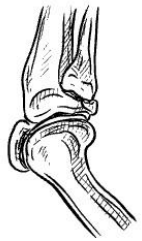
بسم الله الرحمن الرحيم

PATHOLOGY



MID | Lecture #2

MSS & Skin tumors Pt.2

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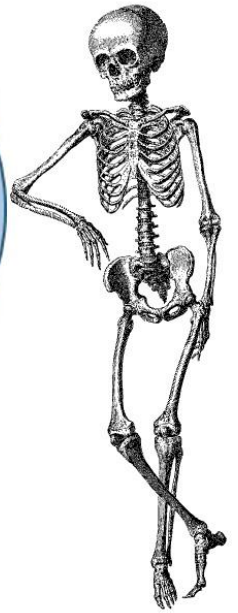
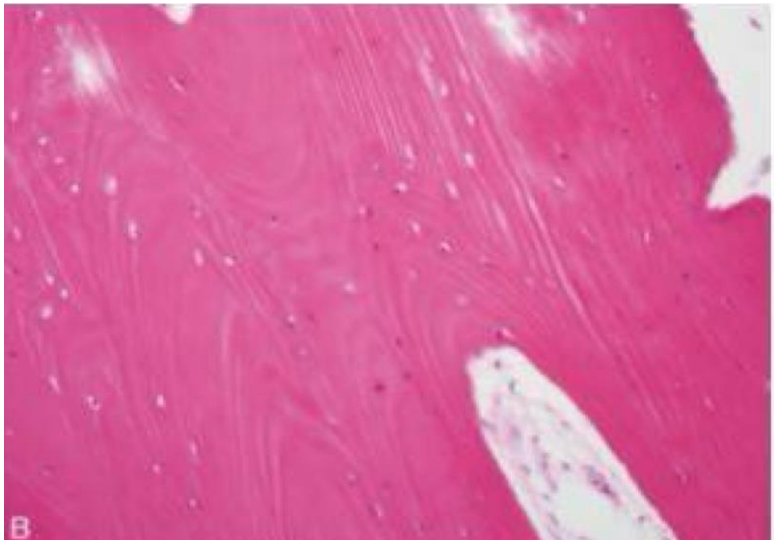
Reviewed by : Leen Mamoon

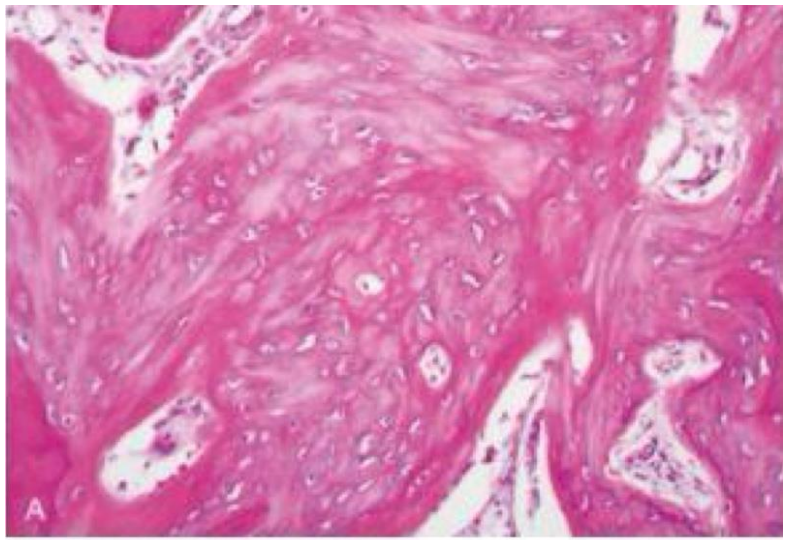
﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا



Click on the LAMELLAR BONE To test yourself in the previous lecture.





"اللهم إني أسألك فهم النبيين وحفظ المرسلين والملائكة المقربين، اللهم اجعل ألسنتنا عامرة بذكرك،
وقلوبنا بخشيتك، إنك على كل شيء قدير وحسبنا الله ونعم الوكيل"

CONGENITAL DISORDERS

✓ While these disorders are not common , they are likely to be observed during pediatric and orthopedic rotations.

There are 2 major categories of congenital disorders of bone :

Wrong Bone

DYSOSTOSIS

- Abnormal condensation & migration of mesenchyme
- Genetic abnormalities of homeobox genes, cytokines and its receptors
  - Aplasia
  - Supernumerary digit
  - Syndactyly & craniosynostosis

DYSPLASIA

Misnomer

- Disorganized bone & cartilage
- Gene mutations that control development and remodeling
- Dysplasia here: not premalignant

CONGENITAL DISORDERS

DYSOSTOSIS

Abnormal formation of bone

- Abnormal condensation & migration of mesenchyme

At some point during bone maturation there was an abnormal concentration , condensation and migration of these (bone) cells .

The causes :

- Genetic abnormalities of homeobox genes which affect inflammatory cytokines, mediators and its receptors

Examples :

- Aplasia

Absence or failure of an organ or tissue to develop normally / Lack of synthesis of certain group of bones (no condensation & migration of mesenchyme) .i.e: 4 fingers instead of 5

- Supernumerary (Extra) digit

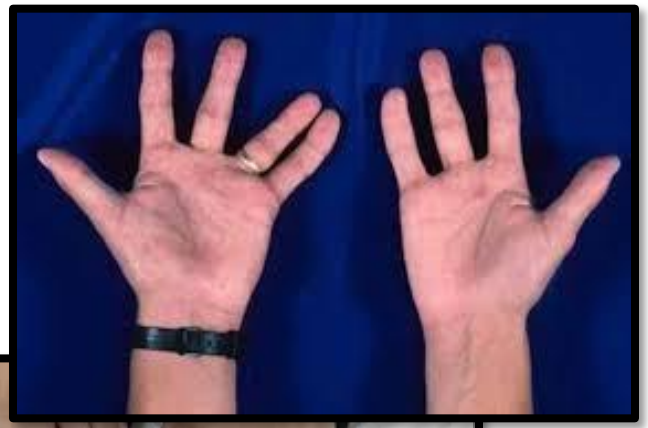
i.e: 6/7 fingers

- Syndactyly & More common than others , fusion of digit
- craniosynostosis Abnormal shapes and formation of skull

DYSOSTOSIS

Test yourself with these pictures :

1



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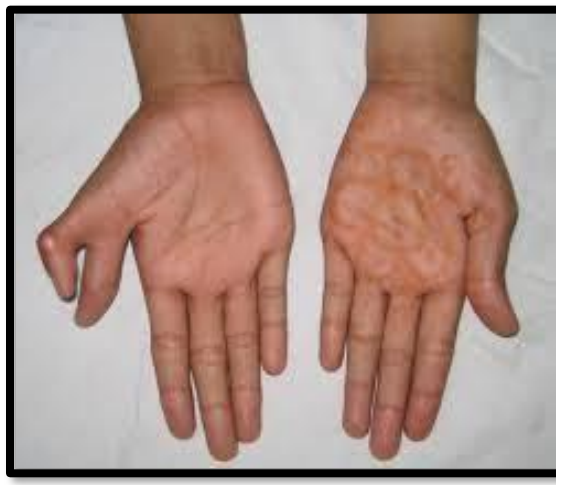

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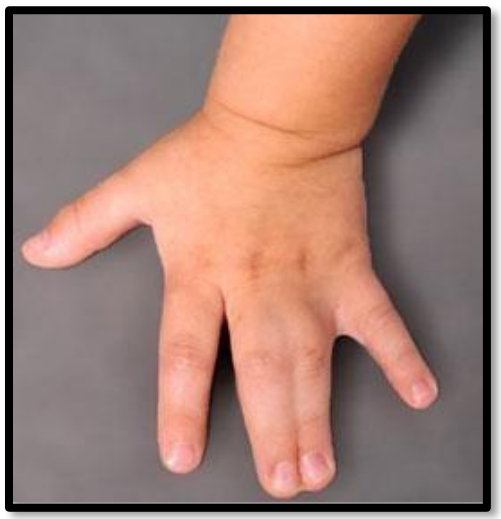

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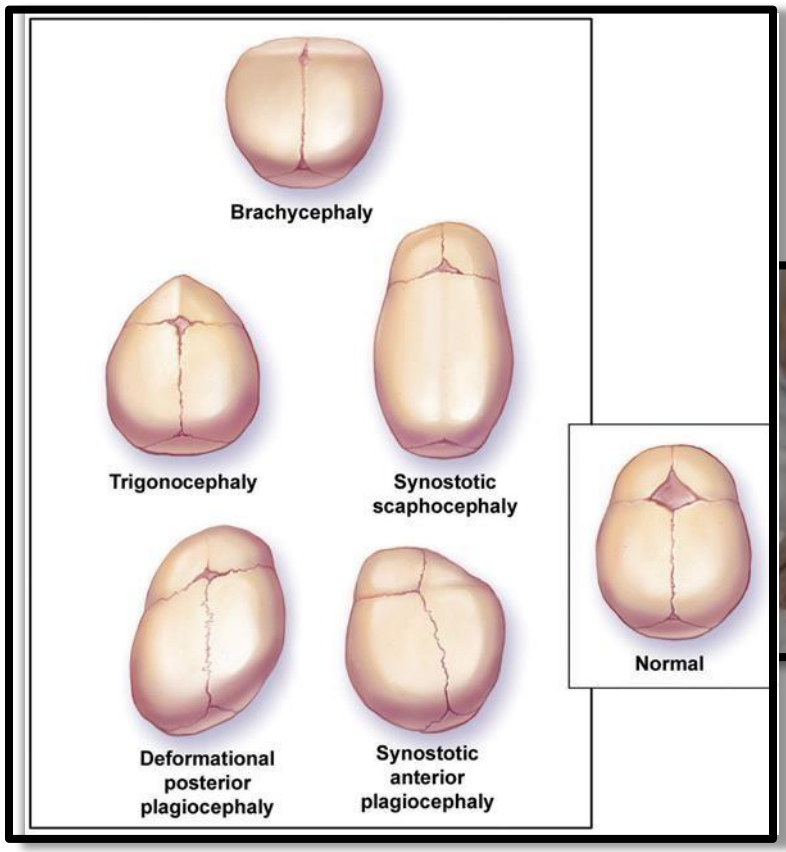


Do not memorize the details in this picture , just know the general concept

Answers for last slide :

1. Aplasia
2. Supernumerary digit
3. Syndactyly
4. Supernumerary digit & syndactyly
5. craniosynostosis

Lecture 2

DYSPLASIAS

- 1) Achondroplasia (dwarfism): most common

Achondroplasia is the most common cause of dwarfism .

Each disorder has mutation in separate genes .

- Mutations in FGFR3

  MEMORISE

  Fibroblast Growth Factor Receptor 3

FGRF3 is the major driver of Achondroplasia .

- No impact on longevity, intelligence or reproductive status

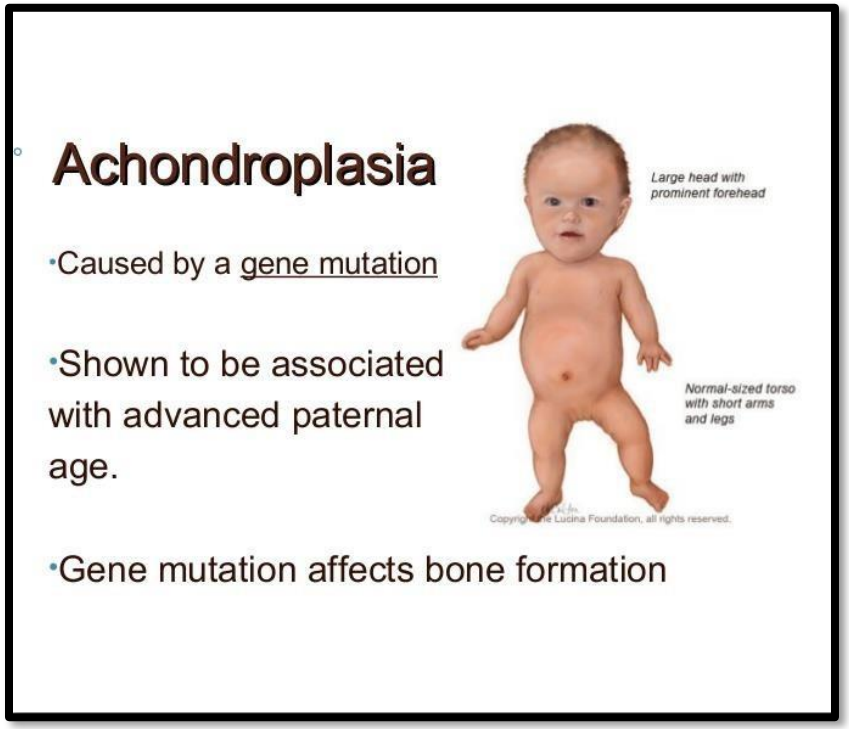
Longevity : life span or life expectancy (normal) .
They die from the same diseases as normal people

DYSPLASIAS

Features :

1.Big head (normal)

2.Short limbs



55- years old

Peter Dinklage: 48-years-old, married with 2 children from USA, New Jersey

"Game of thrones"

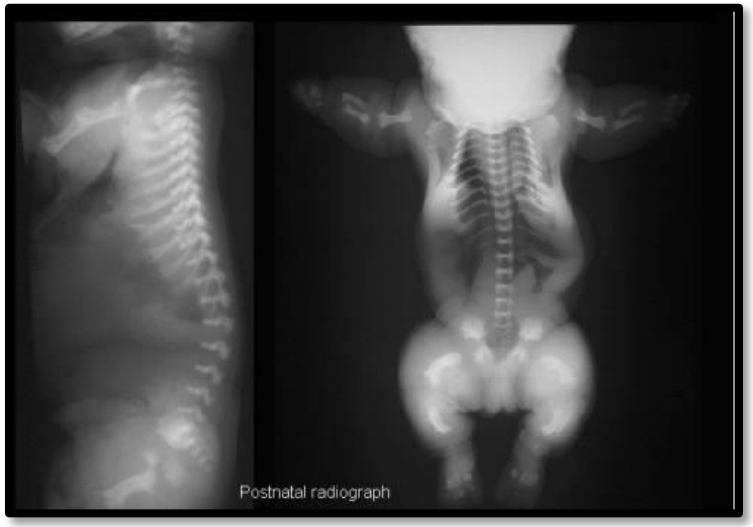
2) THANATOPHORIC DYSPLASIA

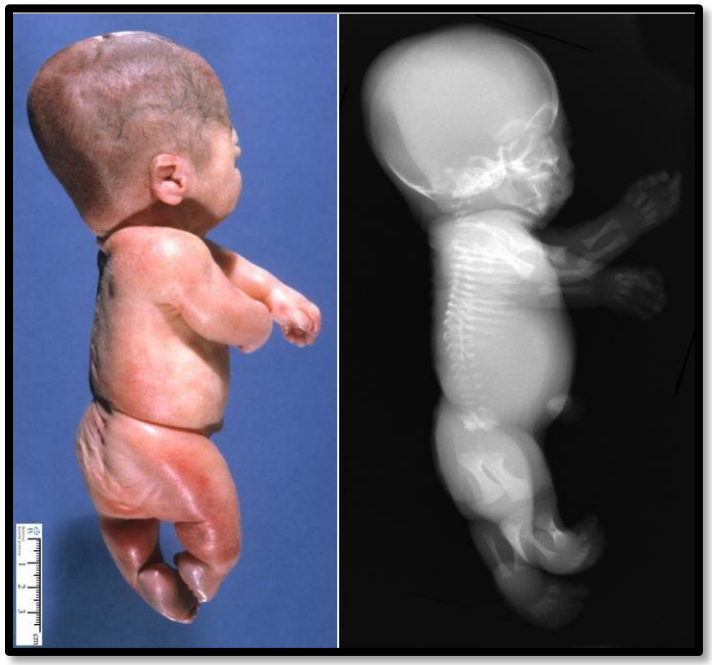
- Most common lethal form of dwarfism
- FGFR3 mutations (different location from Achondroplasia)
- Most patients Die at birth / in uteru or shortly after (small chest leading to resp. insufficiency)

Features:

1.Big head
2.Short limbs
3.Very severe restriction on the chest wall

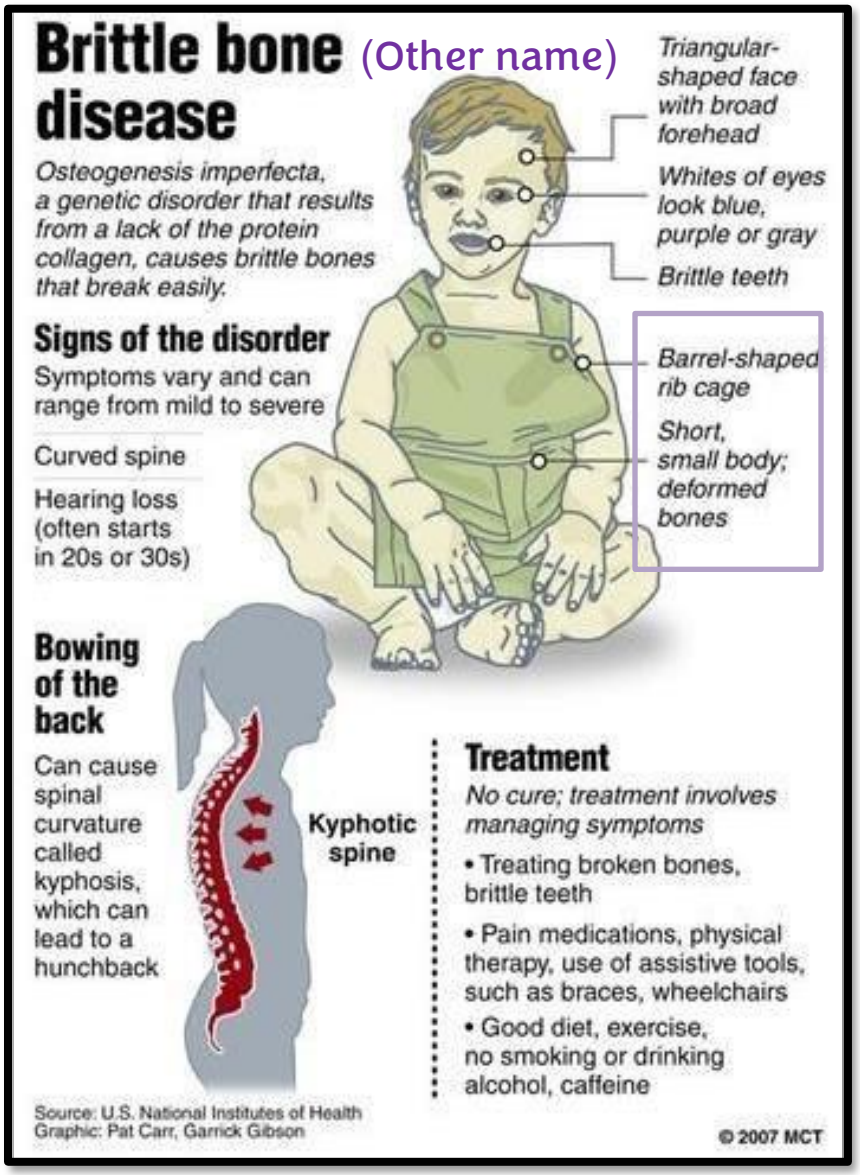
Chest compression & respiratory insufficiency





3) OSTEOGENESIS IMPERFECTA (OI)

Different features:



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
- Too little bone; fragility
- Blue sclera; hearing loss; teeth abnormalities Search why!

> Blue sclera is a clinical sign where the sclera (the white part of the eye) appears bluish due to its thinness and increased translucency.

- Type 2 (lethal)

  They don't survive beyond the first 6 months or 1 year of life

- type I (relatively normal life)

  They have proplems ,they break,but supportive therapy and management will keep them alive.

4) OSTEOPETROSIS

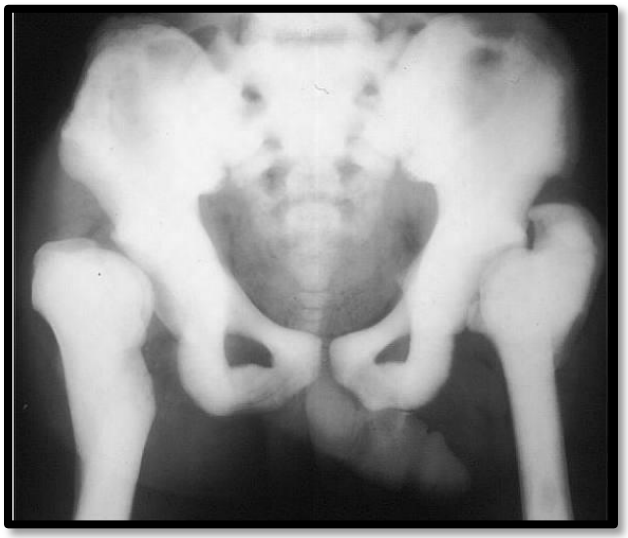
The opposite of osteoporosis , we will talk about later on

Other name:

- Marble bone disease “stone bone”(rigid)(group of disorders); rare

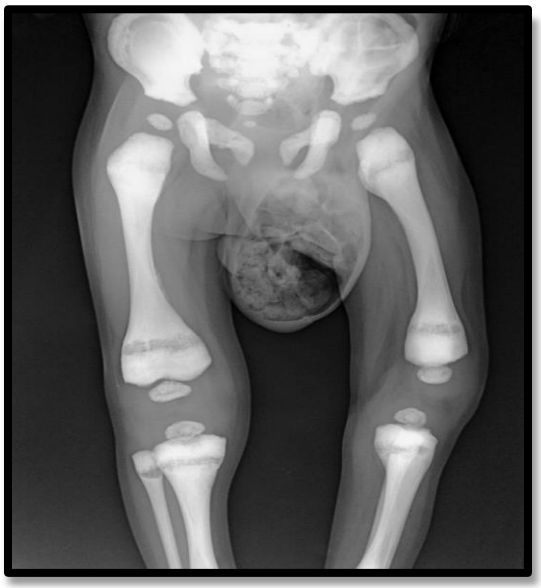
Basic etiology :

- Impaired osteoclast function: reduced bone resorption leading to diffuse sclerosis , diffuse formation of marble bone or stone bone.



All the bones are white .
There is no fatigue .

- Dx: X-ray



- Prone to multiple Fractures and leukopenia in severe forms

If the bone is closed ,even if the bone is open ,the hematopoiesis will be impacted .these are severe forms of leukopenia ,also may lead to immune deficiencies and they will be exposed to more opportunistic bacterial infection.

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

It is essential to distinguish between osteopenia and osteoporosis, which is done by measuring bone mass, Each age has a mean of bone or bone density mass:

Bone less

- **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**
- **Osteoporosis classification : Generalized (much more common) or localized**

✓ In some cases, osteoporosis may affect only a specific region of the body, such as the right upper limb. This can occur due to a previous injury, fracture, trauma, or prolonged immobilization, leading to decreased bone density in that area while the rest of your bones are completely ,This condition is referred to as localized osteoporosis.

Another classification:

PRIMARY OSTEOPOROSIS

Much more common
Increasing with senile (aging) s
Usually occurs in postmenopausal women ,especially who has been pregnant many time

All of us, after the age of 40, we will start having a certain element of osteoporosis

SECONDARY OSTEOPOROSIS

Much less common
Caused by:Hyperthyroidism, malnutrition, steroids

They stimulate the activation of osteoclasts leading to secondary osteoporosis.

Factors:

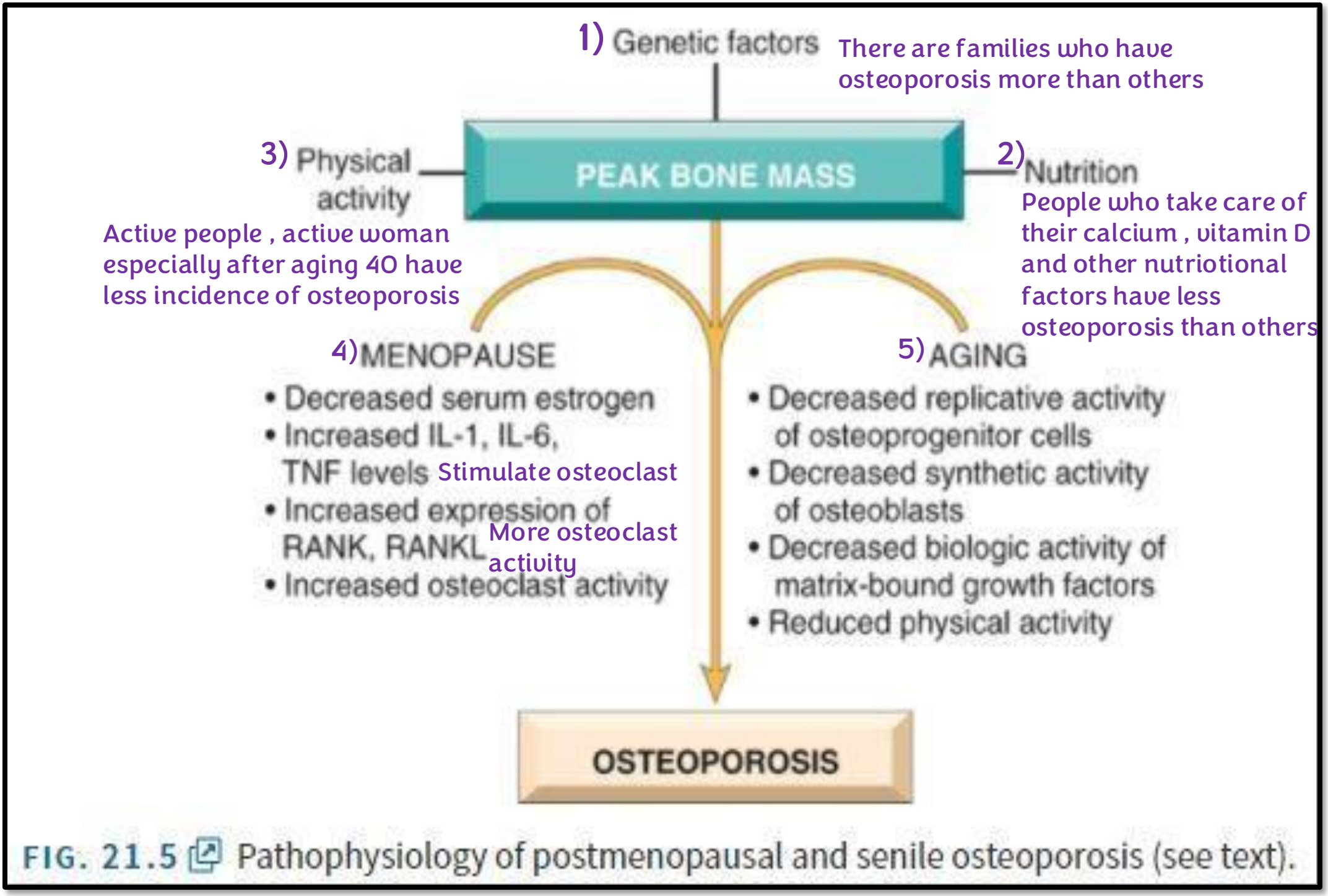


FIG. 21.5 Pathophysiology of postmenopausal and senile osteoporosis (see text).

Normal vertebra

Severe osteoporotic vertebra

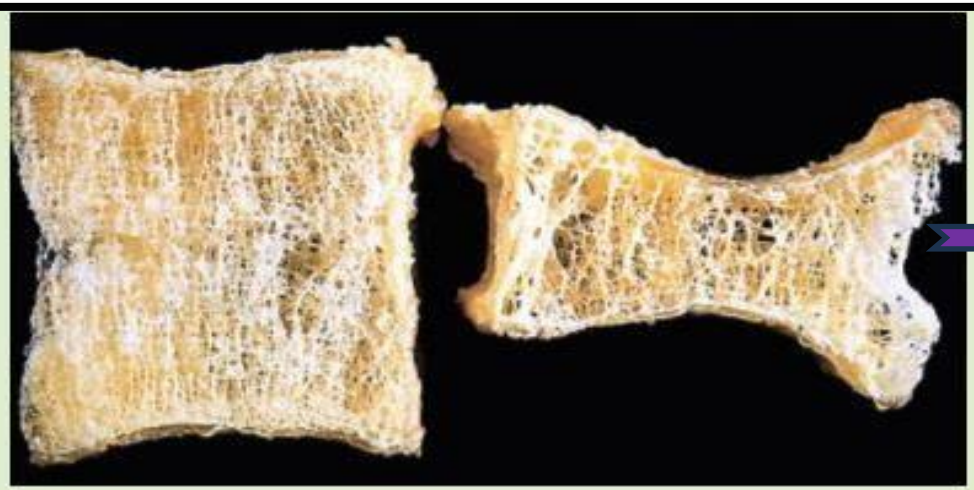


FIG. 21.6 Osteoporotic vertebral body *(right)* shortened by compression fractur.

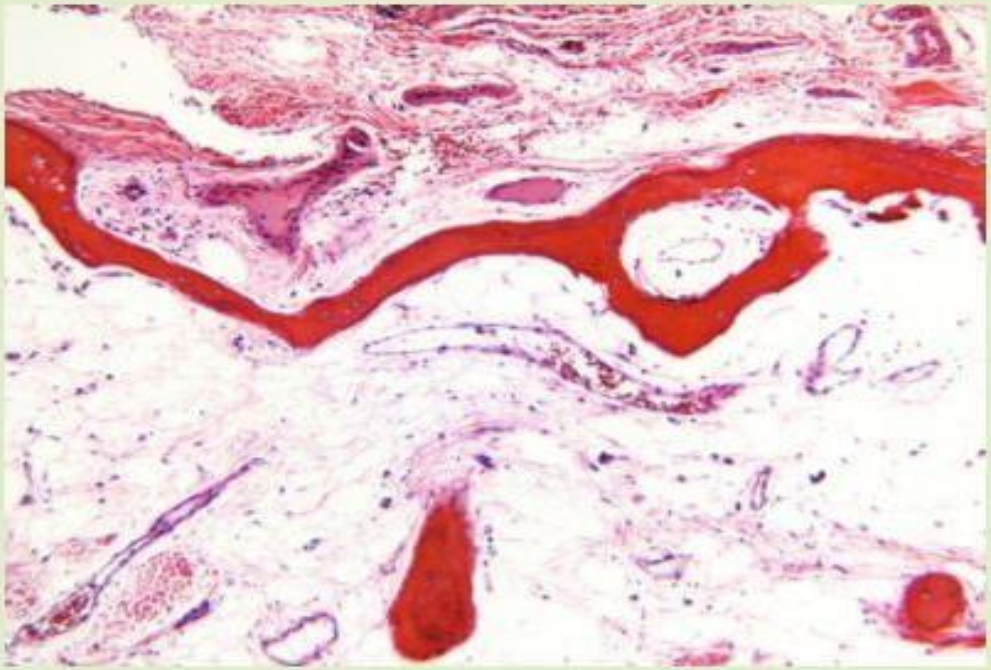


FIG. 21.7 In advanced osteoporosis, both the trabecular bone of the medulla *(b.*

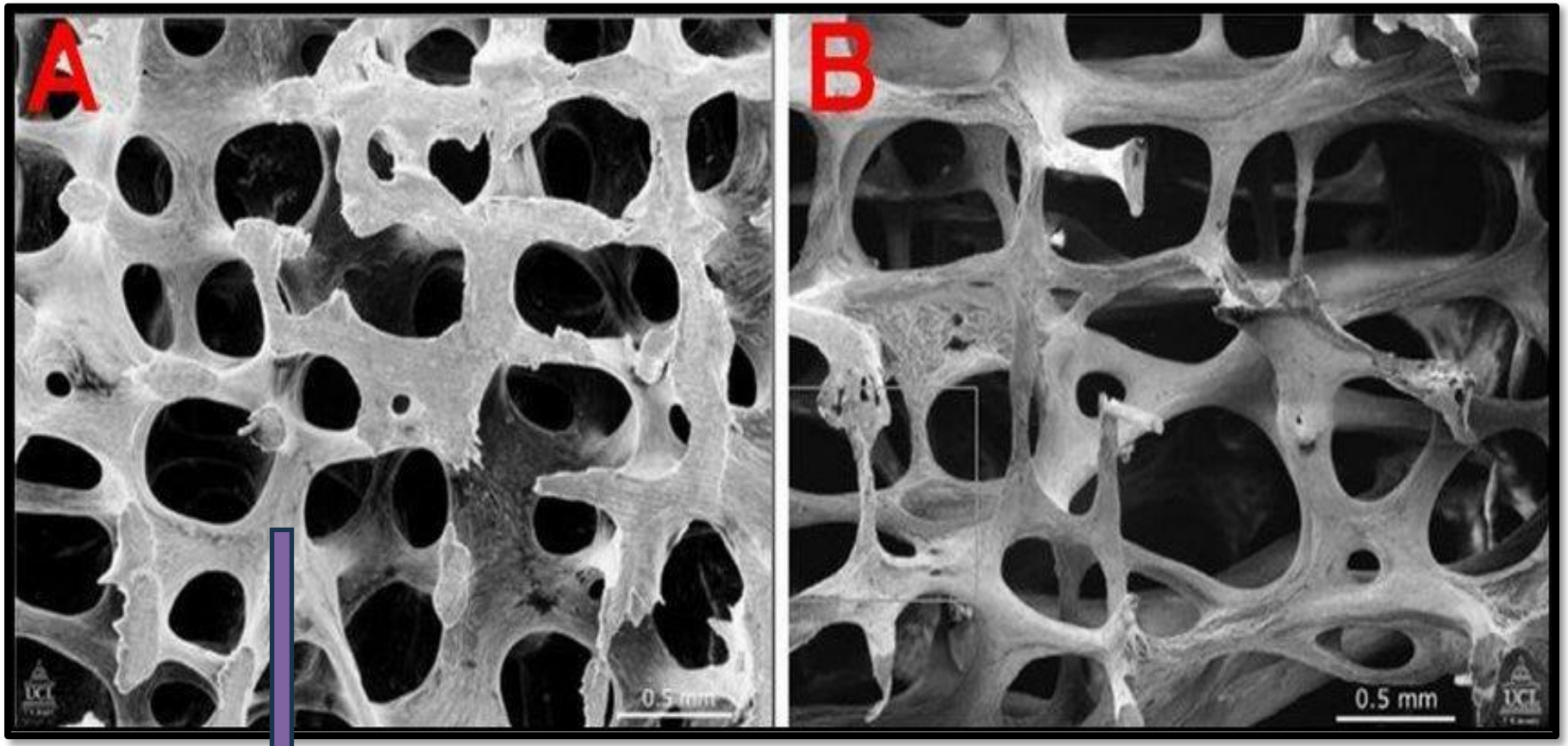
- A gross picture of an osteoporotic vertebra cut in the middle
- Compression fracture in the vertebra → one of the severe complications of osteoporosis

In advanced osteoporosis →
- Decreased number of trabecular bone
- Increased matrix

Normal bone

Osteoporosis

Taken by scanning microscope

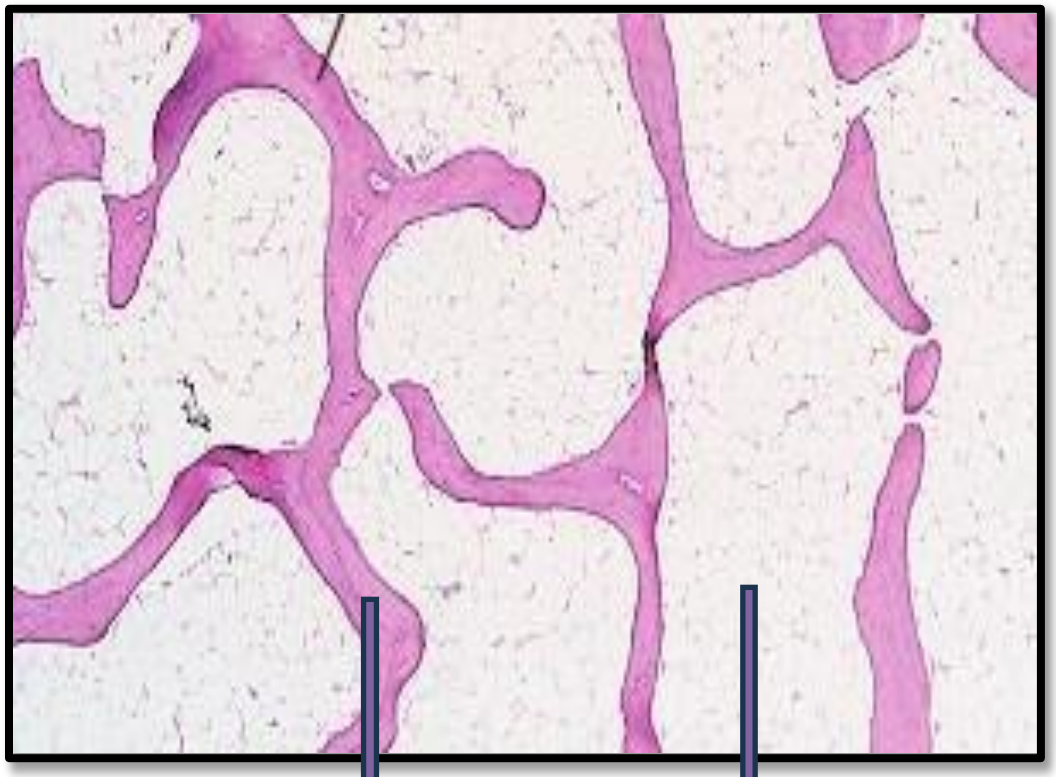


*Thick trabeculi

*Thinner trabeculi
*Fractured
●Very painful and associated with comorbidities

لَا إِلَهَ إِلَّا أَنتَ سُبحانكَ إِنِّي كُنتُ مِنَ الظَّالِمِينَ

Normal bone



Bone trabeculi

Matrix

Osteoporosis

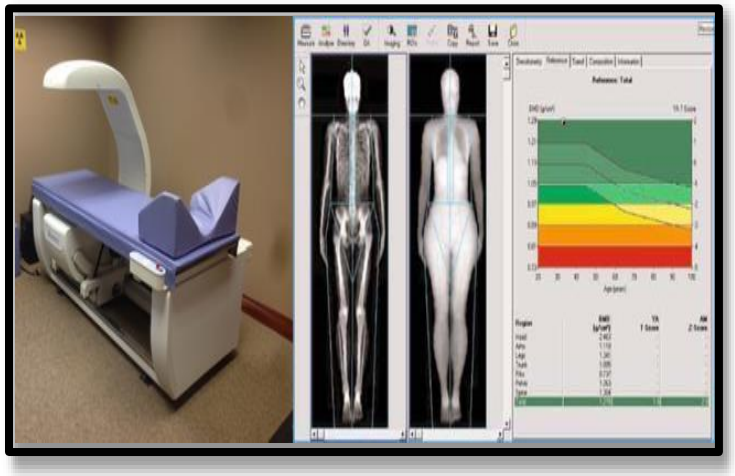
*Thinner trabeculi
(more abundant matrix)
*Multiple microfractures

صَلّ على من نرجُو شَفاعَتَهُ

OSTEOPOROSIS CLINICALLY

- **Vertebral fractures** especially compression fractures
- **Femur and pelvic fractures: immobility, PEs**(pulmonary embolus)**, 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 embolus (PE) (Silent killer) is a blockage of a pulmonary artery by a blood clot usually caused by deep vein thrombosis (DVT).



PREVENTION AND TREATMENT

We mainly care about prevention not treatment

- Exercise
- Calcium especially females approaching menopause and vitamin D
- Bisphosphonates: (Drugs work on) reducing osteoclast activity and (by) induce its apoptosis
- Denosumab (a drug): anti-RANKL; works on blocking osteoclast activation (new expensive potent)
- Hormones (estrogen)Exogenous estrogen replacement therapy.

Side effects :risking DVT,stroke and endometrial hyperplasia

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			

Additional Resources:

1. **OSTEOGENESIS IMPERFECTA**
2. **Achondroplasia**

رسالة من الفريق العلمي:

ذَكّر نَفسَكَ في كُلّ حِينٍ أنّ غايةَ السّعيِ ومُنْتَهَاهُ:
قَبرٌ بِلا وَحْشَةٍ، مُستَراحٌ تحتَ ظِلّ العَرشِ، ومِقعَدٌ
في جَنّةِ الخُلدِ، ثُمّ على الدُّنيا السّلام.

ترضى, اللهم إني أسألك نفسًا مطمئنة
بقضائك و تقنع بعطائك و تؤمن بلقائك

ربي إني أحاول فأعني.