Pathology

teamwork 437

Lecture two (2) : Congenital, developmental, and metabolic bone diseases

Color Index :-

- **VERY IMPORTANT**
- Extra explanation
- Examples
- **Diseases names: Underlined**
- **Definitions**

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Revised by

نَستهِينُ كل غالٍ كي نُحقِقَ الحُلم . .إن سئِمنا لا نُبالي بل نسِير للأمام . . إنّ قِمةَ الجِبالِ تستَحِقُ لا جَرم

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 AETIOLOGY, PATHOGENESIS AND CLINICAL FEATURES OF OSTEOPOROSIS.

OVERVIEW :

All the information here is not mentioned in our slides, but we advice you to read, because it will give you a very well understanding of the lecture.

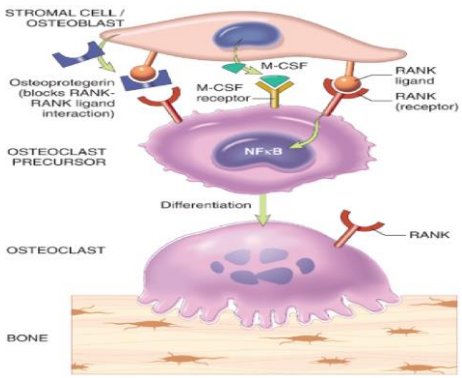
- The bone appears to be stable tissue, **but IT'S NOT!** In fact it's very **dynamic** and subject to constant breakdown and renewal.
- This balance is determined by the relative activates of **osteoblast** which deposit bone, and **osteoclast** which resorb bone.
  - **But how these two cells are regulated?** By several factors that impact their activity:
    1. **RANK and RANKL**
    2. Vitamin D
    3. Parathyroid hormone

- **What is RANK AND RANKL?**

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 "osteoblast", 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.

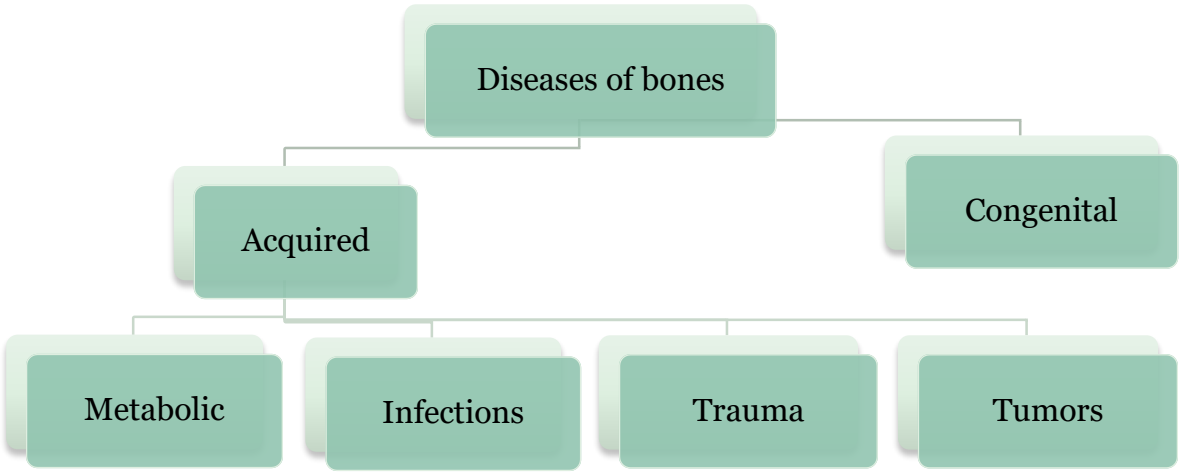


-مثل ما عرفنا ان النسيج العظمي دايماً في حاله تغير، بحيث ان ال osteoblast تجدد العظم، وال osteoclast تحطم العظم عشان يبدا يتجدد أو تنحته عشان ياخذ شكله الصحيح .

- طيب أكيد هذه الخلايا ما تشتغل بشكل عشوائي..بل منظم جداً. كيف؟
- بإختصار يوجد بجدار ال osteoclast <- RANK receptor
- وبالمقابل osteoblast عندها -> RANK ligand بحيث إذا بغت ال osteoblast تنجدد العظم تنادي الosteoclast عشان تكسر لها العظم القديم.
- بالمقابل إيضاً ال osteoblast عندها OPG عشان تثبط وتمنع ال RANK بحيث توقف تنشيط الosteoclast

- بعض الامراض تنتج عن طريق لخبطة بهذا النظام : مثل الosteoprosis

DISEASES OF BONES



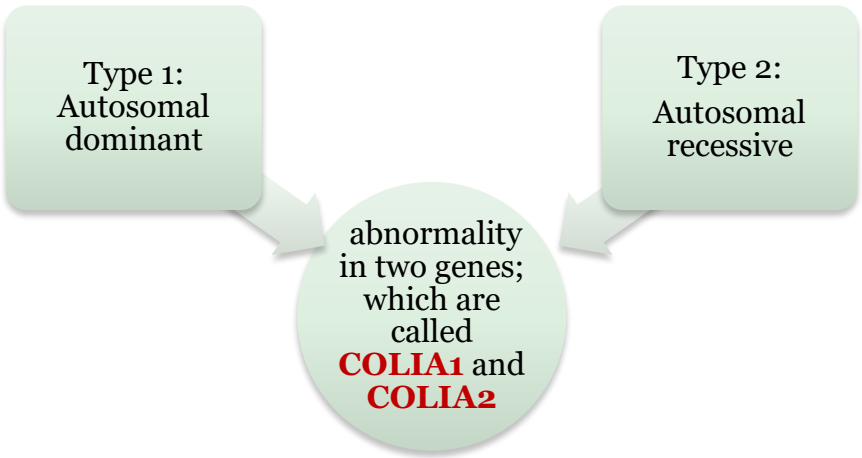
- **Congenital Diseases of Bones :-**

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

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



-COLIA1 is found on **chromosome 17**
-COLIA2 is found on **chromosome 7.**

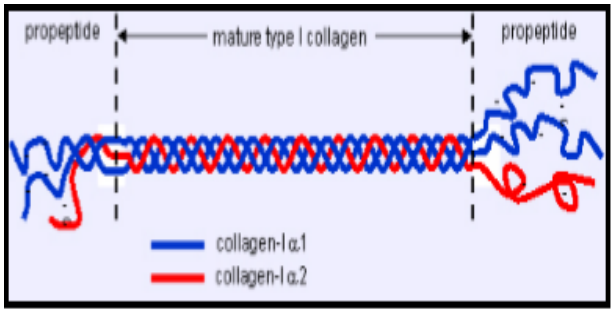
- **The pathogenesis /What is the problem in this disease ?**

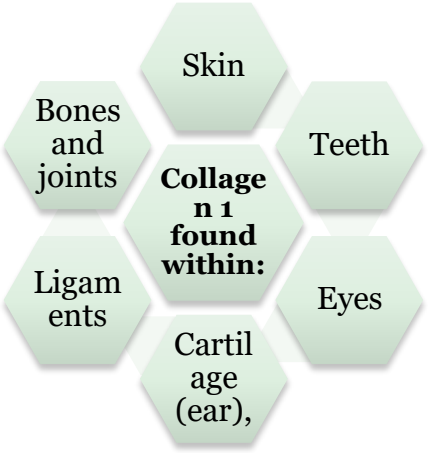
  -These two genes are mutated in this case. Their mutation causes an abnormality in the **structure of the protein collagen 1**. Amino acids chains **alpha 1** and **alpha 2** in the structure of collagen **(type 1)** are defected.

  -**Defect in the synthesis of type I collagen** leading to many abnormalities within organs and tissue that have high contents of collagen (type 1)

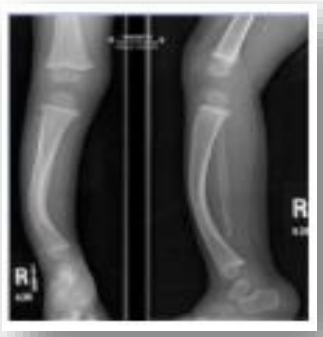
- **What's the difference between type 1 and type 2?**

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.



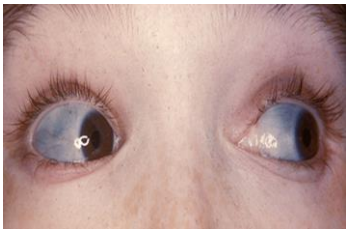


1. Abnormal bone (usually in the long bones).



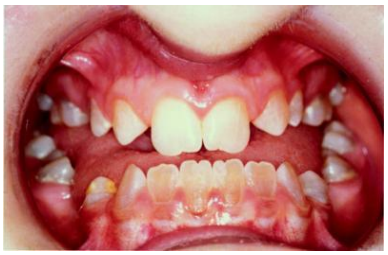
- Prone to pathological fractures due to deficiency with collagen (type1)
- **WHY are there recurrent fractures?** because the bone is **brittle** (due to collagen deficiency). That's why the disease is also called brittle bone disease

2. Blue sclera



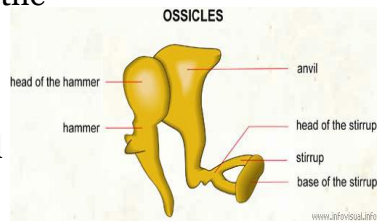
- Superfically, the sclera looks white, however upon closer inspection, there is presence of **blueish tint.**
- Caused by thinning of the sclera due to deficiency of collagen (type 1) resulting in the eye reflecting the blue pigment of **the choroid layer from behind**

3. Teeth deformities



- Deformation and discoloration of the teeth due to deficiency in **dentin** (middle layer of tooth)
- Dentin **is extensively made out of collagen** (type 1), as a result deficient collagen results in not enough dentin material being made.

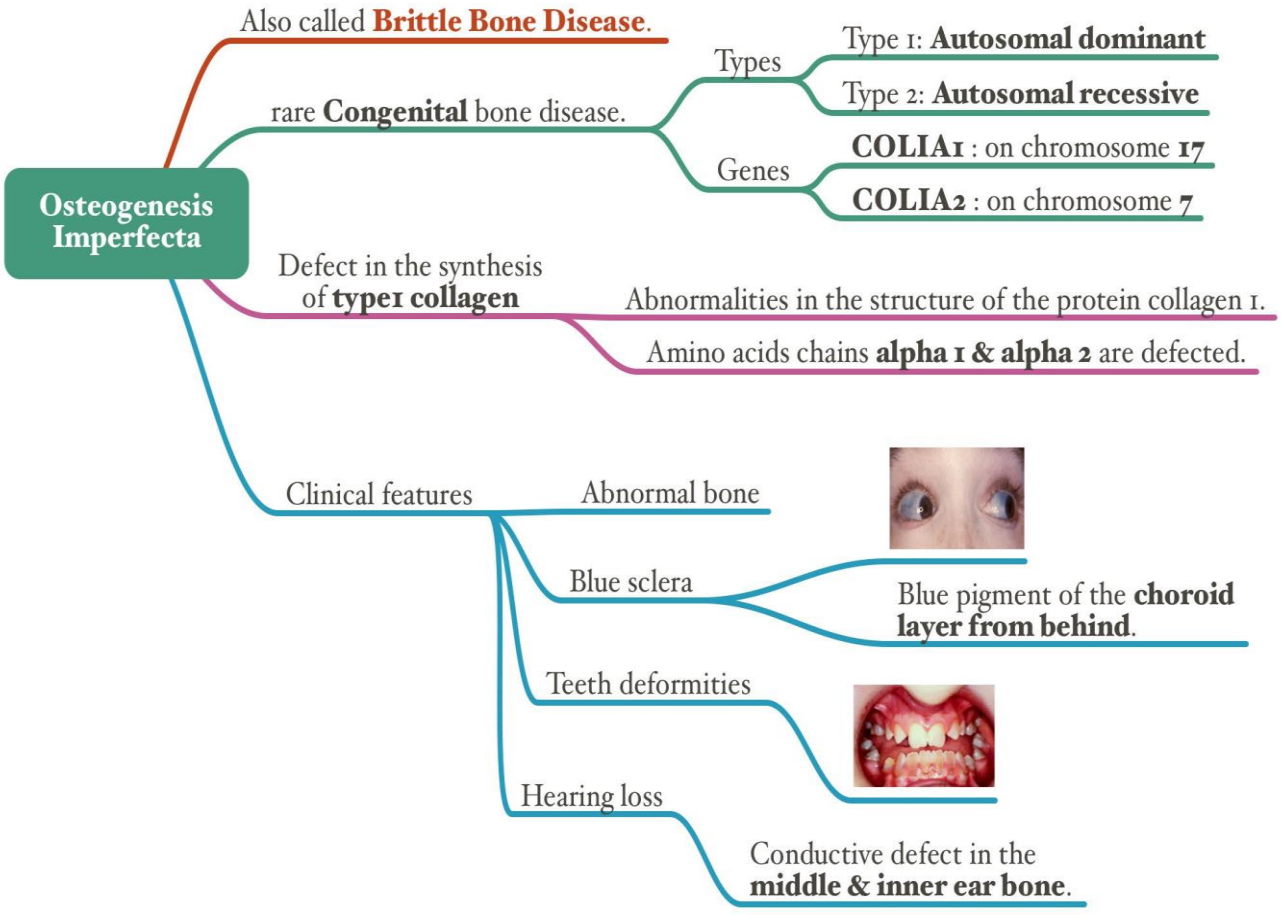
4. Hearing loss



- Related to a **conductive** (NOT NEUROGENIC) defect in the middle and inner ear bones.
- The ossicles (auditory bones) are bones responsible for transmitting sounds by vibrations to the inner ear
- **Osteogenesis imperfecta** causes systemic disease in all the bones including the ossicles, impairing **their functional ability and limiting a person's hearing**

* All of these information has been explained by Dr.rikabi

MIND MAP :



* ال mind maps بتساعدكم كثير بالباثولوجي لأن عندنا كثير امراض ولازم تفرقون بين كل من اسباب المرض والاعراض و ألخ لكل مرض، نصيحة يعد ما تدرسون كل مرض أو تدرسون المحاضره كلها، راجعوا من المايند مابز بترتب افكاركم كثير☺

ACHONDROPLASIA

Overview:

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

-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.

- **What is the clinical features?**
  - Affected individuals have shortened **proximal extremities**, a **trunk** of relatively normal length, and **an enlarged head** with **bulging forehead** and conspicuous **depression of the root of the nose, bowing** of the **legs and neck.**
  - General health, intelligence, or reproductive status are not affected, and life expectancy is normal

  - 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.

- **The pathogenesis /What is the problem in this disease ?**

-It is transmitted as an autosomal dominant trait but many cases arise from spontaneous mutation .

-Usually, there is a mutation on gene that is **located on the short arm of chromosome number 4, fragment 16.3** which is called Fibroblast Growth Factor Receptor 3 (FGFR3)

- **WHAT IS FGFR3 ?** is a receptor with **tyrosine kinase activity** that transmits intracellular.

    1. Signals transmitted by **FGFR3** inhibit the proliferation and function of growth plate chondrocytes.
    2. In this case the gene is **over activated** and over stimulated
    3. and as a result, **the chondrocytes signals will be inhibited prematurely in the growth plates of the long bones**

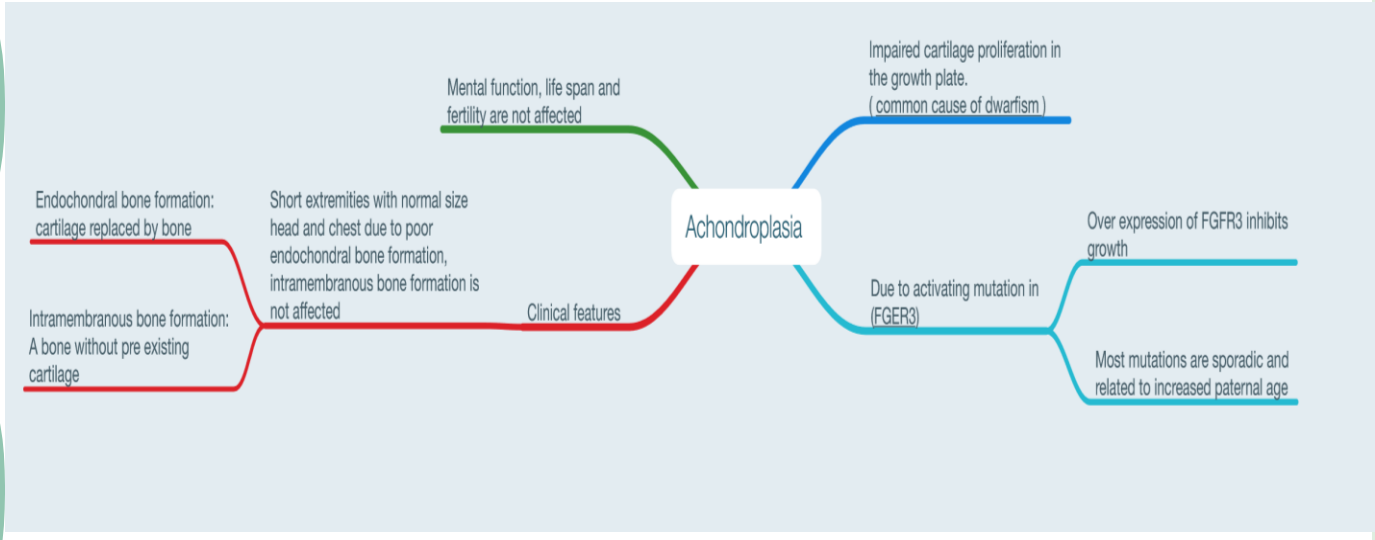
- **SO:** It is characterized by failure of cartilage cell proliferation at the **epiphysial plates of the long bones**, resulting in of longitudinal bone growth and subsequent short limbs.

- **Membranous ossification is not affected**, so the skull, facial bones, and axial skeleton develop normally.

هذا الreceptor وظيفة أنه يستقبل مواد و يثبط وظيفة ال chondrocytes اللي هي مسؤولة طول العظام . ايش فايده هذا ال receptors ان لما نوصل لعمر معين يبدا يوقف الطول وهذا طبيعي .

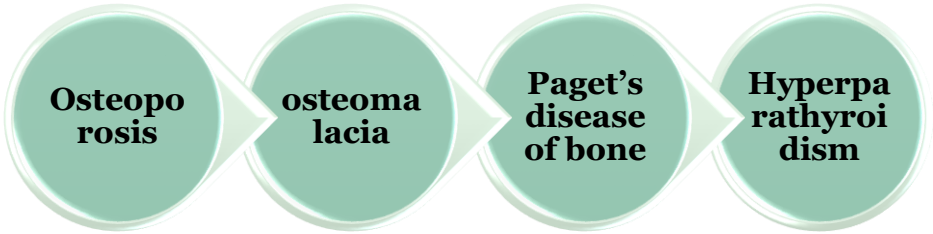
لكن بهذا المرض يكون ال FGFR3 يشتغل بشكل سريع وأكثر بكثير من المفروض, عشان كذا صاحب هذا المرض يكون قصير القامه .

لماذا يكون غالبا فقط ال limbs تتأثر ؟ لأن ال chondrocytes موجوده بال long bones أكثريعني باللimbs



METABOLIC BONE DISEASE

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



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** ; the most important clinically significant osteopenia is **osteoporosis**.

Osteoporosis is an **acquired** condition characterized by **reduced bone mass**, leading to bone fragility and susceptibility to fractures The bone tissue becomes weak "chalk like" يشبه (الطبشور). most commonly in females

Overview :

-The cortical bone is thinned, and the bone trabeculae are thinned and reduced in number.

increased porosity of the skeleton leading to reduction in the bone mass but without distortion of architecture.

-It may be **localized** e.g. disuse osteoporosis of a limb**. or may involve the entire skeleton**, as a metabolic bone disease.

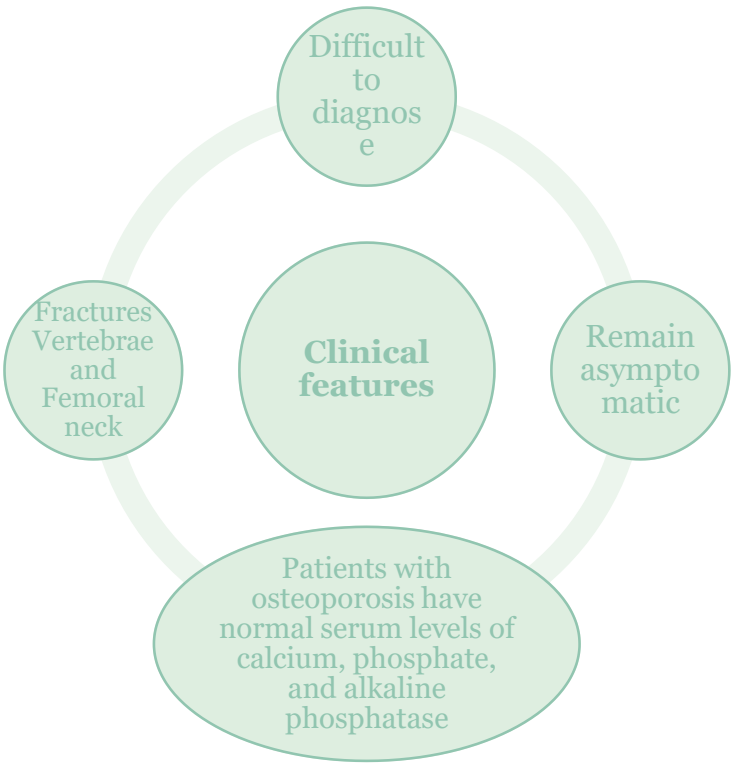
-People with osteoporosis are likely to sustain **three types of fractures** :

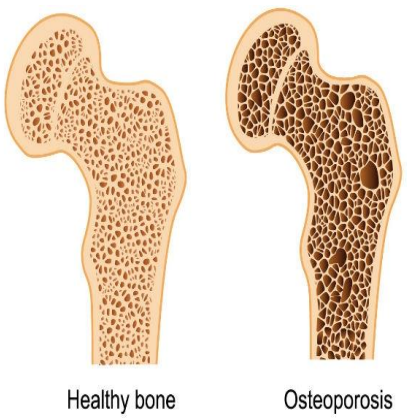
1. Colle's fracture 2. Fracture of the neck of the femur 3. Vertebral compression.

any bone can be fractured from osteoporosis but the three mentioned above are most common.

-We can examine osteoporosis by examining the density of the bone.

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).





- **Pathophysiology:**

Occur when the balance between **bone formation** and **resorption** tilts in **favor of resorption**

Genetic factors | Nutritional effects | Physical activity | Aging | Menopause

-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.

-يعني أكبر وأفضل كميه من التكوين العظمي توصلها في بداية الadulthood فالصغار ما بعد تكون العظم بشكل كامل ونهائي ، والكبار تبدا تضعف الخلايا المكونه للنسيج العظمي.

- لكن السؤال هل تختلف هذه المرحلة من شخص لشخص من حيث افضليه النسيج ؟ نعم، كيف وعلئ اي اساس ؟ علئ اساس الجينات و النظام الغذائي قبل الوصول لل peak و عوامل بيئية. قد ما يكون نظامك ممتاز قد ما بيكون ال peak حقك اعلى وكلما كان ال peak اعلى قلت الأمراض اللي ممكن تصيب العظام.

- Generally it is divided into two types: **primary** osteoporosis and **secondary** osteoporosis.
- **primary osteoporosis :** refers to **senile** osteoporosis and **postmenopausal** osteoporosis.

Why are women at increased risk of osteoporosis after menopause?

1. There is a relationship between **estrogen** and **osteoporosis**. The drop of oestrogen will induce osteoporosis.

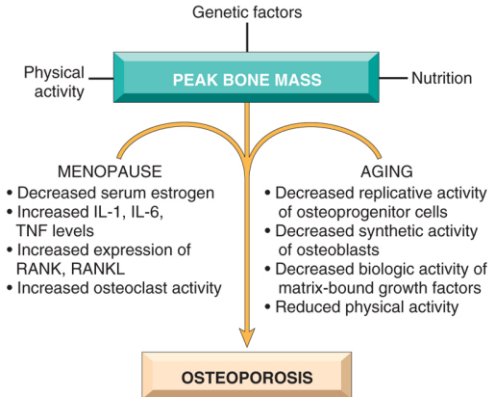
2. They think that the drop in estrogen **->** stimulate some inflammatory cells and will increase the secretion of certain **cytokines** especially tumour necrosis factor (TNF), interleukin 1, interleukin 6 and sometimes interleukin 8.

3. 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.

تذكرون لما قلنا ال RANK L لما يُفرز ينشط وظيفة ال osteoclast? فيه دراسات تعتقد أن عندما يقل نسبة الاستروجين يتنشط هذا ال rankl اللي بدوره بينشط الosteoclast بالتالي بتصير كثافه العظام أقل ومنها بتنشأ osteoporosis

يعني المرأه في سن اليأس معرضه بشكل كبير لهشاشه العظام بسبب نقصان مستولا الاستروجين.

اما بالنسبة للعمر لكل من الرجل والمرأه فهو ايضاً عامل قوي لهشاشه العظام. لماذا؟ بسبب نقصان نشاط ال osteoblast



- **how can you diagnose osteoporosis?**
  - **Plain X ray**: cannot detect osteoporosis until **30% to 40% of bone mass has already disappeared**. s
  - **Dual-emission X-ray absorptiometry (DXA scan):** is used **primarily** to **evaluate bone density**, to diagnose and follow up with osteoporosis.
  - **Biopsy** : from the **iliac crest.**

DXA scan

-It is hard to diagnose osteoporosis, (it's asymptomatic until the skeletal fragility is announced).
-It cannot be detected until we find that 30% to 40% of the bone mass has already disappeared.
-Serum level of calcium phosphorus and alkaline phosphatase are insensitive to osteoporosis.

- **Prognosis :**

-**Osteoporosis** is **rarely lethal.**
-Patients have an increased **mortality rate** due to **the complications of fracture.**

Example :hip fractures can lead to decreased mobility and an additional risk of numerous complications: **deep vein thrombosis** pulmonary embolism and **pneumonia**.

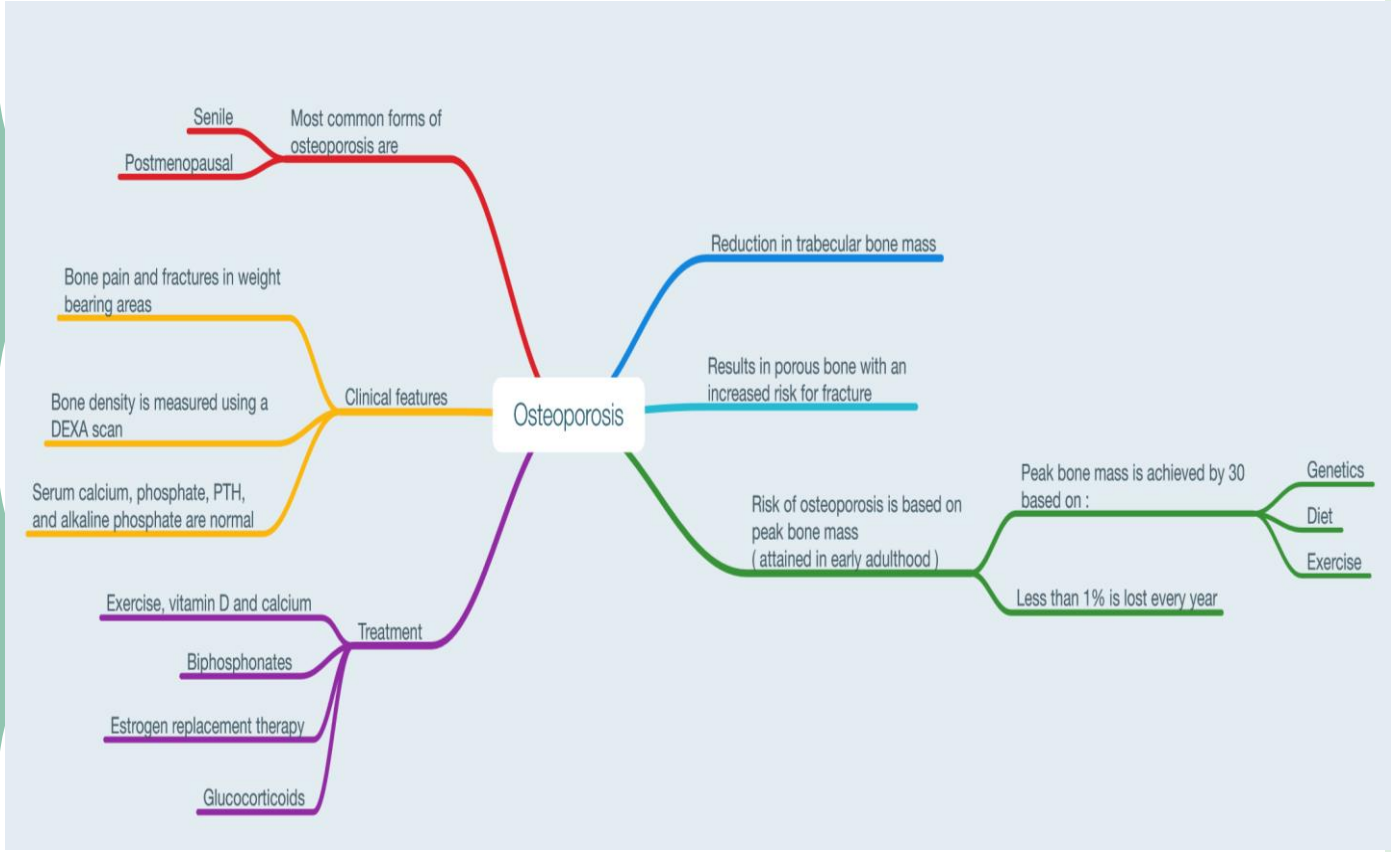
- **Prevention Strategies:**

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

-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.This will provide a good reserve against bone loss later in life. Exercise places stress on bones that builds up bone mass.

MIND MAP:


Osteoporosis
Most common forms of osteoporosis are
Senile
Postmenopausal
Clinical features
Bone pain and fractures in weight bearing areas
Bone density is measured using a DEXA scan
Serum calcium, phosphate, PTH, and alkaline phosphate are normal
Treatment
Exercise, vitamin D and calcium
Biphosphonates
Estrogen replacement therapy
Glucocorticoids
Reduction in trabecular bone mass
Results in porous bone with an increased risk for fracture
Risk of osteoporosis is based on peak bone mass (attained in early adulthood)
Peak bone mass is achieved by 30 based on :
Genetics
Diet
Exercise
Less than 1% is lost every year

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

OSTEOMALACIA AND RICKETS

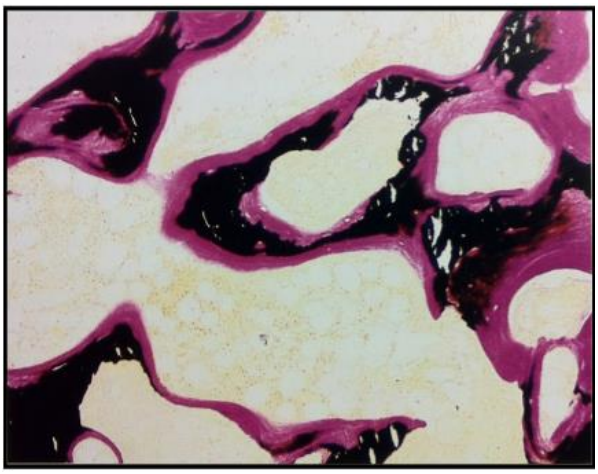
- In **osteomalacia** (in adults) **and rickets** (in children), osteoblastic production of **bone collagen is normal** but **mineralization is inadequate**.

- It results in accumulation of unmineralized matrix (increased osteoid) It is a manifestation of **vitamin D deficiency**

-Deficiency of vitamin D can be caused by:

a) **Insufficient intake**
b) **Malabsorption** due to intestinal diseases e,g: **Crohn's disease**
c) **Renal disease:** vitamin D is activated by the kidney after absorption, so renal failure will affect the activation of vitamin D causing osteomalacia, as well as increase bone resorption

How does it cause bone resorption?
→Decreased renal activation of vitamin D
→Hypocalcemia
→Secondary hyperparathyroidism
→Osteoclastic activation
→Bone resorption



Patient with osteomalacia:

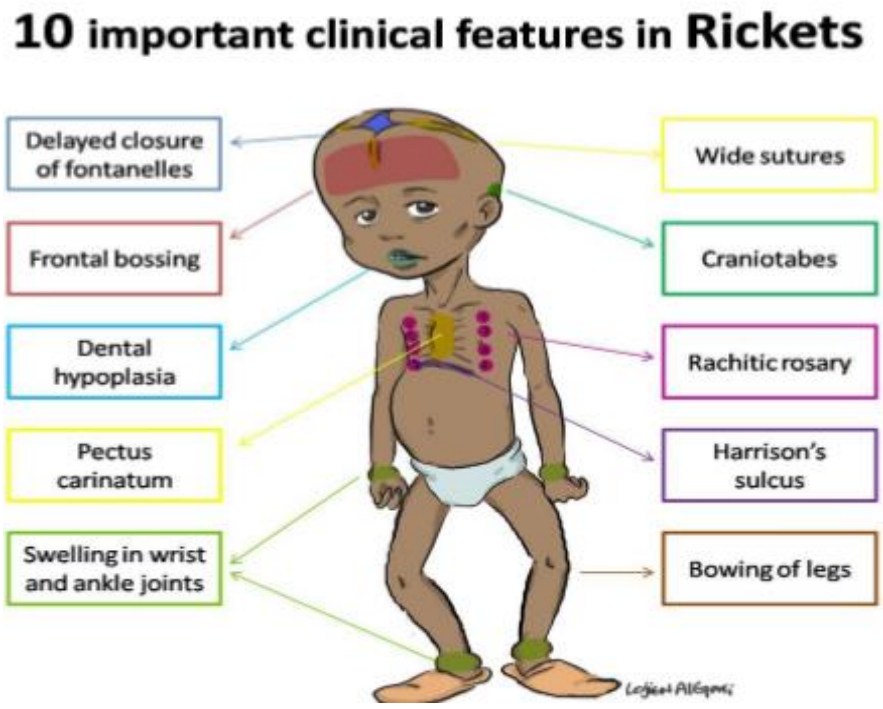
Special stain used for detection of **calcium**: von Kossa stain

Result of micrograph:
- Notice broad zone of **uncalcified matrix** (red)
- Minimal **minerlization present in** center (black)

- **Rickets** refers to the disorder in children, in which it interferes with the

- **Osteomalacia** can be diagnosed through bone biopsy, and X-rays.
- **Osteomalacia** in children is known as Rickets. It could be caused by poverty, by illness, by ignorance in feeding babies, by malabsorption and by malnutrition.

CLINICAL FEATURES OF RICKETS



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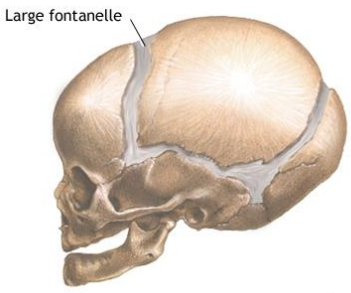
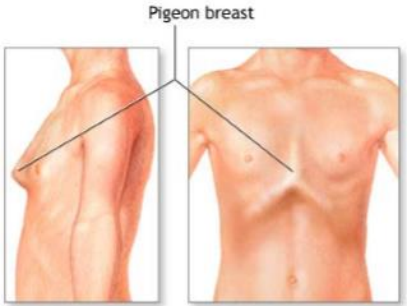
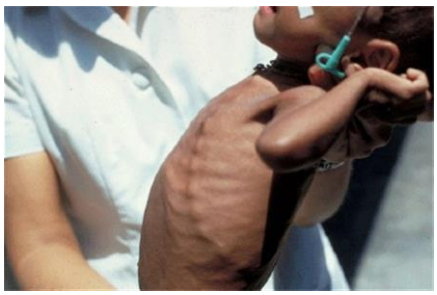


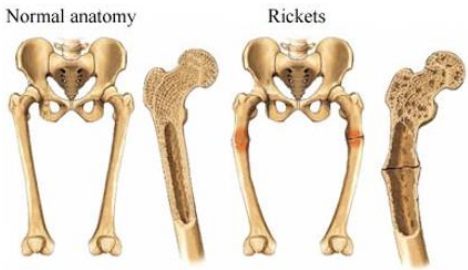
Delayed fontanelle closure: resulting in prominence and bulging of frontal bone



Pigeon chest: deformities of the chest wall causing protrusion of sternum and ribs



Rachitic rosary: expansion of the anterior part of the rib at the costocondral junction

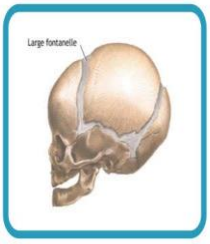


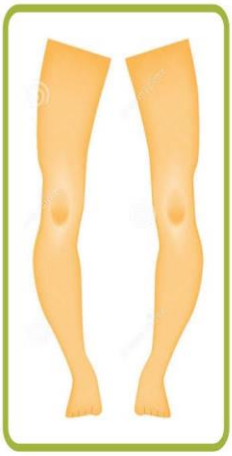
Bowing of the leg: specifically femur and tibia bones

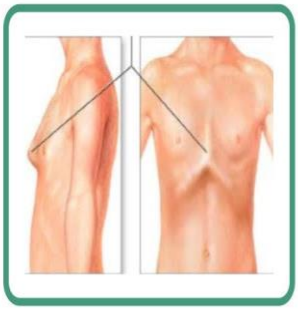
MIND MAP :

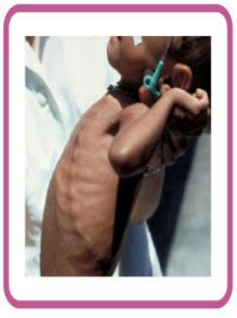
Osteomalacia / Rickets

- **Acquired disease**
- **Inadequate mineralization**
  - **Normal bone collagen**
  - **Vitamin D deficiency**
  - **Low Calcium level**
- Depending on age it called :
  - **Rickets : In children** — Disorder interferes with deposition of bone in the growth plates
  - **Osteomalacia : In adults** — The bone formed during remodeling is undermineralized
- Clinical features
  - Delayed closure of fontanelles
  - Frontal bossing
  - Rachitic rosary
  - Pigeon chest
  - Bowing of the leg







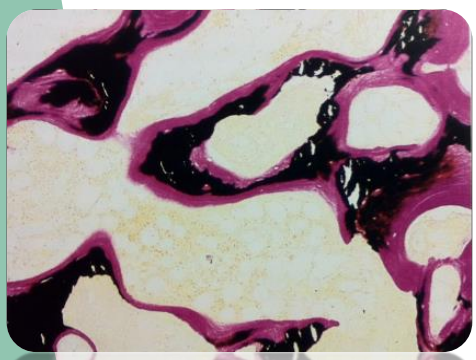


OSTEOPOROSIS VS OSTEOMALACIA

Osteoporosis

- Loss of bone density and mass
- Decreased osteoblastic production
- Thinning of cortical and trabecular bone
- Normal ossification and mineralization process
- Calcium levels are normal

Osteomalacia



- Softening of bone tissue
- Normal osteoblastic production
- Decreased mineralization of bone
- Calcium levels are low
- Vitamin D deficiency

STUDY SMART! AND READ THIS:

	Etiology	Pathogenesis	Clinical features	
Osteogenesis Imperfecta	Congenital Type1: autosomal dominant. Type2: autosomal recessive. COLIA1: on chromosome 17. COLIA2: on chromosome 7.	• Defect in the synthesis of type I collagen. • Amino acids chains alpha 1 and alpha 2 in the structure of collagen (type 1) are defected.	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.	1. Delayed fontanelle closure. 2. Rachitic rosary. 3. Pigeon chest. 4. Bowing of the leg.	

MCQS

- **1) A disease which can lead to growth failure (dwarfism) and permanent intellectual disability?**

A) Achondroplasia

B) Congenital Hypothyroidism

C) Osteogenesis Imperfecta

D) Osteopetrosis

- **2) Overexpression of FDER3 is due to a mutation on the?**

A) Short Arm Of Chromosome 4

B) Long Arm Of Chromosome 4

C) Short Arm Of Chromosome 16

D) Long Arm Of Chromosome 16

- **3) Osteogenesis imperfecta is due to a defect in?**

A) Collagen Type 3

B) Collagen Type 4

C) Collagen Type 1

D) Collagen Type 2

1-b
2-a
3-c
4-b
5-a
6-a

- **4) What type of osteogenesis imperfecta is not compatible with life?**

A) Type 1

B) Type 2

C) Type 3

D) Type 4

- **5) Postmenopausal women will have an increase in which of the following lymphokines ?**

A) TNF, IL1, IL6

B) PDGF, TGF-B, FGF

C) IL-6 , IL1 , FGFR

D) IL-2 , IL-6, TNF

- **6) Which of the following is the most likely disease which will have the following laboratory findings: decreased calcium and phosphate serum levels and increased PTH and alkaline phosphatase**?

A) Rickets/Osteomalacia

B) Osteoporosis

C) Paget Disease Of Bone

D) Osteopetrosis

SAQ

- 1) Why does achondroplasia cause short extremities and a normal sized head and chest?

- 2) Patients with osteogenesis imperfecta will have blue sclera because?

- 3) Patience with osteogenesis imperfecta could suffer from hearing lose because?

- 4) Give two primary reasons for osteoporosis?

- 5) What are the clinical features of osteoporosis?

ANSWERS

- 1) Poor endochondral ossification will lead to short extremities (long bones) and they will have normal intramembranous ossification so the head and chest will not be affected.

- 2) Because they have a defect in collagen type 1 and it will cause thinning of the scleral collagen revealing the choroidal vein.

- 3) Because the bones of the middle ear are easily fractured so the deafness is caused by a conductive defect not a nerve defect.

- 4) 1- Senile 2- Postmenopausal

- 5) Kyphosis, scoliosis, and fractures (e.g. neck of femur, Colle's fracture, vertebral column.)

Some helpful videos:

Osteoporosis:
https://www.youtube.com/watch?v=eYGkT6OrBko

Achondroplasia:
https://www.youtube.com/watch?v=gt-SAjuikLM

Rickets/Osteomalacia:
https://www.youtube.com/watch?v=QHHnaPydYvw

Osteogenesis Imperfecta:
https://www.youtube.com/watch?v=nwsqVT4k3m8

MEMBERS :

Females:

-leader : بثينة آل ماجد

-روان الحربي
-وفاء العتيبي
-الجوهرة الشنيفي
-رزان الزهراني
-رهف الشمري
-روان مشعل
-منيره المسعد
-نوف العتيبي
-رزان الزهراني
-هديل عورتاني
-فاطمة بالشرف
-ابتسام المطيري
-رناد الفرم
-غرام جليدان
-بلقيس الراجحي
-نورة القاضي
-آلاء الصويغ
-ريم القحطاني

Males:

-leader : فيصل الطحان

عبدالجبار اليماني
محمد باحاذق
أحمد الراشد
عبدالله بالعبيد
عبدالله السرجاني
أحمد الحربي
أنس السيف
داود إسماعيل
فهد الفايز
محمد بن معيوف
فهد النحابي
سعد الفوزان
سيف المشاري
تميم الوهيبي
خالد العقيلي
محمد الصويغ
محمد الأصقه
نواف السبيعي
عبدالعزيز المحنا
عبدالله المعيذر
فايز الدرسوني
رشيد البلاع

Kindly contact us if you have any questions/comments and suggestions:

* EMAIL: pathology437@gmail.com
* TWITTER : @pathology437

GOOD LUCK!☺

Resources:-

1- Females slides
2- Robbins reference book

Pathology

teamwork437