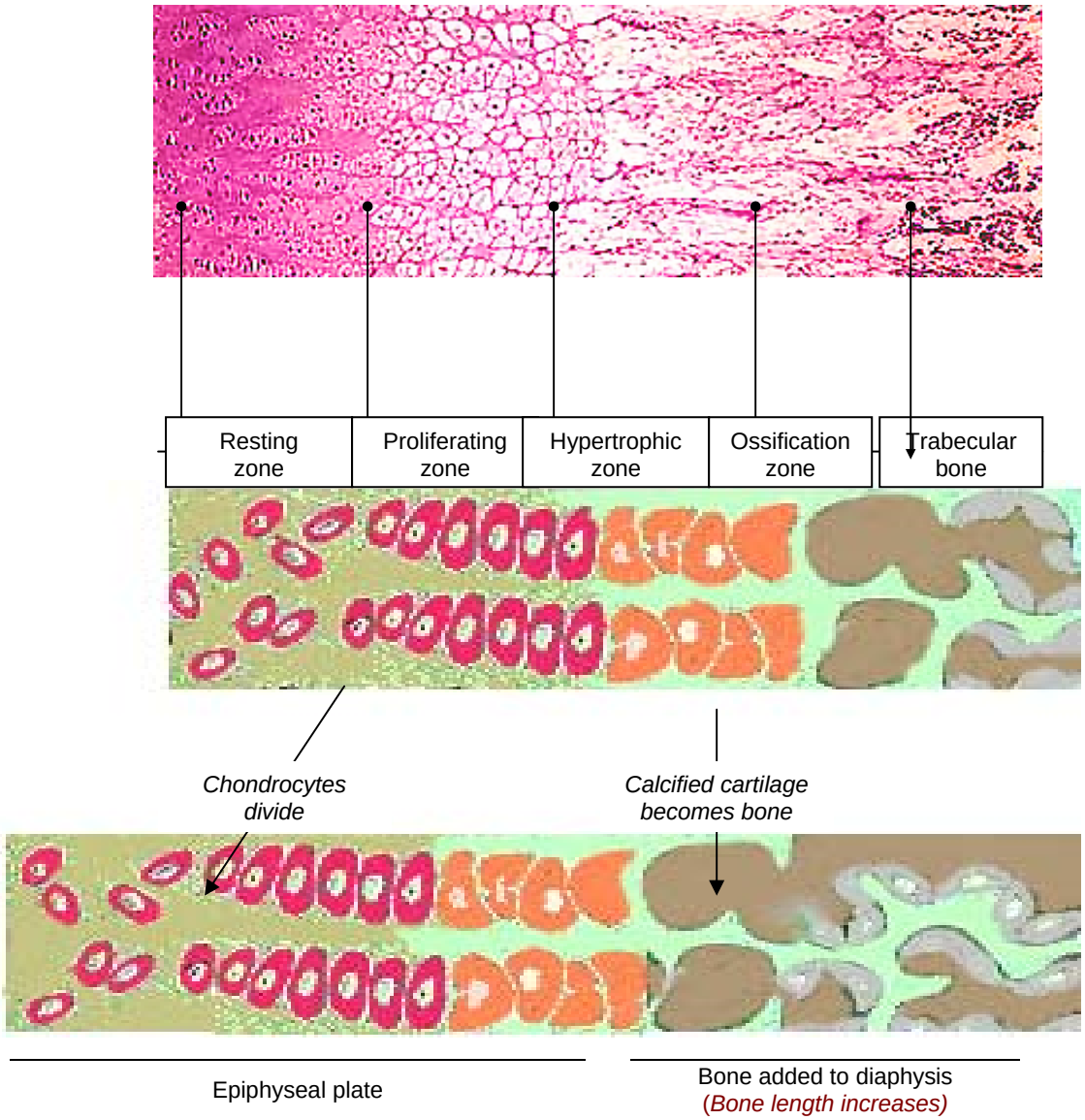
Growth in length

Bones grow in length at the epiphyseal plate regions where there is cartilaginous tissue present between the epiphyses and the diaphysis. The epiphyseal plate consists of four regions (Fig. 9).

1. *Zone of resting cartilage*. This is the outermost zone (next to the epiphysis / away from the diaphysis) which contains chondrocytes that are in a resting stage. This region serves to anchor the epiphyseal plate to the epiphysis.
2. *Zone of proliferating cartilage*. Here the chondrocytes divide and get arranged over one another to form a stack.
3. *Zone of hypertrophic cartilage*. This zone contains chondrocytes that are maturing by undergoing hypertrophy. Columns of enlarged chondrocytes are seen in this region.
4. *Zone of calcified cartilage*. The matrix around the chondrocytes gets calcified in this region. The chondrocytes die and the calcified cartilage is dissolved by osteoclasts. New matrix is laid down by osteoblasts. As new bone tissue is added to the diaphyseal side of the epiphyseal plate, the length of the bone increases while the size of the epiphyseal plate remains the same.

In humans, between the age of 18 to 25 years the chondrocytes of the epiphyseal plate stop dividing, the cartilage gets calcified and is replaced by bone. This is known as *closure of the epiphyseal plates*. In place of the plates epiphyseal lines remain.

Fig 9: Bone: growth in length

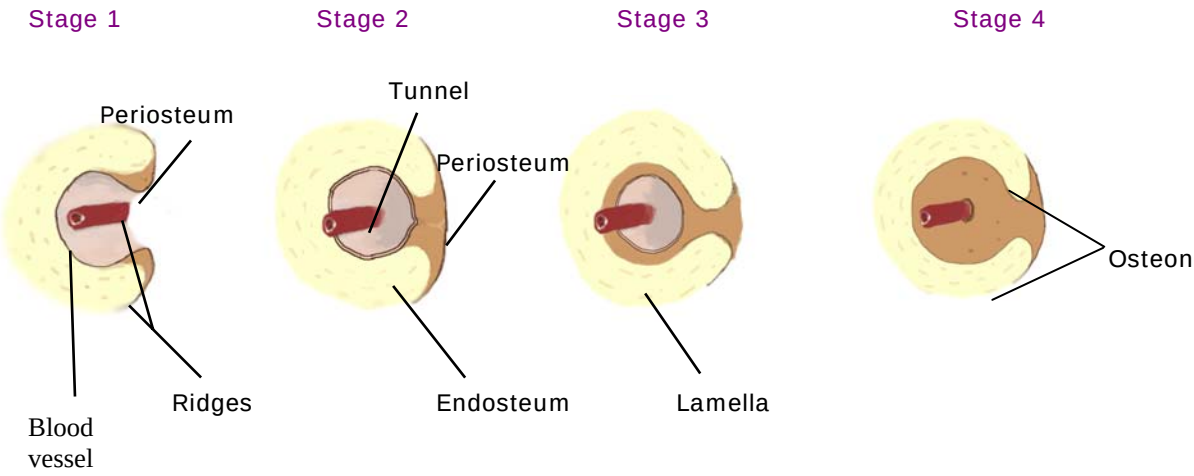


Growth in thickness

Bones can grow in thickness only by *appositional growth.* The following sequence of events occurs during growth in thickness (Fig. 10).

- At the bone surface the periosteal cells near the blood vessels get differentiated into osteoblasts.
- These osteoblasts start secreting the matrix causing the formation of ridges on the sides of the blood vessels with a groove surrounding the blood vessel.
- These ridges grow, meet and fuse enclosing the blood vessel in a tunnel.
- The periosteum lining this tunnel forms the endosteum.
- Cells of the endosteum form osteoblasts which start secreting the bone matrix in a concentric fashion to form the lamellae.
- The osteoblasts form the osteocytes that are surrounded by lacunae.
- In this manner a new osteon is added towards the inner side to reduce the size of the tunnel through which the blood vessels pass.
- The cells of the periosteum also add lamellae on the outer side of this new osteon to give rise to *outer circumferential lamellae*.

Fig. 10: Bone: growth in thickness



Factors affecting bone growth

The following factors are needed for adequate bone growth.

Minerals:

Minerals, such as calcium, phosphorus, fluoride, manganese, iron and magnesium, are needed for bone growth.

Vitamins:

- Vitamin C is essential for the synthesis of collagen and for the differentiation of osteoblasts into osteocytes.

- Vitamin K and vitamin B_{12} are needed for protein synthesis.
- Vitamin A stimulates the activity of osteoblasts.
- Vitamin D is essential for absorption of Ca^{2+} (needed for bone growth) in the alimentary canal.

Hormones:

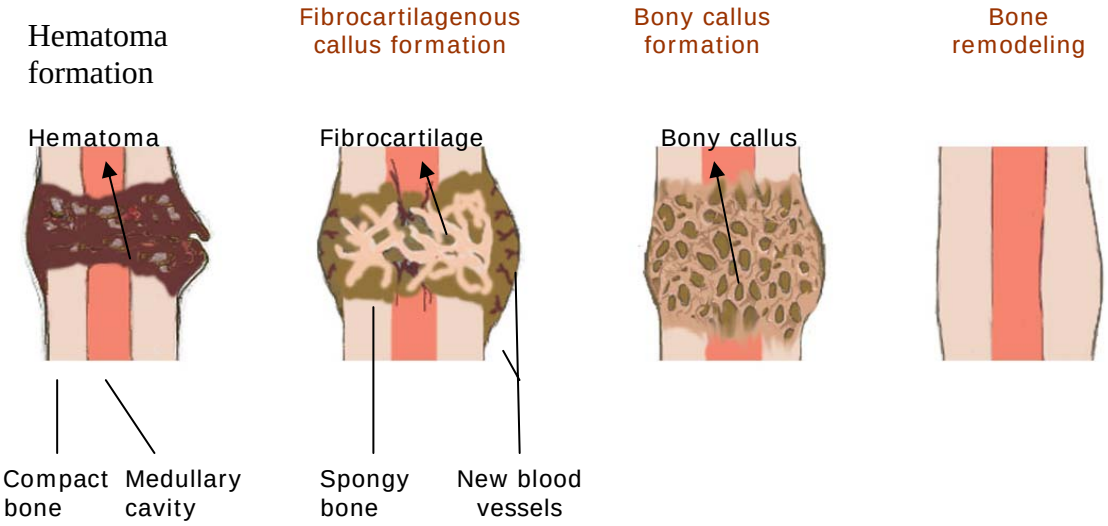
- Growth hormone is needed for the secretion of insulin-like growth factors (IGFs) from the liver and bone tissue.
- IGFs stimulate cell division in the periosteum and the epiphyseal plate. They also stimulate protein synthesis for deposition of bone matrix.
- Thyroxine and insulin are also needed for normal bone growth.
- Sex steroids are needed for the sudden growth of bones (growth spurt) during puberty. Estrogens cause the skeleton to grow in a female pattern. Estrogens in both the sexes (males also have circulating estrogens derived from testosterone) cause the closure of the epiphyseal plates.

Bone repair

Any break in the bone is known as a fracture. Fracture repair occurs by the following four steps (Fig. 11):

1. **Formation of a hematoma**. When a bone breaks, blood vessels in the periosteum, endosteum, medullary cavity or the perforating and central canals get damaged. Bleeding from these vessels result in the formation of a blood clot; this mass along with the injured tissue is known as a *hematoma*. Due to injury to blood vessels, blood supply to neighbouring tissue is disrupted and those cells also start degenerating. Phagocytes and osteoclasts start removing the debris around the hematoma. New capillaries grow into the blood clot (Fig. 11a).
2. **Formation of a callus**. With new capillaries forming, the connective tissue starts growing (granulation tissue) to form a *procallus*. Fibroblasts and osteogenic cells from the periosteum, endosteum and bone marrow invade the procallus. Fibroblasts form collagen fibres connecting the broken ends of the bone. Osteogenic cells (osteochondroblasts) develop into chondroblasts which produce fibrocartilage. This results in the formation of a mass of tissue between the broken ends of the bone, called the *fibrocartilaginous callus* (Fig. 11b).
3. **Formation of a bony callus**. The fibrocartilaginous callus is converted into a bony callus. The osteogenic cells in the adjoining healthy bone regions form the osteoblasts which secrete the matrix. Trabeculae are formed from this tissue, which join healthy regions of the bone with the injured regions. This is called the bony callus formation (Fig. 11c).
4. **Bone remodeling**. In this phase the dead portion of the bone is removed by osteoclasts and spongy bone gets converted into compact bone (Fig. 11d).

Fig. 11: Bone repair



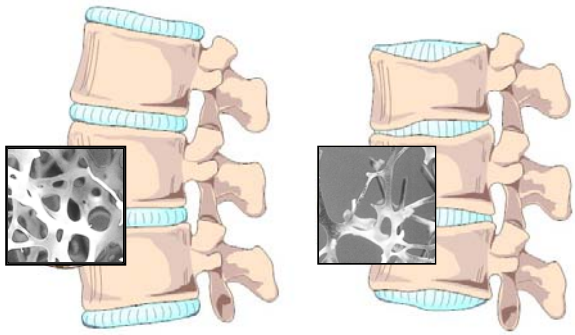
Effect of exercise and ageing on bone tissue

Bones remodel well when subjected to mechanical stress within a limit. If there is no mechanical stress on the bones in the form of gravity or the skeletal muscles pulling at bones, resorption of bones takes precedence over bone formation resulting in weakening of bones. Weight bearing exercises or other forms of exercise that put moderate stress on bones help maintain bone mass. To retard bone resorption during ageing such exercises should be done to maintain healthy bones. Mechanical stress also stimulates the release of hormone calcitonin from the parafollicular cells of thyroid gland which inhibits bone resorption.

Effects of ageing

Circulating sex steroids in adults maintains bone mass by balancing the rate of bone resorption and the rate of bone formation. With age, especially in females, as the levels of estrogens decline after menopause, the rate of bone resorption increases resulting in weakening of bones. This happens due to loss of minerals (demineralization) which reduces the bone mass and due to reduced synthesis of collagen fibres that causes the bones to become brittle (Fig. 12). Synthesis of collagen fibres is also reduced due to reduction in circulating growth hormone levels with age. Loss of bone mass and increased brittleness causes deformed bones, loss of height, loss of teeth, pain and stiffness in bones. These effects of ageing are less pronounced in males because the testosterone levels do not fall so drastically. In males, calcium loss from bones does not occur till the age of 60 years.

Fig. 12: Weakening of bones due to ageing



Normal bone ***Osteoporotic bone***

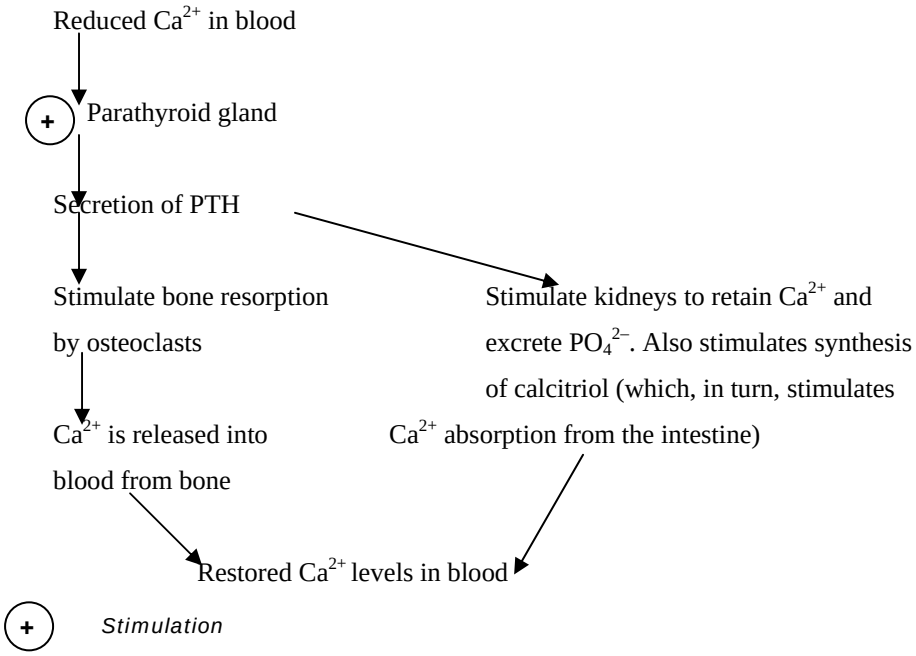
Role of bone in calcium homeostasis

Calcium is an important constituent of our body with many functions:

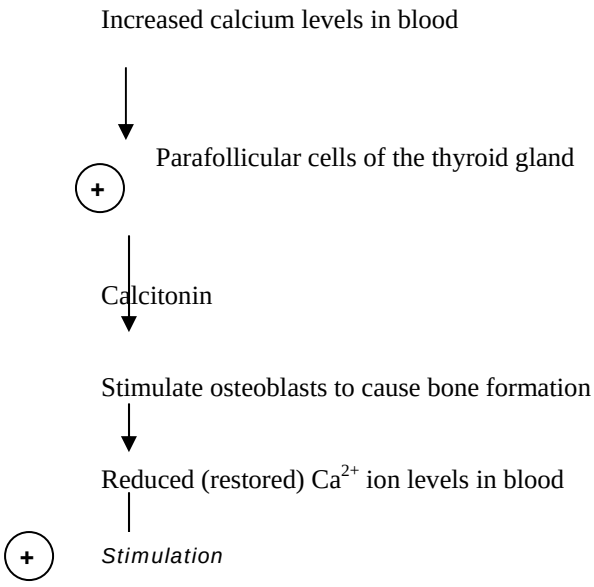
- Ca^{2+} ions participate in blood clotting.
- Calcium is essential for muscle contraction.
- Conduction of nerve impulses is dependent on normal Ca^{2+} ion levels.
- Ca^{2+} ions participate in enzymatic reactions by acting as a cofactor.

Levels of calcium in the blood are regulated around 9 mg to 11 mg/100 ml of blood. An increase in Ca^{2+} ion concentration may result in cardiac arrest and a reduction may cause the respiratory muscles to stop contracting. Bone resorption by osteoclasts release Ca^{2+} into blood and bone formation by osteoblasts causes Ca^{2+} ions to be removed from the blood and deposited in bones. Activities of these two types of bone cells are balanced by the following two hormones through regulation of blood Ca^{2+} levels.

1. Parathyroid hormone (PTH) from the parathyroid gland



2. Calcitonin from parafollicular cells of the thyroid gland



Bone disorders

Rickets and osteomalacia

Osteomalacia is a disorder where bones do not calcify normally. It is also known as "adult rickets" where bones fail to calcify because of a deficiency of calcium. The collagen fibres are formed normally but calcium does not get deposited. So, the bones are "rubbery", soft and deformed. Rickets is caused in children due to lack of vitamin D. Symptoms include bowed legs, and deformities of skull, ribcage and pelvis.

Osteoporosis

This is characterized by loss of minerals from the bones resulting in porous bones that fracture easily. It is more common in post-menopausal women due to absence of circulating estrogens. Other predisposing factors include lack of exercise, cigarette smoking, vitamin D deficiency, and insufficient calcium in diet.

Osteomyelitis

It is caused by the infection of bone with a bacterium, usually *Staphylococcus aureus*, which finds its way into the bone either directly from outside or through an open fracture or from another infected site in the body, e.g. from a urinary tract infection. Symptoms include pus formation, edema, fever, sweating, nausea, etc.

Osteoarthritis

This is an age-related disease where the articular cartilage on the epiphyses of bones degenerate causing friction between bones at joints resulting in painful movements.