MSS

Sheet no.3

Pathology

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***In this sheet, we are going to take some metabolic disorders that impact the bone, they will be explained further more during our future study.**

RICKETS & OSTEOMALACIA

- These diseases are related to Vitamin D, either the quantity is deficient or the metabolism is abnormal so that the impact is low.

  - **Vitamin D deficiency**

    -Normal vitamin D level is around 30 ng/mL, below 30 means that it is deficient/insufficient.

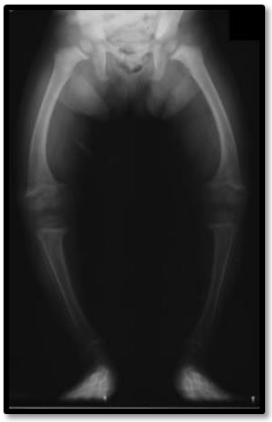
    -Nowadays, vitamin D is involved in everything; carcinogenesis, diabetes...and the treatment for them is by taking vitamin D (to prevent infections, control BP, etc.)

  - **Abnormal metabolism of vitamin D**

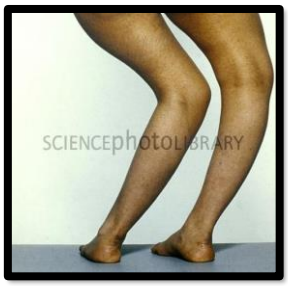
If this occurs in:

- **Children**, it's called **Rickets**
- **Adults**, it's called **Osteomalacia**
- The impact: Decreased or impaired mineralization of bone, unmineralized matrix.
- **Consequences**:

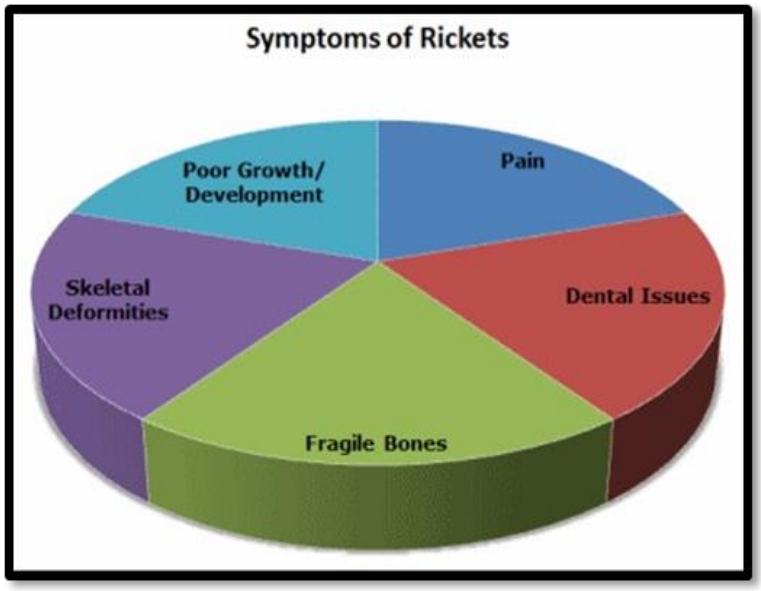
  1- Increase risk of fractures (the bone trabeculae are not strong enough and fragile).
  2- Pain because of microfractures.
  3- Dental issues.
  4- Deformities in the skeleton (the patient cannot stand up because weak bones won't be able to hold your body; bowing of the legs).
  5- Poor growth & development.



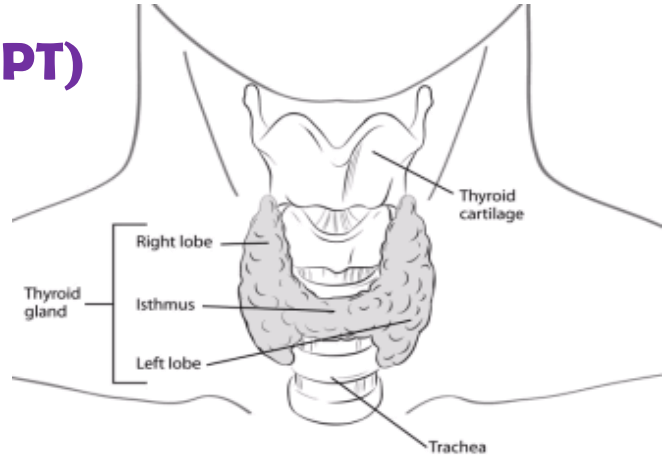
Bowing Legs



Softening of the bone



HYPERPARATHYROIDISM (HPT)



notes:

-We have one thyroid gland which has a right lobe and a left lobe, connected together by isthmus.

-We have 4 parathyroid glands; upper right, upper left, lower right & lower left.

-Parathyroid gland secretes **P**ara**T**hyroid **H**ormone (**PTH**) which stimulates calcium to exit the bone and enter the serum to maintain normal calcium blood levels (8-11mg/dL).

Hyperparathyroidism is where you have <u>increased function or quantity of PTH</u>, which stimulates osteoclasts to increase bone resorption.

Calcium levels are affected.

Hyperparathyroidism Classification

You need to memorize this table
معلش سهل

	Primary	Secondary	Tertiary
Pathology	Hyperfunction of parathyroid cells due to hyperplasia, adenoma or carcinoma.	Physiological stimulation of parathyroid in response to hypocalcemia	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. Cinacalcet (a drug) can be considered in those not fit for surgery.	Treatment of underlying cause.	Usually, cinacalcet or surgery in those that don't respond

➢ Primary:

The disease is in the parathyroid gland itself, it's either:

- **Adenoma** (benign neoplasm) … too much PTH with no control, feedback loops (positive/negative) are not working on the tumor.

Parathyroid hormone is mainly controlled by the negative feedback of calcium levels in the blood to the parathyroid glands. Low calcium levels in the blood stimulate parathyroid hormone secretion, whereas high calcium levels in the blood prevent the release of parathyroid hormone.

- Enlargement (**hyperplasia**) of two or more parathyroid glands causes overproduction of the hormone.
- **Carcinoma**

*__Multiple Endocrine Neoplasia syndromes (MEN syndromes)__, type I (mutation in chromosome 11), type II (in chromosome 10) …. Are the presence of multiple tumors in different organs in the same patient at the same time.
We will take them in the near future, just take a general idea.

➢ Secondary

Most of the time these are due to prolonged hypocalcemia for any reason that affects the gland's function such as:
• **chronic renal failure** • **vitamin D deficiency**
-Hyperplasia happens in the 4 parathyroid glands.
-Sometimes the patient has tolerance so that calcium level isn't as high as the primary but the phosphate here is high.

➢ Tertiary

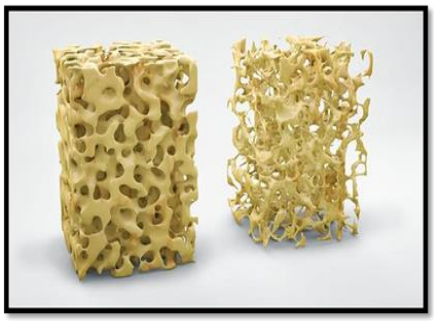
-Complicated and a little bit hard to examine clinically.

-Both calcium and phosphate serum levels are high.

HPT CLINICALLY

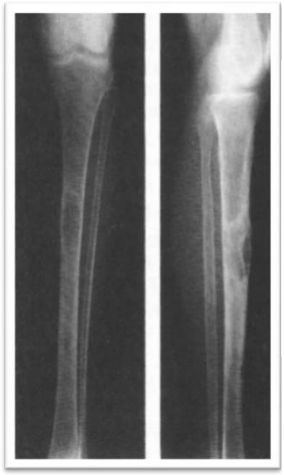
- The following 3 complications are due to <u>prolonged and not treated severe HPT</u>.
- It's one of the causes of **secondary osteoporosis** as mentioned in the previous sheet.
- **Brown tumor** is not a neoplasm but because these patients have multiple fractures and weak trabeculae
  fracture → bleeding → organization and so on, after a couple of months there will be a **sac of multiple cysts filled with blood** and reaction around it in the bone itself.
  *we can easily remove it because it's not a true tumor.
- **Osteitis Fibrosa Cystica (OFC)** A severe case, the mechanism of developing the brown tumor will make a recurrent fibrosis and cyst formation in all the bone, easily identified clinically.

- Also known as **osteitis fibrosa**, **osteodystrophy fibrosa**, and **von Recklinghausen's disease of bone** (not to be confused with von Recklinghausen's disease, neurofibromatosis type I).



Osteoporosis

Brown tumor



OFC

Summary

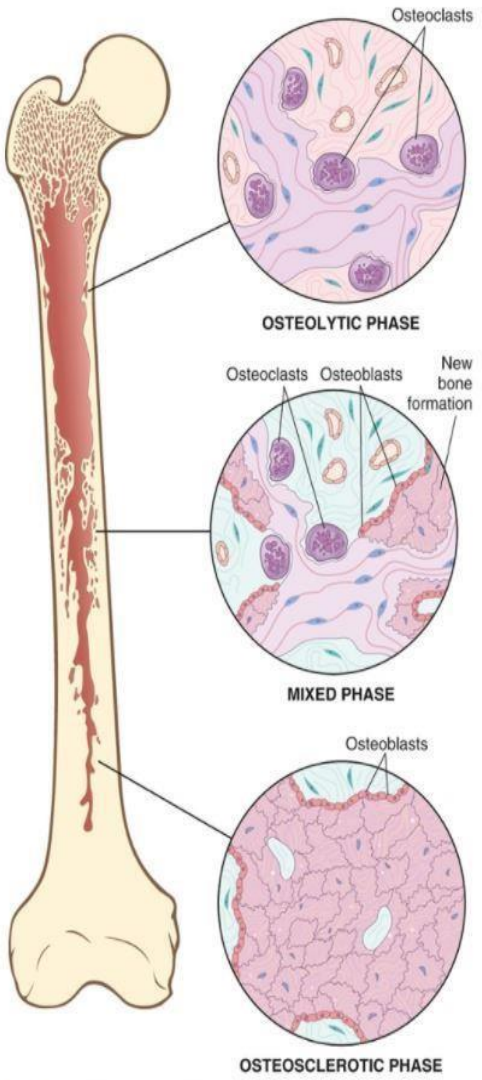
Metabolic Disorders of Bone

- **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.

PAGET DISEASE OF BONE (OSTEITIS DEFORMANS)

***Important**

- A chronic bone disorder with a lot of **bone remodeling**, excessive bone resorption and growth which leads to deformities and potential fractures.
- It's actually a degenerative bone disease rather than osteoarthritis.
- The exact reason is unknown.
- Increased badly, **abnormal formed bone** structure.
- **3 phases**:
  -lytic: osteoclast is dominant.
  -sclerotic:(plastic) osteoblast is dominant.
  -mixed: lytic & sclerotic.
- Easily diagnosed by **x-ray**.
- 1% in USA, not all of them are severe; geographic variation.
- Genetic and environmental factors (we don't know the details of it yet).
- 50% of familial Paget and 10% of sporadic have **SQSTM1 gene mutations** which is responsible of (+RANK…. stimulation & -OPG (osteoprotegerin) …inhibition)
- Viruses (measles and RNA viruses)??
  they are blamed but still there's no evidence yet.
- **Mosaic pattern of bone.**

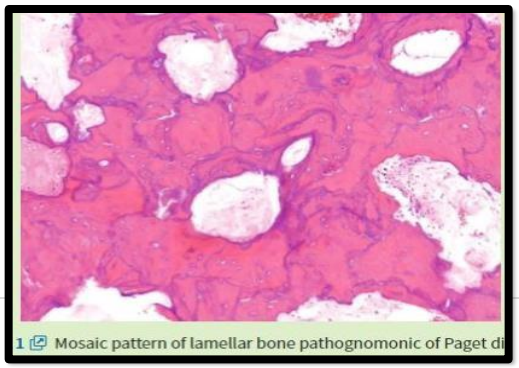


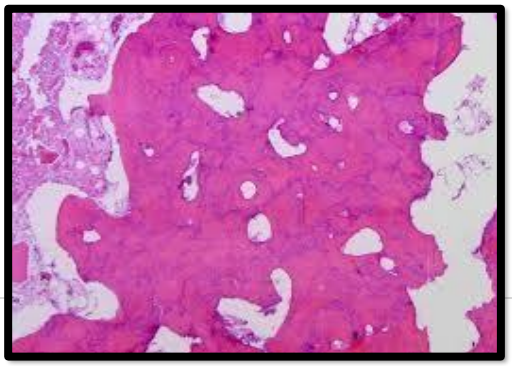
Too many osteoclasts resorbing the bone here so this is the **osteolytic phase.**

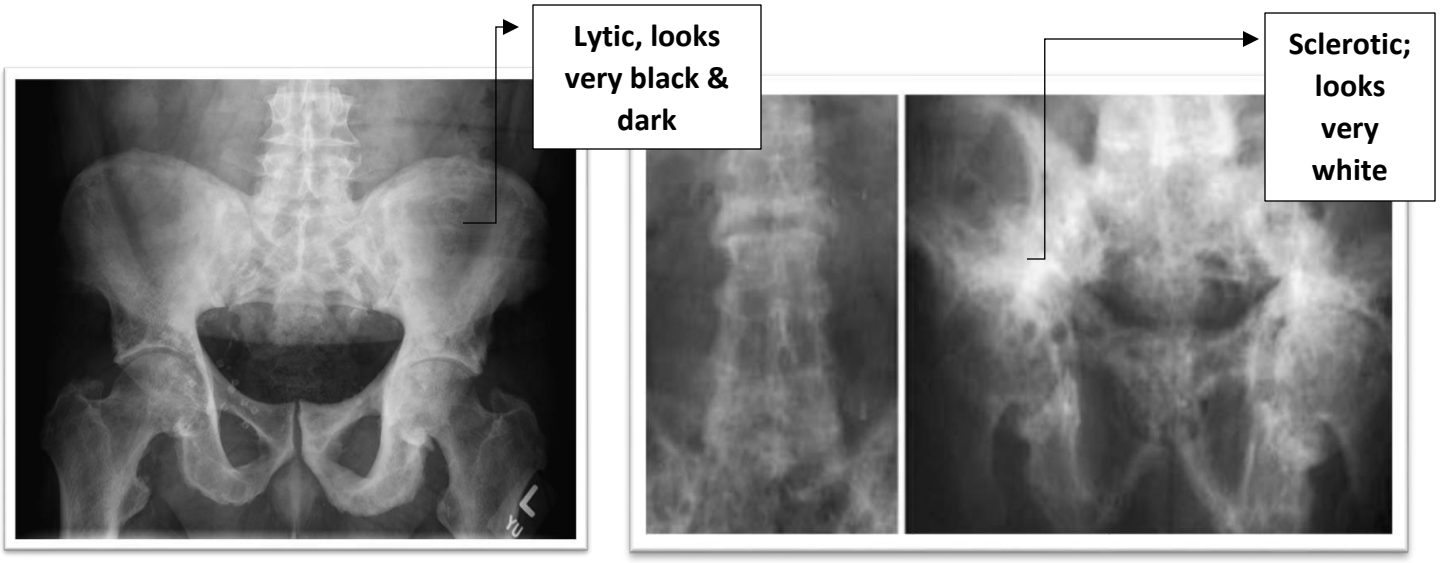
Both osteoclast and osteoblasts are predominant so this is the **mixed phase**.

Too many osteoblasts here, forming the bone in an abnormal way so this is the **osteosclerotic phase**.

- ✓ All this bone is abnormal, the risk is fractures of bone.
- ✓ Higher risk to develop osteosarcoma… (secondary osteosarcoma: arising on the background of abnormal bone).
- ✓ This is lamellar bone, notice the neat organization.
- ✓ **Mosaic pattern of bone** which is a characteristic of Paget's bone disease (under the microscope):







- ✓ These x-rays show abnormal bone, Paget's disease.
- ✓ Cancer can be lytic metastasis (more common) or plastic metastasis.
- ✓ It's very rare to take a core biopsy of bone because this way is just to evaluate the presence or absence of Paget's disease.
  *Normally, nice lamellar bone with equal distribution of matrix and bone.

PAGET CLINICALLY

- ➢ 85% **polyostotic** (affecting 2 or more bones).
  15% **monostotic** (affecting only 1 bone; only the right pelvis or only the femur and so on).
- ➢ Axial skeleton more affected (vertebral body, pelvis and the proximal femur are the most commonly involved).
- ➢ Most cases are **mild and asymptomatic.**
- ➢ Pain: microfractures or nerve compression (which is worst).
- ➢ Severe Paget's of the skull is called: **Leontiasis ossea** (lion face); **platybasia** (invagination of skull base); secondary osteoarthritis; fractures; osteosarcoma (1%).
- ➢ Clinically if Paget's was suspected especially if it wasn't mild, usually it's associated with **increased serum alkaline phosphatase while the calcium and phosphorus are normal**, a pathognomonic/ characteristic of Paget's and there are NO PTH or Vitamin-D problems.

- DX: **x-ray.**
- It's **not a neoplastic disease** but patients are at a higher risk of osteosarcoma.

Leontiasis ossea (lion face); platybasia

****A final note is that ALL these diseases are preventable & treatable.**

Multiple Choice Questions

1- A 4-year-old girl is brought to the pediatrician's office. Her mother says that she noticed that her legs seem unsteady and bowed when the girl stands. She noticed this for the first time 2 months ago. What is the most likely diagnosis?

(A) Osteopenia

(B) Osteoporosis

(C) Paget disease

(D) Rickets

2- A 55-year-old man presents with pain in the left arm. Laboratory studies show elevated serum levels of calcium and parathyroid hormone. An X-ray of the left arm reveals multiple small bone cysts and pathologic fractures. Biopsy of the affected bone discloses numerous giant cells in a cellular and fibrous stroma. The patient undergoes removal of a parathyroid adenoma. Which of the following best describes the pathogenesis of bone pain and pathologic fractures in this patient?

(A) Enhanced osteoblast activity

(B) Impaired mineralization of osteoid

(C) Increased bone resorption

(D) Increased mineralization of bone

(E) Osteoporosis

3- A patient was diagnosed with renal failure in early stage. Parathyroid glands are noticed to be stimulated with no hyperplasia. Which if the following may be found in serum?

(A) High levels of Alkaline phosphatase

(B) Low levels of Phosphate

(C) Low levels of Calcium

(D) Low levels of parathyroid hormone (PTH)

Answers: 1) D 2) C 3) C, this is secondary hyperparathyroidism

Best of Luck