MSS

PATHOLOGY

 # 2

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METABOLIC DISORDERS

Osteopenia: decreased bone mass (1-2.5 SD below the mean).

Osteoporosis: severe osteopenia; > than 2.5 SD below the mean with increased risk for fractures.

Osteoporosis is a very common disease and very expensive on health care systems. Notice that the definition of osteoporosis is designated by numbers, so if the density of the bone is 1-2.5 SD below the mean, this is **Osteopenia** and if the density is more than 2.5 SD below the mean, the case is **Osteoporosis**.

For example: Marry is 45 years old, the bone density of the neck of femur is 2.2 and the mean **(for that age, sex, affected bone)** is 3.3, so she is below the mean by 1.1 SDs, so she has **osteopenia**.

Classifications of osteoporosis:

- **Primary or generalized (much more common).**
- **Secondary or localized.**

PRIMARY OSTEOPOROSIS	SECONDARY OSTEOPOROSIS
Much more common	Much less common
Senile (aging) & postmenopausal	Hyperthyroidism, malnutrition, steroids

So, when we talk about osteoporosis, we mean **generalized**, **postmenopausal**, **primary osteoporosis**. Secondary osteoporosis is much less common (less than 5%).

Very important

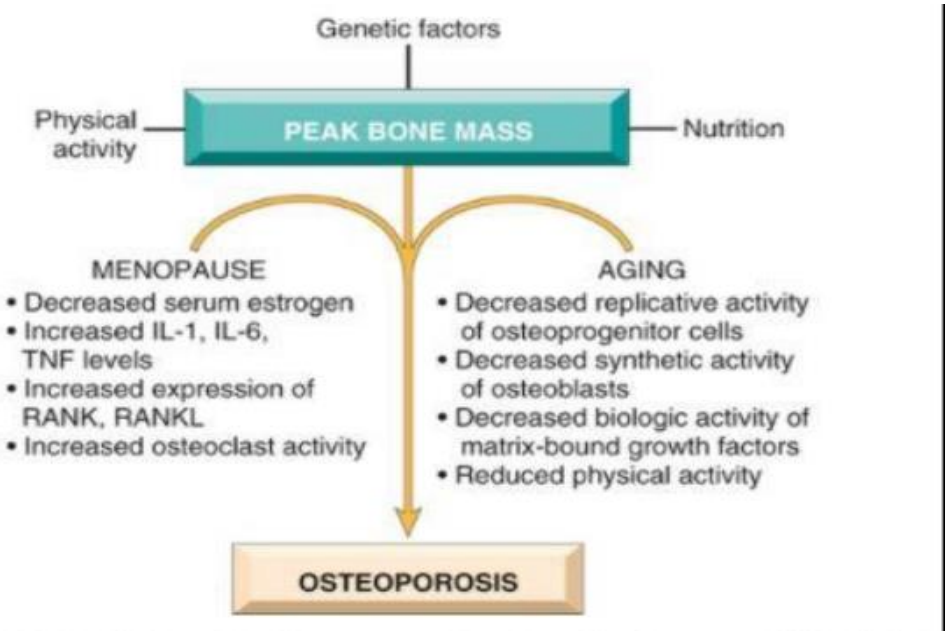


FIG. 21.5 Pathophysiology of postmenopausal and senile osteoporosis (see text).

Pathogenesis of osteoporosis **(primary-generalized)** is **multi-factorial**, there are families that have more risk of osteoporosis than others, they have **genetic predisposition** factors. **Nutritional factor** is more common in areas where females deliver a lot of babies and they do not have proper nutrition specially calcium and diary products. **Physical activity** also plays a huge role in developing osteoporosis, patients who doesn't move or exercise are at a higher risk of developing osteoporosis.

We said before that generalized osteoporosis is associated with **aging**, so why is that?

Multiple mechanisms explain that. **First**: the replicative activity of osteoprogenitor cells **(which form osteoblasts)** is decreased with aging. **Second**, the synthetic activity of osteoblasts (cytoplasmic protein synthesis activity) is decreased with aging. In addition, the biologic activity of the matrix bound growth factors and mediators is decreased. And for sure adult's physical activity decreases. So, this is how **aging** impacts bone density.

Generalized primary osteoporosis is more common in females around and after the **menopausal period**. At this period serum estrogen decreases, and we talked before about estrogen's relationship with RANK ligand and osteoplastic activity. In addition, with menopause, some mediators increase specially **IL-1**, **IL-6** and **TNF** which increase the activity of osteoclasts. Moreover, it was proven that **RANK** and **RANK ligand** which are responsible of osteoclasts maturation (in monocyte macrophage system) are also increased at menopause.

And that's why management of osteoporosis is not easy and expensive, so prevention is important.

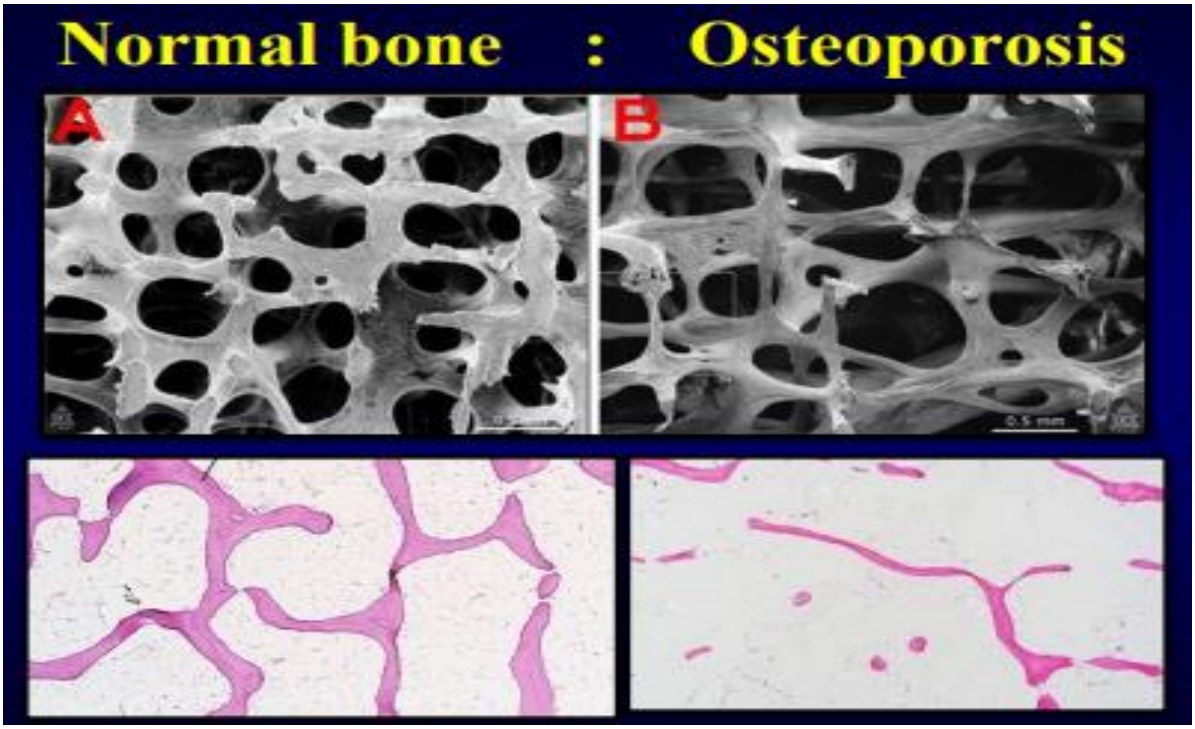
. 21.6 Osteoporotic vertebral body *(right)* shortened by compression fractur.

Vertebral body with compression fraction (multiple micro-fractures)

Severe osteoporosis and the bone density is very low, so when the patient stands up a compression fracture will happen

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

The red parts are the bone trabeculae and notice how it's obviously decreased under microscopic examination.



- *Biopsy is not a common diagnostic way to confirm osteoporosis, there is a device that can measure bone density.*

OSTEOPOROSIS CLINICALLY

Patients with osteoporosis visit the doctor with:

- **Vertebral fractures (specially compression fractures because the bone is very weak, and the density is very low).**
- **Femur and pelvic fractures: immobility, PEs, pneumonia (40-50K death/yr in USA)" those are the bones that have the maximum load"**

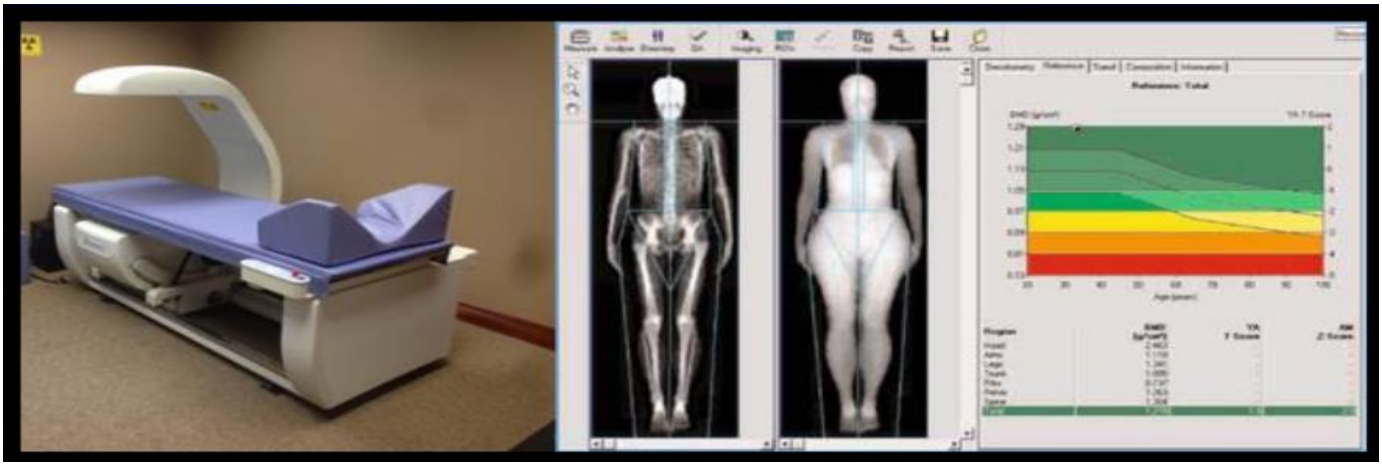
Suppose that a 70-year-old patient, has 10 sons and didn't take calcium or followed any preventive methods during pregnancy, has severe

osteoporosis (3.5 SDs below mean) and fracture of the neck of femur. In hospital she will undergo internal fixation (replacing the head and neck of femur with prosthesis). And she will stay in the hospital **at least** 2 weeks.

Longer stay in hospital will increase the chance of getting hospitalized associated complications. She will be immobilized which lead to deep vein thrombosis in lower limb. In addition, she may develop PEs (pulmonary embolism تجلط شرايين في الرئة) which will kill her.

Note: pneumonia is one of the most causes of death in hospitalized patients.

- **Diagnosis: special imaging technique, bone mineral density (BMD scan): dual-energy X-ray absorptiometry (DXA or DEXA scan) or bone densitometry.**



This is the **DXA scan** (جهاز فحص هشاشة العظم), each bone has a specific number, and the curves above are per age, per sex (females estimates are different from males) so as a doctor, you have to look at the number, then compare it with the mean of the normal bone. Then you decide whether it's within 1-2.5 SDs less than the mean **(osteopenia)** or more **(osteoporosis)**.

PREVENTION AND TREATMENT

It's much better to prevent osteoporosis rather than dealing with it after diagnosis (sometimes it takes years to regulate calcium and vitamin D levels) and it's hard to start physical activity specially if the patient is elderly.

- **Exercise**
- **Calcium & vitamin D**

- **Bisphosphonates (medication): reduce osteoclast activity and induce its apoptosis**

This medicine reduces osteoclast activity by inducing apoptosis which decreases impact of bone resorption. Nowadays, this medication is not being used a lot, that a new, very expensive, potent medication was made **(Denosumab)**.

- **Denosumab: anti-RANKL; blocking osteoclast activation**
- **Hormones (estrogen): risking DVT and stroke**

HRT (hormone replacement therapy) to treat postmenopausal symptoms. However, estrogen can develop some complications like **DVT** (deep venous thrombosis) which is very difficult, critical, and dangerous. DVT is one of the high-risk factors for pulmonary embolism. In addition to that, HRT (especially if estrogen is given alone, not combined with another hormone) increases risk of hypertension and strokes.

So, when you prescribe a drug for menopausal symptoms, **do not give estrogen alone**, give it with **progesterone**.

This method of treatment is much less common today.

https://my.clevelandclinic.org/health/treatments/15245-hormone-therapy-for-menopause-symptoms

you can visit this link to read more about HRT and why we should combine estrogen with progesterone.

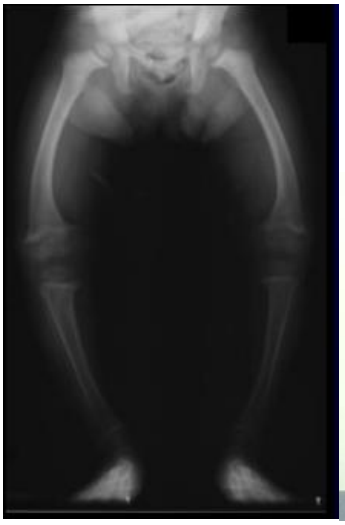
RICKETS & OSTEOMALACIA

Those two **vitamin D related diseases** are not commonly seen those days, they are defined by vitamin D deficiency, either the quantity of it is low, or it's not effective.

We are supposed to do not see these cases today.

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

Vitamin D is responsible of bone mineralization, it enters the calcium to bone, so if vitamin D is deficient, mineralization of bone will be decreased producing weak bone. Patients will suffer from pains, microfractures, their teeth are not formed well, skeletal deformities, more bone fractures and the growth is not normal.



Bowing of long bones تقوس العظام الطويلة

Remember, we shouldn't see similar cases nowadays, because vitamin D deficiency is easily diagnosed and easily treated.

Usually, newborns undergo vitamin D screening.

HYPERPARATHYROIDISM (HPT)

The parathyroid glands are 3-4 pea-sized organs found posterior to thyroid embedded in subcapsular area of thyroid gland, they secretes parathyroid hormone in response to a low blood calcium, which plays a key role in regulating the amount of calcium in the blood and within the bones.

Hyper function of parathyroid gland functions leads to hyperparathyroidism.

Primary (في الغدة نفسها) hyperparathyroidism means the problem is in the parathyroid gland itself **(hyperplasia "increase in the number of cells or tumor "benign or malignant")** adenomas and hyperplasia are much more common than carcinomas. Those patients have high serum calcium and serum phosphorus usually low.

So, if a scenario says that a patient has **high calcium** and **low phosphorus** in serum, you should know that it's **primary hyperparathyroidism**.

So, you diagnose **primary hyperparathyroidism** if you find parathyroid hormone in serum and the **problem** is in the **parathyroid itself**.

For secondary and tertiary hyperparathyroidism, the problem is not in the parathyroid itself. Patients with chronic renal failure always suffer from low levels of calcium in serum. Hypocalcemia lead to positive stimulation of parathyroid hormone causing hyperplasia.

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

HPT must be diagnosed and treated quickly, we shouldn't see long term HPT which is not discovered or treated. However, if this happened, all calcium will leave bone to serum causing bone demineralization and osteoporosis which means more bone fractures.

When bone trabeculae are very weak, they cause multiple microfractures then bleeding, and if a stress was applied to that area, it causes bleeding fractures making a cyst.

Brown tumor: cystic places of blood, osteoporotic bone, weak bone trabeculae and full of blood and looks like a tumor. So, the name (brown tumor) is a wrong name, it's not a neoplasm, it just looks like a mass.

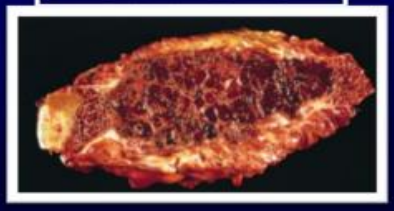
Osteitis fibrosa cystica (OFC): in this scenario, there is no inflammation **(itis)**, it's an abbreviation describing severe untreated hyperparathyroidism of the bone (so weak and unmineralized). Other names: osteitis fibrosa, osteodystrophia fibrosa and von Recklinghausen's disease of bone.

Don't confuse between von Recklinghausen's disease of bone and **Recklinghausen's disease** which is **neurofibromatosis type I**.

HPT CLINICALLY

OSTEOPOROSIS

BROWN TUMOR



OSTEITIS FIBROSA CYSTICA

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.

اِسْتَعِنْ بِاللّٰهِ وَلَا تَعْجَزْ

"Seek ***Allah*** and ***don't*** fail"