Pathology

Team 435

Lecture (1,2): Congenital Disorders, Acquired diseases and Fractures of Bones

Objectives:

- Be aware of some important congenital and developmental bone diseases and their principal pathological features.
- Understand the aetiology, pathogenesis and major clinical features of osteoporosis.
- Be familiar with the terminology used in some important developmental and congenital disorders.
- Appreciate the importance of road traffic accidents with resultant trauma as a major cause of death and disability in the Kingdom.
- Be aware of the mechanisms and stages of fracture healing and understand the difference between trauma induced and pathological fractures.
- Know the factors contributing to delayed fracture healing.

Red: Important Gray: Extra explanation

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Introduction to Bones (recap)

Introduction to bone biology (click here)

The skeletal system is composed of 206 bones. Each Bone is composed of an **Organic Matrix** (35%) and **Inorganic Elements** (65%).
Bone is composed of a **collagen-containing extracellular matrix** (osteoid), synthesized by osteoblasts, that is mineralized by calcium-containing salts (deposition of hydroxyapatite).

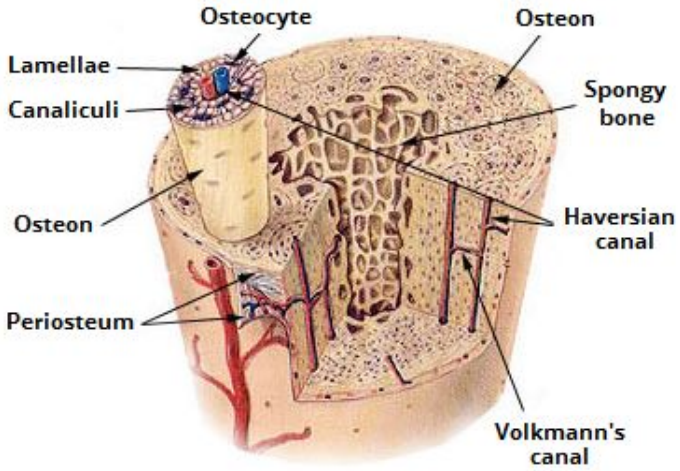
There are two main patterns of bone deposition depending on bone type:

1- Lamellar bone:

The osteoid collagen is deposited in a mechanically strong, parallel stratified pattern. The collagen is deposited in a direction dependent upon the maximal stresses to which the bones will be exposed; giving the maximum strength for the minimum bone bulk.

2- Woven bone (spongy/trabecular):

The osteoblasts deposit osteoid collagen in a haphazard pattern[1]. With its random arrangement of osteoid collagen, the woven (spongy or trabecular) pattern is far **less efficient** and **much more weaker** than **lamellar bone** with a greater tendency to fracture under stress.



[1] بشكل عشوائي

Bone remodeling & modeling:

Bone remodeling or bone metabolism is a **lifelong process** where mature bone tissue is removed from the skeleton (bone resorption) by osteoclasts[2], and new bone tissue is formed (ossification/ new bone formation) by osteoblasts[3]. Many factors play a role such as parathyroid home (PTH), vitamin D and calcitonin.

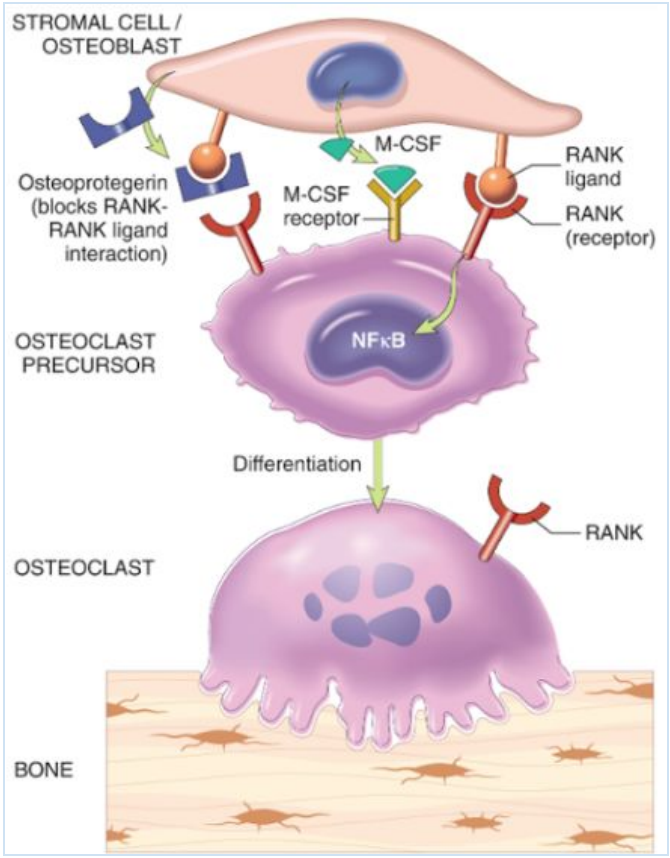
Among the local factors that regulate bone remodeling, the most important are:

1. **RANK** (receptor activator for nuclear factor-κB)[4]:
   Expressed on the cell membrane of pre-osteoclasts and mature osteoclasts.
2. **RANK ligand** (RANKL): Expressed by osteoblasts and marrow stromal cells.
3. **Osteoprotegerin** (OPG).

RANK ligand binds to **RANK** → activation of the transcription factor NF-κB → expression of genes → stimulate **osteoclast** formation, fusion, differentiation, function, and survival.
The actions of **RANKL** can be **blocked** by Osteoprotegerin **(OPG)**, which is a receptor produced by a number of tissues including bone, hematopoietic marrow, and immune cells.

What happens when **OPG** blocks **RANKL**?
Osteoclast activity will decrease.

OPG competitively inhibits **RANK ligand**. **OPG** production is regulated by signals similar to those that stimulate RANK ligand. (hormones, cytokines, growth factors) to influence the homeostasis of bone tissue and bone mass.



[2] They are highly specialized multinucleate giant cells derived from the monocyte-macrophage series capable of removing bone.
[3] Highly specialized cells capable of forming bone that then become osteocytes.
[4] A member of the tumor necrosis factor (TNF) receptor family.

Congenital Disorders of bone and cartilage

Congenital disorders of the skeleton are various and depending on the resulting defect, they can appear at different ages. The most severe disorders produce developmental abnormalities that are evident from the earliest stages of skeletogenesis[5].

Development and growth of skeleton: (Extra to help you understand the diseases mentioned below)

During fetal development, bone can be formed by two ways as following:

	Intramembranous Ossification	Endochondral Ossification
Formed in	Directly in the mesenchyme	Pre-existing cartilage
Examples	The skull and clavicles	Ribs
Bone development	Bone is laid down as woven bone that eventually matures into lamellar bone	The cartilaginous template undergoes ossification at particular sites along the bone known as ossification centers.

- Afterwards, in long bones the cartilage at the epiphysis persists until after puberty allowing growth. This area of persisting cartilage is called the epiphyseal growth plate.
- Once the bones are fully formed further growth occurs by the laying down of further bone onto the pre-existing bone.
- The coordinated actions of the osteoblasts and osteoclasts are paramount[6] in bone development and maintenance. In bone development the action of osteoblasts pre-dominates.
- When the skeleton has reached maturity the bones are continually renewed and remodeled which requires the action of osteoblasts and osteoclasts to be in equilibrium.
- By the third decade osteoclastic resorption begins to predominate with a resultant steady decrease in skeletal mass.

[5] تكون الهيكل العظمي

[6] Important, الأهم

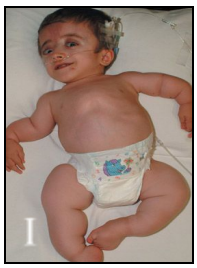
Osteogenesis Imperfecta(OI) سوء تشكل العظام : (also known as brittle bone disease)

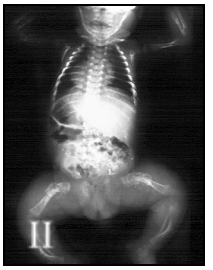
A rare group of genetic disorders that are grouped together because they all have a defect in the synthesis of type I collagen. This disease has 4 major groups , we will only focus on the first two types as type 3 and 4 are rare.

What is Type I collagen?

A major component of the extracellular matrix. Making it important in the structure of different parts of the body, a **defect** in this type of collagen will cause various manifestations affecting these different parts such as **skin, joints, teeth, eyes, ears, ligaments, and bones**.

- **Type I disease is inherited as an autosomal dominant whereas Type II is autosomal recessive.**
  What's the difference between type I and II ? The difference is the severity of the disease.





Type I is compatible with life meaning they usually have a normal lifespan with a modestly increased proclivity[7] for fractures during childhood (decreasing in frequency after puberty).

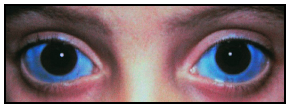
Type II is more severe die in the uterus before birth or immediately postpartum as a consequence of **multiple fractures** that occur before birth.

There is also a similarity between type II and type III, the difference is the fractures in **Type III, occur during delivery.**

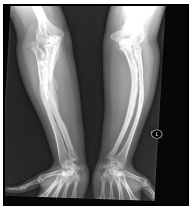
Signs and symptoms of OI (For both type I & II):

The fundamental abnormality in all forms of OI is too little bone, resulting in extreme skeletal fragility[8].

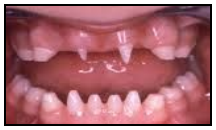
1. **Abnormal ear and loss of hearing:**
   Can be related to conduction defects in the middle and inner ear bones.
2. **Blue sclera (important):**
   It is attributable to decreased scleral collagen content, it causes transparency that allows the underlying choroid to be seen. In other words, The sclera becomes thin that the **blue pigment** which is usually found in the **choroid** becomes visible.



3. **Abnormal bones:**
   Those infected develop lots of pathological fractures (usually in the long bones). They heal very well because the healing process in children is faster. **But why are there recurrent fractures?** because the bone is brittle[9] (due to collagen deficiency) (Hence the name **brittle bone disease)**



4. **Deformed teeth** (small misshapen teeth)**:** Deformed and discolored due deficiency of **dentin**[10].



5. **Abnormal skin:**

   Folds or thinning in some areas and some skin differences such as redness and loss of color.

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[7] Tendency, ميل

[8] ضعف

[9] لين

[10] Dentin is a calcified tissue of the body.

Achondroplasia:

It is the most common form of dwarfism and the most common skeletal muscle dysplasia, it's caused by activating point mutations (mutation in a single gene)

The defective gene (**fibroblast growth factor receptor 3** (FGFR3) on **chromosome 4)** leads to abnormal ossification at the growth plate of bones (that will cause a defect in cartilage synthesis at the growth plates) formed by endochondral ossification but intramembranous ossification is unaffected.

FGFR3 is a receptor with tyrosine kinase activity that transmits intracellular signals that inhibit the proliferation and function of growth plate chondrocytes . therefore, the growth of **normal** epiphyseal plate is suppressed and the length of the bone is stunted (inhibited) leading to dwarfism.

It can be familial (autosomal dominant inheritance) affecting both genders, or sporadic .

Features of achondroplasia:

Achondroplasia affects all bones that develop by endochondral ossification, They have:

- ➢ Normal intelligence.
- ➢ Bowing of legs[11].
- ➢ Abnormal height (short stature).
- ➢ Depression of the of the nasal bridge.
- ➢ Disproportionate shortening of the proximal extremities (short arms and legs).
- ➢ Frontal bossing (protruding forehead) with midface hypoplasia[12].
- ➢ The trunk and head are almost of normal size (Disproportionately large head).
- ➢ The cartilage of the growth plates is disorganized and hypoplastic.

Skin is highly folded, because the skin outgrew the bone size they have making them seem "fat".

Thanatophoric[13] Dwarfism (lethal):

It is the same as achondroplasia but is **more severe** and causes respiratory failure in infants leading to death. It is caused by missense or point mutations of **FGFR3**. Following are some features of this disorder:

- Lethal.
- Extreme frontal bossing[14] of the skull.
- Extreme shortening of the limbs.
- Extremely small thorax, which will be a cause of **fatal respiratory failure**.

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[11] انحناء

[12] A situation in which the upper jaw, cheekbones and eye sockets have not grown as much as the rest of the face

[13] Death-loving

[14] تكون الجبهة بارزة وكبيرة

Osteopetrosis (مرض تصخر العظام):

A group of rare genetic disorders characterized by defective **osteoclast-mediated bone resorption.** Osteopetrosis (literally, "bone-that-is-like-stone disorder") is an appropriate name, since the bones are dense, solid and stone-like (the persisting bone tissue becomes weak over time and predisposed to fractures like a piece of chalk).

Several variants are known, the two most common are:

- ➔ An autosomal dominant adult form with mild clinical manifestations.
- ➔ Autosomal recessive infantile, with a severe/lethal phenotype.

The defects that cause osteopetrosis are categorized into:

- ➔ Those that **disturb osteoclast function.**
- ➔ Those that interfere with osteoclast formation and differentiation.

In some cases the abnormalities have been identified, these include:

- Carbonic anhydrase II deficiency.
- Proton pump deficiency.
- Chloride channel defect.

All of which interfere with the ability of osteoclasts to resorb bone.

Besides fractures, patients with osteopetrosis frequently have:

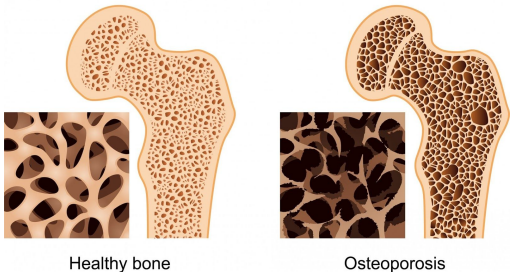
- ❑ Cranial nerve palsies (due to compression of nerves within shrunken cranial foramina)
- ❑ Recurrent infections because of reduced marrow size and activity.
- ❑ Hepatosplenomegaly[15] caused by extramedullary hematopoiesis resulting from reduced marrow space.

[15] تضخم الكبد والطحال

Acquired diseases of bone

The following acquired diseases of bone are all considered **metabolic** bone diseases, the most prominent being osteoporosis.

Osteoporosis:



A **reduction in volume of bone** (reduced bone mass) and an increase in erosion leading to bone susceptibility[16] to fractures. Most common site of these fractures are the **neck of femur** and in the **vertebrae**.

Where does it occur? (Etiology)

Occurs in **both genders**. Severity depends on environmental factors and patients with osteoporosis have 30%-50% less bone density than normal individuals.

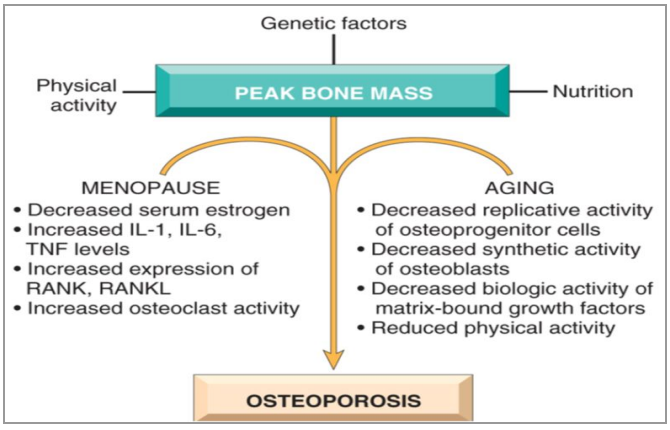
How does it start?

Trabecular bone (found in vertebral bodies and pelvis) is affected **before** cortical bone (found in long bones).

What does it affect?

Osteoporosis does not affect ossification/calcification, however there is a **general reduction in bone mass** and volume. Thus, patients with osteoporosis will have **insensitive (unaffected)** calcium, phosphorus, and alkaline phosphatase levels in serum.The difference is the **decrease in thickness** of the trabecula and cortical bone (Bone mass is decreased without disruption of architecture).

The risk of osteoporosis with aging is related to the peak bone mass earlier in life, which is influenced by genetic, nutritional, and environmental factors. During young adulthood, the greater the peak bone mass, the greater the delay in onset of osteoporosis. When both men and women reach their thirties or forties, bone resorption begins to outpace bone formation. The bone loss, averaging 0.5% per year, is a seemingly inevitable consequence of aging and is most prominent in areas containing abundant trabecular bone —namely the spine and femoral neck. The amount of bone loss with each cycle of remodeling is accelerated after menopause; hence, the vulnerability of women to osteoporosis.



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Morphology:

The hallmark of osteoporosis is a loss of bone.

➢ The **cortices** are thinned, with dilated haversian canals.

➢ The mineral content of the bone tissue is normal.

➢ The **trabeculae** are reduced in thickness and lose their interconnections.

- In **postmenopausal osteoporosis**: Trabecular bone loss often is severe, resulting in compression fractures and collapse of vertebral bodies.
- In **senile osteoporosis**: Cortical bone loss is prominent, predisposing to fractures in other weight-bearing bones (femoral neck)

➢ Osteoclastic activity is present but isn't dramatically increased.

➢ Once enough bone is lost, susceptibility to fractures increases.

Osteoporosis can be divided into two types:

❑ Primary osteoporosis (most common).

❑ Secondary osteoporosis.

Primary osteoporosis:

Primary osteoporosis refers to **senile osteoporosis** and **postmenopausal osteoporosis.**

Let's say a 70 years old woman simply fell from her bed, this is considered a minor trauma and insignificant to a normal person, however because she has osteoporosis she'll acquire a pathological fracture.

- **Senile osteoporosis:**
  - ➔ There is a normal progressive loss of bone mass after around the age of 30 years and so all elderly will have some degree of osteoporosis but bone loss barely exceeds 1% per year.
  - ➔ The higher the initial bone density, the lower the risk of significant osteoporosis.
  - ➔ Women are at higher risk than men, and white people are at higher risk than black people.
- **Postmenopausal osteoporosis:**

Characterized by hormone dependent acceleration of bone loss. Postmenopausal women may lose up to 2% of cortical bone per year and up to 9% of trabecular bone per year for 8-10 years then loose normal rates of bone yearly (1%). **Estrogen deficiency** is thought to have a major role and estrogen replacement at the beginning of the menopausal reduces the rate of bone loss (so it could be a treatment).

Secondary osteoporosis:

Secondary osteoporosis is related to conditions other than menopause or age such as:

➔Reduced mobility (e.g. after fracture or association with rheumatoid arthritis).

➔Endocrine disorders (e.g. Cushing syndrome, diabetes, hyperthyroidism).

➔Cortisone intake (corticosteroids therapy).

➔Soft drinks.

➔Smoking.

➔Alcohol consumption.

All of which take part in the pathogenesis of secondary osteoporosis.

NOTE: Weight bearing exercises decrease the risk of osteoporosis while obesity increases that risk.

Treatment: It can be treated by **hormone replacement therapy**, **oral bisphosphonates**, and **vitamin D**.

Pathogenesis:

Occurs when the dynamic balance between bone formation by osteoblasts and bone resorption by osteoclasts tilts in favor of resorption. Several factors may tip the scales:

- **Age-related changes:**

  With increasing age, the replicative and matrix production activities of osteoblasts progressively diminish alongside with growth factors deposited in the extracellular matrix.

- **Hormonal influences:**

  The decline in estrogen levels associated with menopause correlates with an acceleration of cortical bone and trabecular (cancellous) bone loss.While estrogen replacement can ameliorate some of the bone loss, such therapy is increasingly associated with cardiovascular risks.

  Why are women at increased risk of osteoporosis after menopause?

  Because of the relationship between **estrogen** and **osteoporosis**. The drop of estrogen will induce osteoporosis.

  A drop in estrogen will **stimulate inflammatory cells→ increase the secretion** of **cytokines** especially **tumor necrosis factor (TNF)**, **interleukin 1**,**6** and **8**→ stimulate **RANK** and **RANKL** receptors on the surface of osteoclasts→ osteoclasts will become more **mature**, **active** and cause more **absorption** than usual → **osteoporosis**.

- **Physical activity:**

  Mechanical forces stimulate bone remodeling, thus, reduced physical activity increases bone loss. Decreased physical activity in older persons also contributes to senile osteoporosis. The type of physical activity is important. E.g. resistance exercises such as weight training increase bone mass more effectively than endurance activities such as jogging.

- **Genetic factors:**

  Vitamin D receptor polymorphisms appear to influence the peak bone mass early in life. Additional genetic variables can influence either calcium uptake or PTH synthesis and responses.

- **Calcium nutritional state:**

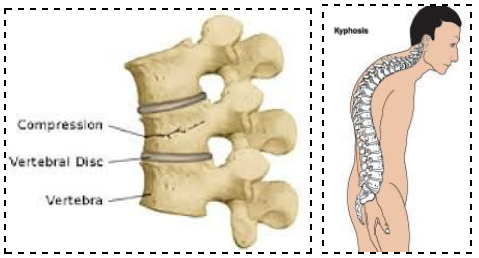
  A majority of adolescent girls have insufficient dietary calcium. This calcium deficiency occurs during a period of rapid bone growth. As a result, girls typically do not achieve the peak bone mass that is expected and are more likely to develop clinically significant osteoporosis at an earlier age.

- **Secondary causes of osteoporosis:**

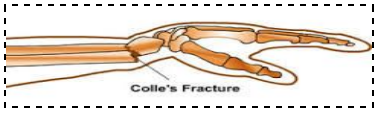
  Prolonged glucocorticoid therapy, which increases bone resorption and reduces bone synthesis. Cigarette smoking and excess alcohol also can result in reduced bone mass.

Clinical Features: The **major** complication of osteoporosis is bone fracture. The sites most commonly affected are:

1. **Vertebral bodies:**
   - ➔ Fractures of the vertebral bodies can be of the crush variety leading to progressive loss of height and considerable pain or of the wedge or triangular shaped type which causes deformity of the spine (kyphosis)
   - ➔ In severe osteoporosis, **the vertebrae is fractured** due to its **weakness**; this is called a **compression fracture**.
   - ➔ The bone volume is reduced → **vacuoles** in the bone → bone will **compress** → **compression fracture**→ back pain and loss of height by severe kyphosis (Dowager's hump)



2. **Distal end of the radius (Colle's fracture[17]):** Which leaves a fork like deformity
3. **The hips (most commonly neck of the femur):**



Which causes major disability and lead to hospital admissions. Secondary complications such as pneumonia and pulmonary thromboembolism are common with hip fractures and account for the high mortality rate associated with hip fractures.

Clinical outcome:

The clinical outcome with osteoporosis depends on which bones are involved:

- Thoracic and lumbar vertebral fractures are common, causing kyphoscoliosis, which compromises respiratory function.
- Femoral neck, pelvis, or spine have pulmonary embolism and pneumonia as common complications.

Paget Disease (Osteitis Deformans)

Osteoclasts are more active than osteoblasts. This means that there is more bone absorption than normal. The osteoblasts try to keep up by making new bone, but they overreact and make excess bone that is very chaotic.

Rickets and osteomalacia:

Both are manifestations of vitamin D deficiency or its abnormal metabolism. The fundamental defect is an impairment of mineralization and a resultant accumulation of unmineralized matrix.This contrasts with osteoporosis, in which the mineral content of the bone is normal and the total bone mass is decreased.

- ➔ *Rickets* refers to the disorder in children, in which it interferes with the deposition of bone in the growth plates.
- ➔ *Osteomalacia* is the adult counterpart, in which bone formed during remodeling is undermineralized, resulting in predisposition to fractures.

Vitamin D is important in the maintenance of adequate serum calcium and phosphorus levels and deficiency impairs normal mineralization of osteoid laid down in the remodeling of bone.

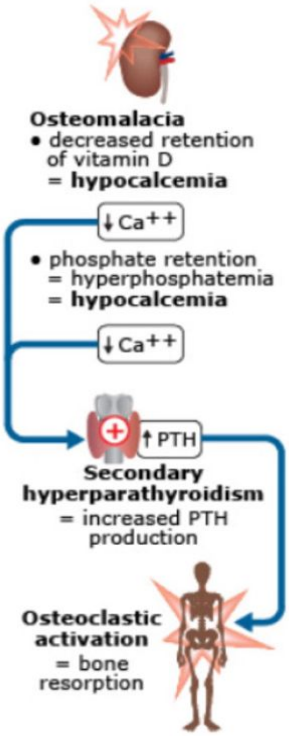
[17] More about it below.

Hyperparathyroidism: (Parathyroid Glands and Hyperparathyroidism)

Leads to significant skeletal changes related to unabated osteoclast activity. NOTE: Fortunately, if PTH levels are brought back to normal, it can completely reverse the bone changes.

There are two types of hyperparathyroidism, which are:

- **Primary hyperparathyroidism:**
  - ❑ It's a common endocrine disorder which is excessive or inappropriate levels of PTH
  - ❑ PTH is directly responsible for the bone changes.
  - ❑ Cause: Adenoma of the gland.
  - ❑ What does it cause?
    - ➔ It's an important cause of hypercalcemia.
    - ➔ It is the most common cause for silent hypercalcemia (asymptomatic).
    - ➔ Osteitis fibrosa cystica ➔ GIT disruption ➔ CS alteration
    - ➔ Renal stones ➔ Osteoporosis



- Secondary hyperparathyroidism:
  - ❑ Occurs in the setting of underlying renal disease (eg. renal failure)
  - ❑ Other than PTH, additional influences are responsible for the bone changes.
  - ❑ Chronic renal failure is the most common disease that leads to this condition.
  - ❑ It is caused by any disease that leads to hypocalcemia.

Parathyroid hormone (PTH) plays central role in calcium homeostasis.

Fractures and Bone healing

Fracture:

A disruption of the continuity of a bone caused by an external element, event, trauma or a disease. Fractures rank among the most common pathologic conditions of bone. The majority are caused by road traffic accidents (the number 1 cause of death in Saudi Arabia is RTA - readers are advised to drive safely)

Motor vehicle accidents (Road Traffic Accidents - RTA):

Trauma due to motor vehicle accidents is a major clinical and social importance. Damage inflicted is related to several factors. the most important of which is the speed of travel, restraint and protection from impacts.

There are three main types of injuries caused by RTA:

1. Injuries caused by sudden deceleration:

   When a body is accelerated and then was suddenly brought to a stop the resulting internal stress may cause severe damage, e.g.:

   - ➢ The aorta may be transected leading to severe internal bleeding.
   - ➢ The brain may sustain internal tearing of white matter tracts.

2. Injuries caused by direct trauma:

   These occur when a body impacts on part of a vehicle or with road surfaces. There may be:

   - ➢ Lacerations to face and hands from windshields glass.
   - ➢ Fracture of sternum and ribs from impact with steering column.
   - ➢ Fracture of legs from collapse of car frame or from impact of car on a pedestrian.
   - ➢ Contusional damage and laceration of liver, spleen and lungs.
   - ➢ Contusions of brain and fracture of the neck from impact damage to the head.

3. Injury secondary to impaired cardiorespiratory function:

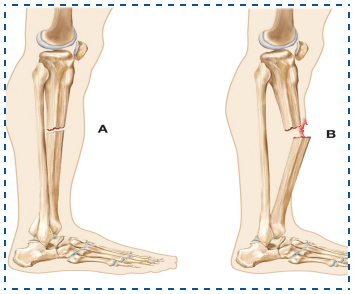
   The blood lose, unconsciousness and interruption of the airway are common in victims of trauma and lead to secondary damage.

   - ➢ Brain is extremely vulnerable to hypoxia, developing neuronal death.
   - ➢ Kidney may develop tubular necrosis.

In general, fractures classified into two major types:

- ❑ Complete or incomplete **closed fractures** (simple fracture).
- ❑ **open fractures** (compound fracture).

NOTE: open fractures are more dangerous than closed fractures because there is hemorrhage in open fractures which lead to infection in that area .



Type of Fractures:

- Greenstick fracture:

  An incomplete fracture of long bones, happens to children most of the time and the fracture heals very well.

- Compound fracture:

  The fracture extends into the overlying skin. Sometime we call it open fracture, which is characterized by swelling and blood oozing out.

- Displaced: In which the fractured bone is not aligned, e.g. in femur bone, bones are displaced.

- Closed simple fracture:

  In which the overlaying tissue is intact. It's linear. If it happens to a child there is no need for cast unlike old people. It has no bleeding or open wounds and has mostly inflammation signs, it also needs an X-ray.

- Comminuted fracture :

  In which the bone is splintered. the bone is broken into many smaller fragments at the site of fracture , it is a closed fracture it also called a fragmented fracture (it could be open fracture).

  * مثل الزاحف اللي يطلع يده من الدريشة وتصدمه سياره ماشيه بالطريق المعاكس وتكسر عظامه الى قطع صغيره *

- Pathological fractures:

  If the break occurs at the site of previous disease (e.g., a bone cyst, a malignant tumor, or a brown tumor associated with elevated PTH). Could be the first sign of malignancy especially in old people. For normal bone to fracture the causative trauma had to be severe. In contrast, trivial or weak trauma that may cause fracture when the underlying bone is abnormal which is a pathological fracture. Diseases causing pathological fractures : الدكتور ذكر هذي الامراض فقط

  1. Metabolic disease:
     - ➔ Osteoporosis (تنخر العظم): particularly in the femur and vertebral column in the elderly.
     - ➔ Osteomalacia: the fractures are often small micro fractures without displacements.
  2. Paget's disease of bone:

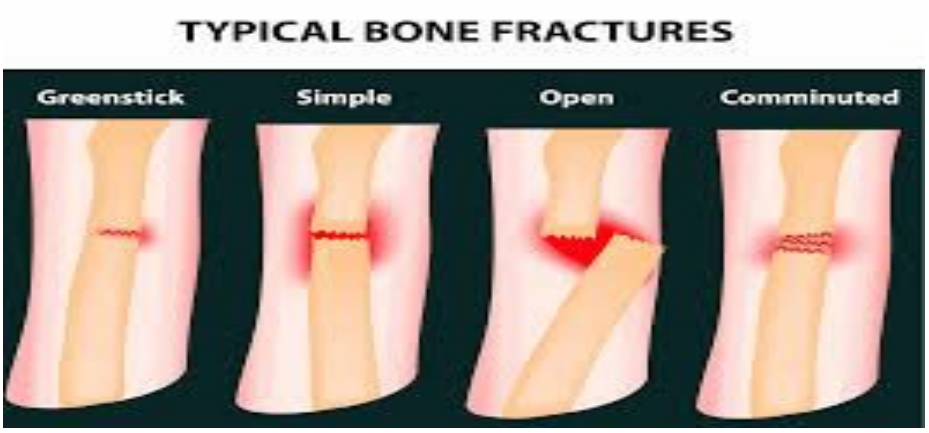
     The pagetic bone being structurally weak despite the increase in bulk.
  3. Metastatic carcinoma in bone is an important cause of pathological fracture.
  4. Osteolytic metastases.
  5. Primary tumor of bone or bone marrow such as giant cell tumor of bone and melanoma.
  6. Some non-neoplastic bone lesions such as bone cyst.
  7. Congenital bone disorders.. The most important disorder is osteogenesis imperfecta.

- Stress fracture:

  Develops slowly over time as a collection of microfractures associated with increased physical activity, especially with new repetitive mechanical loads on bone. It occurs in small bones of the ankle and foot following a very long march and fatigue exercises , it is non-displaced , linear and simple. * بيحدث على المدى الطويل مثل لاعبين كرة القدم أو العسكر *

- Compression fracture:

  Fracture of vertebra, if it's severe it could cause neurological defects, it is commonly caused by osteoporosis and trauma.



Sometime fractures cause deformities (تشوهات) like colles fracture.

Colles fracture:

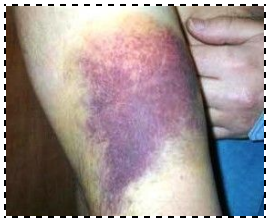
A very famous fracture which occurs in the distal radius that heals badly causing a fork like shape (مثل الشوكه) of the arm, it's usually closed, its common in people with osteoporosis.

Displaced and comminuted fractures frequently result in some deformity; devitalized fragments of splintered bone require resorption, which delays healing, enlarges the callus, and requires inordinately long periods of remodeling and may never completely normalize.

Fracture healing:

Bone fracture heals by granulation tissue formation and fibrous repair, followed by new bone formation in the granulation tissue. The degree of fracture can vary widely as mentioned before in types of fractures.

Fracture healing process:



1st step is the formation of haematoma[18] around the broken ends of the bone, which will result in an inflammatory reaction.

There are 2 cases, the blood is either from the soft tissue or an injured blood vessels which release blood. There will be an increase in white blood cells due to inflammation, but the hematoma is the **initial** problem

2nd step afterwards, is that healing occurs through organization of this haematoma by granulation tissue (which occurs in chronic inflammation).

However, this process is modified because the granulation tissue contains proliferating cells derived from periosteum and endosteum which differentiate into chondroblasts and osteoblasts that lay down new cartilage and immature (woven) bone. And by organization it means that it's trying to be organ like, forming a new tissue, formation of granulation tissue. Formed of:

➔ Fibroblast macrophages. ➔ Chronic inflammatory cells. ➔ Endothelium.

Note: Never confuse between granulation tissue and granuloma

3rd step is Callus formation, callus is the scar which occurs in the bone following a fracture. It's formed by margination of progenitor cells or pluripotent cells[19], pluripotent stem cells are found in the growth plates.

The result is hard tissue called callus surrounding and joining the broken ends of the bone.

- ➢ Bone union occurs when new bone produced in the callus links the bone fragments together.
- ➢ The cartilage and the woven bone are gradually replaced by the lamellar bone (the type found in mature bone).

What Happens?

1. They marginate into the site of vascular granulation tissue and they get transferred into:

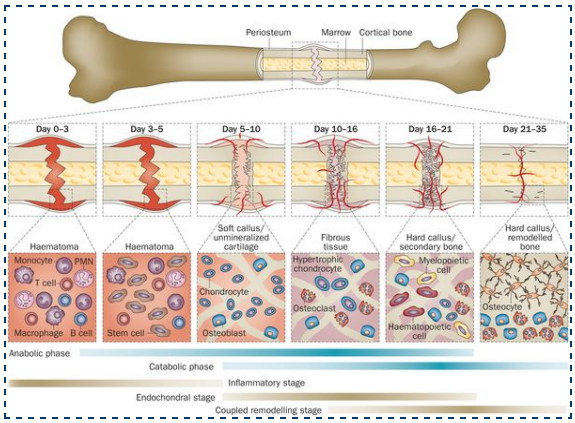
➔ Osteoblasts. ➔ Osteoclasts. ➔ Multinucleated cells. ➔ Cartilaginous cells.

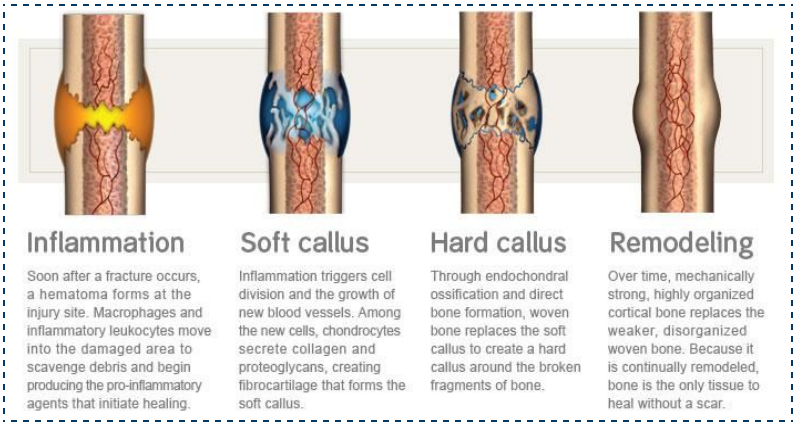
[18] Rupture or disruption of the blood vessels. Those blood vessels could be large, small or capillaries, and there will be blood coming out from the soft tissue and between the fractured pieces of the bone and it will form a very big swelling which is called hematoma.

[19] Capable of differentiating into one of many cell types

2. They marginate into the fracture site and start lining osteoid (connective tissue of the bone) and it will start building the callus, the cartilaginous cells will stay for a while and then they will go away, and it may get ossified.
3. The callus and cartilaginous cells are non classified, non-weight peering (it can't carry weight).

4th step is remodeling. This new bone can be remodeled so that the anatomy can return to close to normal. However, the fracture bone fragments must be aligned and placed together for optimum healing to occur, otherwise the callus may not adequately bridge the gap between them, resulting in a permanent deformity. Delayed or abnormal healing of fractures can lead to non-union in which the fractured bone ends do not join by bone. It usually occurs because of the action of the returning the bone to its original shape or form, which can take a long period of time.





For a proper fracture healing to take place, it is essential that the fractured bone ends be in close apposition that the fractured bone is immobilized that the patient's healing capacity is adequate.

Among the factors that detrimentally affect healing of bone:

- ❏ Poor blood supply to the affected area:

  This is important in certain areas such as the scaphoid bone in the wrist and neck of the femur, both of which can be associated with avascular necrosis of fracture fragments.

- ❏ Poor general nutritional status: Particularly where there is protein malnutrition or vitamin deficiencies.

- ❏ Poor opposition of the fractured bone ends:

  E.g. wide displacement, entrapped viable soft tissue between the bone ends or excessive mobility can also contribute to delayed or abnormal healing.

- ❏ The presence of Infection (a risk in comminuted and open fractures):

  The infection must be eradicated before successful bone reunion and remodeling can occur. ▫

- ❏ The presence of foreign bodies.
- ❏ Large quantities of necrosis bone.
- ❏ Corticosteroid therapy.

What's the aim of treatments of fractures?

It's to ensure fracture appositions of bone ends followed by firm immobilization so that the fractured end can't move during the formation of granulation tissue and callus. When fractured bone ends are not closely apposed or if any of the above local complicating factors are present, ossification of the callus doesn't occur the two bone ends are joined by fiber tissues (ankylosis) which is unstable.

Major complications of bone healing:

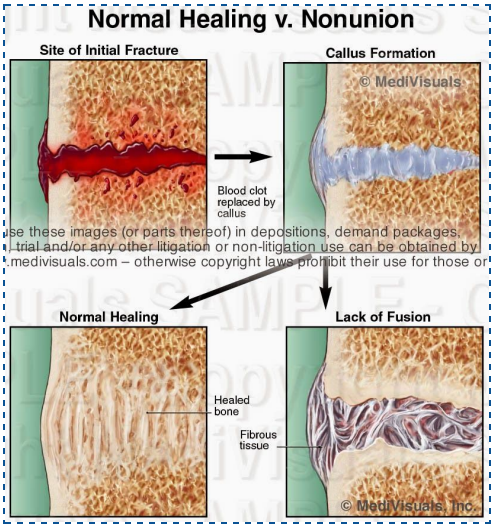
During the process of healing many problems can occur:

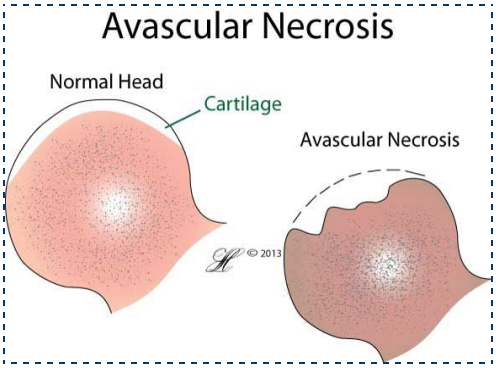
- Secondary osteomyelitis: Commonly occur in compound and open fracture
- Foreign body inside the bone:

  Either because of surgical operation (tools can create a reaction) or because of the contamination of the fracture site, and it may cause a second infection.
- Formation of Pseudarthrosis (مفصل كاذب)

  It will stop at vascular granulation tissue and fibrosis and the area does not heal very well, for many reasons, unsuccessful operation, a foreign body, ischemia or secondary infection and many other reasons.
- It can be malunion or nonunion:
  - ➔ Nonunion: Broken bone which doesn't heal.
  - ➔ Malunion: The fracture heals but not in the optimal position.
- Avascular Necrosis: (necrosis caused by lack of vessels)

  It can occur when there is local ischemia, either because of a rupture of an important blood vessel or because of the structure of the bone itself, it's common in fracture of the head of the femur, because of the femoral artery (treatment is total joint replacement), and the fracture of the scaphoid bone and it doesn't heal, (treatment is removal).





Contact us: Pathology435@gmail.com

Team members

Nouf Altwaijri	Wael Al Oud
Aljohara Almazroue	Abdulaziz AlHammad
Dalal AlHuzaimi	Abdulaziz Redwan
Deema Alfaris	Abdullah AlGhizzi
Ghaida Aljamili	Abdulrahman Thekry
Haifa Bin Taleb	Ahmad Alkhiary
Lina Alshehri	Ahmed Alrwaly
Lina Ismael	Ahmed Al Yahya
Munerah AlOmari	Ammar Almansour
Nojood Alhaidari	Anas Ali
Nouf Alabdulkarim	Faris Alwarhi
Ola Alnuhayer	Khalid Ali Alghsoon
Raghad Almansour	Mana AlMuhaideb
Samar AlOtaibi	Naif Alhadi
Shahad Albeshr	Saleh Alkhalifa
Shahad Aldakhyil	Rayan Almuneef

قال صلى الله عليه وسلم: من سلك طريقاً يلتمس به علماً سهل الله له به طريقاً إلى الجنة.

دعواتنا لكم بالتوفيق.