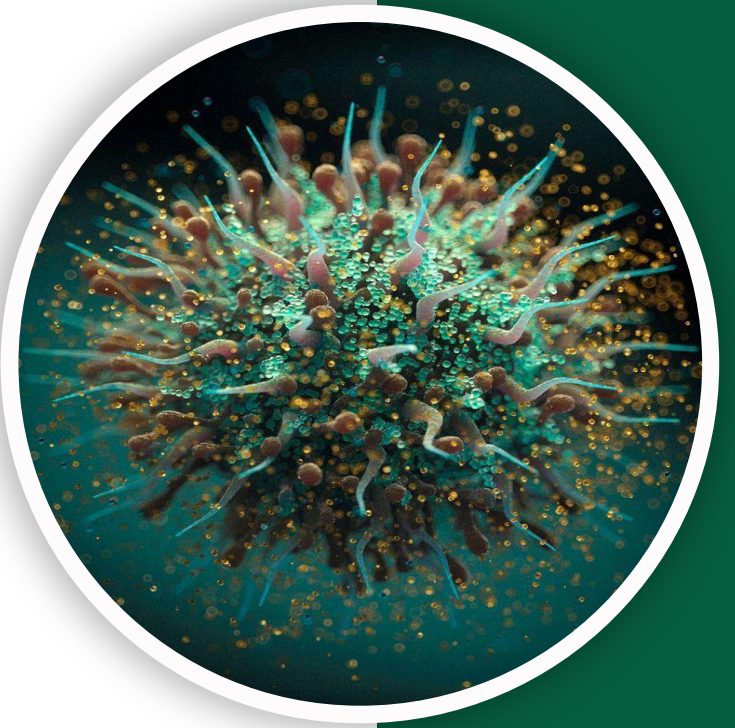
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pathology | MID 2

# MSS & Skin Tumors pt.2

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Batool Zayed

Reviewed by : Maya Almajali

# CONGENITAL DISORDERS

- Although they are not very common, you may notice them during pediatric rotations and sometimes in orthopedic rotations.
- **There are two major categories of congenital disorders of bone:**

## DYSOSTOSIS

- Dys = wrong / ostosis = bone
- Abnormal condensation & migration of mesenchyme
- Genetic abnormalities of homeobox genes, cytokines and its receptors
  - **Aplasia**
  - **Supernumerary digit**
  - **Syndactyly & craniosynostosis**

## DYSPLASIA

- Abnormalities in the organization of the structure of the bone and cartilage.
- **Disorganized bone & cartilage**
- **Gene mutations that control development and remodeling**
- **Dysplasia here: not premalignant**

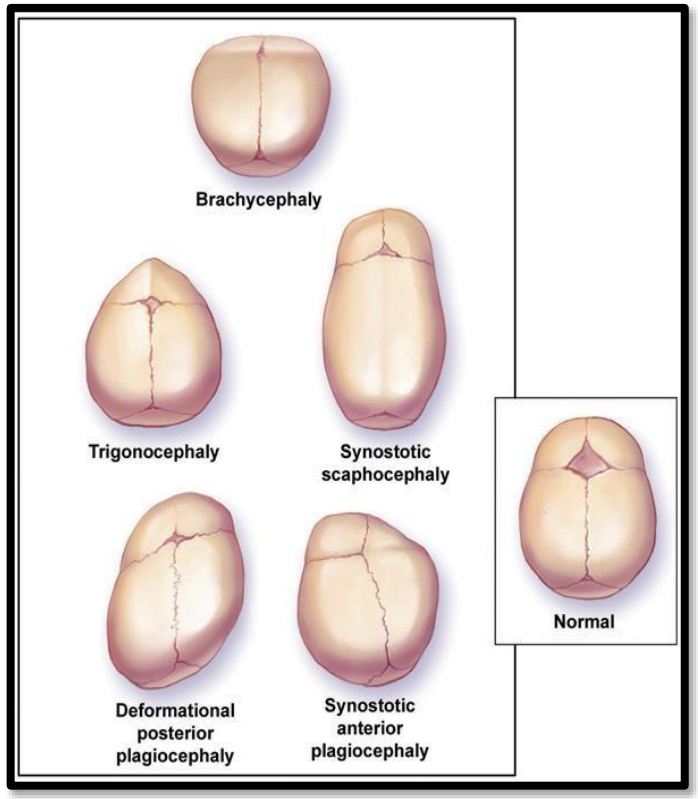
# ✓ DYSOSTOSIS:

- Abnormal condensation & migration of mesenchyme at some points during bone formation or bone maturation.
- **Due to** Genetic abnormalities of homeobox genes, which are affecting many inflammatory cytokines mediators and its receptors
- Examples on dysostosis :
  - **Aplasia is lack of synthesis of certain bone or certain groups of bone** ( no condensation & migration of mesenchyme ) , i.e : four fingers instead of five.
  - **Supernumerary digit** It is a congenital condition where a person has **more than five digits on a hand or foot (extra )** , i.e : six fingers instead of five.
  - **Syndactyly & craniosynostosis** more common than the two previous conditions .
  - Syndactyly is **fusion of digits or toes** .
  - Craniosynostosis is a condition in which one or more of the skull sutures fuse prematurely in an infant, leading to abnormal head shape and potentially restricting normal brain growth. **(Abnormalities in the formation of skull)**

# DYSOSTOSIS

(1) **Aplasia** ; there is an absence of finger .
(2) **Supernumerary digits** ; the presence of an extra finger.
(3) **Syndactyly** of the little & middle fingers.
(4) **Supernumerary digits & Syndactyly**
(5) **Craniosynostosis**

(5)




(1)

(2)

(4)

(3)

❗The details related to craniosynostosis are not required, just know the general concept .

# Lecture 2

# DYSPLASIAS

**1) Achondroplasia (dwarfism): most common**

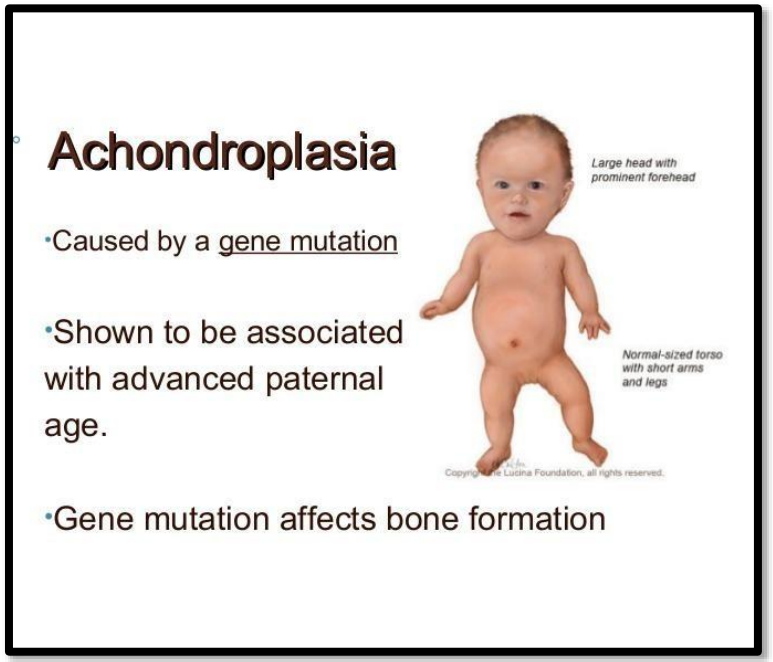
- The common cause of dwarfism (القِزامة) is achondroplasia.
- **Mutations in FGFR3** (fibroblast growth factor receptor 3) which is the major driver of achondroplasia syndrome .
- **No impact on :**

**a) longevity** It means they live like us and die from the same diseases we do; therefore, the achondroplasia they have does not affect their lifespan or life

  - Longevity refers to the length of time an organism lives, typically measured as life span.

**b) intelligence** ( their brain growth is normal )

**c) or reproductive status** ( they have normal reproductive status)




**Peter Dinklage: 48-years-old, married with 2 children from USA, New Jersey "Game of thrones"**

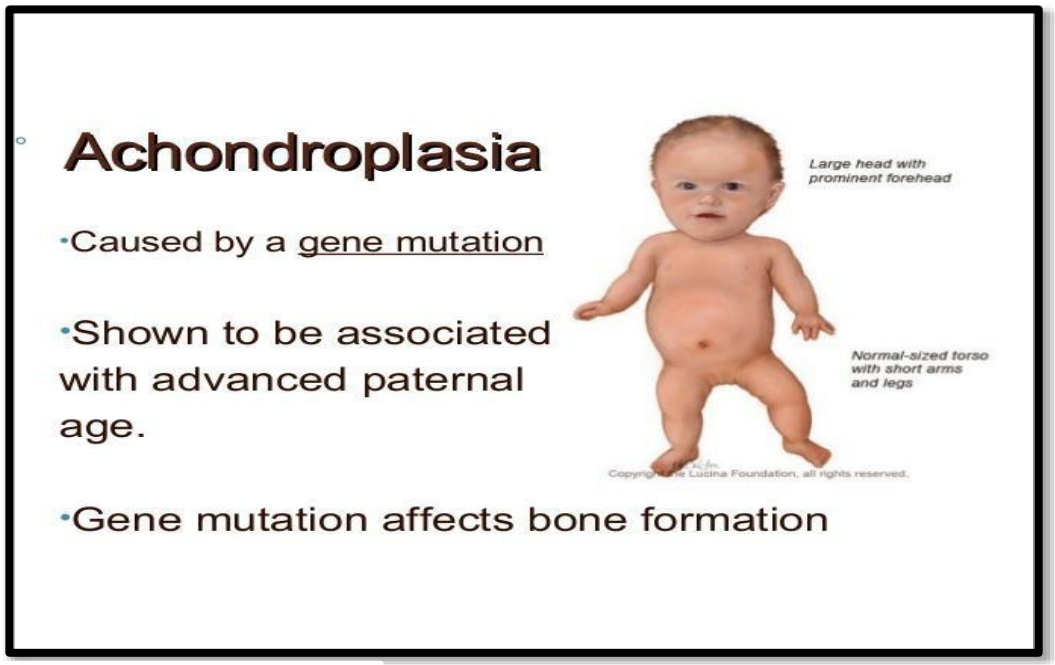
# DYSPLASIAS

- ***The features of achondroplasia:***

a) Big head with mild frontal bossing

(بروز الجبهة).

b) Short limbs and hands.




**Peter Dinklage: 48-years-old, married with 2 children from USA, New Jersey "Game of thrones"**

In the world of Game of Thrones, power belongs to the sharpest mind not the tallest warrior :)

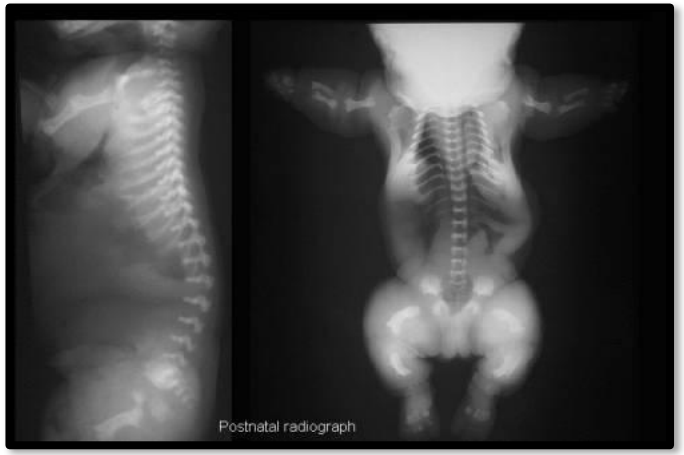
# 2) THANATOPHORIC DYSPLASIA

- **Most common lethal form of dwarfism**
- **FGFR3 mutations (different from Achondroplasia ;** they are in the same receptor group but at different locations**)**
- Most of patients either **Die** in utero **, at birth or shortly after ,** because they can't maintain normal respiration **(small chest leading to resp. insufficiency &** chest compression **)**
- Characteristic features of Thanatophoric dysplasia:

a) Big head

b) Short limbs

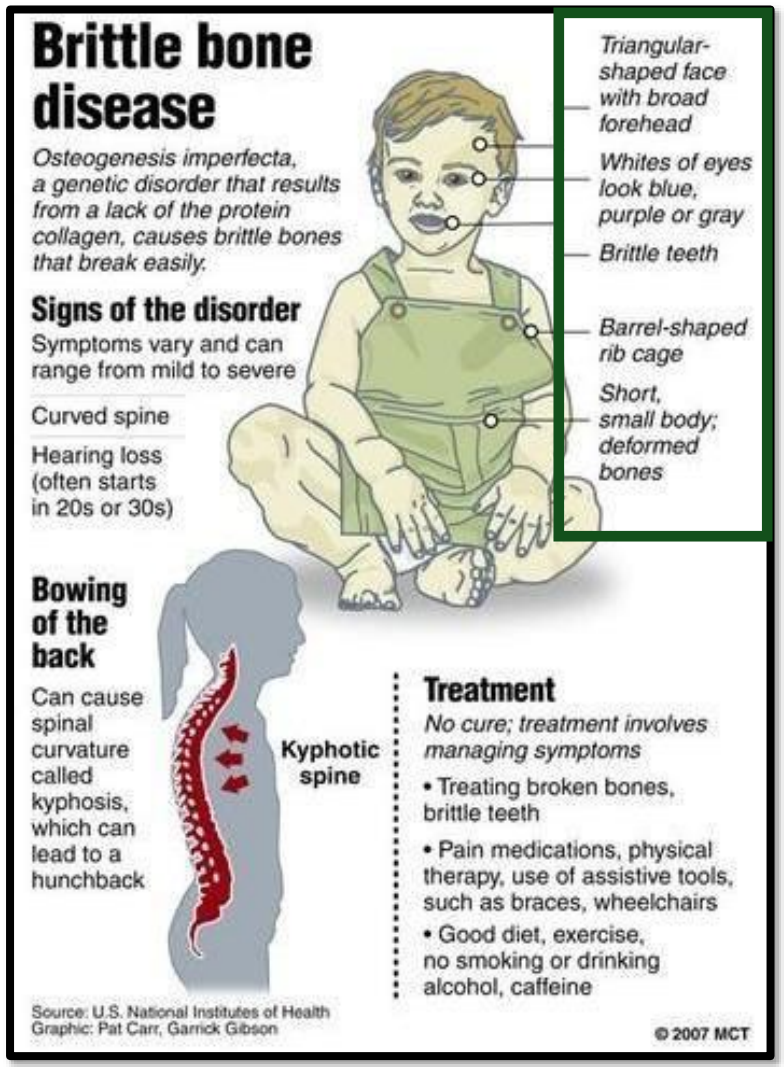
c) Very severe restriction on the chest wall




﴿وَالذَّاكِرِينَ اللَّهَ كَثِيرًا وَالذَّاكِرَاتِ أَعَدَّ اللَّهُ لَهُم مَّغْفِرَةً وَأَجْرًا عَظِيمًا﴾

# 3) OSTEOGENESIS IMPERFECTA (OI)

This diagram explains the different features of OI :




- Layman name : brittle bone disease ; because the bone is abnormal , weak , prone to fractures frequently , simple trauma causing devastating fractures.
- **Most common inherited disorders of connective tissue**
- **Group of disorders; AD** ( autosomal dominant) ; **deficiency of type I collagen synthesis** , this is why the bone is brittle.
- **Too little bone; fragility**
- **Blue sclera; hearing loss; teeth abnormalities**
- **Type 2 (lethal)** they don't survive beyond the first 6 months or 1 year of life **and type I (relatively normal life)** they have problems , but supportive therapy and management will keep them alive.

The professor asked:

**How does type I collagen deficiency in osteogenesis imperfecta lead to the development of blue sclera?**

No need to search, I've got the answer for you ;)

**Ans :** Although osteogenesis imperfecta is primarily known as a bone disorder, type I collagen is also a major structural component of the sclera. Defective or reduced synthesis of type I collagen results in scleral thinning. As the sclera becomes thinner and more translucent, the underlying choroidal vasculature – which has a dark bluish color – becomes visible. This translucency gives the sclera its characteristic blue appearance.

*You can check Robbins and Cotran Pathologic Basis of Disease 11th edition , Chapter 26.*

# 4) OSTEOPETROSIS

- Osteopetrosis is exactly the opposite of osteoporosis that we will talk about later on.
- Other name of osteopetrosis : **Marble bone disease "stone bone"** (rigid) **(group of disorders); rare**
- **Impaired osteoclast function: reduced bone resorption leading to diffuse sclerosis** (diffuse formation of marble bone)
- Osteoclasts need to be functional so that the bone retains some flexibility under shear forces.
- **Dx: X-ray**
- Prone to multiple **Fractures and leukopenia in severe forms**
- Osteopetrosis > impaired bone remodeling > pressure on the bone marrow > impaired hematopoiesis > decreased production of white blood cells > leukopenia

These are classic X-ray images , but they are not normal. All the bones are white in color, and there is no darkness at all.

## Summary

### Congenital Disorders of Bone and Cartilage

Abnormalities in a single bone or a localized group of bones are called **dysostoses** and arise from defects in the migration and condensation of mesenchyme. They manifest as absent, supernumerary, or abnormally fused bones. Global disorganizations of bone and/or cartilage are called **dysplasias.** Developmental abnormalities can be categorized by the associated genetic defect.

- FGFR3 mutations are responsible for achondroplasia and thanatophoric dysplasia, both of which manifest as dwarfism.
- Mutations in the genes for type I collagen underlie most types of osteogenesis imperfecta (brittle bone disease), characterized by defective bone formation and skeletal fragility.
- Mutations in *CA2* and *TCIRG1* result in osteopetrosis (in which bones are hard but brittle) and renal tubular acidosis.

# METABOLIC DISORDERS

More common

Standard deviation

- **Osteopenia: decreased bone mass (1-2.5 SD below the mean).**
- **Osteoporosis: severe osteopenia; > than 2.5 SD below the mean with increase risk for fractures**
- **Generalized (much more common) or localized**

The mean for each particular age is different ،there are certain graphs for each nationality that are validated , you go back to them after calculating the bone mass to diagnose the patient whether in the normal range , having osteopenia or osteoporosis

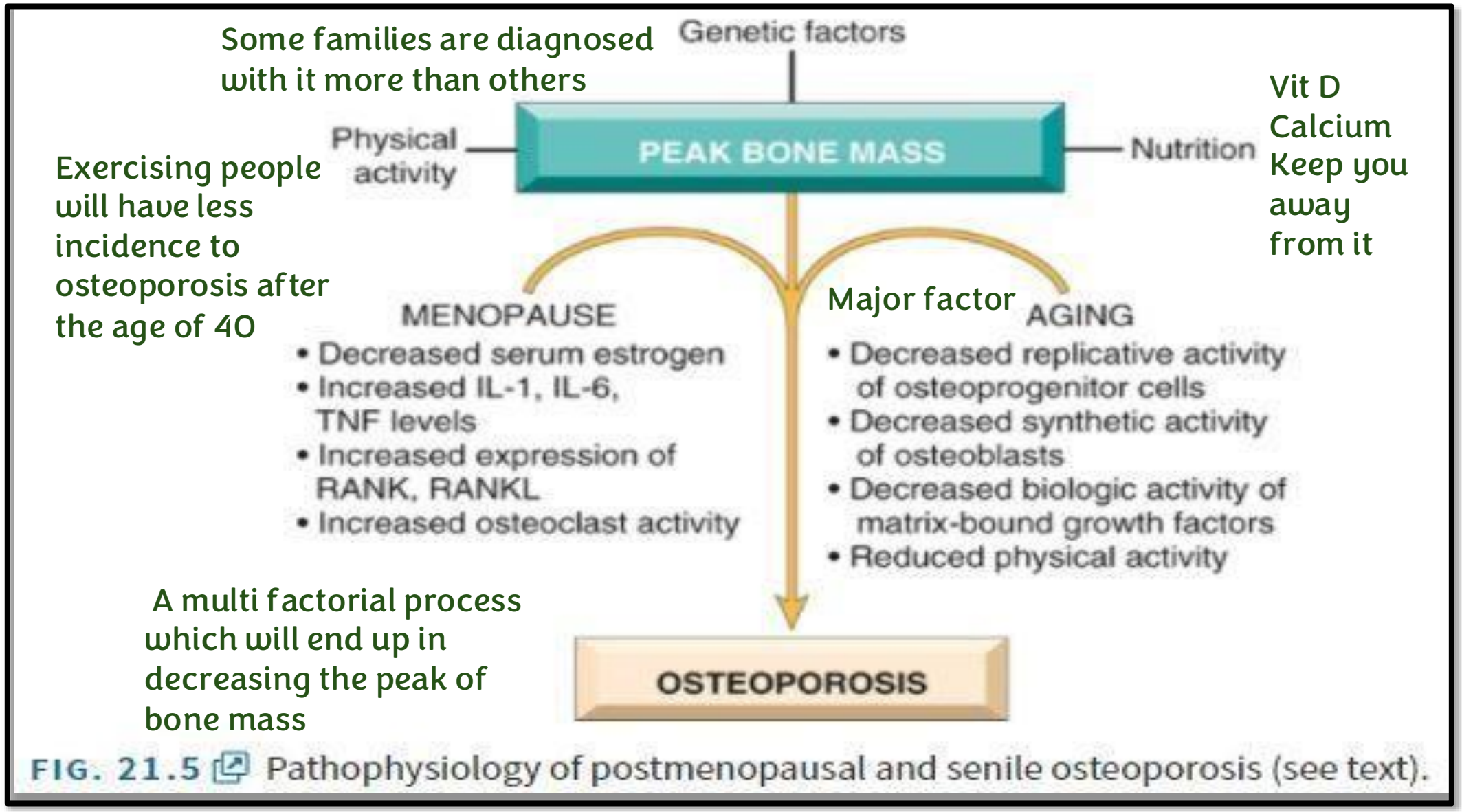
| PRIMARY OSTEOPOROSIS | SECONDARY OSTEOPOROSIS |
|---|---|
| Much more common<br>Senile (aging) & postmenopausal | Much less common Hyperthyroidism, malnutrition, steroids |

Caused by specific metabolic disorders

Especially in multiparous women , because with each pregnancy there is more impact in decreased bone mass

- **Osteoporosis as a general disease affecting the whole community is the generalized primary osteoporosis .**

Some families are diagnosed with it more than others



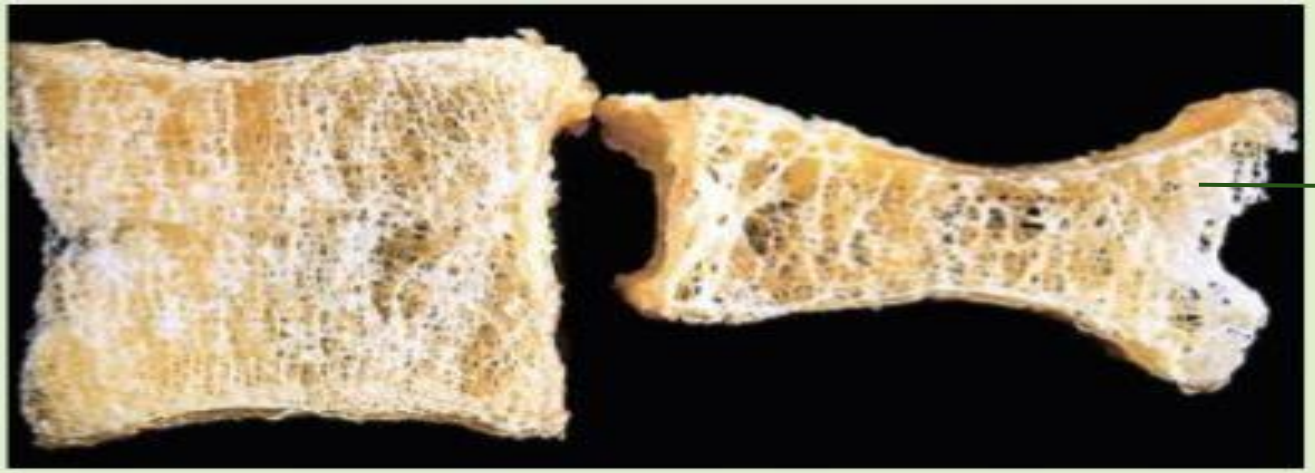

Vit D
Calcium
Keep you away from it

Exercising people will have less incidence to osteoporosis after the age of 40

A multi factorial process which will end up in decreasing the peak of bone mass

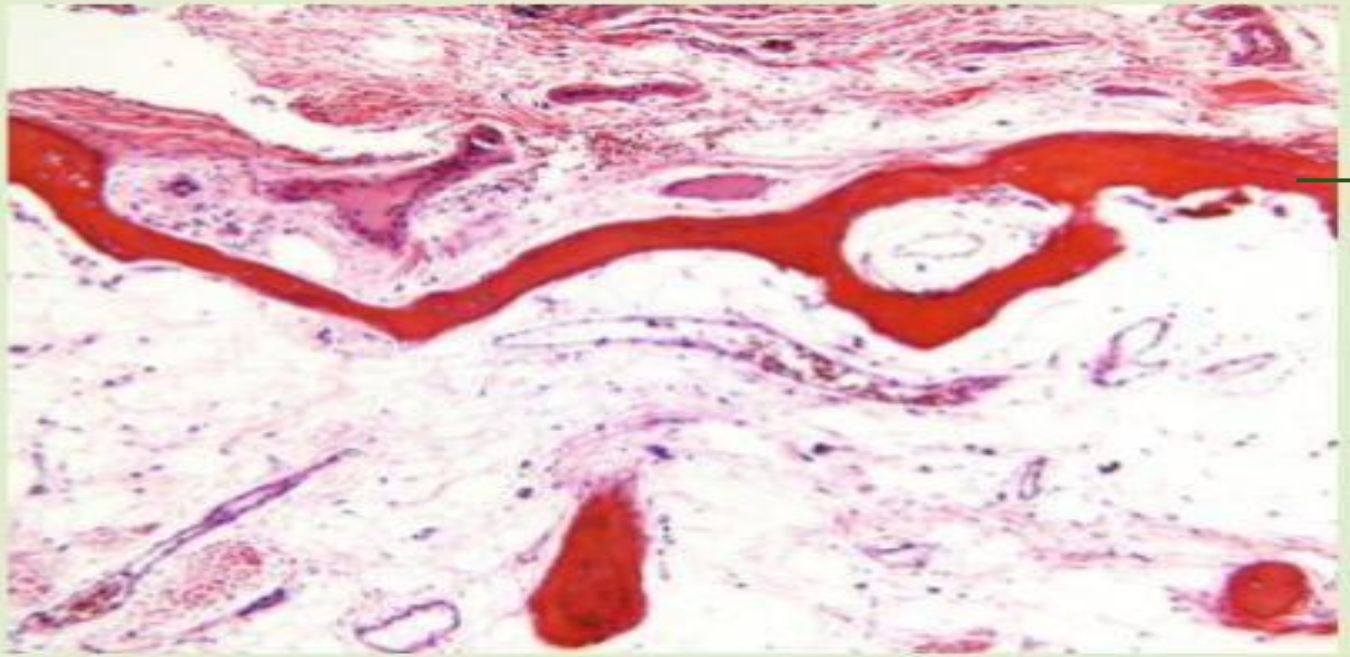
FIG. 21.5 Pathophysiology of postmenopausal and senile osteoporosis (see text).

Normal vertebrae



This vertebrae contains micro fractures leading to compression fractures which is the main cause for severe osteoporosis

FIG. 21.6 Osteoporotic vertebral body *(right)* shortened by compression fractur..



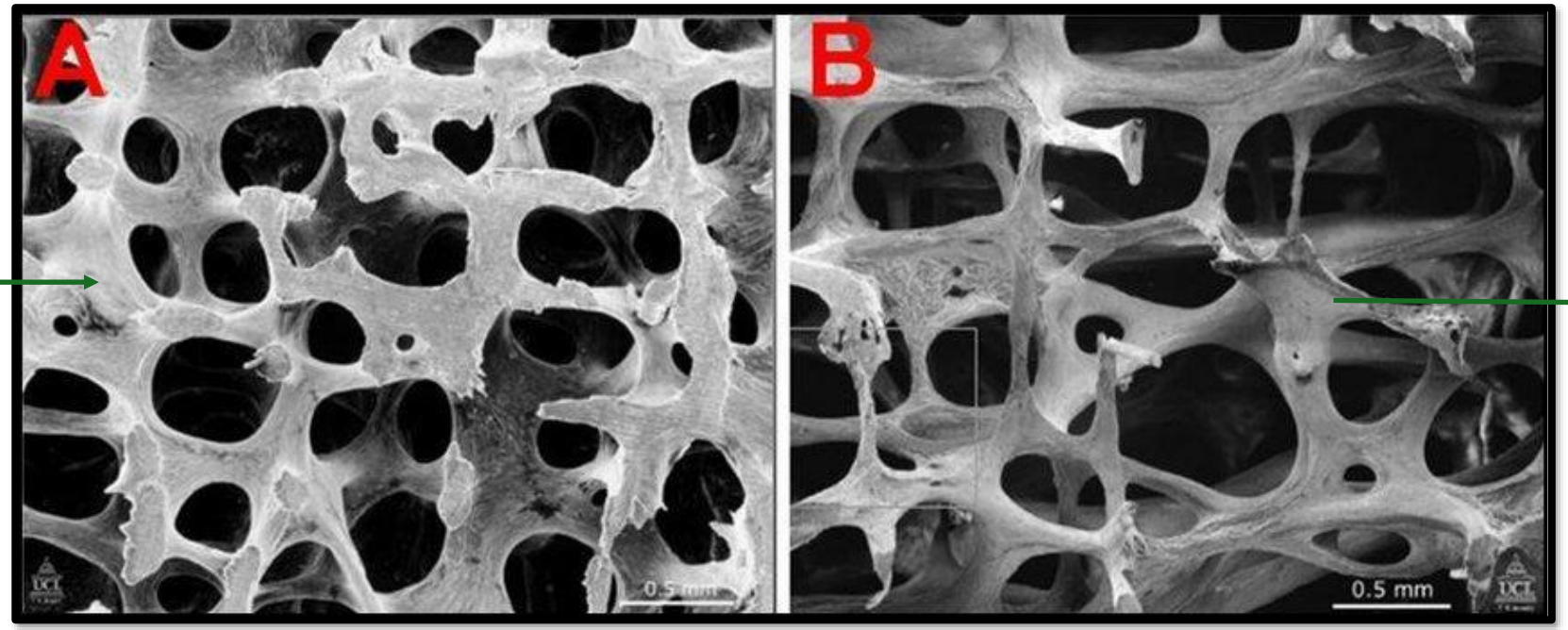
Histologically , thin bone trabeculae and more matrix

FIG. 21.7 In advanced osteoporosis, both the trabecular bone of the medulla *(b..*

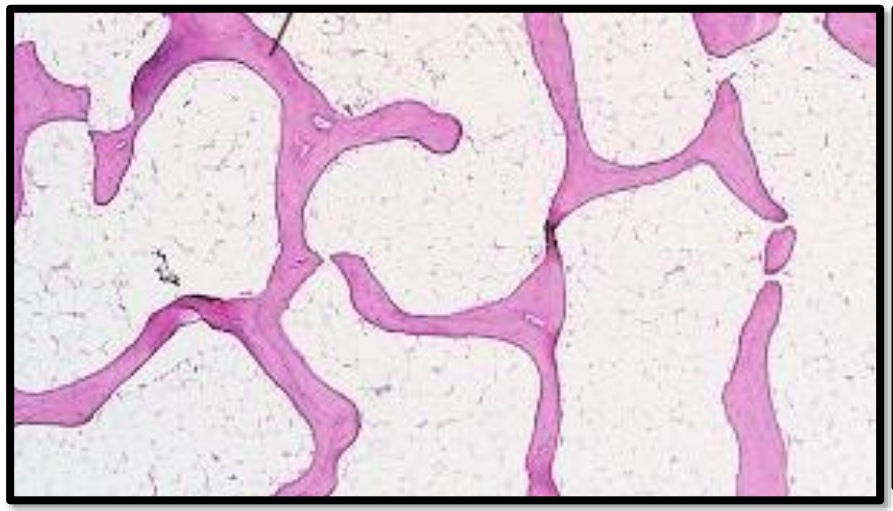
# Normal bone : Osteoporosis

SEM pictures

Thick trabeculae




Thinner and broken trabeculae , very painful and associated with sever comorbidities



More matrix compared with normal bone

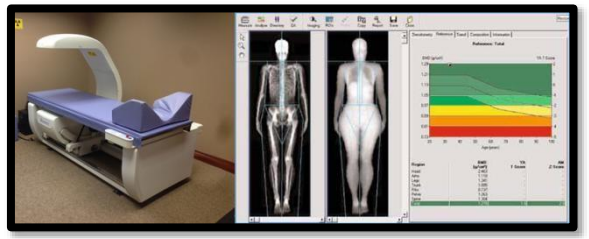
# OSTEOPOROSIS CLINICALLY

- **Vertebral fractures** Specially compression fractures
- **Femur and pelvic fractures: immobility, PEs, pneumonia (40-50K death/yr in USA)**
- **Diagnosis: special imaging technique, bone mineral density (BMD scan): dual-energy X-ray absorptiometry (DXA or DEXA scan) or bone densitometry**

Pulmonary embolism , silent killer , patients are at risk of deep vein thrombosis the major cause of death in hospitalized patients

BMD : Bone mineral density

جهاز قياس هشاشة العظام



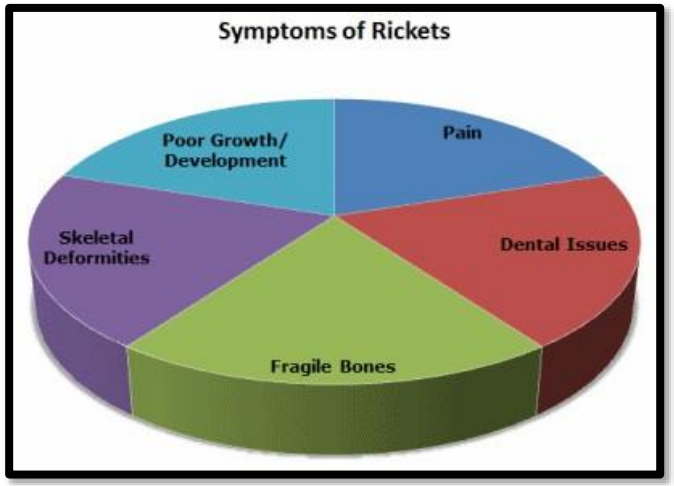
# PREVENTION AND TREATMENT

- **Exercise** Osteoblastic activity is increased, and osteoclastic activity is decreased. The chance for osteoporosis will be much less
- **Calcium & vitamin D (the nutrition)**
- **Bisphosphonates: reduce osteoclast activity and induce its apoptosis**
- **Denosumab: anti-RANKL; blocking osteoclast activation (new expensive potent)**
- **Hormones (estrogen): risking DVT and stroke**

Post-menopausal symptoms

They are rare nowadays

# RICKETS & OSTEOMALACIA




- **Vitamin D deficiency or abnormal metabolism of vitamin D.**
- **Children: Rickets**
- **Adults: osteomalacia**
- **Decreased mineralization of bone, unmineralized matrix**
- **Increase risk of fractures**

Cause pain , dental problems , skeletal deformities and poor growth and development


Affects bone integrity and causes bone pathology

# HYPERPARATHYROIDISM (HPT)

## Hyperparathyroidism classification

*Different causes and features of hyperparathyroidism - raised parathormone (PTH).*

| | primary | secondary | tertiary |
|---|---|---|---|
| pathology | Hyperfunction of parathyroid cells due to hyperplasia, adenoma or carcinoma. | Physiological stimulation of parathyroid in response to hypocalcaemia. | Following long term physiological stimulation leading to hyperplasia. |
| associations | May be associated with multiple endocrine neoplasia. | Usually due to chronic renal failure or other causes of Vitamin D deficiency. | Seen in chronic renal failure. |
| serum calcium | high | low / normal | high |
| serum phosphate | low / normal | high | high |
| management | Usually surgery if symptomatic. Cincacalcet can be considered in those not fit for surgery. | Treatment of underlying cause. | Usually cinacalcet or surgery in those that don't respond. |

NICE have issued guidance for the use of cinacalcet in what they call refractory secondary hyperparathyroidism which is classified as tertiary hyperparathyroidism in this tblable. http://www.nice.org.uk/TA117

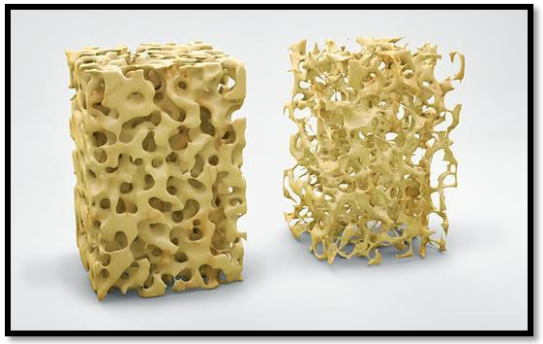
tblable.com

- It is complex to understand it in our level , so just memorize the table

# HPT CLINICALLY

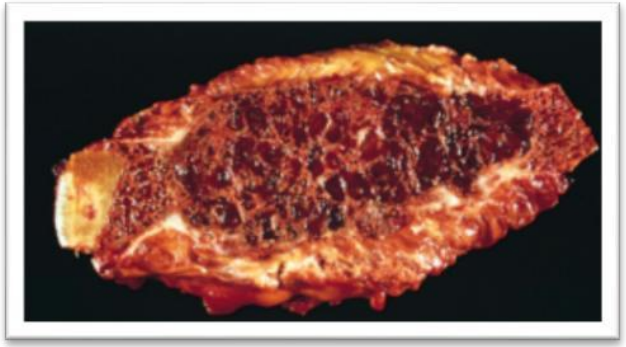
Sometimes , there will be multiple small fractures leading to cystic hemorrhagic area which will miss lead the clinicians that this is a tumor , however its not an actual tumor and the diagnosis of it is the first indication that the patient is having hyperparathyroidism

## OSTEOPOROSIS



A misnomer , it's not actually a tumor

## BROWN TUMOR



## OSTEITIS FIBROSA CYSTICA

Due to severe chronic , untreated , unrecognized HPT

**Abbreviated OFC, also known as osteitis fibrosa, osteodystrophia fibrosa, and von Recklinghausen's disease of bone (not to be confused with von Recklinghausen's disease, neurofibromatosis type I)**

## Summary

### Metabolic Disorders of Bone

- **Osteopenia** and **osteoporosis** represent histologically normal bone that is decreased in quantity. In osteoporosis the bone loss is sufficiently severe to significantly increase the risk of fracture. The disease is very common, with marked morbidity and mortality from fractures. Multiple factors including peak bone mass, age, activity, genetics, nutrition, and hormonal influences contribute to its pathogenesis.
- **Osteomalacia** is characterized by bone that is insufficiently mineralized. In the developing skeleton, the manifestations are characterized by a condition known as **rickets.**
- **Hyperparathyroidism** arises from either autonomous or compensatory hypersecretion of PTH and can lead to **osteoporosis**, **brown tumors,** and **osteitis fibrosa cystica**. However, in developed countries, where early diagnosis is the norm, these manifestations are rarely seen.

# Additional Resources:

# رسالة من الفريق العلمي:

# For any feedback, scan the code or click on it

Corrections from previous versions:

| Versions | Slide # and Place of Error | Before Correction | After Correction |
|---|---|---|---|
| V0 → V1 | | | |
| V1 → V2 | | | |