Normal Bone Health and Bone Disease

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Consultant Hand and Wrist Surgeon
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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)
Anatomy of a long bone

- Knee joint
- Physeal scar – corresponding to physis
- Metaphysis (proximal)
- Diaphysis
- Metaphysis (distal)
- Physeal scar – corresponding to physis
- Ankle joint
Anatomy of a long bone

- Knee joint
- Epiphysis
- Physis
- Metaphysis (proximal)
- Diaphysis
- Metaphysis (distal)
- Physis
- Epiphysis
- Epiphysis
- Ankle joint
Cortical and trabecular system in more detail

Cortical bone

Trabecular bone
Bone composition at a cellular level

Ca$_5$(PO$_4$)$_3$(OH)

Figure 1. Structure of hydroxyapatite

Figure 3. Markers of collagen synthesis
Articular cartilage (Hyaline)
Articular cartilage

- Water, collagen, proteoglycans
- Sparse distribution of highly specialised cells called chondrocytes
- Function is to provide a smooth lubricated surface for articulation.
  - Unlike bone, mainly type 2 collagen
  - Unlike bone, no blood vessels so cartilage heals very slowly after injury.

Example of pathology: Osteoarthritis (wearing of cartilage)
Articular cartilage
Function of bone

- Structural support
- Protection
- Locomotion
- Metabolic
- Haematopoiesis
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

<table>
<thead>
<tr>
<th>Hypocalcaemia (&lt;2.2mmol/L)</th>
<th>Hypercalcaemia (&gt;2.6mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voltage gated ion channels open spontaneously; nerve and muscle cells hyperactive</td>
<td>Voltage gated ion channels don’t open as easily</td>
</tr>
<tr>
<td>→ Tetany (muscle spasms)</td>
<td>→ Depressed nervous system function</td>
</tr>
<tr>
<td></td>
<td>→ Deposition of excess calcium and phosphate (kidney stones)</td>
</tr>
</tbody>
</table>
Normal plasma level = 2.2 to 2.6 mmol/L
Diet – Vit D3

Vit D3 (cholecalciferol)

25-OH-cholecalciferol)

1, 25-Di-OH-cholecalciferol)
Regulation

• PTH >> secreted when low \( \text{Ca}^{2+} \)
  – Kidney
    • Stimulates hydroxylation in kidney
    • Increases resorption of \( \text{Ca}^{2+} \) in kidney
    • Promotes urinary excretion \( \text{PO}_4^{2-} \)
  – Bone
    • Osteoclast stimulation
  – Overall
    • \( \uparrow \text{Ca}^{2+} \)
    • \( \downarrow \text{PO}_4^{2-} \)

• Calcitonin >> secreted when high \( \text{Ca}^{2+} \)
  – Bone
    • Osteoclast inhibition
  – Overall
    • \( \downarrow \text{Ca}^{2+} \)
Primary hyperparathyroidism

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

- Causes symptoms of hypercalcaemia
  - Bones
  - Stones
  - Groans (abdominal)
  - Moans (psychiatric)
Hypoparathyroidism

- Complication of thyroid surgery
  - Injury to parathyroid glands
- Results in reduced level of calcium and associated problems:
  - Muscle spasms and tetany
  - Paraesthesia around mouth/feet
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
Osteoclast
- Recruitment
- Differentiation
- Activation

Quiescence

Mineralization

Lining cells

Resorption

Formation

Matrix synthesis

Reversal

Osteoblast
- Recruitment
- Differentiation
- Activation

Osteoclast
- Apoptosis
- Removal
Bone Remodelling

**BONE REMODELING**

1. Osteoclasts
   - Time: 1, 2, 3, 4, 5
   - Phases: Pre-osteoclasts, Osteoclasts, Osteoblasts, Lining cells

2. Howship’s lacuna
   - Monocytes, Preosteoblasts, Active osteoblasts, Osteoid tissue

**Cells involved in bone remodeling**

- Osteoblasts
- Osteoclasts
- Osteocytes

© www.rheumtext.com - Hochberg et al (eds)
Osteocytes

- Most numerous cells in bone: 10,000 / mm$^3$
- Viable for decades Detect strain & micro-fractures
- Induce new bone remodelling
How does a bone heal after a fracture?

Three stages:

- Inflammation
- Repair
- Remodelling
Bone Healing

• Inflammation:
  – Formation of haematoma
  – Increased capillary permeability leads to release of local inflammatory mediators: interleukins, growth factors, hormones. These include factors which stimulate proliferation and differentiation of stem cells which leads to new bone formation and repair.
  – Minutes to days

• Repair:
  – Callus formation
  – Callus ossifies
  – Lasts weeks

• Remodelling
  – Return to normal structure
  – Lasts months

Fracture Repair
Bone Healing

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

- **Inhibition of healing:**
  - Poor blood supply
  - No stability
  - Malnutrition (reduced callus formation, reduced proliferation of osteochondral cells)
  - Smoking (direct inhibition of osteoblasts)
  - Diabetes
  - Infection
Malunion and non-union
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)*
What causes osteoporosis?

• Imbalance in remodelling
  – Osteoclast > osteoblast
Risk factors for osteoporosis

- Age
- Gender
- Genetic
- Lifestyle
- Low BMI
- Physical inactivity
- Reduced oestrogen in women- Secondary causes.....
Some secondary causes of osteoporosis in adults

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

Osteoporosis - diagnosis

- Based on measurement of BMD in g/cm²
- Usually measured using Dual Energy X-ray Absorptimetry (DEXA).
- Blood tests - normal

### DXA Results Summary:

<table>
<thead>
<tr>
<th>Region</th>
<th>Area (cm²)</th>
<th>BMC (g)</th>
<th>BMD (g/cm²)</th>
<th>T-score</th>
<th>PR (%)</th>
<th>Z-score</th>
<th>AM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>12.97</td>
<td>10.55</td>
<td>0.814</td>
<td>-1.0</td>
<td>88</td>
<td>-0.9</td>
<td>89</td>
</tr>
<tr>
<td>L2</td>
<td>14.64</td>
<td>13.96</td>
<td>0.954</td>
<td>-0.7</td>
<td>93</td>
<td>-0.6</td>
<td>94</td>
</tr>
<tr>
<td>L3</td>
<td>16.00</td>
<td>16.92</td>
<td>1.058</td>
<td>-0.2</td>
<td>98</td>
<td>-0.2</td>
<td>98</td>
</tr>
<tr>
<td>L4</td>
<td>18.05</td>
<td>18.31</td>
<td>1.015</td>
<td>-0.9</td>
<td>91</td>
<td>-0.8</td>
<td>92</td>
</tr>
<tr>
<td>Total</td>
<td>61.65</td>
<td>59.74</td>
<td>0.969</td>
<td>-0.7</td>
<td>93</td>
<td>-0.6</td>
<td>93</td>
</tr>
</tbody>
</table>

Total BMD CV 1.0%

WHO Classification: Normal Fracture Risk: Not Increased
Age Related Bone Mineral Density

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**Age (yrs)**

**Bone Mass**

- Peak Bone Mass
- T-score
- Z-score
- +2.5 SD
- -2.5 SD
- Mean

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*Z-score*
Age and Gender in Peak Bone Mass

- **PBM**
- **Accelerated Bone Loss**

**Bone Mass** vs **Age (yrs)**

- **Male** (blue line)
- **Female** (red line)

**Factors Contributing to Bone Loss**

- **Genetics**: 60 - 80%
- **Lifestyle**
- **Hormones**: 20 – 40%
- **Nutrition**
## Osteoporosis Management

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Effect on BMD</th>
<th>Effect on Spine #</th>
<th>Effect on Hip #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>A</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Calcium (+/- Vit D supplements)</td>
<td>A</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Dietary calcium</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Reduced EtOH</td>
<td>C</td>
<td>C</td>
<td>B</td>
</tr>
<tr>
<td>Falls prevention</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Hip protectors</td>
<td></td>
<td></td>
<td>B</td>
</tr>
</tbody>
</table>
## Anti-fracture Efficacy Of Pharmacological Interventions For Osteoporosis

(when given with calcium and colecalciferol)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Vertebral</th>
<th>Non-vertebral</th>
<th>Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risedronate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>+</td>
<td>+ *</td>
<td>-</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>+</td>
<td>+</td>
<td>+ *</td>
</tr>
<tr>
<td>Denosumab</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IV Zoledronic acid</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IV Ibandronate</td>
<td>+</td>
<td>+ *</td>
<td>-</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>PTH (1-84)</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* In selected patient groups

**1st line**

**2nd line**

**Specialist**
## Osteoporosis treatments

<table>
<thead>
<tr>
<th>Bisphosphonates</th>
<th>PTH analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>e.g. alendronate, ibandronate, risedronate, zoledronate.</td>
<td>e.g. teriparatide</td>
</tr>
</tbody>
</table>

**Mechanism of action:**
- Bisphosphonates: reduce bone breakdown i.e. aim to inhibit osteoclast function and induce apoptosis of osteoclasts.
- PTH analogues: increase formation of new bone i.e. aim to increase osteoblast activity.
Osteomalacia / Rickets

Vitamin D deficiency in adults / children

Significant differences to osteoporosis

But

Osteomalacia is a secondary cause of osteoporosis
Fig. 5.9
Illustration of the difference between osteoporosis and osteomalacia. In osteoporosis the amount of bone is decreased but the ratio of matrix to bone mineral is normal. In osteomalacia, the amount of bone is normal but the ratio of matrix to bone mineral is decreased.
Osteomalacia/Rickets

• Osteomalacia – Vitamin D deficiency. Leads to insufficient calcium and phosphate and so new osteoid cannot be mineralised.
• Causes bones to be softer and more pliable (therefore more prone to deformation/fracture)

• Rickets is essentially the same problem (only seen before growth plate disappears → deformity)

• Deficiency may be due to malnutrition, reduced sun exposure or gut malabsorption
Vitamin D deficiency - Causes

- Inadequate sunlight
  - Frail / unwell / nursing homes
  - Cultural / clothing / darker skin
- Inadequate diet
  - Vegan / lacto-vegetarians
  - Lactose intolerance
- Malabsorption
  - Small bowel resection
  - Cystic fibrosis
- Medication
  - Phenytoin, rifampicin
- Low levels in breast milk
- Multiparosity
- Abnormal Vit D Metabolism
  - Liver Disease
  - Renal disease (=renal osteodystrophy)
- Hypophosphataemia
- Rare causes
  - Hypophosphaetaemic Rickets
    - X-Linked
  - Congenital 1-alpha hydroxylase deficiency
  - Congenital Vit D resistance
Treating osteomalacia/rickets

• Treatment
  – Vitamin D!!!!!
    • **Oral D2/D3**(requires good renal function)
      – Eg. Fultium D3
      – Calcichew D3 forte......etc
      – 600 – 2000 IU vitamin D daily maintenance
    • **Oral 1-alphacalcidol**
    • **Oral calcitriol**
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
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
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
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
Bone metastases

• **Cancers** which may metastasise to bone include:
  – Breast
  – Kidney
  – Thyroid
  – Prostate
  – Lung

• **Common sites** for bone mets are:
  – Vertebrae
  – Pelvis
  – Proximal femur/humerus
  – Ribs
  – Skull

Lytic v Sclerotic v Mixture
Bone metastases

• Presentation
  – Pain
  – Pathological fracture
  – Spinal cord compression
  – Elevated alkaline phosphatase and calcium

• Treatment
  – Bisphosphonates
  – Radiotherapy
  – Surgical
  – Chemo/hormone therapy in some cases

Bone Mets to Left Shoulder
Summary of biochemical changes in bone disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Calcium</th>
<th>Phosphate</th>
<th>Alk Phos</th>
<th>PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteomalacia</td>
<td>low</td>
<td>low</td>
<td>high/normal</td>
<td>high/normal</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Paget’s</td>
<td>normal</td>
<td>normal</td>
<td>high</td>
<td>normal</td>
</tr>
<tr>
<td>Primary Hyperparathyroidism</td>
<td>high/normal</td>
<td>low/normal</td>
<td>high/normal</td>
<td>high</td>
</tr>
<tr>
<td>Renal osteodystrophy</td>
<td>normal or low</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Bone Metastases</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>low</td>
</tr>
</tbody>
</table>
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