2008-1-7 Number 7 Question: Outline the regulation of plasma calcium concentration. Outline the mechanism of action of biphosphonates for the management of hypercalcaemia.

Normal Calcium: 25,000 mmol (400 mmol/kg)

Distribution:

- Readily exchangeable pool (1%) (ECF esp plasma)
  - Total plasma [Ca2+] = 2.12-2.65 mmol/L
  - Ionised [Ca2+] = 1.2 mmol/L
    - Only the plasma free Ca is physiologically active and regulated by homeostatic mechanisms
  - Two pools
    - Diffusible (55%)
      - 45% free/ionised
        - Active form (above)
      - 10% complexed
    - Non-diffusible (45%)
      - protein bound (esp to albumin)
      - pH-dependent (↑ binding with ↑ pH)
- Poorly exchangeable pool (99%)
  - Bone/teeth (as hydroxyapatite, phosphates, carbonates)

ECF and hence plasma Ca is the result of a balance between dietary intake, gastrointestinal absorption and excretion, renal excretion and exchange with bone Ca.

Normal Losses:

- Kidneys (40%) → 2.5-7.5 mmol/day
  - Filtration of 250 mmol/day
  - 95% reabsorbed by tubules
    - PCT 65% with Na
    - TAL of LoH 20%
    - distal nephron 10%
  - 5% excreted
  - ↑ reabsorption at LoH/distal nephron
    - PTH
    - 1,25-dihydroxy-vitamin D
- GIT in faeces (60%) → 6-14 mmol/day

Regulation:

1. Calcitonin
   - 32 AA peptide with 1 disulfide bond it is the hormone of Procalcitonin
   - Released from Parafollicular cells (C-cells) of thyroid
   - Release Stimuli: Hypercalcaemia, gastrin, beta-agonists, dopamine, oestrogen, CCK, glucagon and secretin
   - Effect:
     - Increases osteoblast function/Inhibits osteoclast function
     - ↓intestinal calcium reabsorption
     - inhibition of renal Ca and PO4 reabsorption
2. Vitamin D
   - Fat soluble sercosteroid from either
     - diet or

        - synthesis in skin of cholecalciferol from cholesterol then processed in liver and activated in PCT of the kidney
    - Release stimuli
        - ↑ concentration of PTH causes ↑ 1-alpha-hydroxylase activity in kidney or ↓ Ca or PO4
    - Effect:
        - ↑ bone release of Ca/PO4
        - ↑ intestinal and renal reabsoption of Ca and PO4
        - negative feedback on PTH release
3. Parathyroid hormone
    - Polypeptide hormone secreted from the parathyroid gland
    - Release stimuli:
        - ↓ Ca (primary or due to ↑ PO4) sensed by CaSR (Ca sensing receptor) in PT chief cell
        - ↓ vitamin D levels
    - Effect:
        - ↑ Ca/PO4 reabsorption due to ↑ osteoclast activity
        - ↑ Vit-D production by kidney (effect on 25 alpha hydroxylase)
        - ↑ illeal Ca reabsorption
        - ↑ renal reabsoption of Ca/Mg from DCT and TAL loop of henle
        - ↓ PCT phosphate reabsorption

Bisphosphonates

- Indication: Hypercalcaemia
- Action:
    - Analogues of pyrophosphate in which P-O-P bond is altered to P-C-P bond that is unhydralysable.
    - Deposition of the analogue to the bone prevents osteoclast liberation of Calcium

Examiner Comments

The main points expected for a pass were:
• The components of plasma calcium are diffusible Ca (free and complexed) and nondiffusible Ca (protein bound). Only the plasma free Ca is physiologically active and regulated by homeostatic mechanisms. Plasma free Ca is also affected by plasma pH and albumin concentration.
• The distribution of Ca in the body and the fact that ECF Ca is less than 0.1% of total body Ca. ECF and hence plasma Ca is the result of a balance between dietary intake, gastrointestinal absorption and excretion, renal excretion and exchange with bone Ca.
• Tight hormonal regulation of GIT absorption, bone exchange and renal excretion mainly by parathyroid hormone and calcitriol.
Also expected were details of the actions of PTH on bone and the kidney and the actions of calcitriol on the gut and bone. No candidates described the feedback control mechanisms involving PTH and calcitriol. Additional marks were given for mention of other hormones that have a lesser effect on plasma Ca concentration.
The second part of the question on the mechanism of action of biphosphonates was poorly answered.