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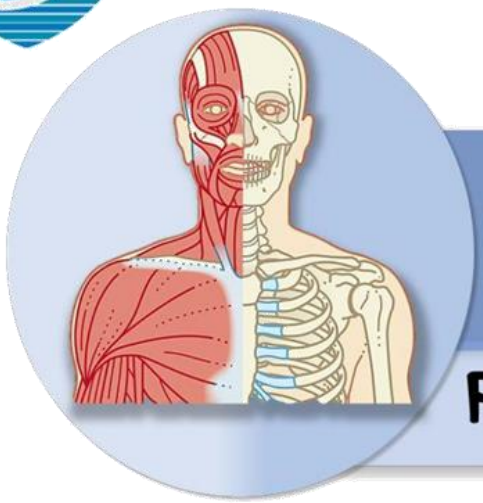

MSS system

Pathology

◉ Sheet ○ Slide

Number:	#3
Done by:	Awaisheh
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Doctor:	Mousa Al-Abbadi

**This sheet was written from Section 1's lecture, in the first 10 mins the Dr. repeated all the previous material relating to osteoporosis from the previous lecture, so please make sure to review the material from sheet no.2 before reading about how to prevent and treat osteoporosis in this sheet for a clearer understanding.*

Prevention and Treatment of Osteoporosis:

Mainly preventive procedures include:

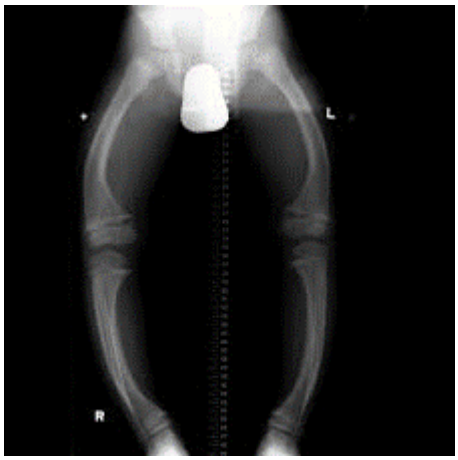
- **Physical exercise**
  (Extra info from Robbins: exercises such as weight training are more effective stimuli for increasing bone mass than repetitive endurance activities such as bicycling for load magnitude influences bone density more than the number of load cycles)
- Appropriate **calcium** and **vit D** intake

Of course, prevention is much preferred over being idle until treatment is required, nevertheless, procedures used mainly for treatment include:

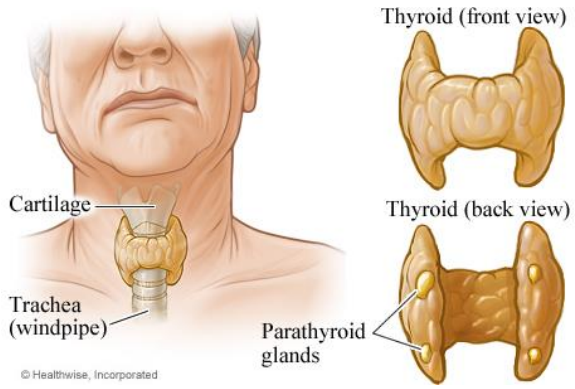
- **Bisphosphonates**: they are pharmacologic agents that decrease bone resorption by **reducing osteoclast activity** and inducing their **apoptosis**.
- **Denosumab**: an **anti-RANKL antibody** that blocks osteoclast activation.
- **Menopausal hormone therapy (oestrogen)**: has been used to prevent fracture, but complications like Deep Venous Thrombosis (**DVT**) and **stroke** are prominent risk factors.

Rickets and Osteomalacia (related to vit. D deficiency)

a) Both rickets and osteomalacia are manifestations of **vit D deficiency or its abnormal metabolism**.
b) Rickets refers to the disorder in children, in whom it interferes with the **deposition** of bone (*new bone*) in the growth plates.
c) Osteomalacia is the adult counterpart, in which bone formed **during remodelling** is undermineralized, resulting in a higher risk of fractures.
d) The main defect is an impairment of mineralization and a resultant accumulation of unmineralized matrix.
e) Leads to:
   - Skeletal deformity
   - Pain
   - Dental issues
   - Fragile bones/fractures
   - Abnormal growth and development



Hyperparathyroidism



Parathyroid glands are located in the neck behind the thyroid where they continuously monitor and regulate serum calcium levels. ParaThyroid Hormone raises Ca serum levels by increasing bone resorption, which can reduce the bone density. Severe parathyroid activity can thus lead to osteoporosis.

Increased function in the parathyroid glands (**hyperthyroidism**) can occur due to:

a) **Hyperplasia** (1^{ry}/2^{ndry}) in all four glands, due to many different causes
b) **Adenoma** (1^{ry}), usually in one of the glands only. Because it is neoplastic, it is greater in size → increased function (remember that the parathyroid hormone's function is to raise Ca serum levels) → raised Ca levels. But due to it being neoplastic with many mutations, it becomes unresponsive to hypercalcemia, or in other words, it **loses** the susceptibility to **negative feedback inhibition**, therefore, the neoplasm's hyperactivity proceeds without regulation.
Summary: adenoma → ↑activity → ↑PTH → ↑bone resorption to ↑Ca serum levels → ↓bone density.
c) **Carcinoma** (1^{ry}), but this occurs very rarely.

Primary (**1^{ry}**) hyperthyroidism occurs when there is **hypercalcemia** with an unresponsive gland (**no neg. feedback**).
Treatment is by surgical removal.

Secondary (**2^{ndry}**) hyperparathyroidism occurs when there is continuous **chronic hypocalcemia** most commonly (but not restricted) due to chronic renal failure → ↑Ca excretion → **(+) stimulation of PTH secretion** → hyperplasia.
Treatment is by managing the underlying cause or by surgical removal.

*We are not required to study tertiary hyperparathyroidism for the tests and the Dr did not mention it further.

Ultimate result: excessive bone resorption → osteoporosis.

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
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.

Question:
Why is it so important to keep Ca levels high and risk getting weaker bones with a higher chance of fractures and other morbidities?
Answer: Ca is essential for functional heart contraction. Therefore, severe hypocalcemia is lethal.

Helping info from Robbins about PTH not mentioned during the lecture:
Excess production and activity of PTH result in increased osteoclast activity, bone resorption, and osteopenia.
• Osteoclast activation, increasing bone resorption, and calcium mobilization. PTH mediates the effect indirectly by increased RANKL expression on osteoblasts.
• Increased resorption of calcium by the renal tubules.
• Increased urinary excretion of phosphates.
• Increased synthesis of active vitamin D by the kidneys, which in turn enhances calcium absorption from the gut and mobilizes bone calcium by inducing RANKL on osteoblasts.

Symptomatic, **untreated** primary hyperparathyroidism (بكير "زأطنا" ما) manifests with three interrelated skeletal abnormalities:

a) **Osteoporosis** (generalized): the correlative radiographic finding is a decrease in bone density.
b) **Brown tumours:** the bone loss predisposes to recurring **microfractures** and secondary haemorrhages that elicit an influx of macrophages and an ingrowth of reparative fibrous tissue, creating a mass of reactive tissue, known as a **brown tumour** (Fig. 21.9). *BEWARE! IT IS NOT A NEOPLASM!* The brown colour is the result of the vascularity, haemorrhage, and hemosiderin.

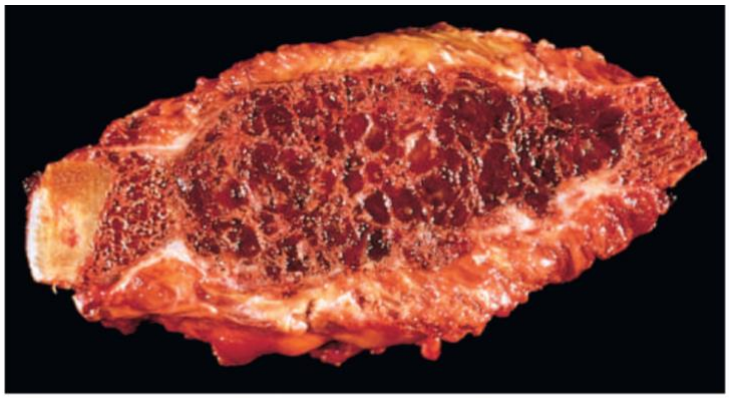


Fig. 21.9 Resected rib, harboring an expansile brown tumor adjacent to the costal cartilage.

c) **Osteitis fibrosa cystica** (aka von Recklinghausen's disease of bone, not to be confused with von Recklinghausen's disease of neurofibromatosis type I): the **combination** of increased bone cell activity, peritrabecular fibrosis, and cystic brown tumours is the hallmark of severe hyperparathyroidism and is known as **generalized osteitis fibrosa cystica**.

As bone mass decreases, affected patients are increasingly susceptible to fractures, bone deformation, and joint problems. **Osteitis fibrosa cystica is now rarely encountered because hyperparathyroidism is usually diagnosed on routine blood tests and treated at an early stage.** Restoration of PTH levels to normal can completely reverse the bone changes.

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's Disease of Bone (Osteitis Deformans)

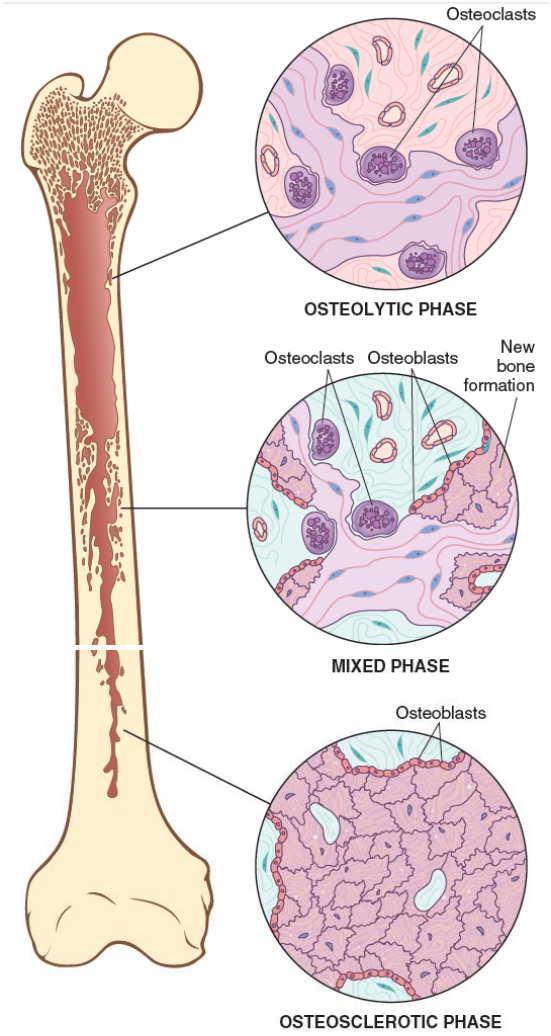


Fig. 21.10 Diagrammatic representation of Paget disease of bone demonstrating the three phases in the evolution of the disease.

**Note: Don't confuse with Paget's disease of the breast or Paget's of vulva.*

Paget disease is a condition of **increased, but disordered and structurally unsound, bone**. The primary **cause of this disease is mostly unknown**. Is it genetic? Environmental? Infection? No single factor seems to be the fundamental cause.

This unique skeletal disease can be divided into three sequential phases:

(1) an initial osteolytic stage with increased osteoclast activity,

(2) a mixed osteoclastic–osteoblastic stage, which ends with a predominance of osteoblastic activity and evolves into

(3) a final osteosclerotic stage (Fig. 21.10).

Pls note: these stages are not sequential, even all three can occur simultaneously and in the same bone!

Pathogenesis

Current evidence suggests **both genetic and environmental causes** of Paget disease. Approximately **50% of familial** Paget disease and **10% of sporadic** cases harbour mutations in the ***SQSTM1* gene**. The mutations increase the activity of NF-κB, which, in turn increases osteoclast activity. Activating mutations in ***RANK*** (**+**) and inactivating mutations in ***OPG*** (**-**) account for some cases of Paget disease.
Cell culture studies have shown that infection of osteoclast precursors with viruses such as **measles** or other **RNA viruses** can lead to increased bone resorption.
An intriguing aspect is the striking geographic variation in the prevalence. An estimated 1% of the U.S. population older than age 40 is affected.

Paget's leads to **increased risk of fractures**, accompanied with severely heightened levels of **pain**.
Paget's also increases the risk of tumours occurring in the bone, specifically **osteosarcomas**, which are common in children and elderly with 55 yrs of age or more. They usually take place in the distal femur and proximal tibia (around the knee joint)

Paget's is usually **diagnosed clinically and by radiology** (x-ray). Note how in the two pictures to the right, the normal bones of the hip (upper) show clear borders and uniform density, while the bones of someone with Paget's (lower) show **irregular bone density**, due to the three stages of Paget's occurring in diffuse areas all over the area.