ISOMETRIC CONTRACTION

Contraction is said to be isometric when the length of the muscle does not shorten during contraction. This can be measured by clamping both of the muscle so that they cannot move and by incorporating a force meter at one end which does not vary in length under load. A change in force measured while muscle remains constant is called isometric contraction i.e tension drops.

e.g of isometric control is when we attempt to pick up a weight that is too heavy: the muscle tenses but does not shorten. When muscle under an isometric contraction, the contractile unit shortens (actin and myosin filaments slide past each other) but other passive parts of the cell attached to the contractile unit i.e. the tendon and connective tissue are stretched so there is no nett movement. The passive parts that are stretched by the contractile unit are called series elastic component (SEC) of the muscle (tendons, connective tissue and hinged arm of the cross bridges.

SKELETAL SYSTEM

3 types of bone cells - osteoblast - precursor cells
- osteocytes
- osteoclasts

Summary of function of Bone & Bone cells

1. They function to help maintain, thru homeostatic regulation, a constant ionic environment, within the organism e.g. release of calcium.
2. They support & protect soft tissues and organs including the bone marrow.
3. Together with the aid of muscle and tendons, bone aids the animal in movement.

BONE CELLS

Osteoblast

They are columnar cells that vary greatly in size from 15-150μm in length, although most fall within a range of 20-30cm. These cells cover the surfaces of newly forming bone. Osteoblasts are polarized in that the nucleus is located farthest from the bone surface. The cytoplasm contains abundant endoplasmic reticulum with some having dense granules (ribosomes) on their outer surface. Mitochondria often lie in close opposition to the granular endoplasmic reticulum, Golgi apparatus is also present.

Histologically osteoblasts are characterised by their strong cytoplasmic basophylia that ranges directly with cell activities. The basophilia is due to the presence of ribonucleic acid (RNA). These granules (RNA granules) are decreased in number when the osteoblast is in the resting stage. Alkaline phosphatase is confined to the external surface of the osteoblast plasma membrane. Acid phosphatase is present in the osteoblast lysosome.

Osteoblasts participate in the ossification process and are readily observed when new bones are being formed.

Osteocytes

They are osteoblasts that become entrapped and embedded in growing bone. They are situated within the flat oval lacunae and have cytoplasmic processes extending thru apertures into the canaliculae of bone to connect directly with other bone cells.

The cytoplasm is slightly basophilic with few mitochondria and a small Golgi network. It also contains fat globules and glycogen. Acid phosphatase and other lysosomal enzymes are present.
Osteocytes participate in osteolytic osteolysis and bone formation.

Osteoclasts
They are usually multinucleated giant cells observed at site of bone resorption and in eroded cavities of bone called **Howship's lacunae**. They are polarized like osteoblast. They contain numerous mitochondria. Lysosomes are found in abundance in regions where bone is being resorbed (bone resorption, dissolution, removal of mineral and intercellular matrix. osteoclasts are highly motile and capable of migrating along surfaces of resorbing bones and also of entering the blood streams.
Osteoclasts arise from precursor cells in bone marrow or spleen.

MEMBRANES
Anatomical evidence shows that in the normal state, osteons and trabeculae are separated from the vascular compartment by a membrane composed of osteoblast, osteocytes (and their filaments).
This membrane is thought to serve as a barrier to the free flow of ion and other substances between body fluids and the crystalline surfaces of bone. It may also regulate or facilitate the transfer of nutrients to and from sites of bone formation and resorption.

INTERCELLULAR MATRIX
Composition - osteogenic cells (osteocytes and osteoblasts) synthesize and release organic components of the intercellular matrix which subsequently calcify and form bone.
1. **Bone mineral**
2. **Collagen** (a fibrillar protein) constitutes 90-95% of total
3. **Amorphous ground substance** composed mainly of MPS mucopolysaccharide (Chondroitin sulfate), fatty acid, phospholipids and other substances.
4. **Water**

Adult bone contains approximately 25% water, 30% organic matter, 45% ash (37% calcium, 18.5% phosphorus).
On dry weight basis, the mineral content is 65-70% while the organic fraction is 30-35% (95-99% is collagen which upon heating is converted to aqueous **Gelatin**.

COLLAGEN
This is a fibrous protein synthesized by fibroblast and related cells such as osteoblasts of bone cells and chondroblast of cartilage. It is found in all tissues of the body. Collagen formation occurs both intra- and extracellularly.

Intracellular pathway for collagen formation
- Synthesis of protocollagen molecules
- hydroxylation of some proline and lysine residues
- glycoxylation of hydrolysine residues.

- formation of procollagen monomers
- extrusion of procollagen trimers in helical configuration

Extracellular formation of collagen
There is limited proteolytic hydrolysis of procollagen to form tropocollagen which subsequently forms the matrix fibrils.
The amino acid component of collagen contains $^1/_3$ glycine, $^1/_3$ proline and hydroxyproline, while the remaining is lysine hydroxylysine.
Collagen is considered to be crystalline in nature due to the ordered aggregation of the collagen macromolecules and to the high degree of structural regularity of the collagen fibrils.

GROUND SUBSTANCE

This is the extracellular and interfibrillar amorphous component of all connective tissue. It is interspersed between collagen fibers and connective tissues. It is continuous with the interstitial fluid and exhibits varying degrees of condensation. It consists mainly of protein polysaccharide (chondroitin sulphate), glycoproteins, non-structural protein, electrolytes and water.

BONE MINERAL (BONE SALTS)

These are deposited within the interstitial substances and are calcium, phosphates, OH^-, carbonate, citrate and water. Others are Na, Mg, K, Cl^- and F^-.
It is generally accepted that the crystalline structure of bone minerals is that of the apatite series and is approximated by the formula of hydroxyapatite i.e. $Ca_{10}\ (P0_4)_6\ (OH)_2$

CALCIFICATION MECHANISM

Osteoblasts synthesize and secrete organic components into the intercellular space and these components are required for bone mineralization.
Note: Proper mineralization requires that an adequate supply of inorganic ions is available and that the synthesis and elaboration of appropriate organic constituents by the osteoblasts have occurred.

Calcium and Phosphorus
Ca is present in the body mainly in the form of calcium phosphate ($Ca_3(PO_4)_2$). The concentration of Ca and PO_4 ions in the ECF are considerably greater than those required to cause precipitation of hydroxyapatite. However inhibitors are present in almost all tissues of the body as well as in plasma to prevent such precipitation. One of such inhibitors is **PYROPHOSPHATE.** Therefore hydroxyapatite crystals fail to precipitate in normal tissues except in bones despite the state of super saturation of the ions.

Mechanism
The initial stage is the **secretion of collagen** molecules (collagen monomers) and ground substance by osteoblasts. Then the **collagen monomers polymerize** rapidly to form collagen fibers and an **osteoid is formed**. (An osteoid is a cartilage-like material differing from cartilage in that salts readily precipitate in it). Some of the **osteoblasts then become**

entrapped in the **osteoid** as it is formed and they **become quiescent and are called osteocytes**.
Ca salts now begin to precipitate on the surfaces of the collagen fibers within a few days after osteoid formation.
This Ca precipitation first appear at intervals along each collagen fiber forming minute nidi to rapidly multiply and grow over a period of days and weeks into the finished product i.e. hydroxyapatite crystals.
Note: Initial Ca salts deposits are not hydroxyapatite crystals but amorphous compound (non crystalline) i.e. a mixture of salts such as $CaHPO_4.2H_20$, $Ca_3(PO_4)_2.3H_20$and others. These salts are over a period of weeks or months converted into hydroxyapatite by a process of substitution and addition of atoms, or reabsorption and reprecipitation.

Deposition and Absorption of Bone

Bone Deposition by Osteoblasts

Bone is continually being deposited by osteoblast and continually being absorbed where osteoclasts are active. Osteoclasts are found on the outer surfaces of the bone in the bone cavity. A small amount of osteoblastic activity occurs continually in all living bone (on about 4% of all surfaces of bone at any given time in an adult) so that some new bone is being formed constantly.

Bone absorption

This is a function of the osteoclasts bone is continually absorbed in the presence of these osteoclasts. The osteoclasts are normally active on <1% of the bone surfaces of an adult. Parathyroid hormone (PTH) controls the bone absorptive activity of osteoclasts. Bone absorption occurs immediately adjacent to the osteoclast.

Bone resorption

This is the removal by degradation and dissolution of the entire complicated structure of bone.
The components of the organic matrix are degraded and released and bone salts are solubilised.

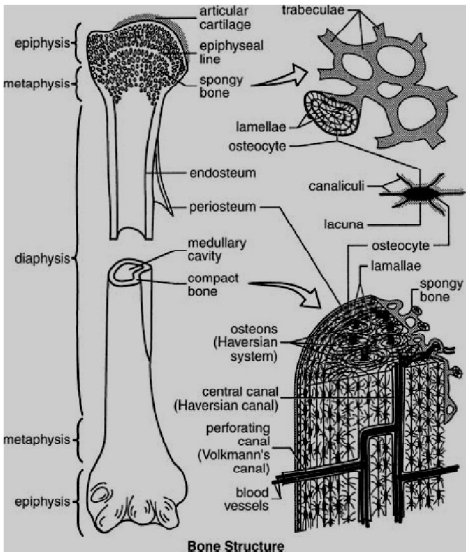
Mechanism of Resorption (Osteoclastic osteolysis)

Osteoclast sends out villus-like projections towards the bone, forming a ruffle border adjacent to the bone.
The villus secretes 2 types of substances:

1. A proteolytic enzyme released from the lysosomes of the osteoclasts e.g. collagenase.
2. Several acids e.g lactic and citric acid released from the mitochondria and secretory vessicle.

These enzymes digest and dissolve the organic matrix of the bone and the acid cause dissolution of the bone salts.
Osteoclastic cells also imbibe by phagocytosis, minute particles of bone matrix and crystals, eventually also dissoluting these and releasing the products into the blood.
Note: normally (except in growing bones), rate of bone deposition and absorption are equal to each other so that the total mass of bone remains constant.
Osteoclastic activity in about 3 weeks creates a tunnel of about 0.2-1mm or several mms long. The tunnel is then invaded by osteoblasts and new bones start to develop. This

continues for several months. New bone is laid down in successive layers of concentric circles lamellae on the inner surface of the cavity until the tunnel is filled. Bone deposition ceases when the bone begins to encroach on blood vessels supplying the area (blood vessels are in Haversian canal) and each new area of bone deposited in this way is called an **OSTEON**.



Osteocytic Osteolysis

This occurs as a result of the ability of osteocytes to resorb bones from the surfaces of the lacunae which they reside. Replacement of the resorbed lacunar bone is also carried out by the osteocyte and **these 2 osteocytic processes i.e. bone removal and replacements are responsible for bone remodelling.**

Osteoclastic and osteoytic osteolysis are both stimulated by PTH. Relative contribution of these 2 processes to bone removal under stress of Ca deficiency, have not been resolved satisfactorily.

REGULATION OF BONE METABOLISM AND HOMEOSTASIS

Several input factor influence the rate of bone turnover and renewal, bone growth, bone resorption, Ca and Phosphorus concentration in blood, the degree of intestinal Ca and P absorption, and the reabsorption of these elements by the kidney tubules.

Of significance among these factors are the gonadal hormones (estrogen and androgens), thyroid hormone, hydrocortisone, growth hormone (GH), vitamin A and ascorbic acid. Most of these are prominent in the normal growth and maturation of bone tissues, and their deficiency or excess can exert profound effects e.g.

- ascorbic acid deficiency will lead to impaired collagen synthesis.
- excess vitamin A in the body will lead to production of excessive bone resorption because there will be a release of lysosomal digestive enzyme.
- deficiency of vitamin A leads to inhibition of osteoclastic activity resulting in abnormal bone

resorption pattern.
- GH defifiency will lead to dwarfism while excess will lead to gigantism in growing individuals
or acromegaly in adults.
Maintenance of blood Ca level is very important because the bone represents an available reservoir. Abnormaly low or high blood Ca concentration will lead to acute or chronic pathological states. The prominent factors for homeostatic regulation of Ca and Phosphorus metabolism are Parathyroid hormone (PTH), Calcitonin and vitamin D.

PTH AND CALCITONIN

Parathyroid gland secretes PTH that influence blood Ca levels. Parathyroidectomy in most animal species results in a rapid decline of blood Ca.
Parafollicular C- cells of the thyroid gland in mammals' produce calcitonin which also has a central role in Ca homeostasis. The action of calcitonin is the opposite of PTH, functioning in the same way as the insulin-glucagon system in the control of blood sugar. When blood Ca levels are high, calcitonin is secreted and apparently acts by inhibiting bone resorption to cause a rapid decrease in blood Ca level presumably to normal.
PTH affects bone resorption by stimulating osteoclastic and osteocytic osteolysis, thereby increasing the number of osteoclasts on the bone surface. PTH has a phosphaturic effect i.e. it inhibits reabsorption of phosphate by the kidneys.

Effects of PTH

1. It directly stimulates the membrane-bound enzyme adenylate cyclase which catalyses the formation of 3,5 adenosyl monophosphate (cyclicAMP or cAMP).
2. PTH also increases Ca movement into responsive cells and these cellular Ca in conjunction with cAMP may be the immediate effector of PTH action on osteocytes, osteoblasts and osteoclasts.

Note: there is no direct effect of PTH by the stimulation of osteoclasts. Osteoblast responds directly to PTH by the stimulation of adenylate cyclase activity and inhibition of collagen synthesis. PTH causes shrinkage of the osteoblast that covers the bone surface thereby exposing bone surface to osteoclastic action.
Calcitonin (anti-hypercalcemic hormone), inhibits osteoclastic bone resorption and this action is mediated by the production of cAMP.

Vitamin D

Deficiency leads to rickets in young animals and osteomalacia in adults. This is characterised by the depressed mineralization of the skeleton while the synthesis of uncalcified matrix, the osteon and osteoid continues. It results in bone with low ash or mineral content in relation to its wet weight, dry weight or total nitrogen content. Other causes of vitamin D deficiency are renal tubular defects, steatorrhoa (maladsorption by intestine) chronic uremia.
Biochemically, in rickets and osteomalacia, blood Ca is normal or low while blood phosphate is low and alkaline phosphatase is either high or normal. Vitamin D which is derived from diet or ultra-violet irradiation of skin is first hydroxylated in the liver to 25-hydoxylcholecalciferol form and subsequently to 1,25-dihydroxylcholecaciferol [1,25-$(OH)_2D_3$]in the kidney. 1,25-$(OH)_2D_3$ is considered to be the hormonal form of vitamin D

(it meets the usual criteria for hormone i.e. produced at one site and causes a response elsewhere and its production is feedback regulated). It is produced in the kidney and elicits its effect in the intestine, bone and other tissues. Its rate of formation is related to the Ca, phosphate and/or PTH levels in the blood and of Ca and Phosphorus needs of the animal.

The major site of action of 1,25-$(OH)_2D_3$ is the intestines where it increases the absorption of Ca. The mechanism appears to involve the stimulation of the synthesis of macromolecules that constitute essential parts of the Ca transport system e.g. of the macromolecule is vitamin D-dependent calcium-binding protein (CaBP)

Vitamin D and its metabolites have a direct effect on the kidney, increasing Ca and phosphate reabsorption. A vitamin CaBP is present in the distal tubule. Receptors for 1,25-$(OH)_2D_3$ have been identified in the bone, pancreas, kidneys, intestine, parathyroid gland and the shell gland of laying hens.

Vitamin D and 1,25-$(OH)_2D_3$ have a direct effect on the intestinal absorption of phosphate.