COMMONWEALTH OF AUSTRALIA

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Drugs Affecting Bone

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Objectives

At the end of this lecture you should have gained:

• An understanding of bone metabolism and factors regulating
  – Bone remodelling
  – Mineral homeostasis

• Knowledge of drugs used to treat disorders of bone
  – Mechanism of action
Bone Function

• **Mechanical**
  – Provides structural support
  – Protects organs
  – Sites of attachment for muscles

• **Metabolic**
  – Reservoir of calcium (98-99%) and phosphate (85%)
  – Acid-base balance

• **Synthetic**
  – Production of white and red blood cells
Bone Structure

Compact Bone & Spongy (Cancellous Bone)

- Lacunae containing osteocytes
- Lamellae
- Canaliculi
- Osteon of compact bone
- Trabeculae of spongy bone
- Osteon
- Haversian canal
- Periosteum
- Volkmann's canal

Cortical bone/ trabecular bone

Image from National Cancer Institute SEER Training module http://training.seer.cancer.gov/anatomy/skeletal/tissue.html
Bone Structure

- 80% cortical bone
- 20% trabecular (spongy, cancellous) bone
  - Larger surface area
- Metabolically active
  - Not inert!

Tetracycline

- Broad spectrum antibiotic
- When consumed during tooth development stage yellow/brown/blue discolouration of dentin
- Binds to calcium ions (calcium orthophosphate)
- Fluorescent yellow – UV – brown
- Also used widely in pig farming


Courtesy A/Prof Liz Tudor
Bone Constituents

- **Cells**
  - Osteoblasts
  - Osteocytes
  - Osteoclasts

- **Matrix**
  - Osteoid
    - Organic, unmineralised bone matrix
    - Collagen-I
    - Proteoglycans, ostecalcin, osteonectin
  - Mature bone tissue is mineralised
    - Hydroxyapatite (calcium phosphate)

Why is bone remodelled?

• Bone growth during **skeletal development**
  – Endochondral ossification
  – Intramembranous ossification

• Respond to **mechanical stress**
  – Mechanical loading
  – Stress related micro-fractures

• Mechanism to **regulate calcium** in the extracellular fluid
Bone Remodelling

• In adults:
  – 25% of trabecular bone remodelled per year
  – 3% cortical bone remodelled per year
  – 10% total bone per year

• Remodelling is affected by:
  – Ageing
  – Physical factors (exercise, loading)
  – Hormones (oestrogen)
  – Drugs (corticosteroids)

• Processes that affect bone remodelling preferentially affect trabecular bone
  – femoral neck and vertebral bodies
Bone Remodelling

Osteoblasts

Osteoclasts
Bone Remodelling

- Five Phases:
  - Activation
  - Resorption
  - Reversal
  - Formation
  - Quiescence

Rat osteoclast and resorption pit

Images: Bone cell gallery UCL Research Dept of Cell and Developmental Biology
http://www.ucl.ac.uk/cdb/research/arnett/gallery_bone1

Histological stain of bone section
Factors Regulating Bone Remodelling

• **Parathyroid hormone**
  – increased osteoblast activity and increased osteoclast activity

• **Oestrogen**
  – decreased osteoclast activity

• **Glucocorticoids**
  – increased osteoclast activity and decreased osteoblast activity

• Sequestered cytokines when released
  – increased osteoblast activity

• **Calcitonin**
  – decreased activity of osteoclasts
Dexamethasone decreases OPG and increases RANKL.

Protein

\[
\text{Dexamethasone concentration (log M)}
\]

mRNA

\[
\begin{array}{c|c|c}
\text{hFOB} & \text{MS} \\
- & + & - & + \\
\end{array}
\]

- OPG-L
- \(\beta\)-actin

Hofbauer L C et al. Endocrinology 1999;140:4382-4389
Bone Mineral Homeostasis

- Bone main reservoir of calcium and phosphorous
- Serum calcium levels precisely controlled
  - Involved in signal transduction
  - Gradient across cell membranes
    - Low concentrations!

- Regulated by:
  - Parathyroid Hormone (PTH)
  - Vitamin D
  - Calcitonin
Factors Regulating Bone Mineralisation

• **Parathyroid hormone (PTH)** increases plasma Ca by:
  – Increasing calcitriol (Vitamin D) synthesis (INDIRECT)
  – Mobilising calcium from bone
  – Reducing renal calcium excretion

• **Calcitonin** (from thyroid gland)
  – decreases osteoclast activity and calcium resorption from bone
  – Inhibits calcium reabsorption in kidney
Vitamin D Synthesis

Cholecalciferol  
Calcifediol  
Ergocalciferol

7-dehydrocholesterol  
cholecalciferol (vitamin D3)  
25-hydroxyvitamin D  
Calcitriol

UVB  
Skin  
Liver  
Kidney

Dietary intake  
Fortified foods, supplements (D2 or D3), fish oils (D3)

Ibhar Al Mheid et al. Eur Heart J 2013;eurheartj.eht166
Factors Regulating Bone Mineralisation

• **Vitamin D family**
  – dietary precursors are converted to **calcitriol** in kidney

• **Calcitriol**
  – increased plasma calcium
    • increased intestinal absorption
    • decreased renal excretion
    • increased osteoclast activity
1. Parathyroid gland releases parathyroid hormone (PTH).
2. PTH stimulates Ca\(^{2+}\) release from bones.
3. Ca\(^{2+}\) level increases.
4. Active vitamin D increases Ca\(^{2+}\) uptake in intestines.
5. Blood Ca\(^{2+}\) rises.
7. Calcitonin.
8. Stimulates Ca\(^{2+}\) deposition in bones.

Homeostasis: Normal blood calcium level (about 10 mg/100 mL)
Disorders of Bone

- **Hypocalcaemia**
  - Vitamin D deficiency
  - low serum Ca
- **Hypercalcaemia**
  - some malignancies
  - high serum Ca
- **Hypophosphataemia**
  - nutritional deficiency states
  - low serum phosphate
- **Hyperphosphataemia**
  - renal failure
  - high serum phosphate
- **Osteoporosis**
  - aging, post menopause, corticosteroid use
Bone Density

Osteoblasts: Increased bone density

Osteoclasts: Decreased bone density
Osteoporosis

• **Osteoporosis**
  – reduction in bone mass more than 2.5 standard deviations below the norm for healthy 30 year old women
    • Post menopausal
    • With ageing
    • Following glucocorticoid therapy

• **Osteopaenia**
  – reduction in bone mass 1-2.5 standard deviations below the norm for healthy 30 year old women
Osteoporosis and age: Bone density over the life span

http://www.drugdevelopment-technology.com/projects/lafoxifene/
Osteoporosis

- Reduction in bone mass with loss of both cells and matrix
- Loss of trabeculae and thinning (below)
  - reduces cross-sectional area so that loads on bone are relatively greater

Images: Bone cell gallery UCL Research Dept of Cell and Developmental Biology
http://www.ucl.ac.uk/cdb/research/arnett/gallery_bone1
Drugs Used in Bone Disorders

• **Anti-resorptive** agents:
  – Bisphosphonates
  – Selective oestrogen receptor modulators (SERM)
  – RANK Ligand inhibitors
  – Calcitonin

• **Anabolic** agents:
  – Parathyroid hormone
  – Oral calcium
  – Oral vitamin D analogues
Bisphosphonates – Structure

- Enzyme resistant analogues of pyrophosphate (P-O-P)

A: Inorganic pyrophosphate and Bisphosphonate structures

B: Non-Nitrogen Containing Bisphosphonates

- Etidronate
- Clodronate
- Tiludronate

Relative potency: 1, 10, 10

C: Nitrogen Containing Bisphosphonates

- Alendronate
- Risedronate
- Ibandronate
- Pamidronate
- Zoledronic acid

Relative potency: 500, 2000, 1000, 100, 10,000

Mayo Clinic Proceedings 2008 83, 1032-1045 DOI: (10.4065/83.9.1032)
Bisphosphonates – Mechanism

- Inhibit recruitment of osteoclasts
- Promote apoptosis of osteoclasts
- Incorporated into bone matrix and ingested by osteoclasts during bone resorption
- Accumulate at site of bone mineralisation - remain for long periods

- Oral administration daily/weekly
- IV administration
- Poorly absorbed – low bioavailability
- Adverse GI effects - oesophagitis
Bisphosphonates – Risk & Benefit

Benefits
Reduced fracture risk

Risks
Oesophageal cancer?
Atypical fractures?
Osteonecrosis of the jaw?

Box 1 | Bisphosphonate effects

Estimated benefits per 10,000 patients
Fracture prevention
- 125–1000 osteoporotic fractures prevented per 3 years’ treatment

Estimated harms per 10,000 patients
Esophageal cancer
- No additional cases in years 0–3
- 5 additional cases per year beyond 3 years’ treatment
- Risks uncertain beyond approximately 7 years’ treatment

Atypical fractures
- 0–2 additional cases per year

Osteonecrosis of the jaw
- Risks uncertain

Atrial fibrillation
- Probably no increased risk

The figures presented are derived from different study designs with different populations and include no measures of uncertainty. They should therefore be compared and interpreted with caution.
Oestrogen

• Hormone Replacement Therapy (HRT) to prevent bone density loss
• Decreases bone resorption by decreasing osteoclast proliferation, differentiation and activation
• Promotes osteoclast apoptosis
• Increases life span of osteoblasts and osteocytes
• Does not increase bone mass but maintains mass and slows bone loss
• Administered with a progestagen
• Increased risk of cardiovascular disease and breast cancer
Oestrogen Receptor Modulators

- Selective oestrogen receptor modulators (SERMs)
- Have replaced HRT in treatment of osteoporosis
- Raloxifene
  - Agonist at oestrogen receptors in bone and cardiovascular tissue
  - Antagonist at oestrogen receptors in mammary tissue and uterus
  - Once daily oral administration
  - Increased risk of DVT and pulmonary embolism
Denosumab

- Denosumab
  - Human monoclonal antibody binds RANKL
  - Inhibits RANKL activity
  - Reduces osteoclastic differentiation, survival, activity

- Treatment has been shown to decrease bone turnover markers and increased bone density in post menopausal women

Strontium Ranelate

- Anti-resorptive and anabolic
- Dual action bone agent
- In 2014, following review, EMA Pharmacovigilance Risk Assessment Committee found increased incidence of myocardial infarction
- TGA issued black box warning
  - Cardiovascular effects
- Last line of treatment – severe osteoporosis

Calcitonin

– Decreases osteoclastic resorption and mobilisation of calcium from bone
– Natural – porcine/human calcitonin (discontinued)
– Synthetic salmon calcitonin (salcatonin)

– Given by S/C or I/M injection, or nasal spray
– Used in Paget’s disease and hypercalcaemia associated with neoplasia
– With other agents in osteoporosis
Bone Anabolic Agents

• **Parathyroid Hormone**
  – Paradoxical behaviour
    • PTH acute exposure promotes osteoblast development and activity
    • Continuous or high exposure to PTH promotes osteoclast activity
  – Severe osteoporosis – alternatives unsuitable

• Once daily S/C administration of Teriparatide favours bone anabolism, whilst continuous high exposure to PTH favours bone catabolism
Bone Anabolic Agents

• **Oral Calcium**
  – Oral calcium salts used as adjunctive therapy in osteoporosis
    • Calcium carbonate (40%)
    • Calcium citrate (21%)
    • Calcium gluconate (9%) - IV
  – Side effect:- GI disturbances

• **Vitamin D**
  – Used in treatment of deficiency states
    • Rickets (children) and osteomalacia (adults)
    • Endocrine dysfunction (hypoparathyroidism)
    • Chronic renal disease (where calcitriol cannot be generated in kidney)
  – Oral administration of Calcitriol or cholecalciferol (D3) or ergocalciferol (D2)
Drugs used to maintain or restore bone density

Inhibiting Osteoclastic Activity

Anti-resorptive agents:
- Bisphosphonates
- Selective oestrogen receptor modulators
- RANKL inhibitors
- Calcitonin

Promoting Osteoblastic Activity

Bone anabolic agents:
- Parathyroid hormone
- Oral calcium
- Oral vitamin D analogues
Suggested treatment options for women with osteoporosis

MJA 180:290-303 2004

BMD = bone mineral density.
*T score = number of standard deviations (SDs) from mean BMD for a young adult population.
Summary

• Bone is a metabolically active tissue
• Biology of bone remodelling
• Biology of bone mineralisation
• Drugs used to maintain bone mass
  – Bisphosphonates
  – Selective oestrogen receptor modulators
  – RANKL inhibitors
  – Calcitonin
• Drugs used to increase bone mineralisation
  – PTH
  – Calcium
  – Vitamin D analogues
Additional Reading:


• PubMed