Normal Bone Health and Bone Disease

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CAME Learning Technology Unit

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Learning Outcomes

- Understand the structure and function of bone and articular cartilage
- Explain the role of osteoblasts and osteoclasts in normal bone remodelling
- Understand the relationship between calcium, vitamin D and parathyroid hormone and the clinical consequences of altered levels of calcium and PTH
- Describe the bone's response to injury and the normal healing process for a fracture
- Link the clinical features, investigation and management of metabolic bone disease including:
  - Osteoporosis
  - Osteomalacia/ Rickets
  - Paget's disease of the bone
  - Bone metastases
  - Hyperparathyroidism (primary and secondary)

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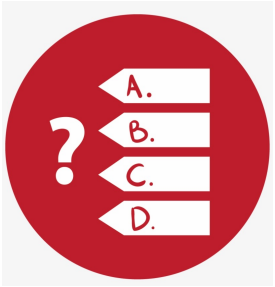

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Bone Health SBAs

- Regarding the healing of a bone following a fracture, which of the following processes occurs during the repair phase?

A. Callus formation
B. Inflammation
C. Haematoma formation
D. Remodelling
E. Stem cell stimulation

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Bone Health SBAs

- Which of the following conditions is most likely to cause hypercalcaemia?

A. Hypoparathyroidism
B. Osteomalacia
C. Pagets disease
D. Renal Osteodystrophy
E. Metastases

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Bone Health SBAs

- Bisphosphonates are commonly used in the treatment of osteoporosis. In which of the following conditions are they also used?

A. Multiple myeloma
B. Chondral tumours
C. Hypoparathyroidism
D. Open fractures
E. Tumours secreting calcitonin

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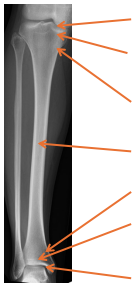
Anatomy of a long bone



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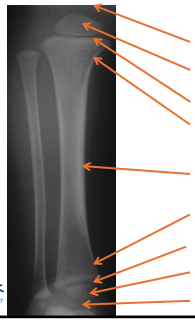

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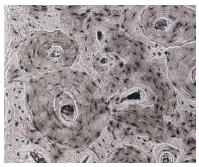
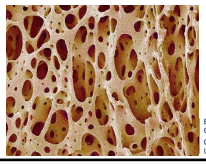
Cortical and trabecular system in more detail



Cortical bone



Trabecular bone

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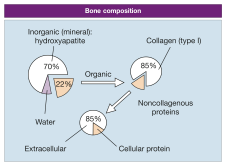
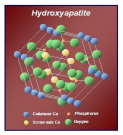
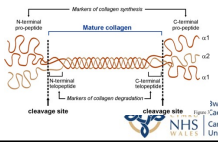
Bone composition at a cellular level





$Cas(PO_4)s(OH)$



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The Skeleton

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Function of bone

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Metabolic function of bone: calcium homeostasis

- Calcium homeostasis refers to the regulation of calcium ion concentration in the extracellular fluid.
  - Normal plasma calcium level is 2.2-2.6 mmol/L
- Tight regulation crucial due to the function of calcium ions: stabilisation of voltage gated ion channels

Hypocalcaemia (<2.2mmol/L)	Hypercalcaemia (>2.6mmol/L)
Voltage gated ion channels open spontaneously; nerve and muscle cells hyperactive	Voltage gated ion channels don't open as easily
→ Tetany (muscle spasms)	→ Depressed nervous system function → Deposition of excess calcium and phosphate (kidney stones)

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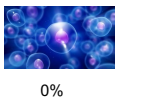

0%

1%

99%

50% bound to albumin

50% free

Normal plasma level = 2.2 to 2.6 mmol/L

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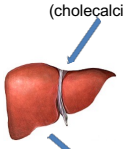
Diet – Vit D3

Vit D3 (cholecalciferol)



1, 25-Di-OH-cholecalciferol)

25-OH-cholecalciferol)

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Regulation

- PTH >> secreted when low Ca^{2+}
  - Kidney
    - Stimulates hydroxylation in kidney
    - Increases resorption of Ca^{2+} in kidney
    - Promotes urinary excretion PO^{4-}
  - Bone
    - Osteoclast stimulation
  - Overall
    - ↑ Ca^{2+}
    - ↓ PO^{4-}
- Calcitonin >> secreted when high Ca^{2+}
  - Bone
    - Osteoclast inhibition
  - Overall
    - ↓ Ca^{2+}

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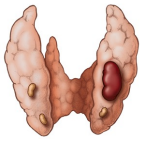
Primary hyperparathyroidism

- Enlargement of one or more of the parathyroid glands
- PTH hypersecretion
  - elevated blood calcium levels
- Adenoma (benign)
- Causes symptoms of hypercalcaemia



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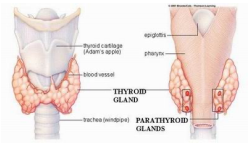
Hypoparathyroidism

- Complication of thyroid surgery
  - Injury to parathyroid glands
- Results in reduced level of calcium and associated problems:



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Bone turnover

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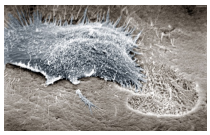
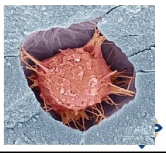
Bone remodelling

- Bone is a dynamic tissue
  - Replace ischaemic or microfractured bone
  - Ensure correct calcium homeostasis
- Relies on
  - Osteoclasts
  - Osteoblasts
  - Osteocytes
- Controlled by
  - transcription factors
  - cell signalling pathways





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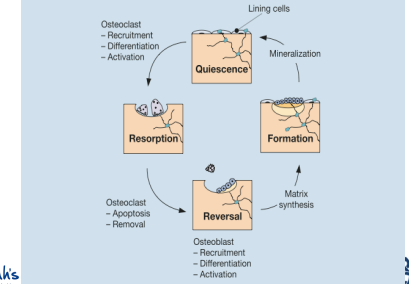

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Bone Remodelling

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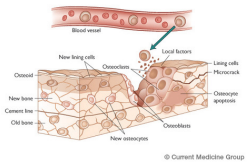
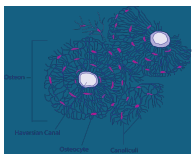
Osteocytes





- Most numerous cells in bone: 10,000 / mm³
- Viable for decades Detect strain & micro-fractures
- Induce new bone remodelling

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Bone HEALING

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Primary v Secondary

PRIMARY	SECONDARY

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Primary Bone Healing?

Three stages:

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Factors affecting bone healing

- Promotion of healing:
  - Good blood supply
  - Mechanical stability
- Inhibition of healing:

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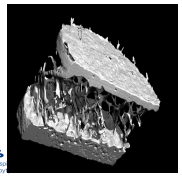
Osteoporosis

A disease characterised by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk.

World Health Organisation (WHO)



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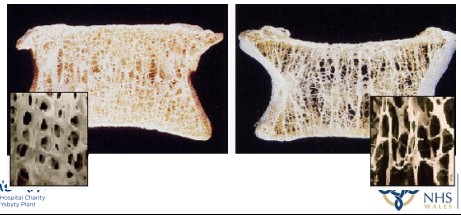
What causes osteoporosis?

- Imbalance in remodelling
  - Osteoclast > osteoblast



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Risk factors for osteoporosis

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Some secondary causes of osteoporosis in adults

Endocrine / Metabolic	Nutritional	Drugs	Disorders of Collagen	Other
Hypogonadism Hyperparathyroidism Thyrotoxicosis Cushings Prolactinoma Acromegaly Hypopituitarism IDDM Hypophosphatasia	Calcium deficiency Vitamin D deficiency Malabsorption Malnutrition Cholestatic liver disease Gastric operations	Glucocorticoids Aromatase Inhibitors Androgen Deprivation Therapy Depoprovera GnRH agonists Heparin Phenytoin Carbamazepine Excess Thyroxine	Osteogenesis Imperfecta Ehler Danlos syndrome Marfans syndrome Homocystinuria	Rheumatoid Arthritis SLE Multiple Myeloma Immobilisation Chronic Kidney Disease Renal Tubular Acidosis Mastocytosis Organ Transplantation

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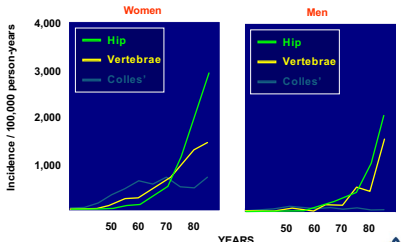
Fracture incidence and age



Adapted from Cooper, C. (2003). "Epidemiology of osteoporosis." Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism: 387-313.

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Osteoporosis - diagnosis

- Based on measurement of BMD in g/cm^2
- Usually measured using Dual Energy X-ray Absorptiometry (DEXA).
- Blood tests - normal

DXA Results Summary:

Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T - score	PR (%)	Z - score	AM (%)
L1	12.97	10.55	0.814	-1.0	88	-0.9	89
L2	14.64	13.96	0.954	-0.7	93	-0.6	94
L3	16.00	16.92	1.058	-0.2	98	-0.2	98
L4	18.05	18.31	1.015	-0.9	91	-0.8	92
Total	61.65	59.74	0.969	-0.7	93	-0.6	93

Total BMD CV 1.0%
WHO Classification: Normal
Fracture Risk: Not Increased

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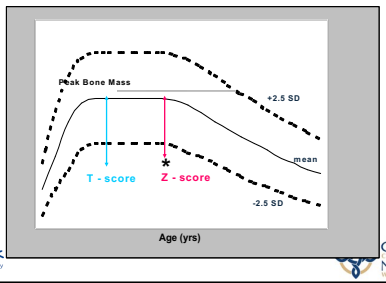
Age Related Bone Mineral Density



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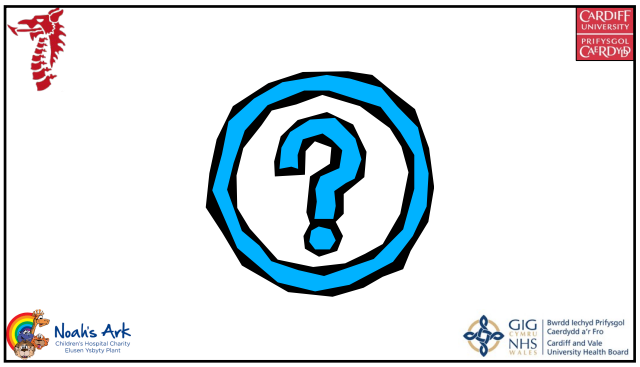

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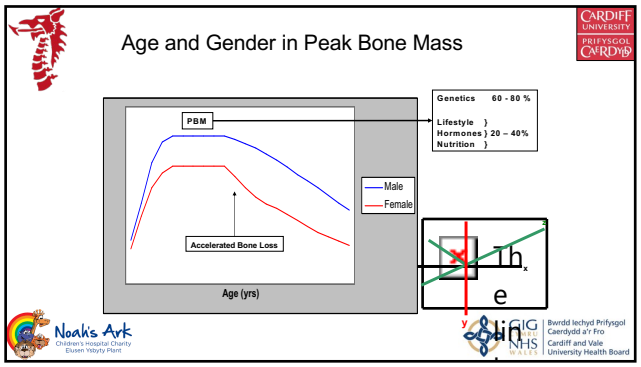

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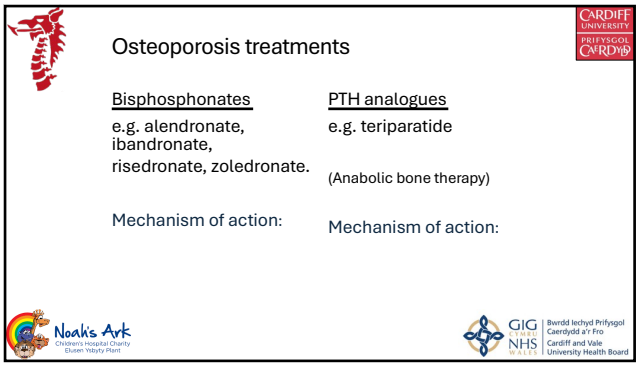

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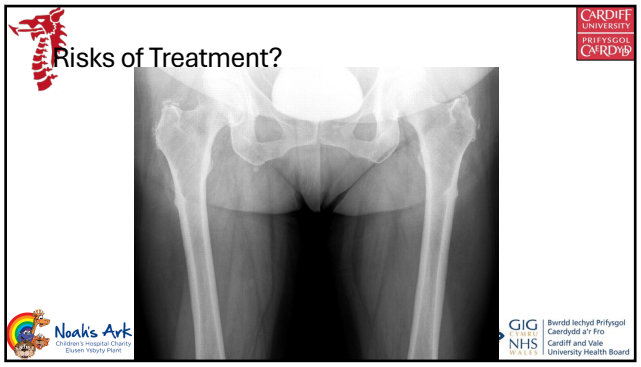

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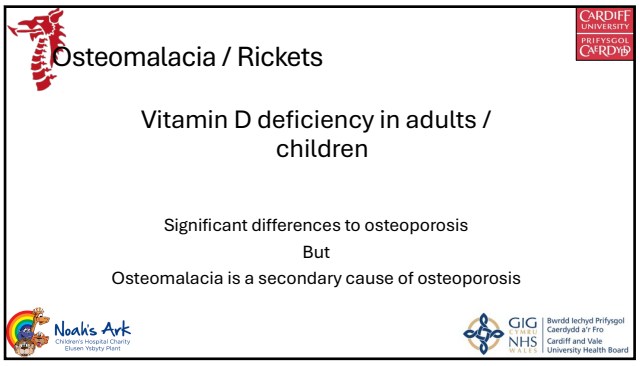

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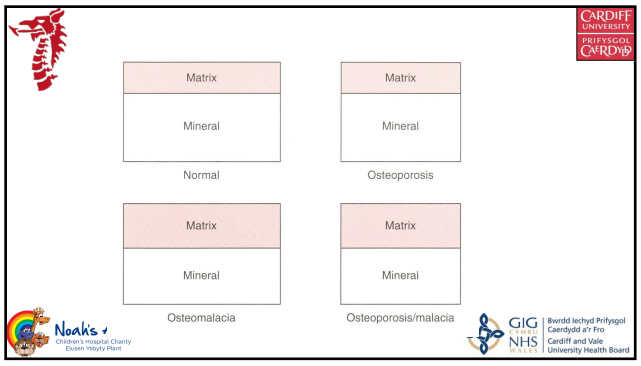

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Osteomalacia/Rickets

- Osteomalacia = Vit D deficiency
  - Low calcium
  - Poor mineralisation
- Rickets in children

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Treatment

- Vitamin D

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Paget's Disease

- Disordered bone metabolism
  - Osteoclast overactivity
  - Followed by compensatory osteoblast activity
  - Leads to disordered 'woven' mosaic bone
  - Weaker than normal bone
- Second most common bone disorder in elderly
  - 70-90% asymptomatic

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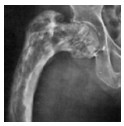

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Paget's disease

- Symptoms
  - Direct
    - Bone pain
      - Deep, constant, boring pain
      - Worse on weight-bearing
    - Pathological fracture
    - Sarcomatous change – rare
  - Indirect
    - High cardiac output
    - Compression effects depending on site

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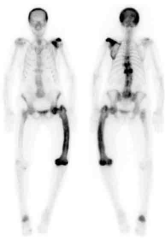
Paget's

- Diagnosis
  - X-ray
    - Incidental / directed
  - Blood tests
    - High alkaline phosphatase (NB. liver disease)
    - Normal calcium, vitamin D, PTH, phosphate
  - Urinary hydroxyproline increased
  - Isotope bone scan – increase uptake



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Paget's

- Treatment
  - Not everyone!
    - Symptomatic
    - In danger of nerve compression
    - Around a weight-bearing joint
  - Bisphosphonates
    - Risedronate – 30mg daily 2 months
    - Zolendronate – 5mg x 1 infusion

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Bone metastases

- Cancers which may metastasise to bone include:
- Common sites for bone mets are:

Lytic v Sclerotic v Mixture

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Bone metastases

- Presentation
- Treatment

Bone Mets to Left Shoulder

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Summary of biochemical changes in bone disease

Condition	Calcium	Phosphate	Alk Phos	PTH
Osteomalacia				
Osteoporosis				
Paget's				
Primary Hyperparathyroidism				
Renal osteodystrophy				
Bone Metastases				

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Summary

- Bone tissue undergoes a continuous process of remodelling
- Osteoporosis results when bone resorption exceeds that of bone formation, resulting in a higher fracture risk
- Risk factors for osteoporosis are numerous, and include age, gender, family history, smoking, alcohol and drugs such as prednisolone
- Osteomalacia is caused by vitamin D deficiency which leads to reduced calcium and phosphate levels and reduced bone mineralisation
- Paget's disease is caused by disordered bone remodelling and has a characteristic appearance on x-ray
- Primary hyperparathyroidism is caused by an excess of PTH secretion, leading to hypercalcaemia
- Secondary hyperparathyroidism is caused by chronically low calcium levels, due to renal dysfunction
- Bone metastases can originate from several types of cancers and may be lytic or sclerotic

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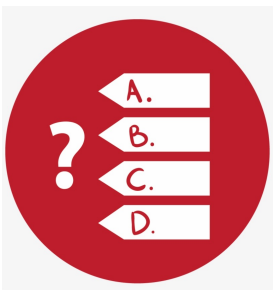

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