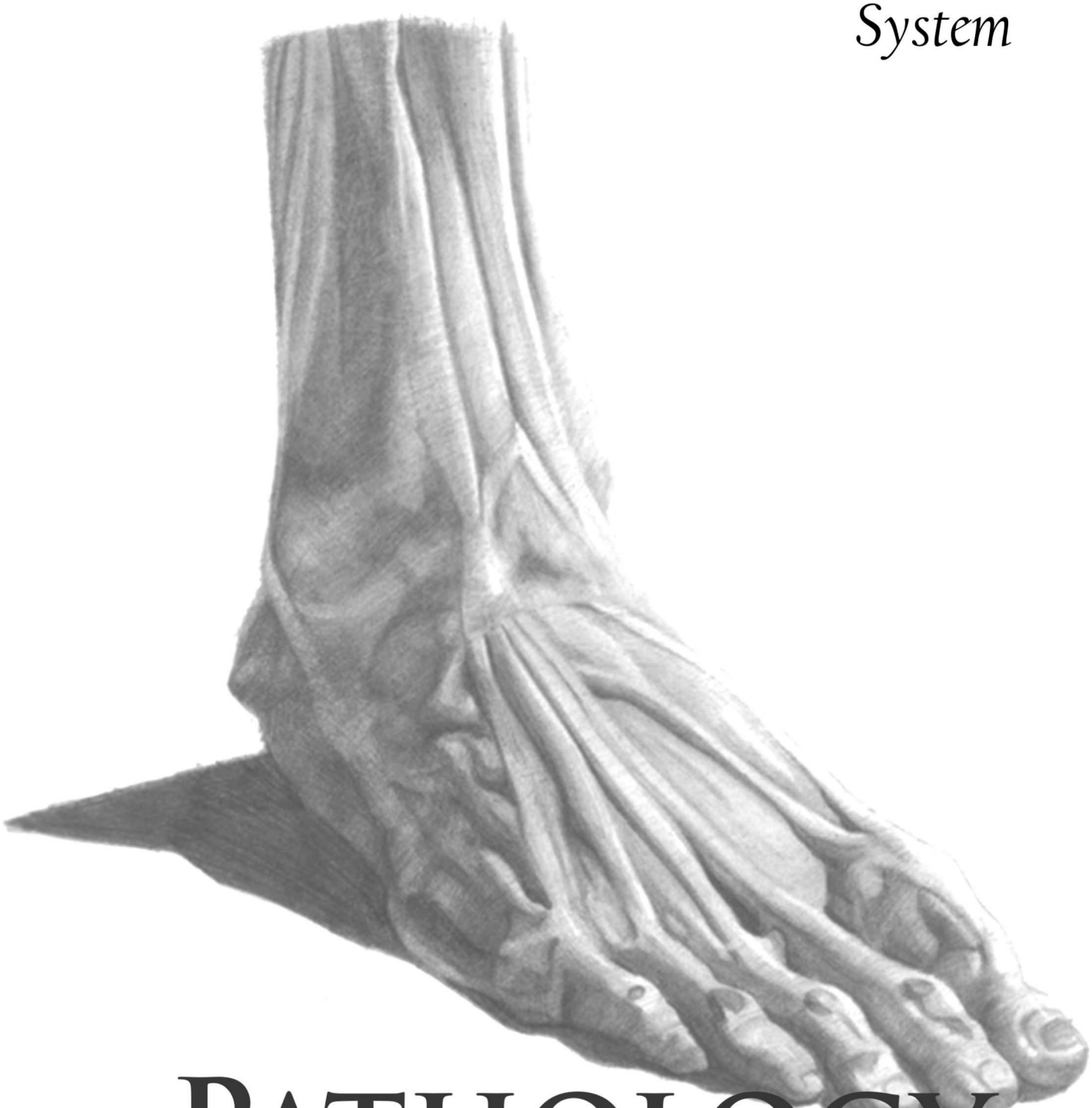
Medical Committee
The University of Jordan

The Skin and
MUSCULOSKELETAL
System



PATHOLOGY

SLIDES ☐
SHEET ■
LECTURE # 1

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Bone related diseases

-Congenital bone diseases

-Congenital is different than inherited, inherited refers to the transfer of a mutated gene from the parents to the offspring but Congenital can be inherited but mainly refer to a new mutation or a new gene abnormality during embryogenesis in the fetus.

-The opposite of congenital and inherited is Acquired diseases that occur during life not during embryogenesis.

-congenital bone diseases are divided to:

1. Localized congenital diseases: affecting part of the body such as a limb.
2. Generalized (Systemic) diseases: either isolated in the bones (affecting bones only) or a part of complex syndromes affecting many things including the bone.

- Congenital bone diseases usually occur by a mutation in **Homeobox genes** which is responsible for the general traits and involved in the regulation of the anatomical development of the body shape (morphology) ,every species has it is own homeobox genes responsible for making their body structure .

- After the mutation in the homeobox genes occur it's manifested in the fetus by 3 ways:

1. Failure of migration of the mesenchymal stem cell (cells that differentiate into bone, cartilage, adipose tissue ...etc) during embryogenesis, for example these mesenchymal stem cells are supposed to reach the leg during migration but they fail to do that so the fetus will lose the limb .
2. Mesenchymal cell reach the desired location but they don't develop into the desired cell, for example it reaches the leg but the mesenchymal cells fail to become bone or cartilage cell and this causes deformity.

3. Mesenchymal cells reach the location and differentiate to the desired cell but the cell (cartilage or bone cell) fails to secret the desired material so it's a functional deformity.

Localized congenital bone diseases

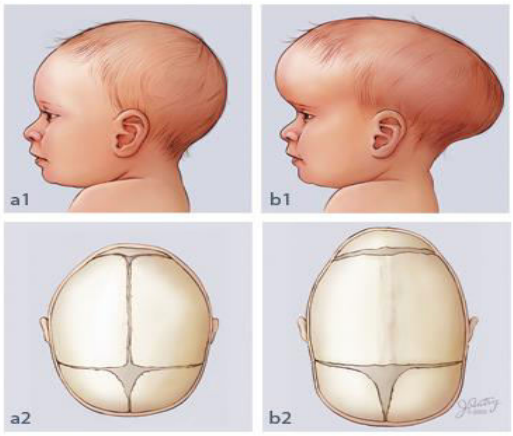
Caused from abnormal migration which includes :

1. **Dysostosis** which is an abnormality of bone formation (Dys :abnormal /Osto : bone) the most important form of Dysostosis is craniofacial Dysostosis with noticed abnormality in face where the face is too small and the skull is huge .

2. **Bone Aplasia** or **bone Agenesis:** this one will result in an absent bone of the limb or the whole limb will be absent.

3. **Bone Supernumerary**: the formation of an extra bones most commonly the formation of extra finger or rib.

4. **Abnormal bone fusion** : also occur in the skull , the skull bones of the baby are not fused and they are separated by sutures to help in the process of delivery if the skull bones were fuse the head of the baby will be rigid and this will not help in delivery .These sutures are fused around 6 months of age , the abnormality occur in premature closure of these cranial sutures which cause an abnormal growth of skull , the normal pattern of skull bone growth is within the suture line but in this deformity the skull bone will grow perpendicular to the suture line so the babe will have an abnormal ,large head and the babe will suffer with



intracranial pressure and vision impairment this condition is called **Craniosynostosis** .(cranio : skull /Syn : fusion /Osto :bone)

5. **Phocomelia** (شكل الفقمة) : it is a sever and complex deformity characterized by shortened and absent bones of the limbs (upper and lower) , also fusion might occur between the bones so the outcome would be that the fingers will pass directly from the shoulder there is no arm so he looks like a فقمة , the main causes of phocomelia are :
    - Side effect of a drug called thalidomide which was manufactured in Germany it was used to treat tuberculosis, cancer, leprosy (wide spectrum of action) .This drug is extremely teratogenic causing phocomelia.
      Note: this drug did not cause phocomelia in the USA because there was restrict rules for using it, however, worldwide the drug causes phocomelia because these restrict rules were absent.
    - Genetic causes which are extremely rare

-Abnormalities in functions that interfere with bone or cartilage mineralization or in the growth factors and their receptors in this case we call it **Dysplasia** usually this abnormality is Generalized (In the whole body) because the growth factor or it's receptor in needed everywhere in the body.

Dysplasia can also occur as a result of mucopolysaccharidoses which are a group of diseases(example : hurler syndrome) caused from deficiency in the enzymes responsible for macromolecules metabolism and they are called storage diseases ,Bone cells are affected by those diseases that's why they will not function normally .

Generalized congenital bone diseases

1- **Osteogenesis Imperfecta** (تكون العظم الناقص)

-it is a group of disease ranging from mild (common) to severe (rare) but they share a common feature that's there is mutation in the gene that codes for collagen type 1 causing an abnormality in α1 and α2 chains ,so the defected collagen will eventually undergo premature degradation, this type of collagen is a crucial part of bone matrix and in this abnormality the bone will become thin and very easy to fracture (the deficit in type 1 collagen may be in the amount or in the quality).

Major types of osteogenisis imperfecta include:

1- OI type 1: the most common type, in this type the patient has a normal life expectancy but his skeleton is deformed, he has an increased frequency of fractures mainly during childhood and it decreases after puberty.

2- OI type 2 : very sever with abnormal and little amount of collagen type 1 , the fetus will suffer from sever fractures inside the uterus because as the baby moves in the uterus he will have fractures in the ribs which will damage the heart .That's why this type causes death in utero or immediately postpartum .

-Collagen type 1 in addition to being essential in bones it's also essential in other parts such as the skin, sclera (**white part of the eye**), teeth. So a patient suffering from OI will present with extra skeletal symptoms like:

1- Blue sclera: because the sclera is so thin it will reflect the choroid veins located under it.
2- Hearing loss: because of loss of conduction due to deformities in middle and inner ear bones (the bones in the ears must be of normal shape to conduct sound waves).
3- Misshaped teeth : as a result of dentin deficiency

2-**Achondroplasia** (A: absent / chondro: cartilage/plasia: genesis)

-it's a congenital disease which is the main cause of dwarfism (التقزم) characterized by a mutation in the gene that codes for fibroblast growth factor receptor type 3 (FGFR-3) , the receptor normal function is to inhibit chondrocyte differentiation and proliferation thus inhibiting bone formation ,at normal conditions the activity of this receptor is regulated but in this mutation the FGFR-3 will be mutated and abnormally active all the time so bone formation will be inhibited.

-Normally bone ossification starts from a cartilage plat then the cartilage later in life ossify to form bones and the chondrocytes differentiate to bone cells, but in Achondroplasia there is very little amount of cartilage since chondrocytes proliferation is inhibited by FGFR-3 and consequently very little amount of bone will be formed .So this patient will have abnormally short and bowed limbs.

-Achondroplasia affects bones that are formed by endochondral ossification (bones of the limbs) so the patient will have normal skull and trunk since they are formed by intramembraneous ossification.

-Achondroplasia is autosomal dominant meaning that a mutation in one allele of the gene is enough to cause the disease so it is heterozygous .Achondroplasia most commonly arise in congenital way and not inherited from the parents but if the patient who has Achondroplasia had a baby it will be inherited to him.

There are 2 forms of Achondroplasia mutation:

1- Heterozygous mutation: most common, occur by mutation during embryogenesis. The patient will have normal life expectancy but with shortened limbs.
2- Homozygous mutation: rare, in this type both alleles of FGFR-3 are mutated either 2 of them were mutated during embryogenesis (extremely

rare) or one of the alleles was mutated during embryogenesis and the other was inherited from the parents .In this type the baby will not live because he has sever bone deformities including the bones of the thorax so the baby will not breathe after delivery and he will die from Fatal respiratory failure in perinatal period.

Thanatophoric dwarfism: which is a variant form of Achondroplasia caused from a mutation in the same gene (FGFR-3) but this mutation includes the extracellular domains of FGFR-3 causing sever inhibition of chondrocyte differentiation and the embryo will die in utero as well as the embryo will have very small rib cage so the embryo cannot breath and die early in life .

Main differences between OI and Achondroplasia is that OI has multiple deformities with one limb being shorter than the other , bowed limbs , blue sclera .But Achondroplasia patient have normal head and trunk with short limbs (dwarf) .

3- **Osteopetrosis** (osteo :bone /petrous :Rock)

it means the formation of rock like bone, it is a rare congenital disease characterized by decreased Osteoclast activity which is normally responsible for bone resorbtion (destruction of old bone cells to provide the body with important minerals like Ca++) in this disorder since osteoclast is defected , Osteoblasts will keep synthesizing new bone and their action is not opposed by osteoclasts leading to the formation of thick bone matrix .

Causes: The exact cause of decrease osteoclast activity is Unknown but there are some things that can contribute to the disease like a Defect in carbonic anhydrase 2 enzyme which is required by osteoclasts for producing H+ in the bone to create an acidic medium important for dissolving Calcium Hydroxyapetite (the mineral of bone) as osteoclasts work on them .Carbonic

anhydrase deficiency is only in rare cases of Osteopetrosis ,in other cases the cause is Unknown.

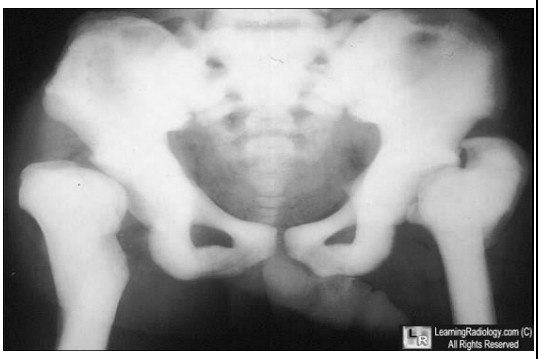
Complications:

1- Bones are easy to be fractured: Surprisingly even though the bones are thick yet they are not well built and haphazard ,also there is no turnover of old bones cells by osteoclasts so these cells will persist and become weak with time making bones easy to be fractured.
2- Nerve injuries : Since some nerves pass through the bone especially in the skull at the cranial foramina and because the bones will become thick they will comprise these nerves causing cranial nerve palsy .
3- Deafness: because of loss of normal conduction in middle and inner ear bones. (deformities in these bones)
4- Recurrent infections : as the bone thickened the bone marrow inside of it decrease in size , as we know the bone marrow is the major site of hematopoiesis for the synthesis of blood cells including White blood cells responsible for immunity defense against infections , when the bone marrow decrease in size the white blood cells drop and the patient will have recurrent infections , anemia (decrease RBC) , increase bleeding tendency (decrease platelets)
5- Hepatosplenomegaly: since the bone marrow has decreased in size, hematopoiesis will happen in the liver and spleen (like in the early form of life) so there will be an increased work demand on these organs and they will become hypertrophic .

Diagnosis:

1. On the X-ray the bones will appear extremely white because of unopposed bone synthesis by osteoblasts..

2. Increase serum levels of alkaline phosphatase



Treatment: bone marrow transplant because osteoclasts are formed from Monocytes that come from the bone marrow, bone marrow transplantation holds a promising future for the treatment of this disease.

A microscopic picture for Osteopetrosis shows only a bone matrix which is very residual and small bone marrow which is not normal.

Acquired bone diseases

1- **Osteoporosis** (osteo : bone / pore : منخل)

It is a disease characterized by decreased bone mass making the bone prone for fracture .On microscopic examination the bone looks porous and spongy.

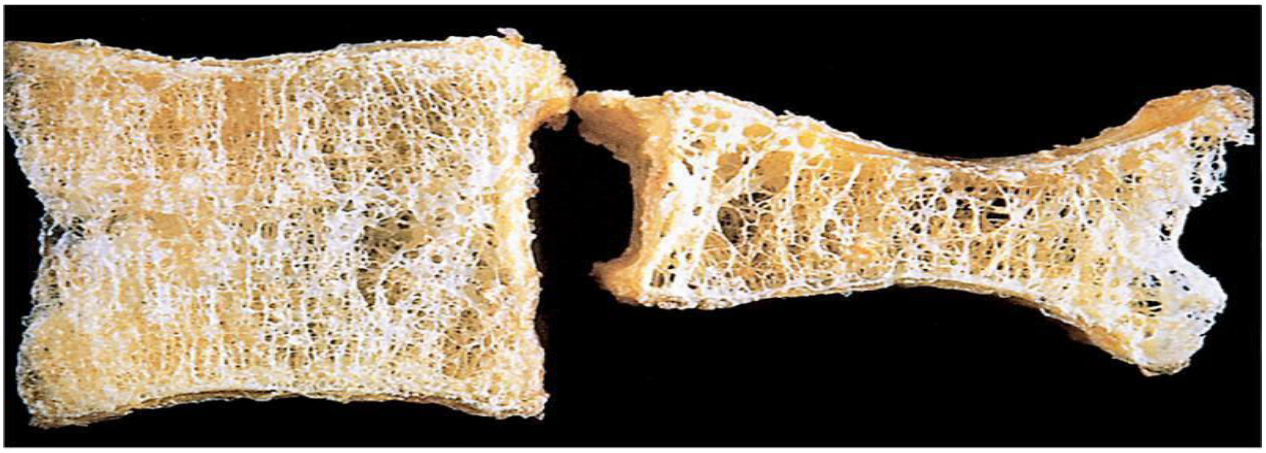
-Osteoporosis can either be:

1- localized: in a certain limb ,the most clear example is disuse osteoporosis when someone has a bone fracture he will immobilize the limb and the limb will have decreased osteoblast activity ,consequently decreased bone mass because of decreased physical activity .

2- Generalized (more common): it is divided into

A- Primary(more common) : the disease will only occur in the bone without any systemic disease

B- Secondary: caused from a systemic diseases that affects many things including the bone like hyperparathyroidism, metastasis, and vitamin C deficiency.



-in the figure above there is a normal vertebrae (left) and an osteoporotic vertebrae (right), normally in bone we have trabecular bone inside and we have longitudinal and horizontal lines but in osteoporotic bone we only find the longitudinal lines and it's porous .The vertebrae are normally stacked above each other so the osteoporotic one will become pressured and it will decrease in size (because it is weaker than normal bones).

Primary osteoporosis

Occurs in postmenopausal women and in old age people in both men and women.

- Bone density is determined by genetic and life style of the person in the early stage of life .During childhood and teenage life the bone continues to ossify and increase in length then in the age of 20 bone growth stops and instead building up of bone mass will start so at this time the amount of exercise , diet , lifestyle will affect the bone mass , if the person at this stage smokes or don't exercise he will have osteoporosis in the old age , diet intake at this time is also important particularly Ca++ and vitamin D (vitamin D can be obtained from eating fishes or mainly by getting exposure to the sunlight) . So at this time you build your own bone.
  Note: after having osteoporosis at old age you cannot change it by taking Ca++ or vitamin D so try to avoid it at early age

-Weight bearing bones including femur and spine will most likely develop osteoporosis and fractures and these fractures are very bad because they take a

long time to heal and the healing process cost a lot also they can result in many complications like ischemia and deformities so it takes a large area of research.

Pathogenesis of primary osteoporosis

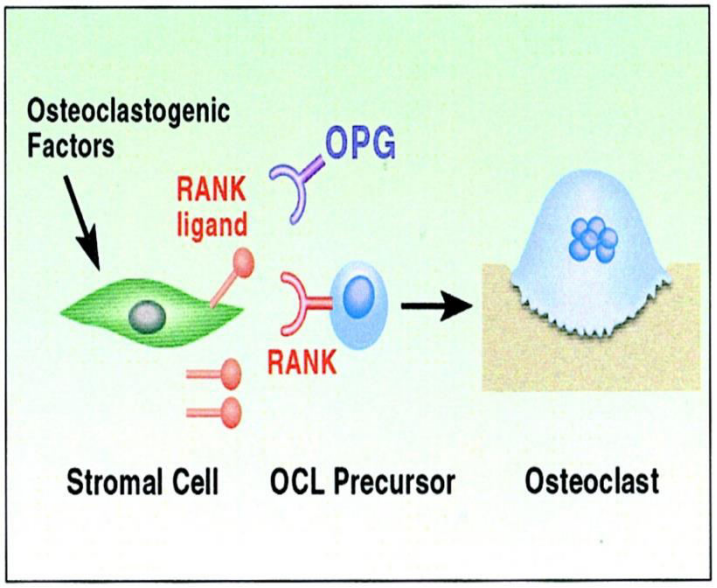
In bone tissue we have many local factors affecting bone growth and bone remodeling and they include:

A- RANK (receptor activator nuclear factor Kappa B) which a receptor found on osteoprogenitor cell (monocyte)

B- RANK Ligand: This is secreted from osteoblasts and it will bind to RANK on osteoproginotor cell and stimulate the differentiation of monocyte to osteoclasts.

C- M-CSF (macrophage-colony stimulating factor) : which is secreted from osteoblasts and stimulate osteoclast formation (like RANK ligand).

D- OPG (osteoprotegerin): which antagonize RANK ligand and inhibits the formation of osteoclasts.



In osteoporosis there is an increase in RANK ligand, M-CSF and a decrease in osteoprotegerin which will increase the activity of osteoclasts consequently decrease bone mass.

-Postmenopausal women starts in the 50 age ,they have decreased serum estrogen and increased serum chemokines (IL-1 ,IL-6 ,TNF) which will increase the expression of Rank and Rank ligand leading to increase osteoclast function → increase bone resorbtion --> osteoporosis

-Senile osteoporosis occurs in both men and women at an old age because people at old age tend to be lazy , they don't exercise and they have low physical activity , since physical activity is important for osteoblast function

and activity , decrease in physical activity will cause osteoporosis at old age and that's the cause of osteoporosis .

Secondary osteoporosis

There is an obvious disease that affects the body and increase bone resorbtion like:

A- Hyperparathyroidism : parathyroid hormone stimulates osteoclasts and in this disease it causes osteoporosis
B- High cortizon which is used as an inhibitory for inflammation and increase bone resoarbtion
C- Intake of drugs like chemotherapy and alcohol

2- Paget's disease

-it's a disease characterized by repetitive sharp attacks of excessive breakdown and formation of bones followed by disorganized bone remodeling , this cause the affected bone to be weakened , pain and deformities .

So paget's disease has 3 phases:

First phase there will be sharp attacks of bone resorbtion from osteoclasts

Second phase the osteoblast starts to make up for the lost bone and synthesize bone but at the same time osteoclast remain active (which is not normal)

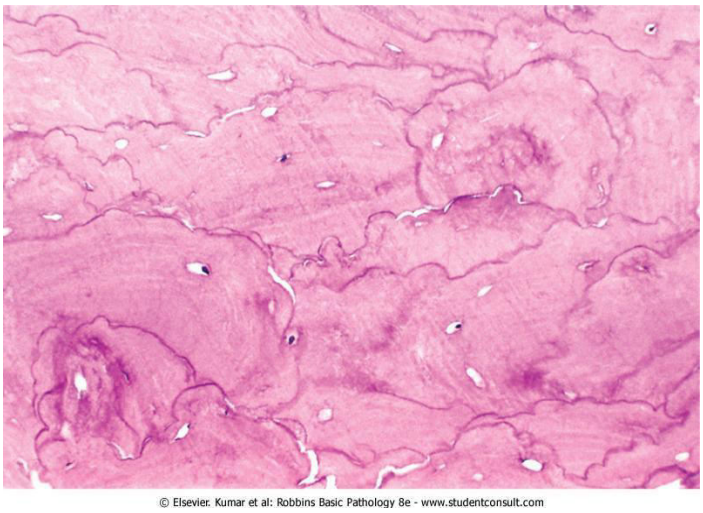
Third phase osteoclast stop and disorganized bone remodeling will occur.

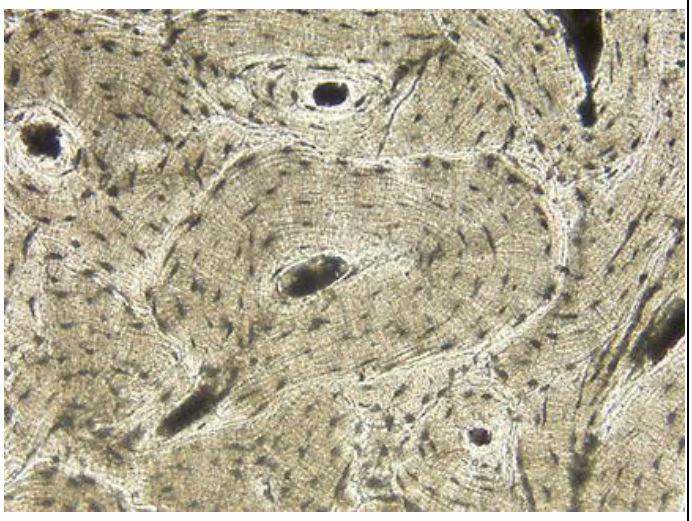
-it comes later in life never in children or teenagers , it occurs in mid adults and increase in tendency with age , mainly it's related to white people and UK has the highest prevalence of this disease in the world .

Pathogenesis :

Sir james pagets thought that the cause of the disease is inflammation and then they discover the presence of paramyxoviruse antigens (not the whole virus) in osteoclasts and they assumed that the presence of these antigens cause an increase in the production of IL-1 ,IL-6 as well as M-CSF in paget bone which cause abnormal osteoclast activity but still they don't know the exact mechanism by which the virus causes this because they couldn't isolate the whole virus from the osteoclast they have only found small antigens of the virus .They have also thought that it's related to the genetic makeup of white people making osteoclast very sensitive to normal concentration of RANK ligand and vitamin D but all of these are still in hypothesis .

Morphology





-The slide on the left show paget bone tissue and the slide on the right show normal bone tissue notice that that in paget bone tissue the osteoclasts are obvious and the place where they resoarb bone is white and this is called the Howship lacunae and they are located inside of it .Paget bone tissue has a very important morphology which is a mosaic pattern due to disorganized bone remodeling.

- The morphology in the second phase of paget disease there will be a lot of osteoblasts along with osteoclasts , there will be extensive blood supply to the paget bone from the bone marrow because osteoblast require a lot of blood for their function (need energy) , so you will see a lot of fibroblasts ,connective tissue ,RBC .Paget disease patients have very high energy expenditure and sometime it

causes heart failure , and if you put the stethoscope on their bones you can hear their heart beat because of the high energy demand in that area .

The morphology in the third phase we will see an increased bone matrix like in osteopetrosis but here it has a different pattern which is the mosaic pattern (puzzle).

-Paget disease can either affect one bone (one region) and it's called monostotic and it makes 15% of the case or it is polystotic (more than one bone) which is more common.

-patient with Paget disease have increased proliferation of the cells in the bone which will increase the risk of mutations , so in 1 % of the people with this disease they can develop cancer called Paget sarcoma/ osteosarcoma

Review

Disease	Type	Description
Craniosynostosis	Congenital Localized	Premature fusion of cranial sutures causing the skull bone to grow perpendicular to the suture line
Osteogenesis imperfecta	Congenital Generalized	Mutation in α1 and α2 chains of collagen type 1 leading to the formation of fragile bone and extra skeletal manifestations .
Achondroplasia	Congenital Generalized	Mutation in FGFR-3 leading to permanent inhibition of bone growth and dwarfism
Osteopetrosis	Congenital Generalized	Decrease osteoclast activity leading to a tip in the balance toward excess bone formation.
Osteoporosis	Acquired either Localized in disuse osteoporosis Generalized in senile and post menopause	There is a tip in the balance between osteoblasts and osteoclasts activity toward osteoclasts causing decrease in bone mass , affected by genetic ,nutritional ,physical activity of young age
Paget disease	Acquired either monostotic or polystotic	3 phases : bone destruction -> bone formation -> disorganized bone remodeling , the patient will experience pain disorganized bones and in rare cases it can develop to paget sarcoma

Dedication to Rakan Radi

Special thanks goes to Mohammad nawaiseh and Mo'nes badaineh for helping me out with this sheet .