Congenital, developmental and metabolic bone diseases.

Editing File

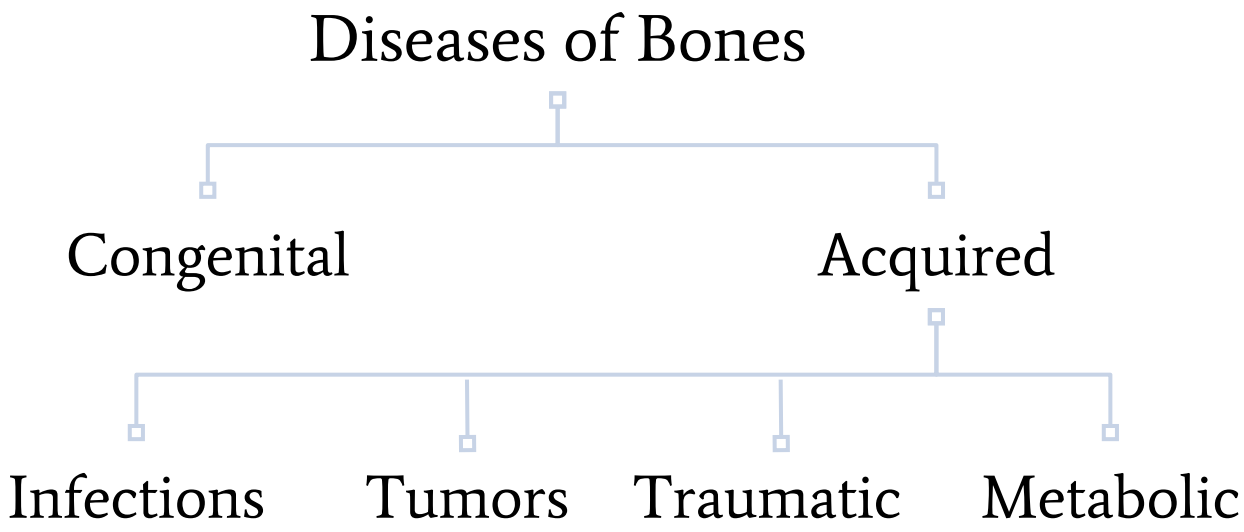
Black: original content
Red: important
Green: ALRIKABI's notes
Grey: Explanation
Blue: Only in the boys slides
Pink: only in the girls slide

Reviewed by Razan AlRabah & Khalid Alknani

Objectives

- ➔ Be aware of some important congenital and developmental bone diseases and their principal pathological features.
- ➔ Be familiar with the terminology used in some important developmental and congenital disorders.
- ➔ Understand the etiology, pathogenesis and clinical features of osteoporosis.

Diseases of Bones



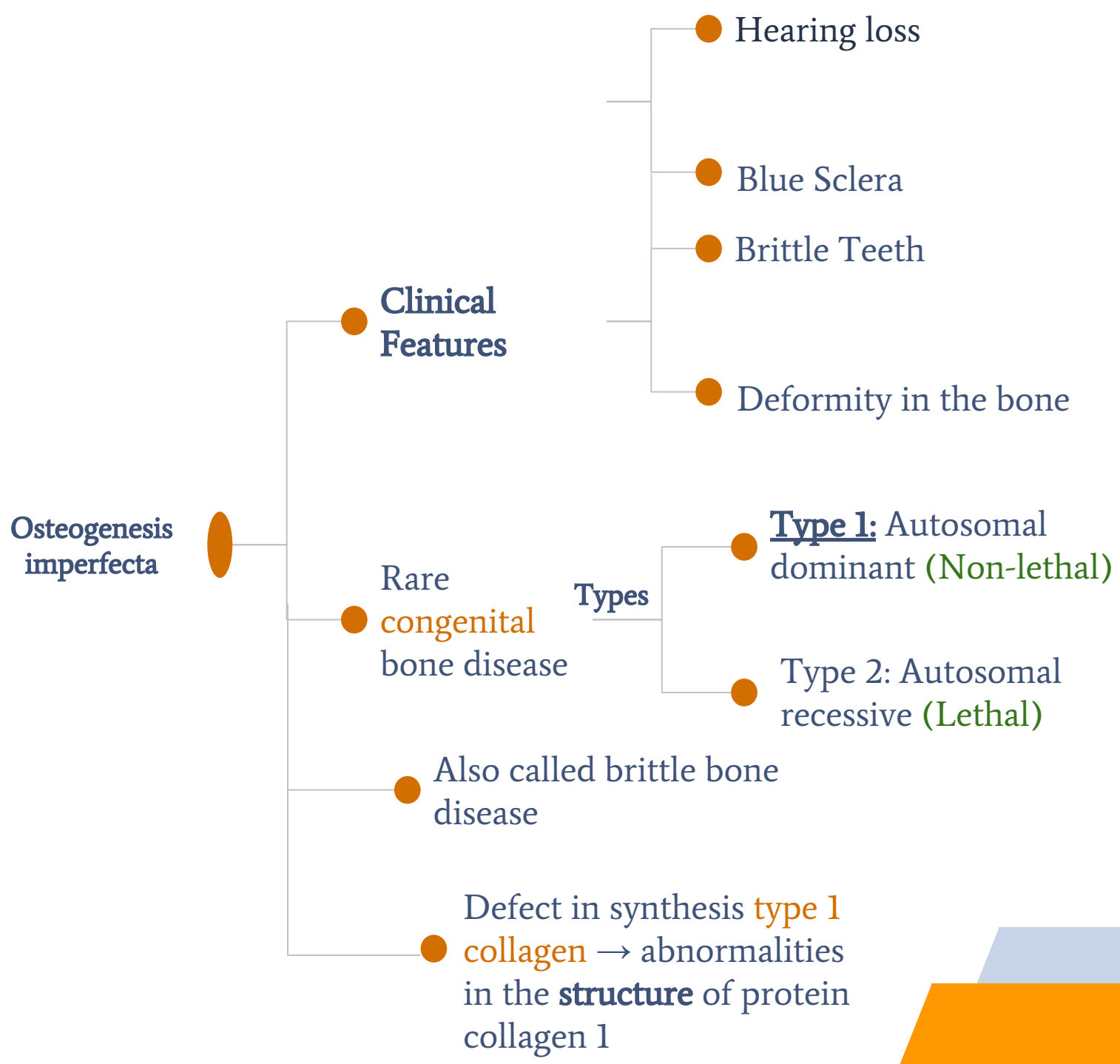
Congenital Diseases of Bones

Localized or the **entire skeleton.**

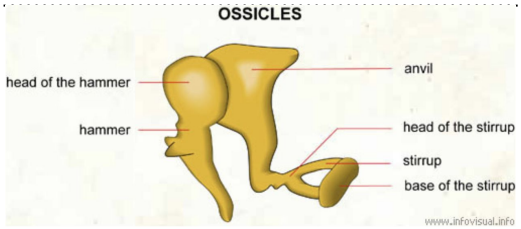
Dysostoses	Dysplasia
A disorder of the development of bone, It can be: **- Aplasia**: e.g. congenital absence of a digit . - **Extra bones, abnormal fusion of bones** e.g. premature closure of cranial sutures.	**Example:** - Osteogenesis imperfecta - Achondroplasia - Osteopetrosis NOTE: skeletal dysplasia is different than dysplasia that we studied in neoplasia (skeletal dysplasia: abnormality in bone formation)

Osteogenesis imperfecta
(brittle bone disease)

- Group of **genetic disorders** characterized by brittle bones caused by **abnormality of number of genes**.
- Defect in the synthesis of **type I collagen** leading to too little bone resulting in extreme skeletal fragility with susceptibility to fractures.
- they are some severe forms of osteogenesis imperfecta where the deficiency is very prominent and the infant may die in utero.

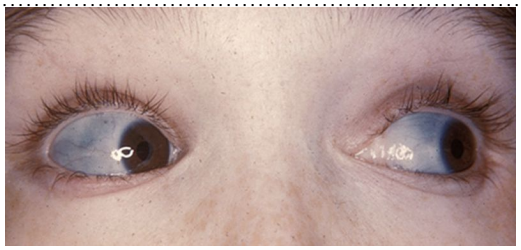


Osteogenesis imperfecta
(Clinical Features)

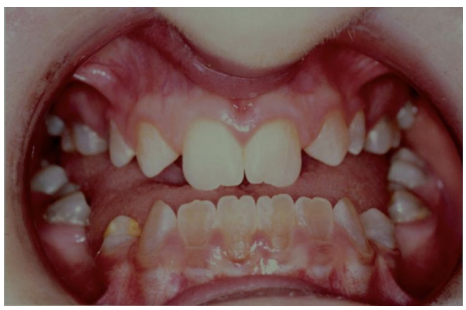


Hearing loss:
weakness in the middle ear's **ossicles***
Osteogenesis imperfecta causes systemic disease in all the bones including the ossicles, **impairing their functional ability and limiting a person's hearing.**

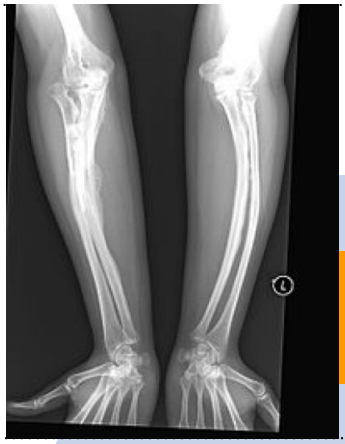
*(ossicles : Three small bones in the middle ear)



Blue sclera:
The sclera of the eyes is **slightly bluish**. Caused by thinning of the sclera due to deficiency of collagen **(type 1)** resulting in both eyes reflecting the **blue pigment** of the choroid layer from behind.



Brittle teeth:
They are brittle, irregular, sharp and sometimes with discoloration.



Deformity in the bone:
Makes the patient susceptible fractures, due to deficiency in collagen type 1.

Achondroplasia

- The **most common** skeletal dysplasia and a major cause of dwarfism.
- NO mental retardation, or sexual problems (infertility) and **normal** intellectual capability.

1) Pathogenesis:

- Autosomal dominant (Genetic) or spontaneous mutation (environmental).
- Usually, there is a mutation on gene **located on chromosome number 4,** which is called Fibroblast Growth Factor Receptor 3 (FGFR3).

What is FGFR3? a receptor with tyrosine kinase activity that transmits intracellular signals.

- Signals transmitted by FGFR3 inhibit **proliferation** and **function** of growth plate chondrocytes.
- In this case the gene is over activated and over stimulated.
- As a result, normal growth of epiphyseal plate is **suppressed** (premature closure of the epiphyseal plate)

- So: It is characterized by failure of cartilage cell proliferation at the epiphyseal plates of the long bones, resulting in failure of longitudinal bone growth and subsequent short limbs.
- **Membranous ossification** is **not affected**, so that the skull, facial bones, and axial skeleton develop normally.

Achondroplasia (Cont.)

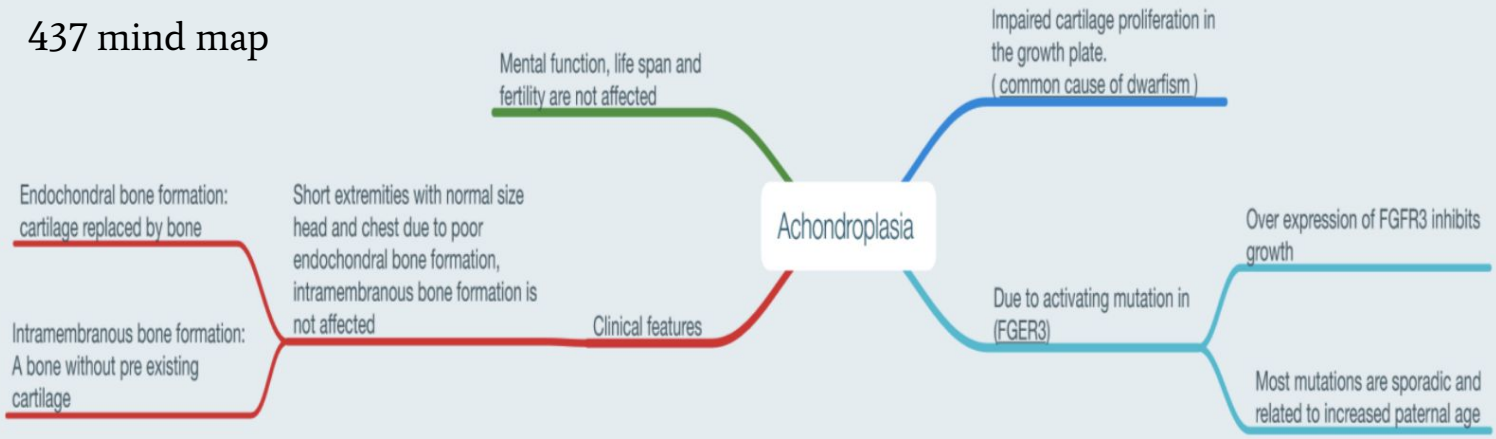
2) Clinical features:

- Affected individuals have:
  - shortened proximal extremities
  - trunk of relatively normal length
  - enlarged head with bulging forehead
  - conspicuous depression of the root of the nose.

- General health, intelligence, reproductive status, and life expectancy are not affected.

Thanatophoric Dwarfism: in this disease the mutation in the gene is **very severe** (it is the severe form of achondroplasia). Leads to: restriction in the thorax cage, (the lung is growing normally but the thorax cage is growing abnormally), and this will not allowed the expansion of the lung, this will cause restrictive lung disease, a lot of them they die within the utero or shortly after birth.
The disease is rare.

437 mind map



Metabolic bone diseases

Comprises four fairly common conditions in which there is an **imbalance** between osteoblastic (bone forming) and osteoclastic (bone destroying) activity:

1. Osteoporosis
2. Osteomalacia
3. Paget's disease of bone
4. Hyperparathyroidism

Osteoporosis

Osteoporosis is an **acquired** condition characterized by **reduced bone mass**, leading to: bone fragility and susceptibility to fractures Resorption(osteoclastic) is more than formation(osteoblastic). It may be:

1- **localized** e.g. disuse osteoporosis of a limb.

2- Involving the **entire skeleton**, e.g. metabolic bone disease.

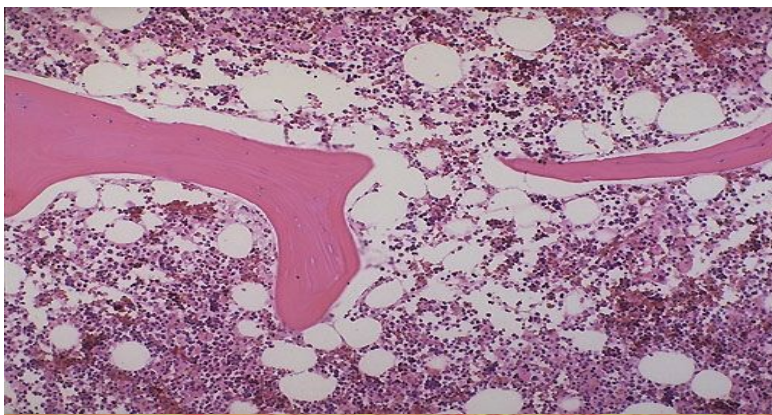
The main problem of osteoporosis that it **can't be detected by X-ray until the patient has lost 40% of his bone mass**.

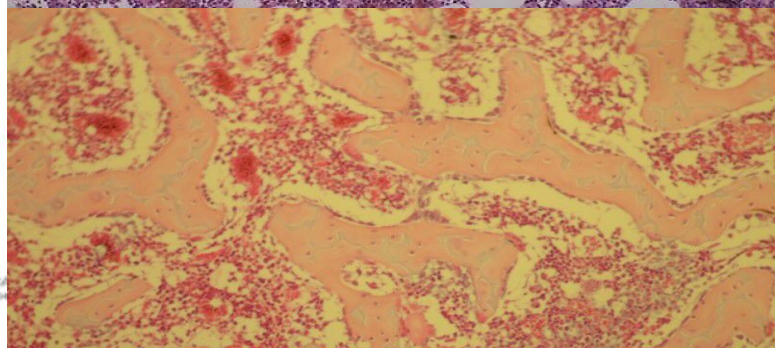
Osteoporosis (Cont.)

1) Morphology

- The hallmark of osteoporosis is a loss of bone.
- The cortices (plural of cortex,compact bone)are thinned, with dilated haversian canals,and a lot of lacunae, and the trabeculae are reduced in thickness and lose their interconnections.
- The mineral (calcium,phosphate) content of the bone tissue is normal.
- Once enough bone is lost, susceptibility to fractures increases.
- In **postmenopausal osteoporosis,** trabecular bone loss often is severe, resulting in **compression fractures** and collapse of vertebral bodies.
- In **senile** (old age related) **osteoporosis,** cortical bone loss is prominent, predisposing to fractures in other weight-bearing bones, such as the **femoral neck.**

Osteoporosis is usually symptomatic. To study it we take bone biopsy from the **iliac crest**. The bone will be black under the microscope, it will be thinner, and there will be wider space in trabecular bone leading to development of symptoms.





Normal

Osteoporotic bone

Osteoporosis (Cont.)

2) Categories of Generalized Osteoporosis

Primary

-**Idiopathic**

-**Post menopausal**: probably a consequence of declining levels of estrogen. In the decade after menopause, yearly reductions in bone mass may reach up to 2% of cortical bone and 9% of cancellous bone. Women may lose as much as 35% of their cortical bone and 50% of their cancellous bone by 30 to 40 years after menopause.

-**Senile.**

Most common forms of osteoporosis are the **senile** and **postmenopausal** types.

-**Environmental factors** may play a role in elderly: decreased physical activity and nutritional protein or vitamin deficiency.

Secondary

- **Endocrine Disorders:**
  - Addison disease.
  - DM (diabetes mellitus) type 1.
  - hypo or hyperthyroidism.
  - acromegaly.

- **Gastrointestinal disorders:**
  - Malnutrition.
  - Malabsorption.
  - Hepatic insufficiency.
  - Vitamin C, D deficiencies.

-**Neoplasia:**
  - Multiple myeloma.
  - Carcinomatosis.

-**Drugs:**
  - Anticoagulants.
  - Chemotherapy.
  - Corticosteroids.
  - Lithium.

-**Others**:
  - Smoking.
  - Immobilization.
  - Anemia.
  - Pulmonary disease.
  - Fracture of the neck of the femur.

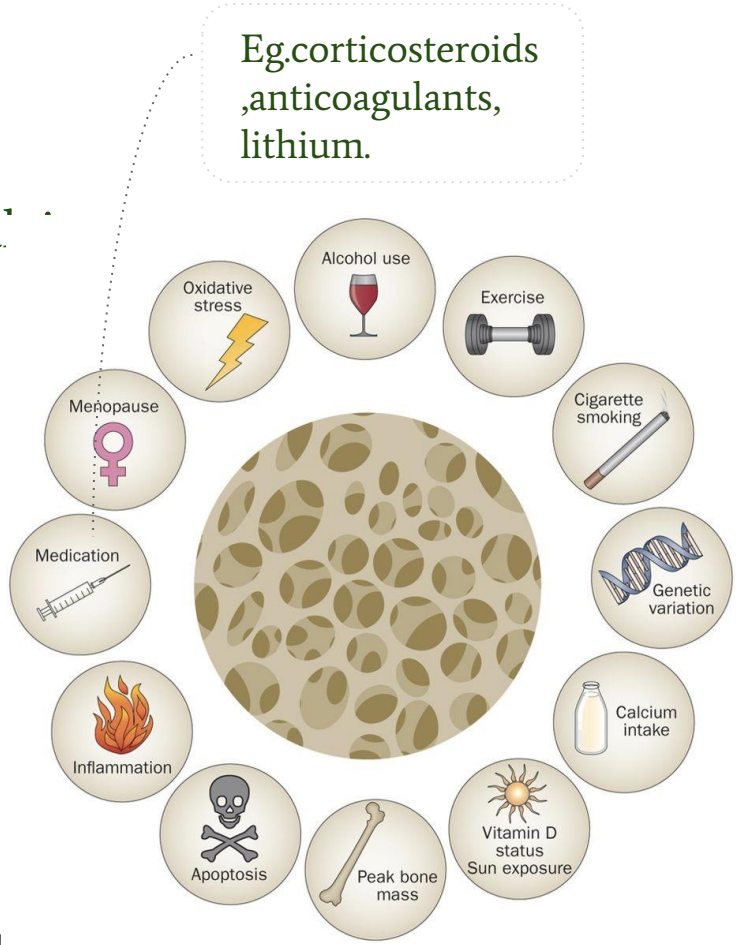
Osteoporosis (Cont.)

3) Pathophysiology:

Occurs when the balance between bone formation and resorption tilts in favor of resorption .

Major Causes of osteoporosis:

- Genetic factors
- Nutritional effects (poor in ca[illegible] and vitamin D)
- Physical activity
- Aging
- Menopause (Low estrogen)



Bone mass peaks during young adulthood; the greater the peak bone mass, the greater the delay in onset of osteoporosis. In both men and women, beginning in the third or fourth decade of life, bone resorption begins to outpace bone formation.

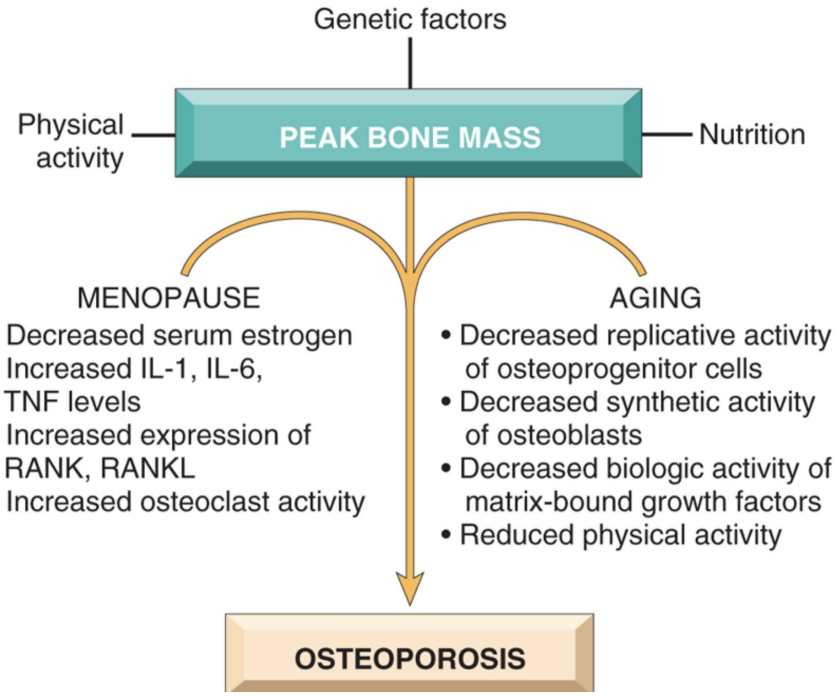
Bone mass peaks : the maximum amount of bone a person has during their life.

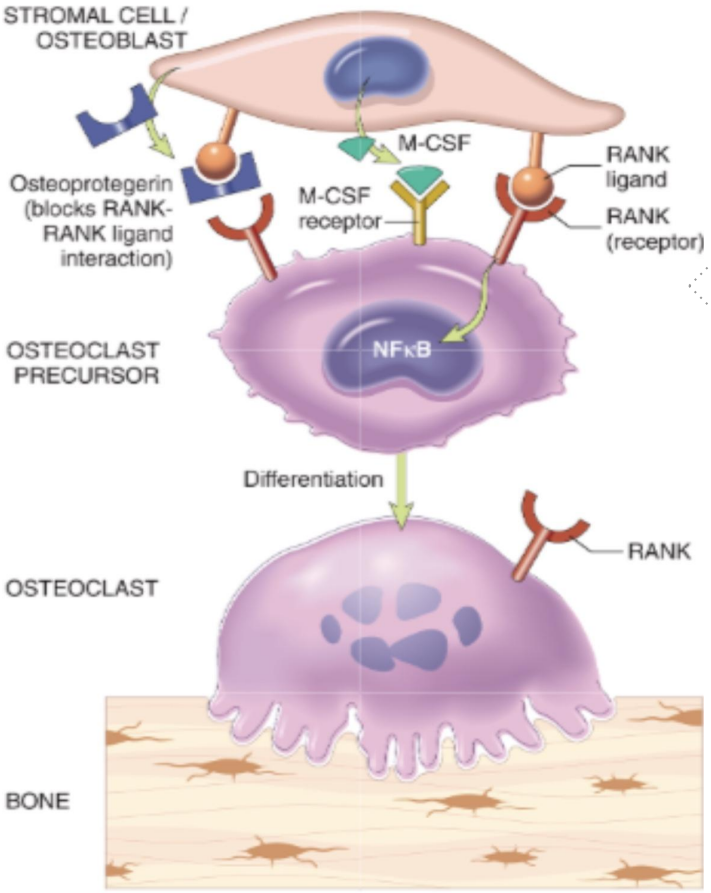
الوقت أو العمر اللي يكون فيه العظم في أكبر كمياته في الجسم أو أكثر كمية ممكن ينمو لها العظم في الجسم .

Osteoporosis (Cont.)

The **postmenopausal** **drop in estrogen** leads to **increased cytokine** production (especially IL-1, IL-6, and TNF), presumably from cells in the bone. These suppress OPG production.

بعد سن اليأس عند النساء يقل الاستروجين —> يزيد تصنيع السايتوكاينز خصوصًا :(IL-1, IL-6, and TNF) فتزيد تصنيع ال RANKL و تصير تفعل osteoclasts أكثر.





Osteoprotegerin (OPG) : **Block** RANK & RANK ligand Interaction . <— اذا صار لهم interaction بتتفعل ال osteoclasts و تكسر العظم .

[Helpful video !!]

Osteoporosis (Cont.)

4) Clinical features:

- Difficult to diagnose
- Remain asymptomatic, leads to sudden fractures.
- **Fractures** (Pathological), most commonly:
  - Vertebrae
  - Femoral neck
- Patients with osteoporosis have **normal** serum levels of calcium, phosphate, and alkaline phosphatase.

Osteoporosis (Cont.)

5) diagnosis

Measure the bone density by radiographic measures :

- **Plain X ray:** cannot detect osteoporosis until 30% to 40% of bone mass has already disappeared .

- **Dual-emission X-ray absorptiometry (DXA scan):**
  is used primarily to evaluate bone density, to diagnose and follow up patient. with osteoporosis.

DXA scan is an example of densitometry

The main problem of osteoporosis.

DXA scan

Osteoporosis (Cont.)

6) Prognosis

- Osteoporosis itself is rarely lethal.
- Patients have an increased mortality rate (معدل الوفيات) due to the complications of fracture.

e.g. Hip fractures can lead to decreased mobility and an additional risk of numerous complications: deep vein thrombosis, pulmonary embolism and pneumonia .

7) prevention strategies

The best long-term approach to osteoporosis is **prevention**:

- **good diet:** children and young adults, particularly women, with a good diet (with enough calcium and vitamin D) and get plenty of exercise, will build up and maintain bone mass.
- **Exercise** places stress on bones that builds up bone mass .

This will provide a good reserve against bone loss later in life.

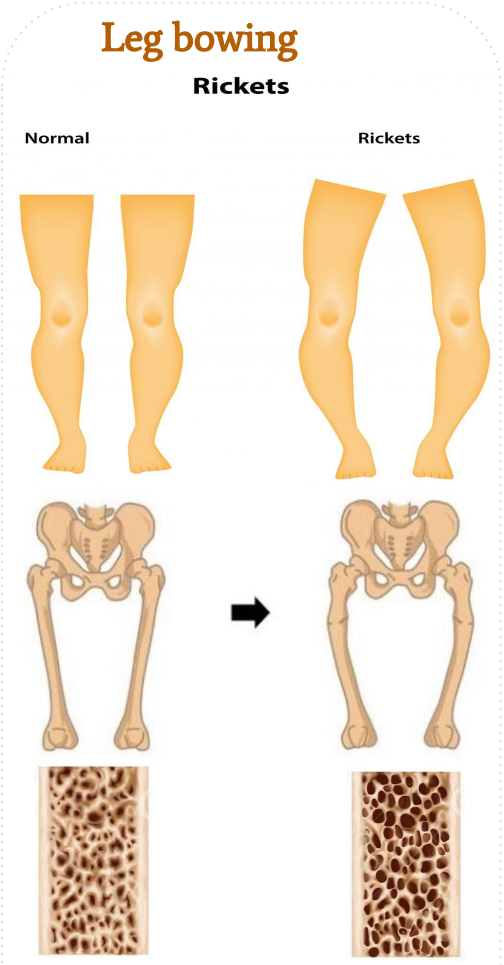
osteomalacia and Rickets

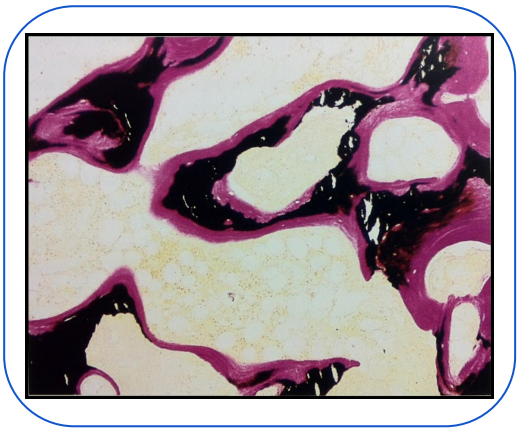
In **osteomalacia** and **Rickets**, osteoblastic production of bone collagen is normal BUT mineralization is inadequate. It is a manifestation of **vitamin D deficiency**.

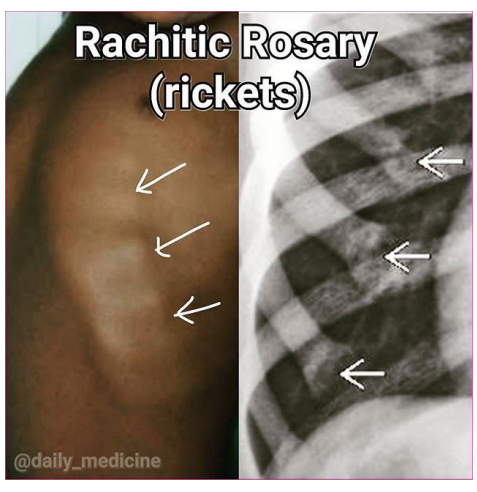
1. Rickets refers to the disorder in children, in which it interferes with the deposition of bone in the growth plates.

Rickets: usually represented by deformity in the bones of the leg caused by brittleness of the bones. another deformity in the cranium (in the skull) showing bossing when the frontal bone become prominent, caused by bad nutrition (low calcium, low vitamin D). People with rickets also have greenstick fracture and looser zone* .

*Looser zone:wide, transverse lucencies traversing part way through a bone)



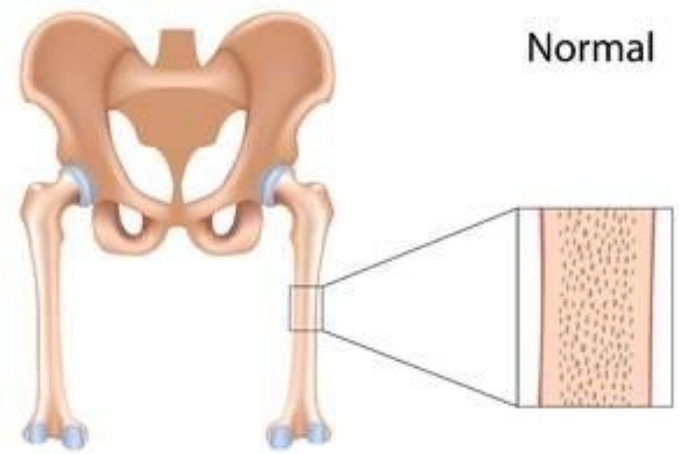


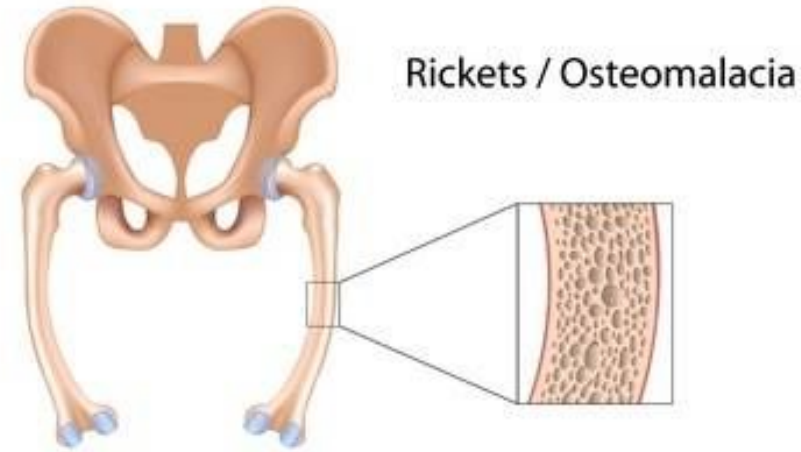


The red part is the osteoid, the black part is the calcified osteoid. Abnormal calcification, abnormal deposition of calcification, abnormality and reduction in the amount of bone which normally calcified in people who have osteomalacia, there is no complete ossification it is still osteoid, it is still connective tissue, and the volume remain the same.

osteomalacia and Rickets (Cont.)

2. Osteomalacia: the adult counterpart of rickets, in which bone formed during remodeling is undermineralized, resulting in predisposition to fractures.





Osteomalacia caused by: Malabsorption (the most important cause), Renal diseases (osteonephrosis), Malnutrition.

Summary

From 437

	Etiology	Pathogenesis	Clinical features	
Osteogenesis Imperfecta	Congenital Type1: autosomal dominant. Type2: autosomal recessive.	• Defect in the synthesis of type I collagen.	1. Abnormal bone 2. Blue sclera 3. Teeth deformities 4. Hearing loss	
Achondroplasia	Congenital • Autosomal dominant trait but many cases arise from spontaneous mutation. • Mutation on gene that is located on the short arm of chromosome 4, fragment 16.3 which is called (FGFR3).	• Failure of cartilage cell proliferation at the epiphysial plates of the long bones.	1. Short proximal extremities. 2. Enlarged head with bulging forehead. 3. Depression of the root of the nose. 4. bowing of the legs and neck. General health, intelligence, or reproductive status are not affected, and life expectancy is normal.	
Osteoporosis	Acquired • characterized by reduced bone mass. • It may be localized or may involve the entire skeleton	• Occur when the balance between bone formation and resorption tilts in favor of resorption. • the greater the peak bone mass, the greater the delay in onset of osteoporosis.	Diagnosis - Plain X ray - DXA scan - Biopsy	Prognosis - Osteoporosis is rarely lethal. - Patients have an increased mortality rate due to the complications of fracture.
Osteomalacia And Rickets	Acquired • Inadequate mineralization. • vitamin D deficiency. • Calcium levels are low.	• Rickets disorder in children, interferes with the deposition of bone in the growth plates. • Osteomalacia is the adult, the bone formed during remodeling is undermineralized.		

Dr. Alrikabi's notes

Congenital Diseases:

1-Achondroplasia (Dwarfism):

A disease does not cause mental retardation, or sexual problems (infertility), normal intellectual capability, inherited (mostly autosomal dominant), the gene receptor responsible for this disease is Fibroblast Growth Factor Receptor 3 (FGFR3) (on chromosome 4) this gene is mutated (abnormal) in this disease, as a result of this abnormality the endochondral ossification which usually starts at the Epiphyseal plate is abnormal, and this will lead to premature closure of the epiphyseal plate. The gene FGFR3 control the endochondral ossification which usually occurs in hyaline cartilage at the epiphyseal plate, the ribs is small, the head is big, the trunk is normal and the upper and lower limbs are very short. The bone is so small that the skin become too big for the bone.

There is very bad type of this disease called Thanatophoric Dwarfism: in this disease the mutation in the gene is very severe, there will restriction in the thorax cage, the lung is growing normally but the thorax cage is growing abnormally, and this will not allowed the expansion of the lung, this will cause restrictive lung disease, a lot of them they die within the utero or shortly after birth. The disease is rare.

2- Osteogenesis Imperfecta (Brittle-Bone disease):

The main manifestation of this disease are pathological fractures, recurrent fractures, this disease has got many forms (5-7 forms), it is caused by abnormality of number of genes, all this genes includes the genetic order to form certain proteins which enters the Collagen Type 1 structure, collagen type 1 is important in the skin, joints, teeth, eye, cartilage (ear), bones. This disease cause subluxation in the joints.

These are the signs of the disease and each sign is related to the organs it affects :

Dr. Alrikabi's notes (Cont.)

1-Deafness —> ear (weakness in the middle ear ossicles)

Parts of the ear:

1-external ear. 2- middle ear. 3- internal ear.

2-Blue sclera (bluish tense): the sclera of the eye is slightly bluish. (Because collagen Type 1 is abnormal in the sclera). The sclera become very thin, it shows reflection of the choroid, the choroid contains a lot of blood vessels and the congestion of these blood vessels and the bluish of sclera.

The eye parts: 1-sclera. 2- choroid. 3- retina.

3-teeth (brittle teeth): they are brittle and irregular and they are sharp and sometimes with discoloration.

4-Deformity in the bone: caused by pathological fractures (the crippling part of this disease).

5- they are some severe forms of osteogenesis imperfecta where the deficiency is very prominent and the infant may die in utero. Lethal forms type 2. (Autosomal recessive). Non-lethal forms (Autosomal dominant).

Metabolic disease:

1-osteoporosis (osteopenia): this characterized by reduction in the bone volume (bone mass), the total bone mass is reduced, sometimes caused by the aging, the amount of calcium and ossification is low. It is usually symptomatic, to study osteoporosis scientifically we take bone biopsy from the iliac crest, The bone will be black under the microscope, and the bone will be more thinner, there will be wider spaces in the trabecular bone this is why the bone is weakened and develop the symptoms. Grossly: there is a lot of lacunae, and there will be fractures called compression fractures, it will cause deformities in the back especially in severe conditions.

The main problem of osteoporosis that it cannot be detected by X-ray unless if the patient has lost 40% of his bone mass.

Dr. Alrikabi's notes (Cont.)

Major Causes of osteoporosis:
1-aging
2-Postmenopausal (Low estrogen)
3-diet (poor in calcium and vitamin D)
4-Smoking increase osteoporosis
5-Certain Drugs like corticosteroids, anticoagulants, lithium.
6- fraction of the neck of the femur.

2-Osteomalacia:
It has two types: in adults (osteomalacia).
In children (rickets).
(In the picture) The red part is the osteoid, the black part is the calcified osteoid.
Abnormal calcification, abnormal deposition of calcification, abnormality and reduction in the amount of bone which normally calcified in people who have osteomalacia, there is no complete ossification it is still osteoid, it is still connective tissue, and the volume remain the same.
Osteomalacia caused by: Malabsorption (the most important cause), Renal diseases (osteonephrosis), Malnutrition.
Rickets: in children, usually represented by deformity in the bones of the leg caused by brittleness of the bones. another deformity in the cranium (in the skull) showing bossing when the frontal bone become prominent, caused by bad nutrition (low calcium, low vitamin D).
People who have rickets also have greenstick fracture and losers zone.

Quiz

1- Which of the following cytokines are responsible for stimulation of osteoclastic receptors ?

A) TNF, IL1, IL6
B) PDGF, TGF-B, FGF
C) IL-6 , IL1 , FGFR
D) IL-2 , IL-6, TNF

2- Which one of the following is associated with Osteoporosis ?

A) Involve the entire skeleton.
B) Loss of calcium in the bone.
C) Reducing of cortical bone and thickened of trabecular bone.
D) Reducing of bone mass and volume.

3- Plain X-ray **can** detect osteoporosis before 30-40% from the bone disappeared ?

A) True
B) False

4- Osteogenesis imperfecta is due to a defect in?

A) Collagen Type 3
B) Collagen Type 4
C) Collagen Type 1
D) Collagen Type 2

5- 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

6- Which one of the following is a congenital disease ?

A) Osteomalacia
B) Osteopetrosis
C) Rickets
D) Osteogenesis imperfecta

1- A | 2- D | 3- B | 4- C | 5- D | 6- D

This lecture was done by

Team Leaders

- Raghad AlKhashan
- Mohannad Ahmad

Team members

- Leena Alnassar
- Reema Alserhani
- Taibah Alzaid
- Lama Alzamil
- Alhanouf Alhaluli
- Sarah AlArifi
- Amiral Alzahrani
- Njoud AlAli
- Ghaida Alshehri
- Deana Awrtani
- Alwaleed Alsaleh
- Muhannad Makkawi
- Naif Alsulais
- Suhail Basuhail
- Ibrahim Alshaqrawi
- Traiq Aloqail

Thank you

Pathology
Teamwork438