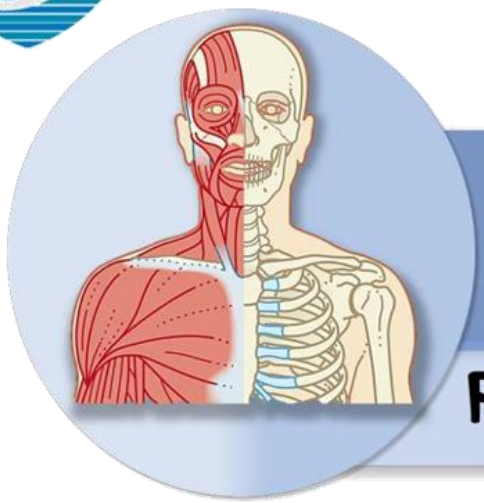

MSS system

Pathology

◉ Sheet ○ Slide

Number:	#2
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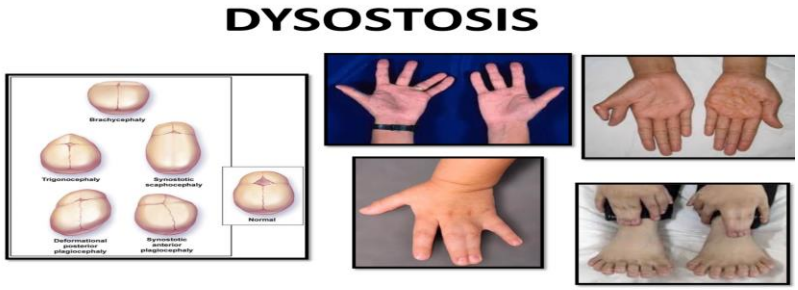
introduction to what we will cover:
-dysostosis is caused by genetic abnormalities in **homeobox genes, cytokines and its receptors**. However, dysplasia is caused by a gene mutation that control development and remodeling.

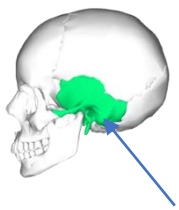
CONGENITAL DISORDERS : **dysostosis** and **dysplasia**, dysplasia is not premalignant (it's not precancerous), it's just an abnormal formation of the bone (badly formed).

DYSOSTOSIS:
Mechanism: Its simply an abnormal condensation and migration of the mesenchyme during fetal growth. So, we will have problems in the formation of bones.

There are multiple disorders due to dysostosis but the most important ones are:



-Aplasia which is simply the lack of formation of a bone or a digit. Ex: missing a finger or missing a toe.
-supernumerary digit (polydactyly); extra bone or digit. Ex: someone having more than 5 fingers.
-**syndactyly:** abnormal fusion of bones. Ex: 2 fingers sticking to each other. Note that it's really important to do a surgery to separate them as soon as possible since it affects bone growth because simply they don't have normal bones like we do.
-**carniosynostosis:** (abnormal formation of cranium): normally the baby has ant. suture, post. suture, 2 lateral sutures and in the middle, there is the fontanel "النافوخ"(which is the place where there is not bone above the brain in order to permit the growth of the brain), It closes after 2 years of birth. (physical growth: weight, size)
In **brachiocephaly** ; absence of lateral sutures , it affects the growth of the temporal bones which are highlighted in green

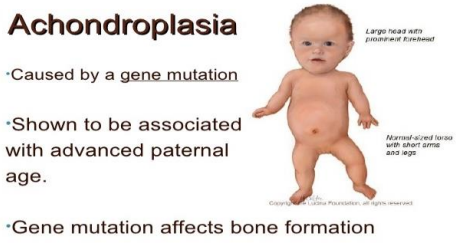


Now let's talk about **DYSPLASIA**.
There are many types, but the most common and important ones are:

1-ACHONDDROPLASIA
This is the proper pathological name and the most common cause of **dwarfism** (there are many causes, but this is the most common)
the mutation is in **FGFR3** (fibroblast growth factor receptor 3)
manifestations: **short limbs** but the trunk and head are normal (trunk can be slightly smaller).
Is there any impact on life expectancy, IQ, reproductive capabilities?? **NO**

Real life example: the actor peter Dinklage from game of thrones , he is 48 years old , married with two kids , notice the normal size of head and trunk but short limbs.

The students asked about the **inheritance** of the disease? the doctor said it's complicated but if a couple with achondroplasia got married the chance of having a dwarf baby is **high** but not 100%. Note that this is a congenital disease not an inherited one.



2-THANATOPHORC DYSPLASIA:
It's the most common **LETHAL** form of dwarfism.
The mutation is in FGFR3 but the locus that the mutation occur in is **different** than achondroplasia.
Very much less common than achondroplasia luckily, its rare.

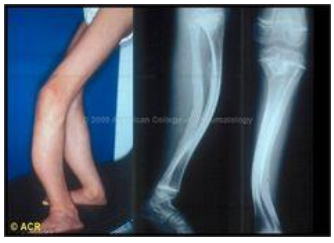
They either die in utero or shortly after why?

Their small chest presses on the lung, so they wont breath properly, eventually they die from respiratory insufficiency.

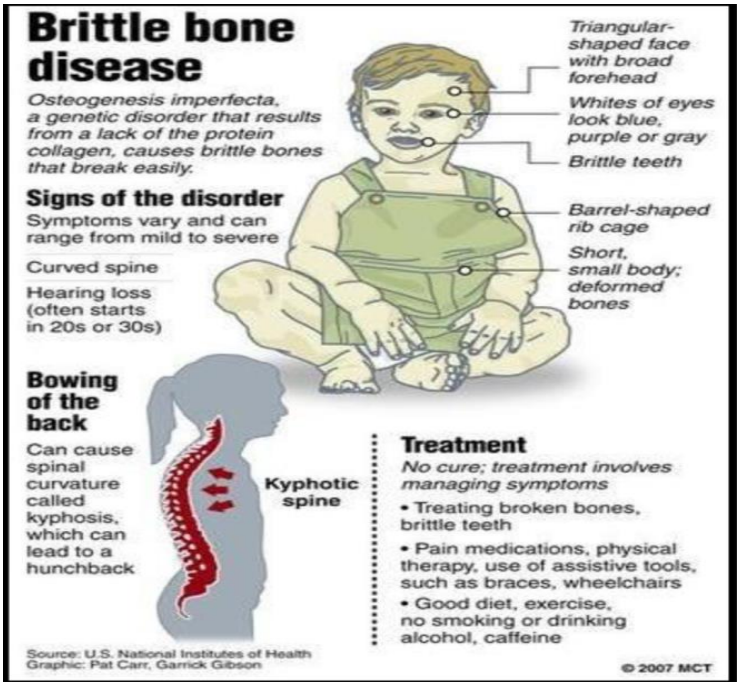
Notice the compressed chest and remember: ITS LETHAL so pay attention if a clinical case came in the exam saying **the baby died in the utero or shortly after birth.**

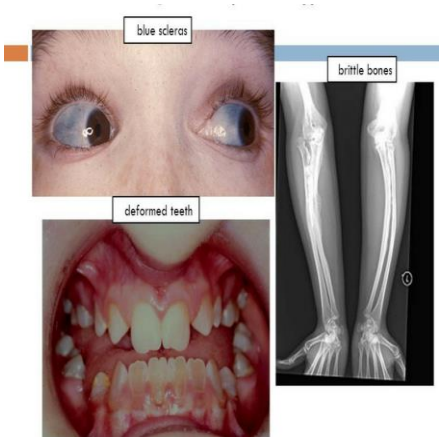
3-OSTEOGENISIS IMPERFECTA (OI)
-*Brittle* bone disease (general name)
-It's the most common inherited disorder of **connective tissue.**
-There are many types (group of diseases)
-It's inherited in an **autosomal dominant trait**
-the abnormality is in the production and synthesis of type 1 collagen which is the main protein in bones due to a **mutation in collagen1 gene**.
-type 1: little deficiency, they can live. type 2: severe deficiency, they die.
-There are subtypes of type 2 (type 2a ,type 2b , type 2c)
-multiple fractures will occur even in the utero (very weak bones)

Fact : one of the deformities is called **phone handle deformity**, because when you scan the femur on the x-ray scan, it will look like the phone handle due to the **fractures** that occurred.



More “clues to identify this type of OI”:
-Hearing loss, weak teeth.
-**Blue sclera** sometimes purple but most common is blue (the sclera is the white part of the eye) **Why?**
Ans: This is due to the **sclera** being thinner than normal because the defective Type I collagen is not forming correctly





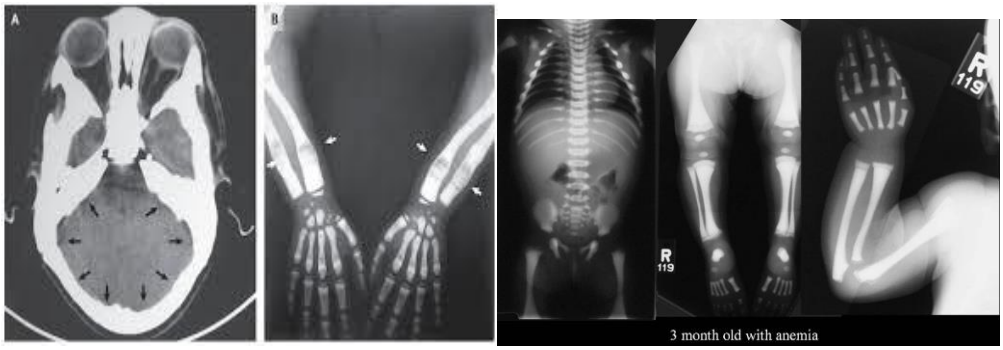
CHECK SLIDE 20

4.OSTEOPETROSIS

-**marble** bone disease (it’s the opposite of osteoporosis) **the osteoclast doesn’t work. (impaired osteoclast function), much lower activity and or doesn’t work** and higher osteoblast activity relatively
-no bone resorption will occur, so the bone will be like marble.
-It’s very rare
-To diagnose it from the x-ray scan, the bone will look really white “too much white, too much calcium, too much ossification” (the normal x-ray scan of the bone has some transparency.)
-No bone marrow no spaces, the trabeculae are fused together (all of the spaces and trabeculae is filled with high calcium amounts), this is bad, any slight force will end up breaking the bone.

-we have said before that one of the functions of bones is transmission of force so how does that work?

-the spongy bone will transmit the force among those thousands of trabeculae so for an example if 5N force hit your arm , the spongy bone will transmit it to the trabeculae “spread the force” so the force will end up being 0.0034N per trabeculae which is okay and will not break the bone rather than a full 5N to a marble bone. (the number is not true it’s just for clarifying things).

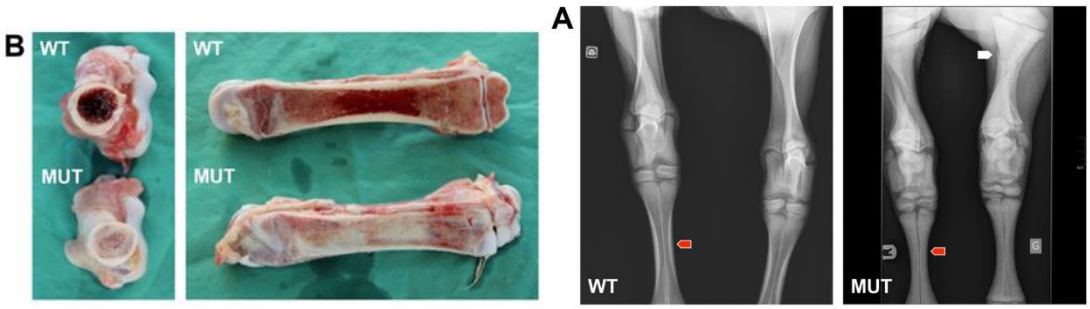


-no bone marrow → no hematopoiesis → leukopenia, anemia and thrombocytopenia (less platelets)
-very severe and diffuse sclerosis (hardening of bone tissue).
they're prone to fracture, their **immunity is weaker** than normal (because of leukopenia), they will have **bleeding disorders** (because of thrombocytopenia they will not stop bleeding from a small wound, it will take more time to stop the bleeding.)

- **The students asked**:
- Does hypocalcemia occur? the dr: I don't think it will happen but check some sources for it, no hormonal impairment, the major impact is in the bone structure and bone function.

- **The students asked**: Can we treat it by steroids? The dr: it's not as easy as u think, the osteoclast is not normal, so I don't know how will the steroids will help, those patients if they survived they will need supportive treatment (therapy). Warning them of falling, being careful… etc..

- Finally, we diagnose it by x-ray scan. This is the best clarifying photo I have found, please observe it really well.



Mutations in **CA2 AND TCIRG1** result in osteopetrosis and renal tubular acidosis.

METABOLIC DISORDERS.

We talked before about the balance between the osteoblast and osteoclast activity, and how it's so important.

Above the age of 40, the balance will be impaired, and a difference in the osteoclasts count to osteoblasts will occur, how big is that difference? that's the thing that we care about the most

Small difference? **Osteopenia**: a little decline in bone mass **(1-2.5)** SD below the mean (I will explain that now)
Big? **Osteoporosis**: big decline in bone mass **(more than 2.5 SD)**

How we determine if our patient has osteoporosis?
Diagnosis: special imaging technique: bone mineral density (BMD scan): dual-energy Xray absorptiometry (DXA or **DEXA** scan) or bone **densitometry**
-it will give us his bone mass compared to the mean of his age in a chart

- if his bone mass lower than the normal mean bone mass of his age by up to **1-2.5** it's still in the **OSTEOPENIA** region.
- if a 60-year-old woman who had a lot of a children and bad nutrition state went through that test, it will probably give bone mass lower than normal of her age by more than 2.5. for an example 3.5 (**OSTEOPOROSIS**).

MAKE SURE TO CHECK THE VIDEOS OF OSTEOPRORSIS AND OTHER SUBJECTS FROM ELEARNING FOR YOUR KNOWLEDGE AND FOR EXAM PURPOSES.

The machine is called **dexa** (the **dexa scan**)

Notice how the patient **is supine**, the thing above will scan his whole body, give the doctor your bone mass compared to the normal mean bone mass of your age group, then the doctor will see how far is your bone mass from the normal **bone mass of your age group** for an example:
Q: Lower than the normal by 1.5 SD? **Osteopenic patient**, it's not very bad compared to osteoporosis and the treatment is less than the osteoporosis.

Q: Lower than the normal by 3, 3.5, 2,6? **Osteoporotic** patient, more dangerous and require more treatment and with more increase risk of fractures. (the decline is more than 2.5 SD)

NOTE: Those numbers are accurate, the scientist proved that the normal that gives a difference statistically is 2.5 after following up with some patients, those numbers also gives them an indication when to prevent and when to treat.

There are two types of generalized osteoporosis:
1- (primary): much more common
Causes: ageing (senile), postmenopausal (why after menopause? Lecture1)
2-Secondary: we know the main reason of the osteoporosis, very less common.
Causes: hyperthyroidism, malnutrition, steroids

Note that we have **generalized osteoporosis** and it has two types mentioned above and "generalized": affecting the whole body.

We have also **Localized osteoporosis**: a patient complaining from a SINGLE bone since he or she was a kid and pain in It and by time it became weaker and developed osteoporosis in THAT BONE ONLY. It's much less common.

FACTORS that develop osteoporosis: (it's multi factorial and not a single factor will develop osteoporosis)

1-GENETIC FACTORS: certain families have genetically stronger bones than others, and those with weaker bones will have A HIGHER risk of developing Osteoporosis than those with stronger, most of the time we don't understand why, but there are definite genetic factors.
2-PHYSICAL ACTIVITY: active people and people who exercise have a lower chance of developing osteoporosis, exercise will help osteoblasts and will delay and sometimes prevent osteopenia and osteoporosis and will lower the intensity and severity of it.

3-**NUTRITION**: calcium, milk, nutrition in general, and people who suffer from starving will have a higher risk of osteoporosis than people in amman for an example.

Note: women have to take calcium supplements from the first pregnancy to prevent osteoporosis before it's too late (at the age of 55 for an example)

4-**MENOPAUSE**: menopause → decreased serum levels of estrogen → it will:

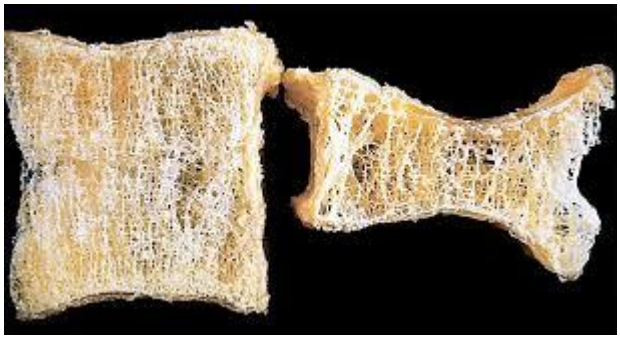
A) It will impact the osteoclast activity.
B) It will increase the levels of IL1 (the most important) and IL6 and TNF. (The students asked: what's the relationship between cytokines and menopause? the dr: I think in menopause the cytokines increase, why? I think its hormonally dependent, but I couldn't link between them so check it up if u want)
C) Increased expression of RANK RANKL, CHECK LECTURE 1 AND THE VIDEOS.
D) osteoclasts activity is increased in menopause regardless of the above.

There may be some overlap like a women who gave birth to a lot of children, no physical activity, bad nutrition state, weak bones genetically , it will greatly increase the risk of osteoporosis.

5- **AGING**: with aging all of the following occur:

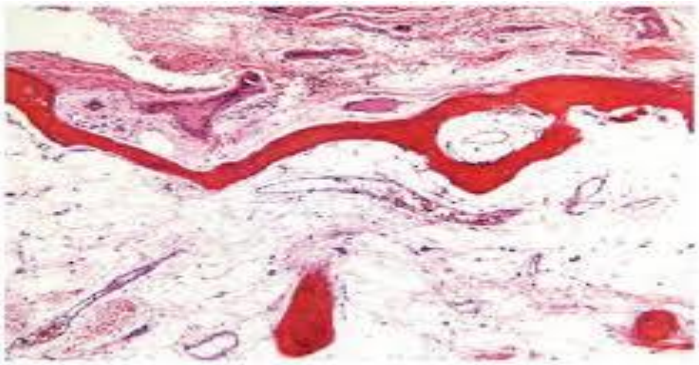
A) Decreased replicative activity of osteoprogenitor cells (that differentiate into the more specialized bone-forming cells (osteoblasts))
B) Decreased synthetic activity of osteoblasts
C) Decreased biologic activity of matrix bound growth factors (they are the environmental factors that if u go to deep in science u will know there are factors and mediators like cytokines)
D) Reduced physical activity.

That is a vertebral body, notice that the right vertebral is osteoporotic and shortened by compression fractures compared to a normal vertebral body on the left, notice that the osteoporotic vertebra has a characteristic loss of horizontal trabeculae and thick ended vertical trabeculae (robins)
On the right: more spaces, on the left: less spaces



Now let's observe a histological appearance

Notice too little bone trabeculae compared to the surrounding matrix, small osteocytes, the diameter and the number of bone trabeculae Is less. (both the trabecular bone of the medulla (bottom) and the cortical bone (top) are thinned))



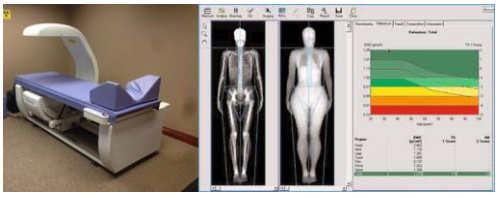
In advanced osteoporosis, both the trabecular bone of the medulla (bottom) and the cortical bone (top) are markedly thinned.

<u>Osteoporosis clinically:</u>

Q: What will happen to a patient who suffers from osteoporosis clinically?
1-Vertebrate fractures: the treatment of them is a really hard process so its better to prevent them by nutrition and physical activity and so on.
2-Femur and pelvic fractures: one of the major causes of death and morbidity of all patients especially females with severe osteoporosis because:
They will be immobilized for a long time in the hospital and no vessel activity will be lower > higher risk of DVT (deep vein thrombosis)

-around 40-50k die each year from complications of femur and pelvic fractures: immobility , pulmonary embolism (the silent killer) (its when a blood clot gets caught in one of the arteries that go from heart to lung) , DVT, also inflammation can occur (pneumonia) and it can kill you. (the lecture ended here but there is the continuation of the slide…

TO DIAGNOSE we DON'T use x ray scan, but we use Special imaging techniques, bone mineral density scan, dual energy x-ray absorptiometry , DXA or DEXA scan or bone densitometry.



NOTE: collagen type 1 is in bones and Type 2 in cartilage
Type 3 in artery walls, skin, intestine , granulation tissue , produced by young fibroblasts quickly before the tougher type 1.
Type 4 in basement membrane along with laminin.

Test yourself

What is the gene abnormality that made the head of that kid look like this?
ans : abnormality in homeobox genes.

1)What is true about the effect of menopause to osteoporosis?

A) Increased estrogen levels
B) Decreased IL1
C) Decreased expression of RANK and RANKL
D) Increased osteoclast activity
E) Increased osteoblast activity

2)all of the following is associated with achondroplasia except

a) patients will be dwarf
b) it has no impact on intelligence
c)the mutation is on FGFR3 and on the same locus as thanatophoric dysplasia
d) no impact on reproductive ability

3)all of the following is true about OI except?

a) teeth abnormalities will occur
b) type 2 is lethal
c)it's the most common inherited disorder of the epithelial tissue
d) deficiencies in collagen type 4 synthesis
e) c+d

4)what is correct about thanatophoric dysplasia?

a) its not a lethal form of dwarfism
b) the mutation is in FGFR3 but different than the one in achondroplasia
c)they die from malignancy
d)the main cause of death is due to respiratory insufficiency
e) d+b

5)all of the following is true about marble bone disease (osteopetrosis) except

a) high osteoclast activity
b) if patients survived they need a supportive treatment
c) the x-ray scan will represent a really whiter look of the bone than normal
d) anemia, thrombocytopenia, leukopenia will occur

7) a 30-year-old woman gave birth of a dead child, the x-ray scan was done and you notice a compressed chest, what is true about the type of dysplasia of the child

A) Its called achondroplasia
B) The child probably suffered from thrombocytopenia
C) It's called thanatophoric dysplasia and the mutation is in FGFR3
D) The baby had really strong marble like bones
E) B+D

GOOD LUCK AND DON'T HESITATE TO ASK ME.

DCEEADC