Basics of Bone

Functions of bone:
- Reservoir of calcium
- Haematopoietic marrow – supplies erythrocytes, leukocytes and platelets
- Mechanical role – attachment of muscles and locomotion
- Protection of viscera

Structure:
- Woven / immature bone – isotropic because of random orientation of collagen fibres. Found in metaphyseal growth, fracture callus and pathological bone (tumours and Paget’s – where there is accelerated turnover)
- Lamellar / mature bone
  - Anisotropic with collagen laid down in parallel sheets / lamella, aligned to the mechanical axis of force
  - Adjacent lamellae are arranged slightly oblique to each other in a herring-bone pattern
- Cortical / compact bone
  - Lamellae arranged in concentric rings are called osteons, around a neurovascular Haversian canal – osteons are 50 microns across
  - Canaliculi run radially in these osteons and are processes from osteocytes that allow for cell signalling by gap junctions.
  - Volkman’s canals run perpendicular to the long axis, and connect the outer periosteal blood supply with the Haversian system.
- Trabecular / cancellous bone
  - Less dense, less elastic and less strong
  - No Haversian systems / osteons
  - Lattice of trabeculae bounded by lamellae again arranged along the axis of force upon the bone, and containing bone marrow elements for haematopoiesis

Components:
- Cellular phase:
  - Osteoblasts – undifferentiated mesenchymal stem cells with high ALP activity and synthetic function. They have 3 fates: become inactive bone lining cells, osteocytes or undergo apoptosis.
  - Osteocytes – 90% of bone cell population and control Ca / PO₄ metabolism, and therefore regulate bone healing and turnover
  - Bone lining cells – inactive osteoblasts recruited for new bone formation. PTH binding results in cAMP-mediated shape change that will expose bone surface allowing osteoclasts to start resorption
- Osteoclasts – arise from haematopoietic macrophage, and will fuse together to form multi-nucleate giant cells. Lie in Howship lacunae (pits) on the endosteal and periosteal surface of bone. Have a brush border for surface area, and contain carbonic anhydrase system (dissolves inorganic hydroxyapatite) and proteolytic enzymes (e.g. TRAP and cathepsin to dissolve organic matrix).

Matrix phase:
- Inorganic – calcium phosphate in the form of hydroxyapatite (Ca_{10}[PO_4]_6[OH]_2), and osteocalcium phosphate (brushite). These mineralise into crystals in the hole and pore regions of collagen fibrils. Inorganic matrix is a reservoir for 99% of body calcium and 80% of body phosphorous.
- Organic phase –
  - Collagen type 1 (tensile strength)
  - Bone specific proteoglycans (compressive strength)
  - Non-collagenous matrix proteins – osteocalcin released by osteoblasts to control osteoclasts; osteonectin released by osteoblasts to regulate mineralisation; osteopontin anchor osteoclasts.
  - Growth factors – BMP (member of TGF-beta family), insulin-like growth factor (IGF I & II), IL1 & 6

**Bone Metabolism**

- Calcium – absorbed by the duodenum via active transport and controlled by calcium binding protein and 1-25-Vit D3, as well as by passive diffusion in the jejunum.
  - 99% of filtered calcium is re-absorbed, with 60% from the proximal convoluted tubule.
  - Recommended daily intake:
    - children 600 mg/day
    - 10-25 1400 mg/day
    - 25-65 750 mg/day
    - lactation 2000 mg/day
    - postmenopause 1500 mg/day
    - fracture healing 1500 mg/day

- Phosphate – as well as being a key compound in inorganic bone matrix, it also functions as a metabolite and as a buffer in the body enzyme systems.
  - Daily requirement = 1000 – 1500 mg/day

- Vitamin D – ingested as naturally occurring steroid in fish oils and plants, or generated in the skin when UV-rays convert 7-dehydrocholesterol into cholecalciferol.
  - Average Caucasian needs 1 hour of sunlight exposure for adequate daily generation.
Activated initially in the liver (25-OH-cholecalciferol), and then in the kidney (1-25(OH)₂-cholecalciferol by 1α-hydroxylase.

- Enhances GI calcium and phosphorous absorption
- Enhances osteoclastic resorption
- Inhibits PTH release
- Inactivated by high Ca-levels by conversion into 24-25(OH)₂-cholecalciferol

Parathyroid hormone – 84 amino-acid peptide secreted by chief cells of parathyroid gland, secreted in response to low Ca-levels.
- stimulates 1α-hydroxylase to activate vitamin D3
- increases reabsorption of calcium in the kidney
- promotes urinary excretion of phosphate
- stimulates osteoclasts - works by activating RANKL (receptor activator of nuclear factor kappa-B ligand) receptor on osteoblasts, which then secrete RANKL and stimulate fusion of osteoclasts into multi-nucleate cells within cutting cones
- overall will increase calcium levels, and decrease phosphate.

Calcitonin – 32 amino acid peptide secreted by para-follicular C-cells in the thyroid gland, in response to raised calcium levels.
- Directly inhibits osteoclasts, by reducing cellular motility, retraction of cytoplasmic extensions and reduction in brush border size.

Oestrogen – inhibits bone resorption

Corticosteroids – reduces GI absorption and increases renal excretion of calcium, resulting in secondary hyperparathyroidism.

Thyroid hormone – increases bone turnover, favouring resorption.

Growth hormone – increases GI calcium absorption

Insulin – type 1 diabetes if poorly controlled may lead to bone loss

Growth factors:
- IL1, IL6, TNFα - stimulate osteoclast precursors
- IGF - activated osteoblasts and produced by osteoblasts
- TGFβ – activates osteoblasts

Physiological changes in bone turnover:
- Bone mass increases up to a peak between age 16 and 25
- After which there is normal loss of bone mass at a rate of 0.3% per year
- Women have an increase in bone loss up to 3% per year for the first decade after the menopause, before it reverts to the same rate of loss in both men and women.