Congenital Disorders, Acquired diseases and Fractures of Bones

Pathology Team 434

Colors of text:
Definitions: Blue.
Examples: Green.
Important: Red.
Extra explanation: Gray. . It is only there to help you understand. If you feel that it didn't add anything to you just skip it.
Diseases names: Underline.

Contents:

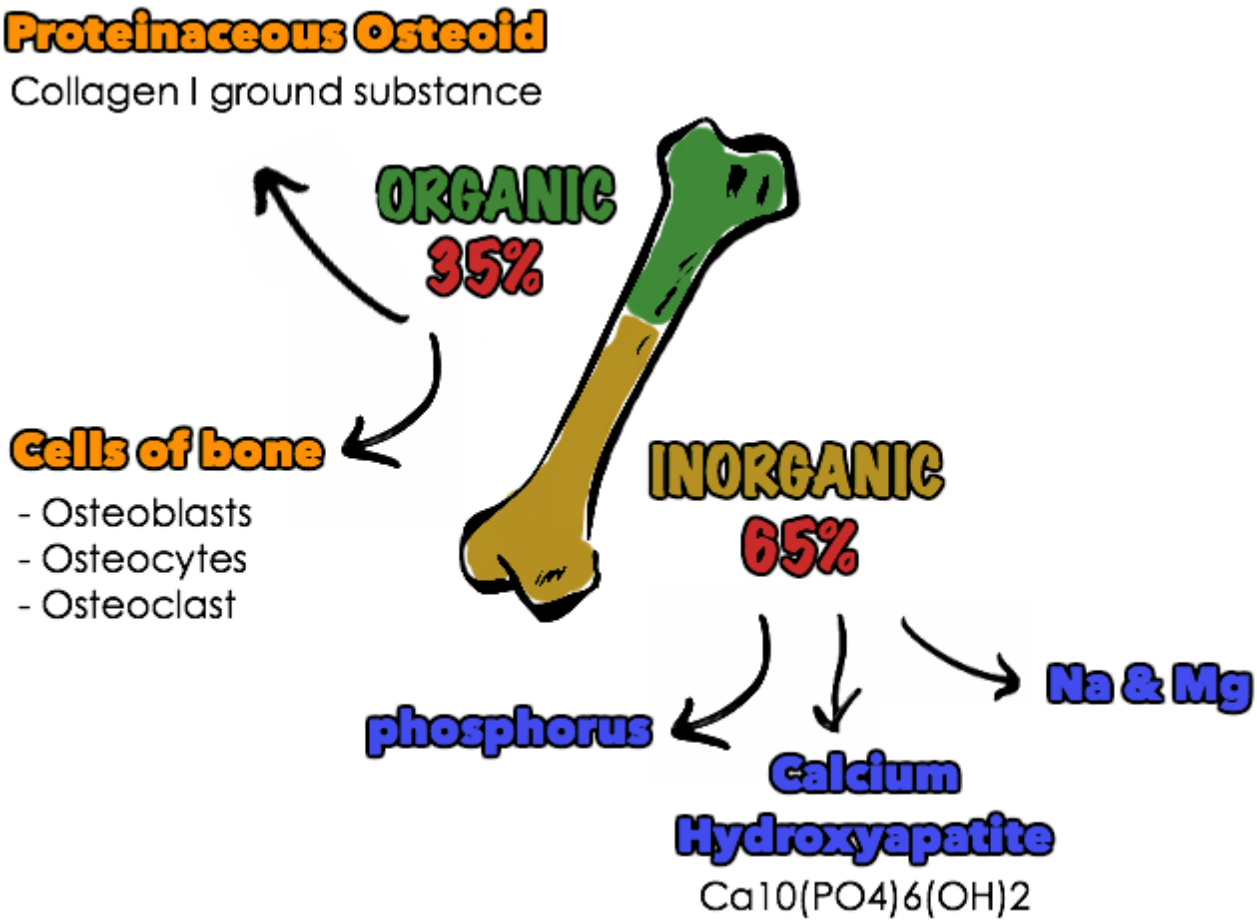
Objectives:

- 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 understands the difference between trauma induced and pathological fractures.
- Know the factors contributing to delayed fracture healing.

Introduction to Bones

Introduction to Bone Biology

The skeletal system is composed of **206** bones. Each Bone is composed of an **Organic Matrix (35%)** and **Inorganic Elements (65%)**.



Bone Remodeling and Modeling

Bone remodeling: (or bone metabolism) is a **lifelong process** where mature bone tissue is removed from the skeleton (a process called **bone resorption**), and new bone tissue is formed (a process called **ossification** or **new bone formation**).

- **Bone-forming cells:** osteoblasts and osteocytes.
- **Bone-digesting cell:** osteoclasts.

OPG, RANK, RANKL pathway + Regulation of Osteoclast Activity.

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

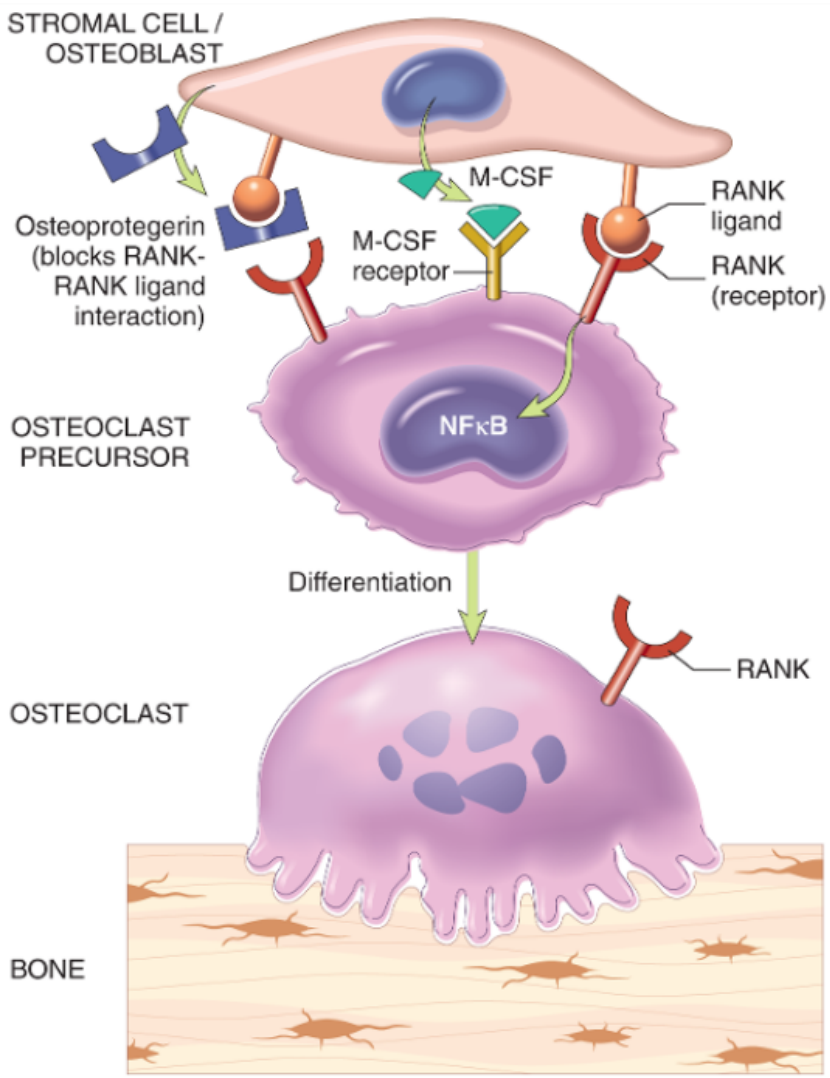
1. **RANK (receptor activator for nuclear factor-κB):** - a member of the tumor necrosis factor (TNF) receptor family - is expressed on the cell membrane of **pre-osteoclasts** and **mature osteoclasts**.
2. **RANK ligand (RANKL):** is expressed by **osteoblasts** and marrow **stromal cells**.
3. **Osteoprotegerin (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 **RANK**? There will be less osteoclast activity.

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.



Congenital Disorders of Bone and Cartilage

Congenital disorders of the skeleton are various. They are manifested at different ages, depending on the affected gene. Some of them are so severe they produce developmental abnormalities from the earliest stages of skeletogenesis.

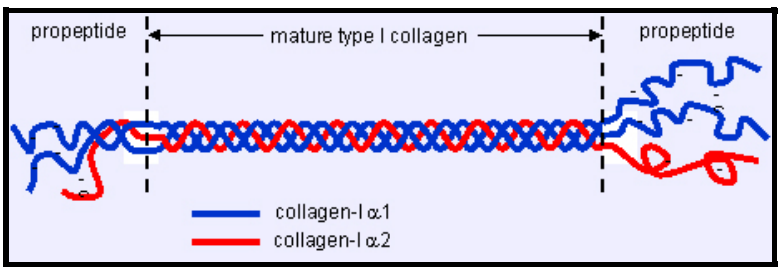
Osteogenesis Imperfecta (OI)

[1]Osteogenesis imperfecta is a rare **congenital** bone disease. Also called **Brittle Bone Disease.** The rate of its incidence is 1-5 infected of 100,000-150,000 childbirths. It has **four** types.

- This disease has four types we will focus on type one and type two. Type three and four are rare and not important for a medical student to know.

Type I disease is inherited as an **autosomal dominant** whereas **type II** is an **autosomal recessive.** In these types there is an abnormality in two genes; which are called **COLIA1** and **COLIA2**.

COLIA1 is found on **chromosome 17** while **COLIA2** is found on **chromosome 7.** These two genes are mutated in this case. Their mutation causes an abnormality in the structure of the protein **collagen 1**. Amino acids chains **alpha 1** and **alpha 2** form collagen 1 are defected. Collagen 1 is important in the structure of the following organs: **Skin , Joints, Teeth, Eyes, Cartilage (ear), Ligaments, and Bones.**



Understanding the pathogenesis and where collagen I is found makes the symptoms understandable, and hence, your life easier.

Symptoms of Osteogenesis Imperfecta (OI):

1. **Abnormal ear and loss of hearing:**

   Can be related to conduction defects in the middle and inner ear bones.

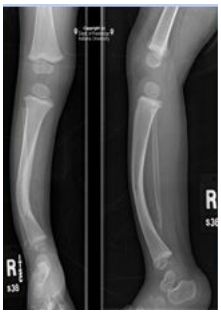
2. **Blue sclera[2] (bluish tense):**

   Superficially it will look white but when examining it closely you will find that it has a **bluish colour** and that is because collagen I is deficient, and because of that deficiency, the **sclera is thin**, therefore reflecting the blue **pigment** which is usually found in the **choroid**.

[1] سوء تشكل العظم

[2] the white outer layer of the eyeball. At the front of the eye, and it is continuous with the cornea.

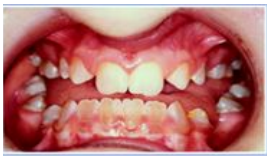
3. Abnormal bones:



Therefore they develop lots of pathological fractures (usually in the long bones). They heal very well because the healing process in children is faster.

WHY are there recurrent fractures? because the bone is brittle[3] (due to collagen deficiency). That's why the disease is also called **brittle bone disease**.

4. deformed teeth:



Teeth are deformed[4] and discolored due deficiency of dentin[5].

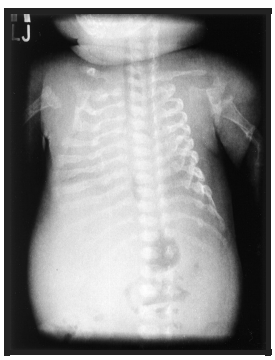
5. Abnormal skin:

Skin has no change in colour but you might find folds or thinning in some areas. In addition, some skin difference such as redness and loss of colour may be observed in some areas.

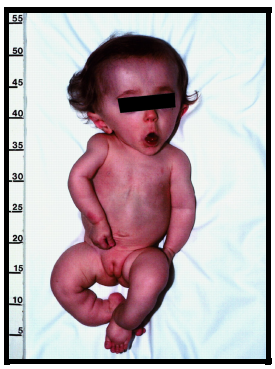
These symptoms are found in osteogenesis imperfecta type 1 and type 2.

Then what's the difference between type I and II ?

The difference is the **severity** of the disease. As **type 1 is compatible with life** they **usually live,** but **type 2 is more severe** and most of affected individuals **die in the uterus** before birth. They usually die from consequence of **multiple fracture** that occur before birth or during delivery.



Embryo with osteogenesis imperfecta type II



Baby with osteogenesis imperfecta type I

[3] لين أو هش
[4] متكونة بشكل خاطئ
[5] عاج الأسنان - hard, dense, bony tissue forming the bulk of a tooth beneath the enamel.

Achondroplasia and Thanatophoric Dwarfism

Achondroplasia is a common disease. Its incidence is **1:15000** live birth. It is the most common cause for **dwarfism**[6].

When you see someone who is a dwarf in most cases he has achondroplasia **but NOT always**. Patients usually have **normal** brain capabilities and mental status; they are NOT retarded.

Their **trunk is of normal size** the problems are in the upper and lower limbs. The upper and lower **limbs are shorter** than usual. Sometimes, there will be bowing[7] of the legs and neck.

We can tell by looking at the pictures that the legs are short and the skin is folded many times. **WHY?** Because the skin is big on them and because they don't have enough bone as it is short so the skin is more than required and therefore it has many folds. (مثل واحد اشترى بنطلون آكبر منه بمقاسين).

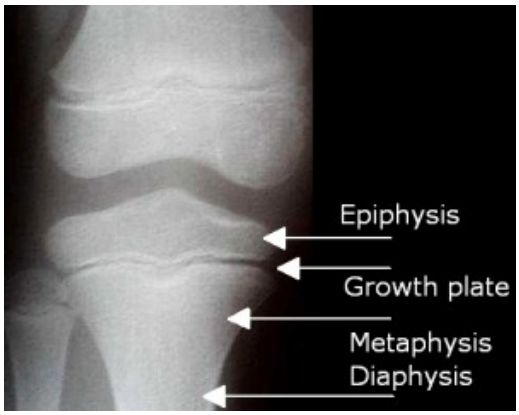
Why do patients get achondroplasia?
It is an **autosomal dominant disease.** There is no sexual preference (it can affect both genders). Usually, there is a **mutation** on a specific gene on **chromosome 4**, which is called **Fibroblast Growth Factor Receptor 3** (**FGFR3**). **FGFR3** is a receptor with **tyrosine kinase activity** that transmits intracellular signals. Signals transmitted by **FGFR3** ***inhibit*** the proliferation and function of growth plate chondrocytes. In this case the gene is **over activated** and **over stimulated**, and as a result, the **chondrocytes** will be inhibited prematurely [8]in the **growth plates** of the long bones.

We know that the long bone consists of three parts which are:

- **Epiphysis:** The very top end of the bone.
- **Metaphysis:** the upper part just below the epiphysis
- **Diaphysis:** The body of the bone or the shaft.

Note: a helpful mnemonic: "**E**piphysis is at the **E**nd of long bones."

[6] القزامة
[7] إنحناء
[8] at an earlier time



Pathogenesis:
An **epiphyseal line of growth plate** is found in children**.** This area controls the growth of bone. It closes down when the growth is complete.
Note: when we look at the picture (an x-ray) and see a gap between the epiphysis and metaphysis that means that the patient is probably young (less than 12-16 years old).
When (**FGFR3**) is mutated: there is a gain of function mutation of this gene, which acts on the growth plate (**the epiphyseal line**) → inhibits chondrocyte proliferation → making the epiphyseal line of growth plate close prematurely[9].
As a result, the bone stops growing and the patient suffers from dwarfism. Achondroplasia affects all bones that develop by endochondral ossification (ossification of cartilage).

Is this disease always inherited?
NO, there can be some **sporadic mutations**[10].

It is not an autosomal dominant trait, it means that something happened to this gene (point mutation) and made it over expressed. This causes an abnormal growth of the chondrocytes, effecting their maturation, and resulting in a premature closure of the epiphyseal line, which makes the bone shorter, and the patient a dwarf.

There is **no treatment** except counselling and reassuring the patient and teach them them how to live with dwarfism.

Thanatophoric Dwarfism (lethal variant of dwarfism).

Features: Thanatophoric means (death-loving)

The God of death in ancient greek was called Thanataphor, and because affected patients died prematurely, this disease was called Thanatophoric Dwarfism.

It is the same as achondroplasia but is more severe and causes respiratory failure in the infant and death.

1. Lethal.
2. Extreme shortening of the limbs.
3. Extreme frontal bossing of the skull. (يعني أن الجبهة تكون بارزة وكبيرة)
4. Extreme small thorax, which will be the cause of **fatal respiratory failure**.

[9] قبل أوانها
[10] طفرة فردية أو حدثت فجأة بدون عامل للوراثة.

Osteopetrosis[11]

[Osteopetrosis.]

Osteopetrosis is 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.

يعني إن العظم يكون متصخر ويشبه الطباشير فيكون قابل للتكسير و التفتت بسهولة و هذا بسبب عدم قدرة الـ osteoclast على امتصاص العظم.

The defects that cause osteopetrosis are categorized into those that disturb osteoclast function and those that interfere with osteoclast formation and differentiation. The precise nature of the osteoclast dysfunction is unknown in many cases. Nevertheless, in some cases the abnormalities have been identified. These include **carbonic anhydrase II[12] deficiency**, **proton pump deficiency** and **chloride channel defect**, all of which interfere with the ability of osteoclasts to resorb bone.

Several variants are known, the two most common being an autosomal dominant adult form with mild clinical manifestations, and autosomal recessive infantile, with a severe/lethal phenotype. 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, and hepatosplenomegaly caused by extramedullary hematopoiesis resulting from **reduced marrow space**. Because osteoclasts are derived from marrow monocyte precursors, hematopoietic stem cell transplantation holds the promise of repopulating recipients with progenitor cells capable of differentiating into fully functional osteoclasts. Indeed, many of the skeletal abnormalities appear to be reversible once normal precursor cells are provided.

SUMMARY

Congenital Disorders of Bone and Cartilage

- Abnormalities in a single or group of bones are called *dysostoses* and can result in the absence of bones, supernumerary bones, or inappropriately fused bones; some of these result from mutations in homeobox genes affecting localized migration and condensation of primitive mesenchymal cells.
- Abnormalities in bone or cartilage organogenesis are called *dysplasias*; these can be caused by mutations that affect signal transduction pathways or components of the extracellular matrix:
  - Achondroplasia and thanatophoric dwarfism occur as a consequence of constitutive FGFR3 activation, resulting in defective cartilage synthesis at growth plates.
  - Osteogenesis imperfecta (brittle bone disease) is a group of disorders caused by mutations in the genes for type 1 collagen that interfere with its normal production, with resultant bone fragility and susceptibility to fractures.
  - Osteopetrosis is caused by mutations that interfere with osteoclast function and is associated with dense but architecturally unsound bone owing to defective bone resorption.

[11] تصخر العظم

[12] chemical substance essential for bone resorption and osteoclast differentiation

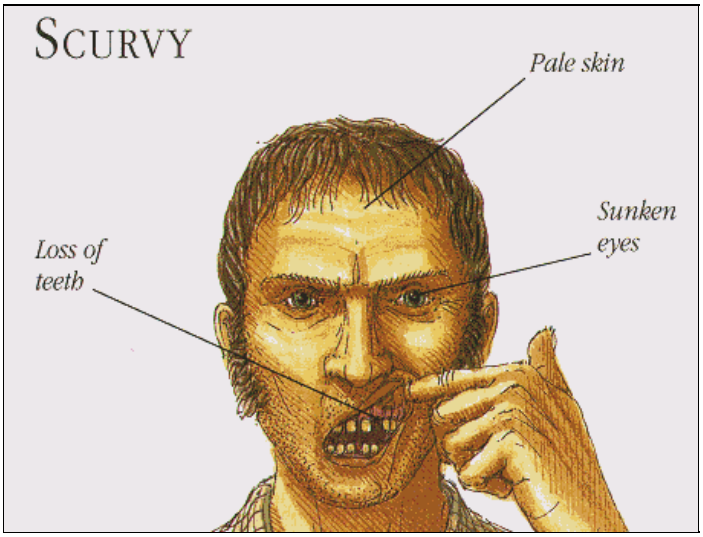
Acquired Diseases of Bone

Acquired diseases of bone: many **nutritional**, endocrine, and other disorders affect the development of the skeletal system. Nutritional deficiencies causing bone disease include:

1. Deficiencies of **vitamin C** (involved in **collagen cross-linking**; deficiency causes **scurvy**).
2. Deficiencies of **vitamin D** (involved in **calcium uptake**; deficiency causes **rickets** and **osteomalacia**).

Many of these disorders are characterized by **inadequate osteoid**, also called **osteopenia**[13]; the most important clinically significant osteopenia is **osteoporosis**.

Scurvy Disease: it is caused by a **deficiency of vitamin C,** characterized by swollen bleeding gums[14] and the opening of previously healed wounds.



- metabolic bone diseases are **common** and they can be seen in **adults** and **children**.
- metabolic bone diseases are concerned with three things: **calcium**, **phosphorus** and **3-alkaline phosphatase.**
- **3-alkaline phosphatase (ALP):** is an enzyme that has three isoenzymes the first one is in the **liver**, the second one is found in the bone in the **osteoblast** and can be increased in certain bone diseases as in **paget's disease.**

Two disorders are common metabolic bone diseases:

1. **Osteoporosis:** which is very common in clinical practise and most doctors come across it whether in paediatrics, internal medicine, surgery or OB/GYN.
2. **Osteomalacia:** Deficiency in vitamin D.

[13] نقص العظم أو الهشاشة

[14] gums : اللثة

Osteoporosis

Osteoporosis[15]: is characterized by reduced bone mass, increase in erosion[16], making bone vulnerable[17] to fracture. Most fractures related to osteoporosis occur in the **neck of femur**. Osteoporosis can occur in **both genders** but **most commonly in females** and white people are at higher risk than black people. After the age **50** all people have osteoporosis it can be **mild** or **severe** according to the environmental factors.

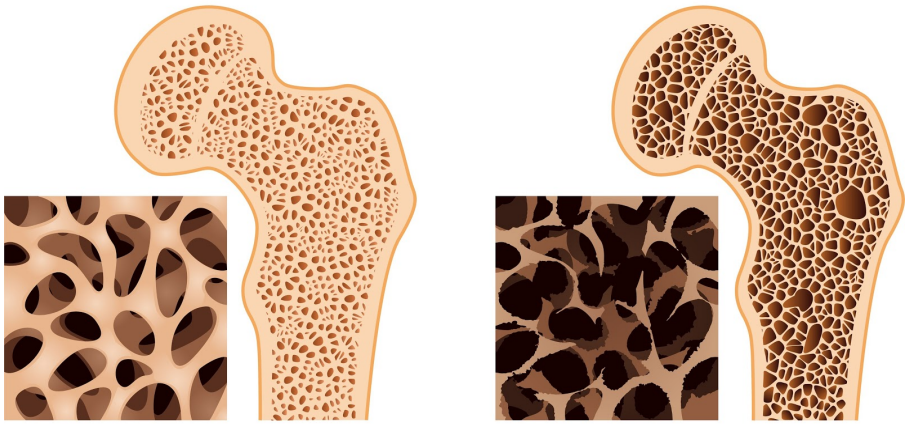
- **Trabecular bone** is affected **before** cortical bone. It's found in greater amount in **vertebral bodies** and **pelvis**.
- **Cortical bone** is found in the greatest amount in the **long bones**.

Patients with osteoporosis has a skeleton which is less dense than a normal skeleton by **30-50%**.

The bone is composed of a **connective tissue** called **osteoid** (**A collagen**). **Osteoid** is formed by **osteoblasts**, and resorbed by **osteoclast**. Osteoid needs to be mineralized by the deposition of **calcium phosphate** (**Hydroxyapatite**) on it. The deposition of calcium phosphate ossifies[18] the osteoid.

Note: osteoid is the bone with the organic material only (collagen I). After mineralization (addition of inorganic materials) it is called bone.

In osteoporosis, the ossification is normal but there is a **general reduction** in bone mass and volume. So in patients with osteoporosis, there will be an increase in **calcium**, **phosphorus** and **alkaline phosphatase** levels in serum, the difference is the decrease in the thickness of the **trabecula** and **cortical bone** (Bone mass is decreased without disruption of architecture).



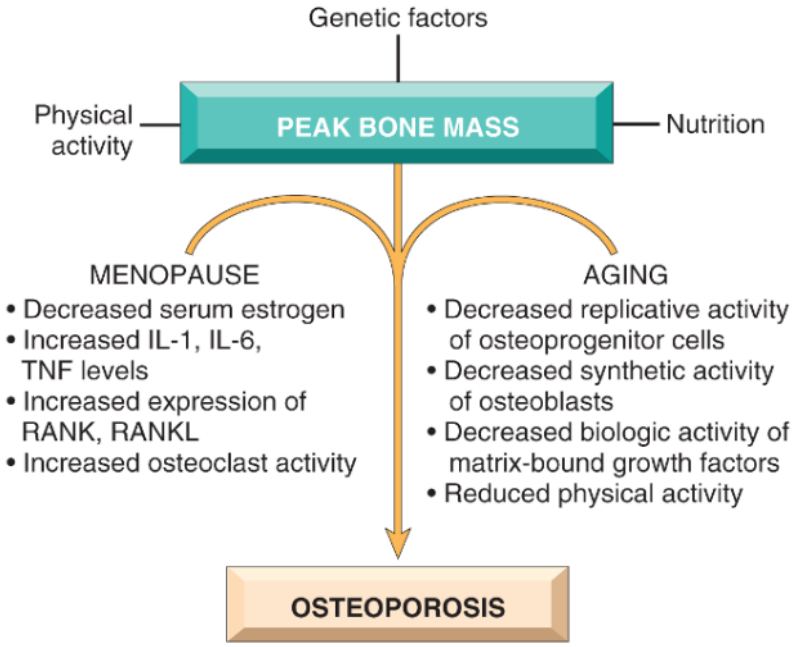
Healthy bone Osteoporosis

[15] Osteoporosis : هشاشة العظام

[16] تآكل

[17] vulnerable : عُرضة

[18] turn into bone or bony tissue.

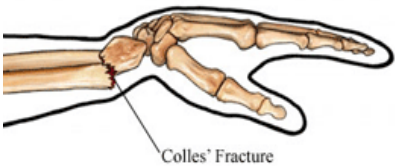


Generally it is divided into two types: **primary osteoporosis** and **secondary osteoporosis**.

Primary osteoporosis:

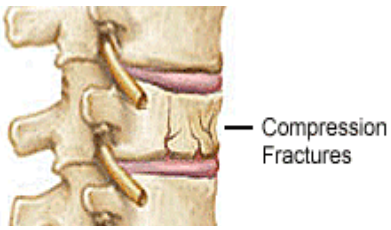
primary osteoporosis refers to **senile**[19] osteoporosis and **postmenopausal** osteoporosis.

- a 70 years old woman fell from her bed.Although this is considered a minor trauma, she had **pathological fractures**
- Fractures can happen anywhere but occur most commonly in the **neck of the femur** and the **wrist** -which is called **colles fracture-** and it's a fracture of the distal end of the radius and you see a deformity in the hand.



Osteoporosis can affect any bone but mainly the **long bones** and the **vertebral column**.

In severe **osteoporosis**, the vertebrae is fractured due to its weakness; this is called a **compression fracture.** The bone volume is **reduced** so there will be vacuoles in the bone, and over a period of time, this bone will compress and form a compression fracture, which will cause pain. Most of patients with compression fractures have **osteoporosis**.



Why are women at increased risk of osteoporosis after menopause?

There is a relationship between **estrogen** and **osteoporosis.** The drop of oestrogen will induce **osteoporosis**. They think that the drop in **estrogen** will stimulate some **inflammatory cells** and will increase the secretion of certain cytokines especially **tumour necrosis factor (TNF)**, **interleukin 1**, **interleukin 6** and sometimes **interleukin 8.** theses cytokines stimulates certain receptors on the surface of **osteoclast**. These receptors are called **RANK** and **RANKL.** When these receptors are stimulated, the osteoclast will become more **mature**, **active** and cause **more absorption** than usual and the end result will be osteoporosis.

[19] senile : شيخوخة

Secondary osteoporosis:

Related to **Alcohol**, **smoking**, **soft drinks**, **cortisone intake (corticosteroids)**, and **endocrine disorders** (e.g. diabetes) all take part in the pathogenesis of secondary osteoporosis.
Weight bearing exercises[20] decrease the risk of osteoporosis.

treatment: Hormone replacement therapy, oral bisphosphonates, and vitamin D.

Diagnosis:

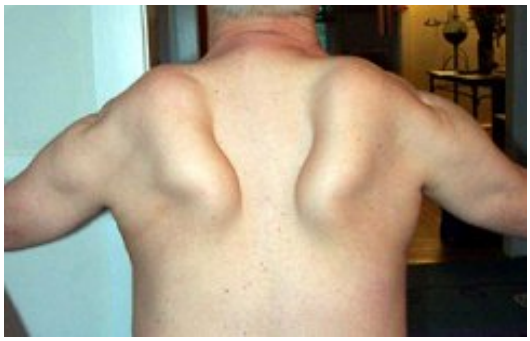
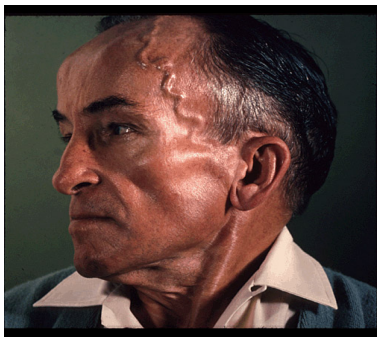
It is difficult to diagnose. **Plain X-ray** can detect it only when 30% - 40% of bone mass is already lost. Another method is called **DXA scan**. We can use **densitometry**[21] and see if the bone mass is decreased by a known reference rate. (bone loss rarely exceeds 1% per year).

[20] حمل الأثقال.. يعني السباحة لن تفيد
[21] مقياس كثافة

Categories of Generalized Osteoporosis

Primary
Postmenopausal
Senile
Secondary
Endocrine Disorders
Hyperparathyroidism
Hypo or hyperthyroidism
Hypogonadism
Pituitary tumors
Diabetes, type I
Addison disease
Neoplasia
Multiple myeloma
Carcinomatosis
Gastrointestinal Disorders
Malnutrition
Malabsorption
Hepatic insufficiency
Vitamin C, D deficiencies
Idiopathic disease
Drugs
Anticoagulants
Chemotherapy
Corticosteroids
Anticonvulsants
Alcohol
Miscellaneous
Osteogenesis imperfecta
Immobilization
Pulmonary disease
Homocystinuria
Anemia

Paget Disease (Osteitis Deformans)

This unique skeletal disease is characterized by repetitive episodes of **frenzied**, **regional osteoclastic activity** and **bone resorption**, followed by exuberant bone formation (*mixed osteoclastic-osteoblastic stage*), and finally by an **apparent exhaustion** of cellular activity (*osteosclerotic stage*).

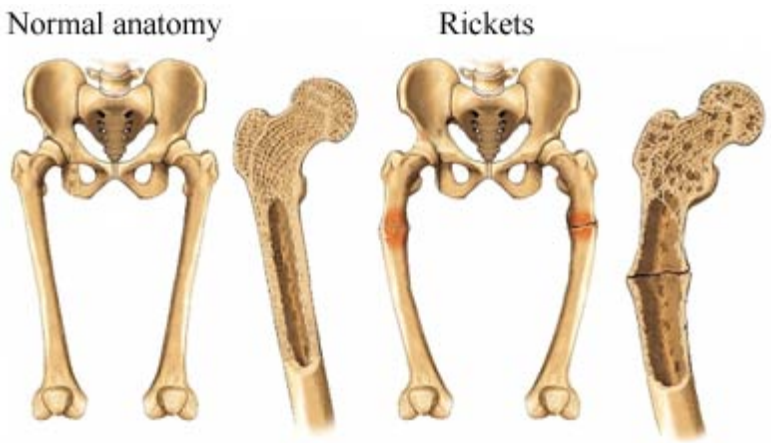
- The net effect of this process is a *gain in bone mass*; however, the newly formed bone is **disordered** and **weak**, so bones may become **enlarged** and **misshapen**[22].

In other words: T=this disease has three stages:

1) increased osteoclasts
2) mixed with both osteoclasts and osteoblasts
3) increased osteoblasts and no osteoclasts

Associated with **paramyxovirus** infections in susceptible patients.

Rickets and Osteomalacia



Osteomalacia: (vitD deficiency) is a metabolic bone disease that occurs in adults. osteoblastic production of bone collagen is normal but mineralization is inadequate [23]which results in accumulation of unmineralized matrix (increased osteoid).

Rickets: (vitD deficiency in children) osteomalacia affecting children where the skeleton is not fully developed(osteofied). It is caused by "Vitamin D" metabolism abnormalities which leads to inadequate mineralization of the **epiphyseal cartilage** as well as the osteoid.

---

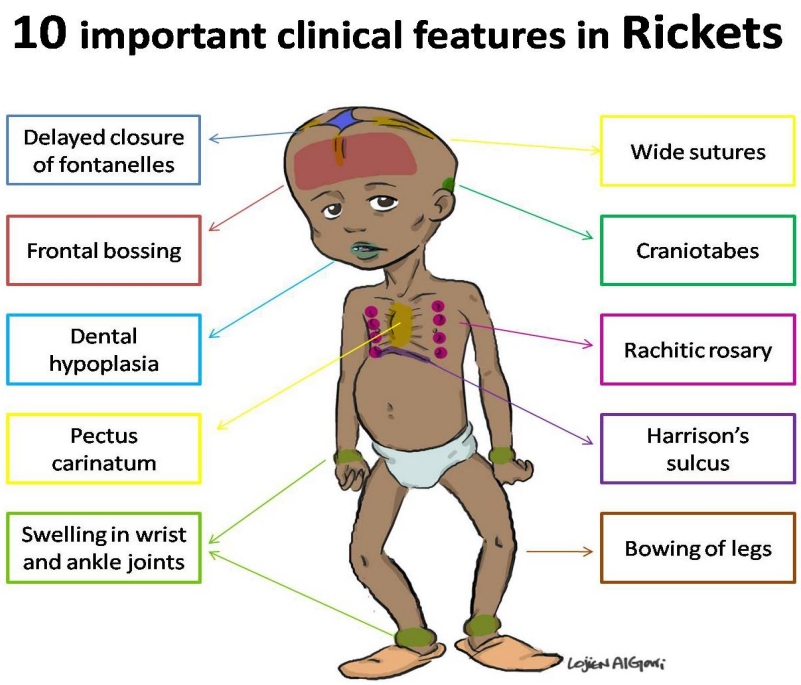
[22] مشوه

[23] Poor

Deficiency of vitamin D caused by:

1) insufficient intake (nutritional *status or diseases)*
2) Malabsorption due to intestinal diseases.
3) Renal diseases.

Remember: Vitamin D is always associated with calcium absorption. Therefore, a lack in vitamin D will affect Ca absorption.

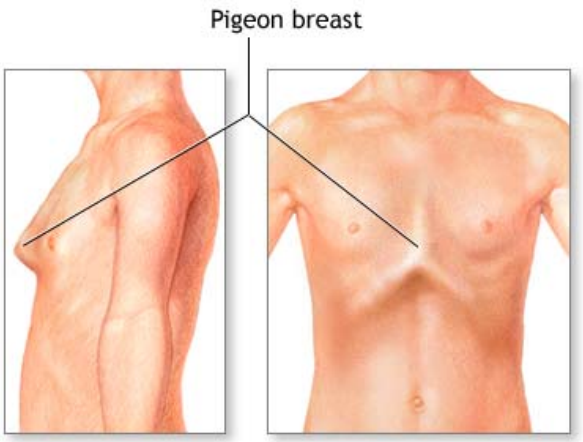


Osteomalacia leads to characteristic structural deformities:

1. Distortion in the skull bone, Gaps in the skull.
2. Abnormality in the rib cage known as "**pigeon chest**"

-No bowing of legs in osteomalacia.

Other Rickets characteristics: gap in skull , large head , bowing head , **pseudofracture**.



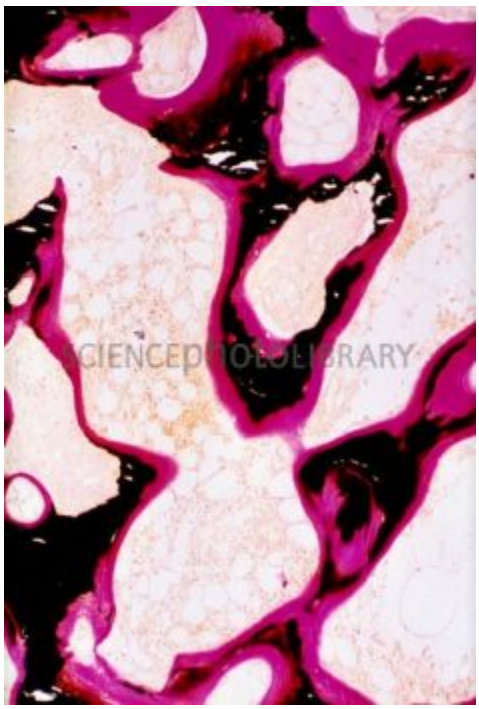
Pigeon breast: s a deformity of the chest characterized by a protrusion of the sternum and ribs.

What is the difference between osteomalacia and osteoporosis?

- **Osteomalacia:** Normal collagen production but inadequate mineralization. Thus, trabeculae of the bone is soft and weak.
- **Osteoporosis:** a slow mechanism that increases bone erosion[24] with poor new bone formation. Therefore, bone mass is reduced but **without** distortion (loss) of architecture.

osteomalacia is caused by lack of vitamin D and abnormal calcification of the bone, so here there is no reduction in the volume but a reduction in the calcified bone (the amount of calcium). Opposite to that, there is a reduction in the volume of bones in osteoporosis.

When noticing the shaft of a normal person you will find the bone's trabecula are normal thickness and have a **black colour** because the stain that used to stain **calcium** (makes calcium have a black colour).



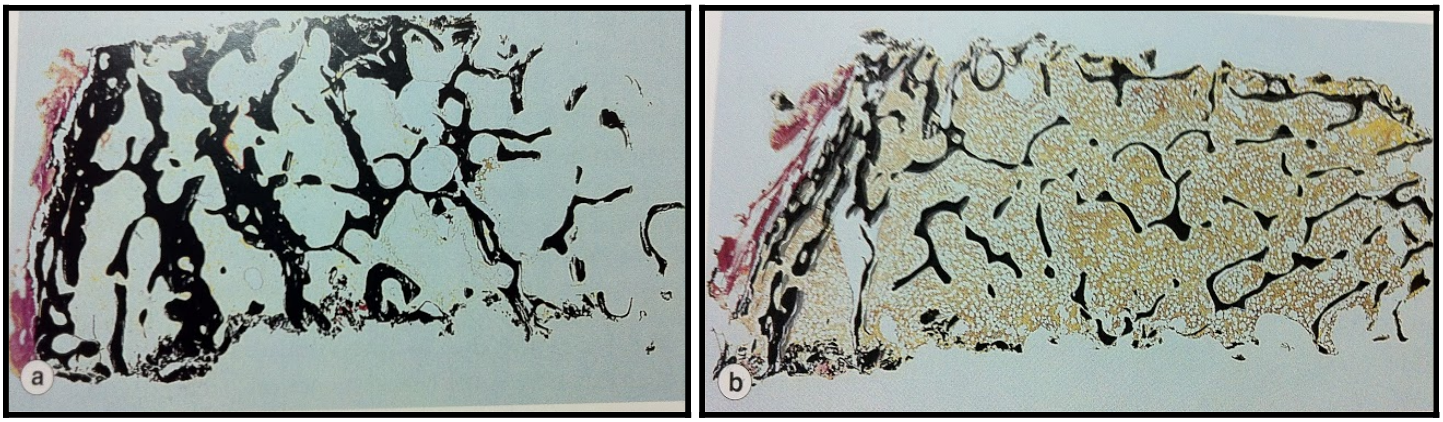
Red = osteoid
Black = calcified osteoid

Vitamin D is activated by the kidney after absorption. Renal failure will impair the activation of vitamin D causing **osteomalacia**. This is called **renal osteodystrophy**.

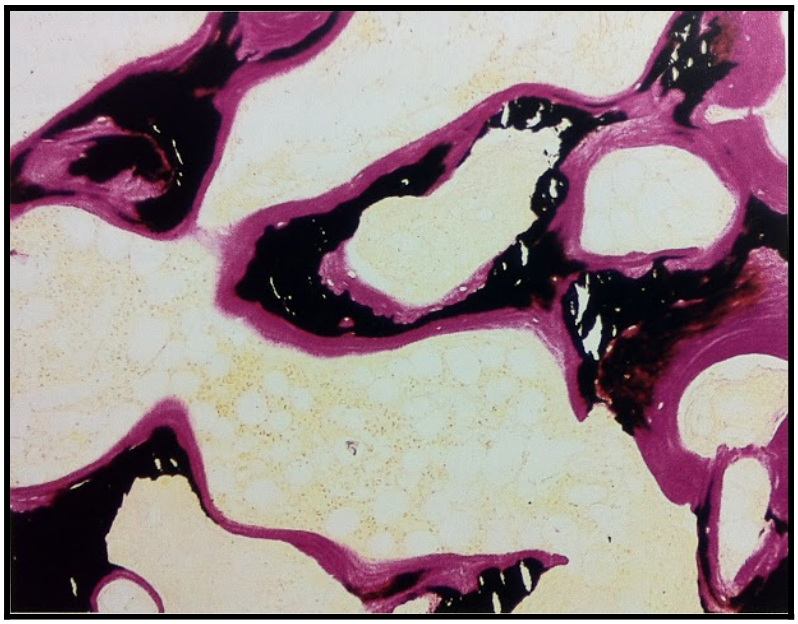
- Osteomalacia is called (**renal osteodystrophy**), When secondary to renal disease.

Decreased renal activation of vitamin D → hypocalcemia → secondary hyperparathyroidism → osteoclastic activation → bone resorption.

[24] تآكل



Osteoporosis. (a) Micrograph of a resin section of a bone biopsy from the iliac crest, showing normal cortical and trabecular bone. It has been stained with a silver method. which stains calcified bone black. **(b)** Micrograph of bone from a patient with osteoporosis. When compared with **(a)**, which shows the bone mass of a normal patient of the same age, it is obvious that the cortical zone is narrower, and that the trabeculae are thinner and less numerous.



Osteomalacia. Micrograph of iliac crest bone embedded in acrylic resin without prior decalcification from a patient with osteomalacia. Note the broad zone of unmineralized osteoid (red) and the central zone of mineralized bone (black), in this section stained by the **von Kossa silver technique**.

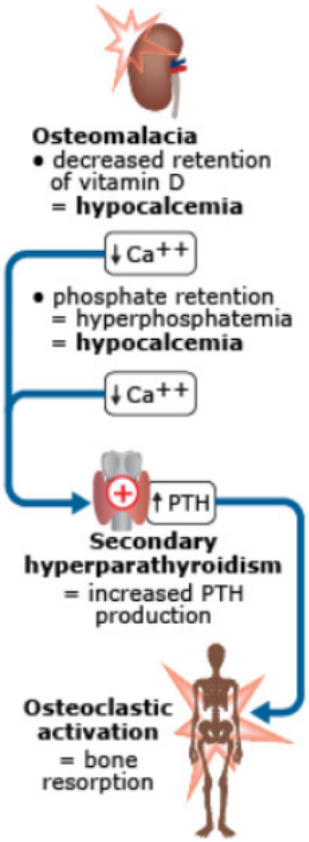
---

losers zone: Common fracture which occur in the **tibia**: you will find the bone not calcified and there are subcortical fractures (not complete) that's why it's called losers fractures.

Once we have this in a child we suspect that he has malnutrition which will lead to rickets, so these fractures occur to patients with osteomalacia (the difference between it and a greenstick fracture that in the greenstick fracture there will be deformation of the bone) these fracture usually does not occur in adults .

Hyperparathyroidism

Parathyroid Glands and Hyperparathyroidism



- **Primary hyperparathyroidism:**
  - **Adenomas** are the most common cause of **primary hyperparathyroidism**.
  - *Hyperparathyroidism* can occur as a **paraneoplastic syndrome** of **lung and renal cell carcinomas.**
  - The excess production of parathyroid hormone (PTH) leads to **hypercalcemia**.
  - *Primary hyperparathyroidism* is often **asymptomatic**, but may cause **osteoporosis** and **osteitis fibrosa cystica**, **metastatic calcifications**, or neurologic changes.

- **Secondary hyperparathyroidism:**
  - is caused by any disease that results in **hypocalcemia**, leading to increased secretion of PTH by the parathyroid glands.
  - The condition can result from **chronic renal failure** and **vitamin D deficiency** or **malabsorption**.

SUMMARY

Acquired Diseases of Bone Development and Mass

- Nutritional deficiencies can affect bone integrity by altering the quality of the organic matrix (e.g., vitamin C is involved in collagen cross-linking) or by influencing bone mineralization (e.g., vitamin D is involved in calcium uptake).
- Osteoporosis results from decreased bone mass and is clinically significant because it predisposes bone to fracture. Although osteoporosis is multifactorial, the two most common forms are *senile osteoporosis* due to aging-related losses of osteoblast function, and *postmenopausal osteoporosis* due to increased osteoclastic activity caused by the relative absence of estrogen.
- Paget disease may result from a paramyxovirus infection in genetically susceptible persons and is caused by aberrant and excessive osteoclast activity, followed by exuberant—but structurally unsound—osteoblast deposition of bone.
- Primary or secondary (due to renal failure) overproduction of PTH (*hyperparathyroidism*) results in increased osteoclast activity and bone resorption, leading to fractures and deformities.

Fracture and Bone healing

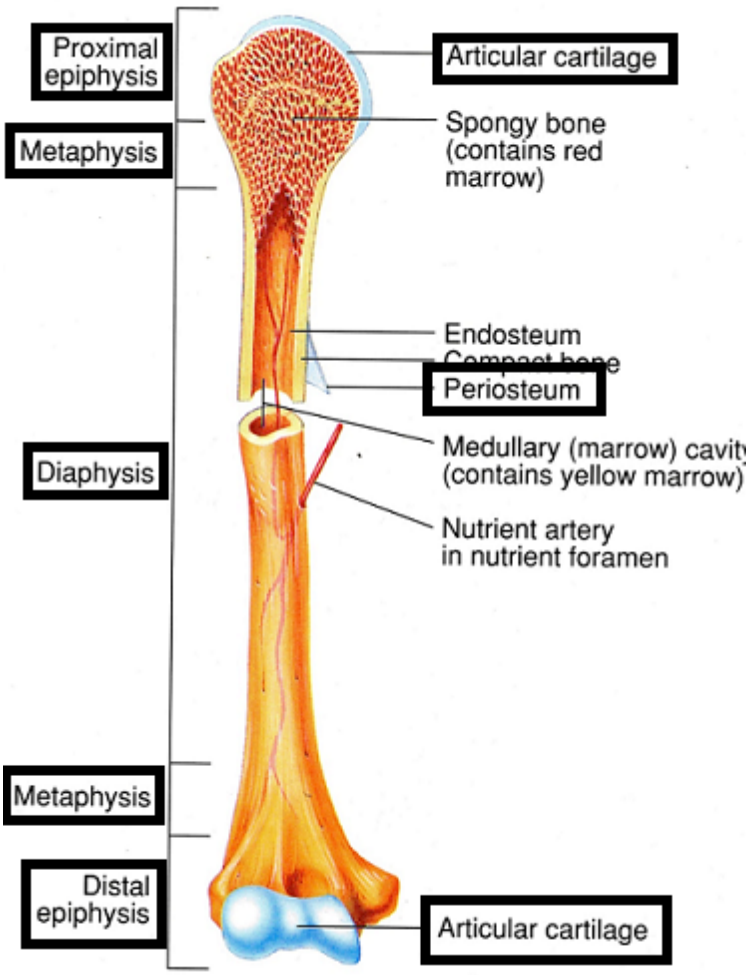
Fracture: a disruption of the continuity of a bone caused by an external element, event, trauma or a disease.

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)

The bone consist of:

1. **Metaphysis:** (between epiphysis and diaphysis).
2. **Diaphysis:** (the shaft / body).
3. **Epiphysis:** (has centers for ossification and bone production, has epiphyseal line that is the growth plate of bone, it has the osteoprogenitor cells, it usually remains open until the ossification is complete, in children the epiphyseal line is open especially in long bone).

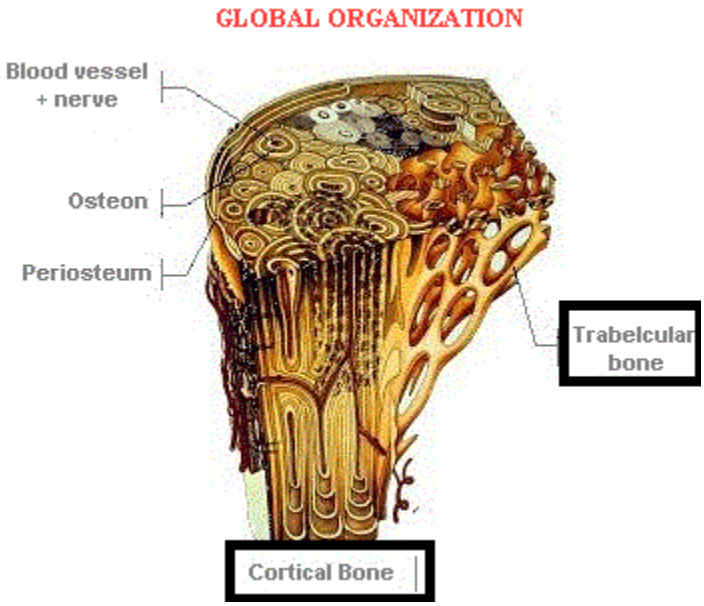
The bone is covered with **articular cartilage** and **periosteum**.



We should know the structure of bone because tumors could occur in certain parts of the bone and help us in differential diagnosis.

We have two types of bone:

1. **Cortical / lamellar** صلب: Formed of **haversian canals** that contain osteocytes (not active). The active ones are the **osteoblast** that form the **osteoid** (connective tissue in bone) and **osteoclasts** (mono or multi nuclear) are responsible for desorption and remodeling of bone (نحت).
2. **Trabecular**: (woven bone is bone that has trabeculae / found in the medulla).



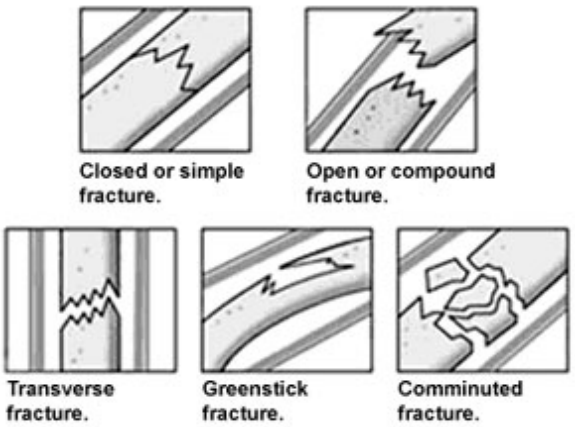
The bone marrow has **progenitor stem cells (red bone marrow)** and **fat (yellow bone marrow)**.

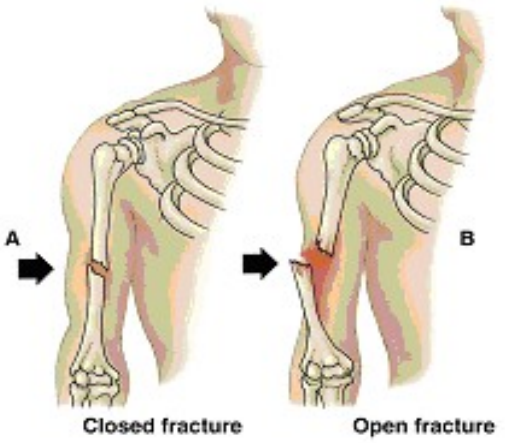
- Bone marrow biopsy is an important diagnostic tool.

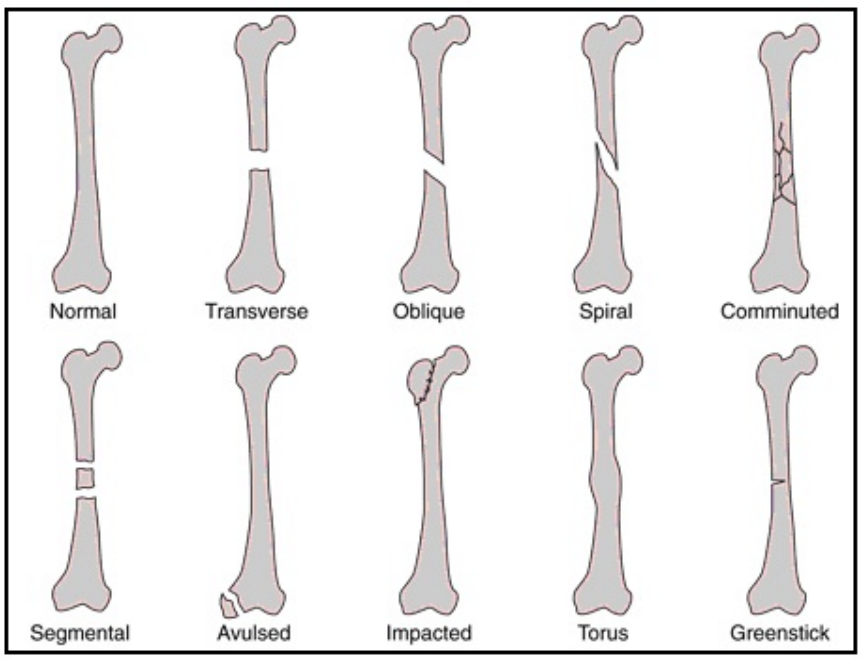
Types of fractures

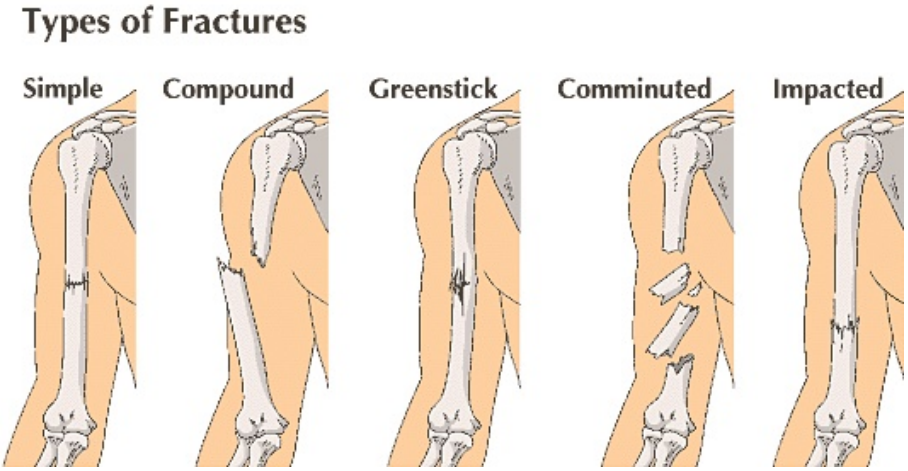
Note: pictures are very helpful for understanding the types of fractures; memorization is not recommended.

Fracture are generally classified into two major types **closed fractures** and **open fractures**.









- **Green stick fracture:** Is an incomplete fracture of long bones and is usually seen in children; the bone is still intact.

- **Displaced / compound fracture:**
  Both part of bone are not opposed , they are displaced, sometime we call it compound (open).
  when there is displacement and rupture of the skin. These kind of fractures are prone to infection. Open fractures are characterized by swelling and blood oozing out.

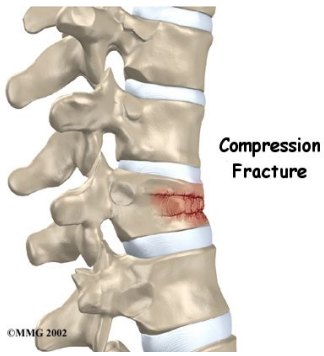
Note: open fractures are those exposed to air: the bone comes out of the skin.

- **Closed simple fracture:** linear. if it happens to a child it may not need a cast and it will heal on its own but if it happens to an old person it needs a cast[25].
  - ❏ closed fracture that has **NO** bleeding or open wound; it is simple.
  - ❏ called close fracture because it is occur in tissue only (doesn't get out).
  - ❏ It has swelling , hemorrhage , loss of function , pain when moving , hematoma formation.
  - ❏ It needs an X-ray.

- **Splintered or comminuted fracture:**
  The bone is broken into many smaller fragments at the site of fracture. It is also called a fragmented fracture. It is a closed fracture .

- **Stress fracture:**
  It occur in small bones of the ankle and foot following a very long march and fatigue exercises. it is nondisplaced , linear and simple

- **Compression fracture:** (fracture of the vertebrae) if it is severe it could cause neurological defects , it is commonly caused by osteoporosis and trauma.



[25] جبس

Pathological fractures: Fractures that occurs because there is a disease in the bone, that means a minor trauma can causes a fracture.

People with diseases are prone to fractures these diseases include:

- Metabolic diseases: osteoporosis or osteomalacia.
- Endocrine: hyperparathyroidism.
- Bone Cysts.
- Inflammatory: osteomyelitis.
- Tumors: primary cancer of bone: osteosarcoma.

- Children with **osteogenesis imperfecta** have multiple fractures even inside uterus (congenital disease).

Sometimes fracture cause **deformities**[26] like **colles fracture**.

Colles fracture: a very famous fracture which occur in the **distal radius** that heals badly causing a **fork like shape** of the arm (شكل الشوكة) (it is common in people with osteoporosis).
Colles fractures can be treated with closed reduction

[26] تشوهات

Fracture healing

When there is a fracture, the shaft is discontinued (forming a gap in the bone). In addition, rupture of blood vessels around the bone and injury in soft tissue is usually present.

So the **First step** of healing is formation of **hematoma**[27].

Second step: organization of hematoma. 3 days after fracture there is an organized hematoma (Hematoma with clotted blood and migration of **fibroblast** and **inflammatory cells** and proliferation of **blood vessels** [vascular granulation tissue], .

Third step : Stimulation of **osteoprogenitor cells**

Inflammatory cells release cytokines (Platelet drive growth factor and fibroblast growth factor) **PDGF**, **FGF** and **TNF**. These cytokines will stimulate **osteoprogenitor** cells which are spindle cells which are capable of transforming into **osteoblast**. Within a week, the tissue will be called **Soft Tissue Callus**.

At the site of fracture, there are osteoblast and chondrocyte. **Chondrocyte** will go away and **Osteoblasts** start forming **osteoid** (connective tissue which is found in bone and it is a form of **collagen I** but it *doesn't* have calcium that means it is not ossified)

Finally, the osteoid will get **ossified** (mineralized) and there will be trabecular and cortical bone. The tissue now is called **Bony Callus**.

[27] Blood clot

Clinical cases

Pathological Fracture

A person come to the emergency and can't move his leg , after doing an x-ray they find lytic bone lesion and fracture of the femur (abnormal bone). we should treat the fracture and take a biopsy of the bone. The biopsy shows a metastatic tumor from lung cancer.

- Most common tumor of bone is metastatic.

Closed Fracture

A women with a fractured ankle : we could see extreme swelling / hemorrhagic area and hematoma formation ورم دموي which is an accumulation of blood within the soft tissue and loss of function (can't move).
Diagnosis: This is a closed fracture because there is no bleeding or open wound.
Further examination: So we do x-ray to determine which bone is fractured.

Osteomalacia

A **71 years old** patient with constant diarrhea after tests you'll find he has **iron deficiency**, **anaemia** and **calcium**, **phosphorus** levels are decreased sometimes **alkaline phosphatase** level are increased.

This patient has malabsorption (chronic diarrhea) caused by a gastrointestinal disease and this induced **osteomalacia**.

- If he was a child it would be called **Rickets**.

Osteoporosis

This man has kyphosis (حدبة) because the vertebra are compressed and he has many compression fractures, we can tell that this compression has led to some deformity of the vertebral column in a degree that the folds of the skin has increased (**WHY?** because the vertebra has become in a spongy form and became more compressed so the length of it has decreased resulting in excessive skin which will fold) and complaining of back pain he went to a lot of doctor with no use. we use pain relievers but we have to make sure that the patient understand that it is a chronic diseases which needs a long term treatment and we use substances that increase calcium in the bone and sometime physiotherapy and treat the fracture when they happen and a simple exercise.

MCQs

1- Which one of the following is an etiology of Osteogenesis imperfecta:

a. Deficiency of type II collagen formation
b. Deficiency of type I collagen formation
c. Mutation of fibroblast growth factor receptor 3
d. Malnutrition

2- Which one of the following is true for Achondroplasia :

a. Is an acquired disease
b. Is an autosomal recessive trait
c. Is an autosomal dominant trait
d. Is a dysostosis

Remember: it may caused by a sporadic mutation . "mutation that happened for one child due to advanced paternal age"

3- Which one of the following is NOT a characteristic of osteogenesis imperfecta :

a. Presence of blue scleras
b. Deformed teeth
c. Hearing loss
d. Failure of cartilage cell proliferation at the epiphyseal line

4- Which one of the following cells is mainly affected in Osteopetrosis :

a. osteoprogenitor cells
b. Osteocyte
c. Osteoblast
d. Osteoclast

5- Which one of the following is NOT a congenital disease:

a. Osteomalacia
b. Osteopetrosis
c. Achondroplasia
d. Osteogenesis imperfecta

6- The main etiology of primary osteoporosis:

a. Reducing of the secretions of progesterone hormone
b. Aging
c. Alcoholism
d. Endocrine disorders

7- Which one of the following is associated with Osteoporosis :

a. Involve the entire skeleton
b. Loss of calcium concentration in the bone
c. Reducing of cortical bone and thickened of trabecular bone
d. Reducing of bone mass and volume

8- Which of the following cytokines are responsible for stimulation of osteoclastic receptors :

a. PDGF - IL-8 - IL-6
b. TNF , IL-8 , IL-6
c. TNF - TGF-β – IL-1
d. PDGF , IL-2 , IL-8

9- Which of following strategies can provide the best overall long-term reduction in risk of fracture from osteoporosis in women?

a. Supplement the diet with calcium and vitamin D after menopause.
b. Begin estrogen replacement therapy after a fracture.
c. Increase bone mass with exercise in childhood and young adulthood.
d. Limit alcohol use and avoid use of tobacco

10- After a minor fall, a 63 year old woman sustains a complete right femoral neck fracture. Of the following conditions, the most significant contributing factor for this fracture is:

a. Multiple myeloma
b. Vitamin D deficiency
c. Chronic osteomyelitis
d. Postmenopausal bone loss

11- In a 75 year old male, which of the following processes contributes to the occurrence of osteoporosis?

a. Decreased production of osteoid by osteoblasts.
b. Increased resorption of bone by osteoclasts.
c. Synthesis of chemically abnormal osteoid.

12- A 2-year-old child has a history of multiple bone fractures with minor trauma. Radiographs reveal diffusely and symmetrically sclerotic bones with poorly formed metaphysis. He is treated with bone marrow stem cell transplantation. Which of the following cells in his bones was most likely functionally deficient and replaced following transplantation?

a. Chondroblast
b. Chondrocyte
c. Osteoblast
d. Osteoclast
e. Osteocyte

13- A 5 year old child has a GI tract problem that causes malabsorption of a certain substance. The same disease seen in adults is known as osteomalacia. What condition is also associated with the deficiency?

a. Osteoporosis
B. Osteopetrosis
C. Scurvy
D. Cushing's syndrome
E. Pneumonia of the Lung

14- A 15 year old boy has shortened limbs and ribs, frontal bossing of the forehead, bowing of the limbs, his IQ however is normal. The cells that are affected in his disorder are:

a. Osteoclasts
b. Chondrocytes
c. Osteoblasts
d. Macrophages
e. Osteocytes

15- A patient presents with multiple fractures and blue sclera of the eye. The same disease in infants would result in:

a. Death
b. Tumor of the bone
c. Fractures
d. Blue sclera
e. A C and D

16- Why is the Osteoporosis difficult to diagnose ?

Because it is asymptomatic .Wouldn't be noticed until skeletal fragility is announced with a fracture. Also , it wouldn't be evident in the radiographs until 30%-40% of the bone mass is lost

17- What is the pathogenesis of primary osteoporosis ?
Drop of estrogen hormone à cytokines { TNF, IL-1,IL-6,IL-8} à over stimulation of osteoclastic receptor à over osteoclastic activates " mis balancing of osteoclastic and osteoblastic activates"

The answers:

1. B
2. C
3. D
4. D
5. A
6. B
7. D
8. B
9. C
10. D
11. A
12. D
13. A
14. B
15. E

1-A 45 year-old woman diagnosed with breast cancer, was walking on a wet floor. Suddenly she slipped and had a fracture in her right femur, what is the type of fracture ?
a) pathological b) traumatic c) stress
answer : a

2- A 55 years-old woman diagnosed with anemia and osteoporosis, she had a previous fracture in her left forearm and after 6 week the doctor ordered an x-ray of her forearm and the results showed that the fracture is still unhealed and in a pseudarthrosis appearance , what is the type of complication ?
a) Delayed union b) nonunion c) malunion
answer : b

3- 60 year-old man diagnosed with anemia, experienced a traumatic fracture followed by a severe swelling, what is the type of complication ?
a)Compartment syndrome b)Post-traumatic arthritis c)Infection
answer : a

4- A healthy 20 year-old basketball player is suffering from pain in his left leg that worsens with exercising, walking or standing. On examination, there is a swelling in his left leg. An x-ray was performed and there was a crack in the left tibial bone , what is the type of fracture ?
a)Traumatic fracture b)pathologic fracture c)stress fracture
answer: c because there is no significant past medical history and no trauma

5- An injury that occurs to vertebrae when they are flattened is known as a:
A)spiral fracture
B)pathologic fracture
C)compression fracture
D)linear fracture
Answer: c

6- Osteoporosis most often occurs in:
A)older men of all races
B)older white women
C)older black women
D)teenage males and females
Answer: b females are more susceptible to Osteoporosis than males

7- Which of the following diseases of bones is a loss of bone mass and density:
A)osteoporosis
B)osteitis deformans (Paget's(
C)osteomyelitis
D)osteosarcoma
Answer: a

8- A Colles' fracture is a fracture of the bone of the :
a)Forearm
b)Leg
c)Thigh
d)Foot
answer: a
Explain: A Colles' fracture is a fracture of the bone of the forearm, which results in a dinner-fork deformity at the wrist. It often follows a fall on the outstretched hand.

9- An open fracture is a fracture that :
a)Results in multiple pieces of bone
b)Occurs when a broken bone pierces through the skin
c)Ruptures a blood vessel
d)Damages a nerve
answer: b

10- A swelling is usually present in cases of fractures :
a)True
b)False
Answer : a
Explain: Symptoms of fracture include alteration in shape of bone, swelling, bruising or bleeding over the fracture site, intense pain, tingling and numbness and inability or limited ability to move a limb.

11- In a greenstick fracture :
a)The entire bone is broken through and through
b)Only one side of the bone is broken and the bone is bent
c)The bone is broken into multiple pieces
d)None of the above
answer : b
Explain : In a greenstick fracture, one side of a bone is broken, and the bone is bent on the other side. This type of fracture is often seen in children.

12- A cast is used in a fracture :
a)To keep the bones in position while the fracture heals b)To keep the fracture site warm c)Both of the above
d)None of the above
answer: a
explain: A cast is applied over a fracture so that the fractured bone is kept in position while it heals

13- In some fracture surgeries, a metal rod is inserted into the bone:
a)True b)False
answer: a
explain: In some fracture surgeries, a metal rod, plates, wires or screws are inserted to keep the bone fragments in place while healing.

14- What type of bone tissue surrounds a medullary cavity:
A)compact bone
B)medullary bone
C)spongy bone
D)replacement bone
Answer: c
Feedback: The answer refers to the general appearance, although it is not soft.

15-The type of cells that brings about intramembranous ossification are:
A)osteocyte
B)osteoblasts
C)osteoclasts
D)osteon
Answer: b

16- Woven bone is formed during which of the following situations:
A)puberty
B)fetal development and after fractures
C)the first few months following birth
D)periods of bone decalcification in old age
Answer: b

17- Lamellar bone is bone that
A)arises out of cartilage
B)arises out of collagen and elastic fibers
C)replaces worn out and fractured bone
D)is mature and is organized into thin sheets or layers
Answer: d

18- When a fracture begins to heal, one type of bone cell moves into the fracture site and tears down the damaged bone tissue. Which of the following tears down bone?
A)osteoclasts
B)osteoblasts
C)osteons
D)matrix cells
Answer: a

19- If a 12 year old were to fracture their epiphyseal plate, the result of the damage could be that the bone:
A)grows abnormally brittle
B)may stop growing at the plate
C)may grow much thicker at the site of the injury
D)has greatly increased potential for a sarcoma
Answer: b

20- Following a bone fracture a callus builds around the fracture site. Callus is a:
A)mass of tissue.
B)mass of blood vessels.
C)mass of old broken bone pieces.
D)collection of blood vessels and collagen at the fracture site.
Answer:d

21- Which of the following fractures refers to a fracture of a bone in multiple pieces:
A)complete
B)incomplete
C)impacted
D)comminuted
Answer: d

22- Which of the following fractures is often referred to as being a "greenstick" fracture:
A)complete
B)incomplete
C)impacted
D)comminuted
Answer: b

23- Which of the following fractures goes all the way through a bone, but does not break it into multiple pieces:
A)complete
B)incomplete
C)impacted
D)comminuted
Answer: a

24-The most common bone disease is osteoporosis. The most common consequence of this disease is:
A)fractures
B)bone thickening
C)luxations and subluxations
D)fusion of bones
Answer: a

25- Which of the following fractures is a fracture in a bone already weakened by disease:
A)Pott's
B)Colles
C)Avulsion
D)Pathologic
Answer: d

26- A spiral fracture of a bone most often is the result of a bone:
A)weakened by disease
B)that has been crushed
C)that has been twisted
D)that has been compressed
Answer: c

True and False Questions

5- Which of the following is/are true statements regarding paediatric bone?

a) Paediatric bones are more porous than adult bones
b) Remodelling capacity is highest in younger children
c) Growth plate fractures occur in adults and children
d) The physis is responsible for longitudinal growth of long bones
e) Fracture patterns in children are similar to that of adults

answers:

a) T
b) T
c) F
d) T
e) F

6- Fracture remodelling is dependent on :

a) Age
b) Proximity to the joint
c) Orientation to the joint axis
d) Length of time in cast
e) Dietary calcium intake

answers :

a) T
b) T
c) T
d) F
e) T

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Good Luck!

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