Pharmacology of Parathyroid Gland, Vitamin D & Calcium

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Content

- Calcium metabolism; Ca homeostasis
- Parathyroid glands
- Vitamin D
- Calcium and bone related-diseases

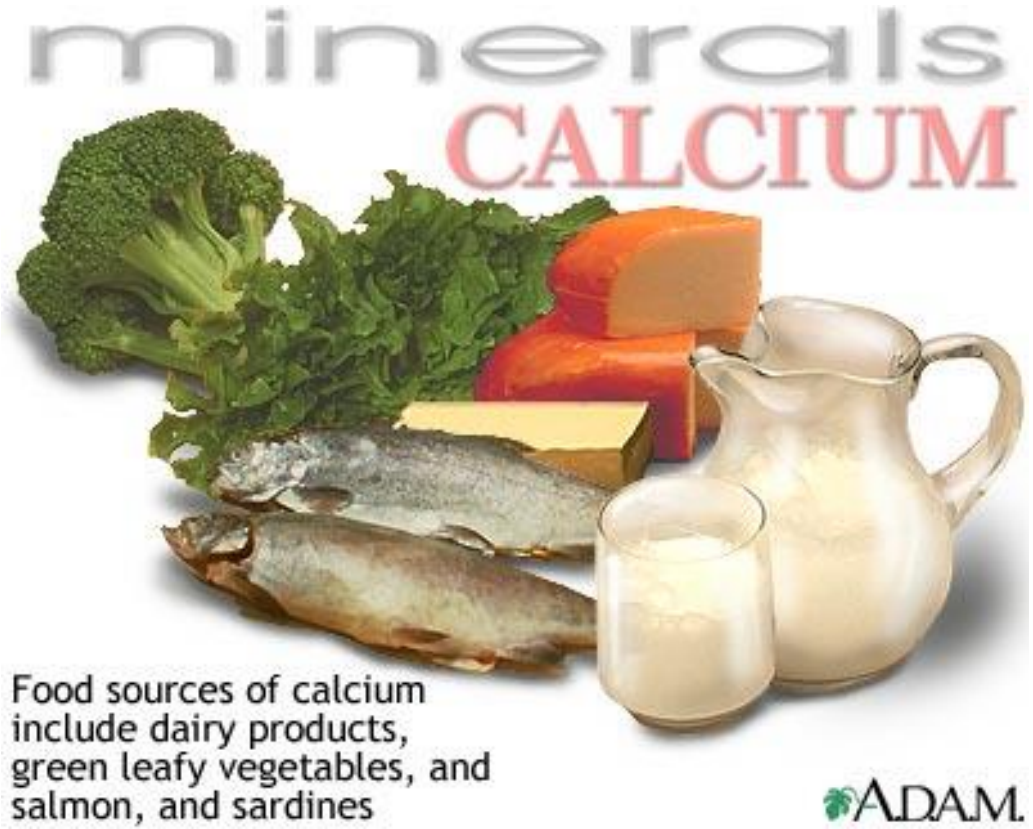
Calcium metabolism or calcium homeostasis

- Is the mechanism by which body maintains adequate levels of Ca
- Disturbance of this mechanism leads to:
  - **Hypercalcemia**
  - **Hypocalcemia**

Importance of Ca in body

- One of **the most important minerals for general cellular function**
- **Ca controls membrane excitation**: there is influx of Ca through specific Ca channels during excitatory process in **nerve & muscle**
- It is necessary for **muscle contraction**
- Ca is a major **constituent of bone & teeth**

Calcium Sources



Calcium Distribution in the Body

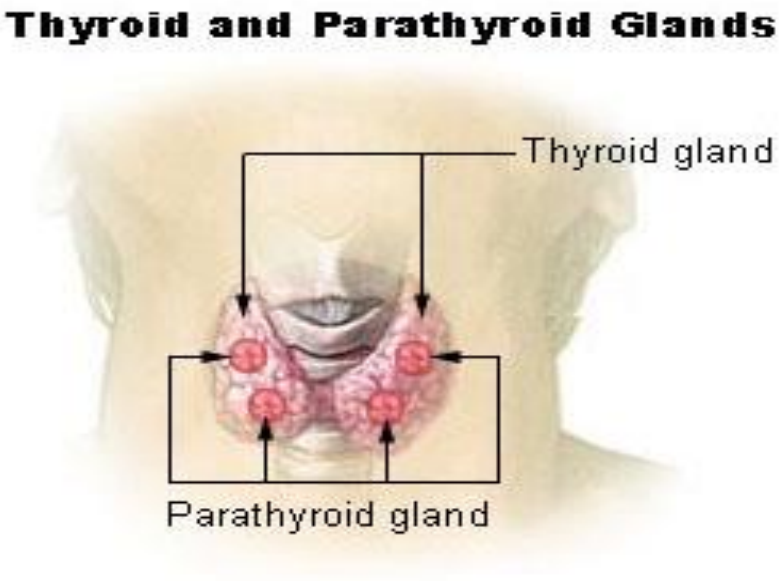
- Average adult body contains **1000g** of Ca
- Over **99%** of Ca is stored in **skeleton**
- The remaining **1%** in **extracellular fluid & cellular cytoplasm**
- The total **Ca in plasma** is about **9-10 mg/dL**

Regulators of Ca homeostasis

1. **Principal regulators:**
   - **Parathyroid hormone (PTH), Vitamin D**
2. **Second regulators:** calcitonin, glucocorticoids & sex steroids (estrogens)
3. **Other ions** such as sodium, fluoride

Parathyroid hormone (PTH)

- Is a single chain peptide hormone, composed of 84 amino acids
- It is produced in **parathyroid glands**



Parathyroid hormone (PTH)

- **When plasma Ca levels are low, PTH secretion increases:**
  - releases of Ca from bones
  - increases Ca reabsorption from kidney
  - stimulates Ca absorption from small intestine
- **If plasma Ca is high**, PTH secretion is inhibited & **Ca is deposited in bones**

Parathyroid hormone (PTH)

1. **Effects on bone:**

- PTH is involved in **remodeling of bone** (bone resorption & formation)

- **Bone resorption** is process by which **osteoclasts** (responsible for bone resorption), breakdown bone & releases minerals

- PTH **increases activity & number of osteoclasts**, which results in **increased Ca in plasma**

Parathyroid hormone (PTH)

2. Effects on the kidney:

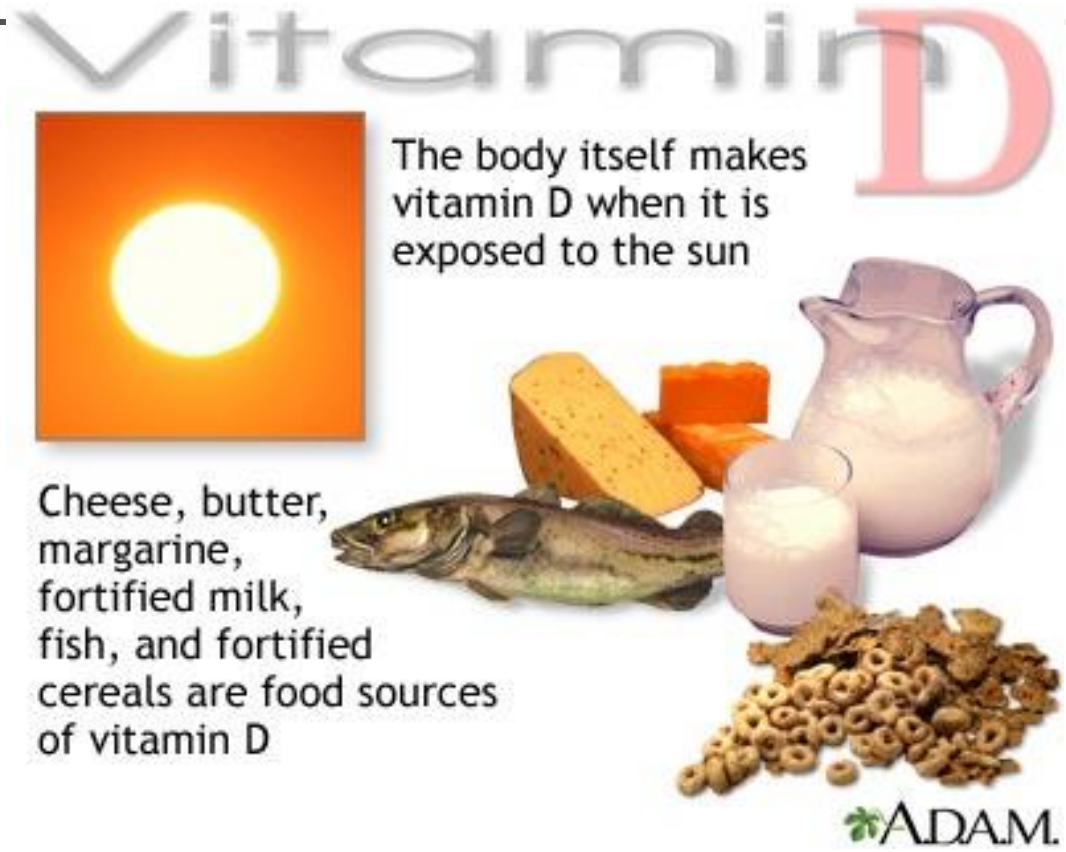
- PTH **promotes active reabsorption of Ca & magnesium by ascending loop of Henle**
- Increases phosphate excretion
- Stimulates synthesis of **1,25-dihydroxyvitamin D (1,25(OH)$_2$D)**

Vitamin D

- Is a prohormone that serves as a precursor to a number of biologically active metabolites
- It is produced in **skin**, from conversion of **7-dehydrocholesterol** to **previtamin D3** by action of **sunlight**, and then is converted to **vitamin D3 (cholecalciferol)**

- Many of **dairy products** in diet are fortified with **ergocalciferol**, **a synthetic vitamin D2** that has activity equal to **vitamin D3**

Vitamin D Sources



Vitamin D

- **Vitamins D2 and D3 are made more active by two hydroxylation reactions:**
  - **1α-hydroxylation in kidney**
  - **25-hydroxylation in liver**

  - to form **1α-25-dihydroxycholecalciferol (calcitriol) (the most active natural form of vitamin D)**

- **Alfacalcidol (one-alpha) requires only hepatic hydroxylation** to become highly active **calcitriol**,
- therefore, it is effective in **renal failure** since defective renal hydroxylation stage is bypassed

Vitamin D

- **Biological actions of vitamin D:**

  - Promotes absorption of Ca & Phosphate from gut

  - Promotes renal tubular reabsorption of Ca and P

Vitamin D

- **Indications:**

  - Prevention & cure of rickets & osteomalacia

  - Psoriasis

  - **Calcitriol** is licensed for management of postmenopausal osteoporosis

Vitamin D

- **Doses and preparations:**

  - **Simple vit D deficiency** can be prevented by taking orally **10 micrograms of ergocalciferol** daily

  - **Alfacalcidol & calcitriol** should be prescribed if patients with **severe renal impairment** require vitamin D therapy

Calcitonin

- A hormone secreted by **parafollicular cells of thyroid gland**
- Effects of **PTH & calcitonin** are antagonistic
- Principal effects of calcitonin are to **lower serum Ca & P** by actions on bone & kidney
- It inhibits osteoclastic bone resorption
- In kidney, it **reduces** both Ca & P reabsorption

Calcitonin

- **It is a useful drug for treatment of:**
  - **Hypercalcemia** (rapid effect)
  - **Paget's disease of bone** (relief of pain & to relieve compression of nerves)
  - Metastatic bone cancer pain
  - Postmenopausal osteoporosis

Glucocorticoids

- **Alter bone mineral homeostasis by:**

  - Antagonise vitamin D-intestinal Ca absorption

  - Stimulate renal Ca excretion

- **Prolonged administration** causes osteoporosis in adults, retarded skeletal development in children

Estrogens

- Estrogens **reduce bone resorbing action of PTH**
- Estrogen administration leads **to increased 1,25(OH)2 D level in blood**
- The principal therapeutic application for estrogen **treatment or prevention of postmenopausal osteoporosis**

Bisphosphonates

- **Action: inhibit activation & function of osteoclasts**
- **Alendronate, pamidronate, risedronate** are licensed for the treatment of osteoporosis
- Others are used in Paget's disease of bone & hypercalcemia due to cancer

Calcium and Bone-Related Diseases

1. Hypocalcemia

- **Features are neuromuscular:** tetany, paresthesis, laryngospasm, muscle cramps, & convulsions
- **Causes of hypocalcemia:**

- Hypoparathyroidism, vitamin D deficiency, renal failure, malabsorption

Treatment of hypocalcemia

1. Calcium (i.v, oral)

- **Calcium gluconate** is preferred for **i.v. use** because it is less irritating to veins (in acute hypocalcemia)

- **Calcium carbonate** is preferred for **oral use** because of its high percentage of Ca, low cost

2. Vitamin D: when rapid action is required, 1,25 $(OH)_2$ D (calcitriol) is vitamin D metabolite of choice, it is capable of raising serum Ca within **24-48 hrs**

2. Hypercalcemia

- Hypercalcemia causes CNS depression, including coma, and is potentially lethal **(cardiac arrest)**
- **Causes of hypercalcemia:**

- Hyperparathyroidism, cancer, hypervitaminosis D, sarcoidosis,

Treatment of hypercalcemia

1. Rehydration with **saline solution** (restores urine flow) & **diuresis** with a loop diuretic such as furosemide (enhance urine flow & increase renal Ca excretion)
2. **Bisphosphonates**
3. **Calcitonin**

Treatment of hypercalcemia

4. **Phosphate**: i.v. should be used only after other methods have failed to control symptomatic hypercalcemia
5. **Dialysis** is quick and effective in severe cases or with renal failure

3. Nutritional rickets

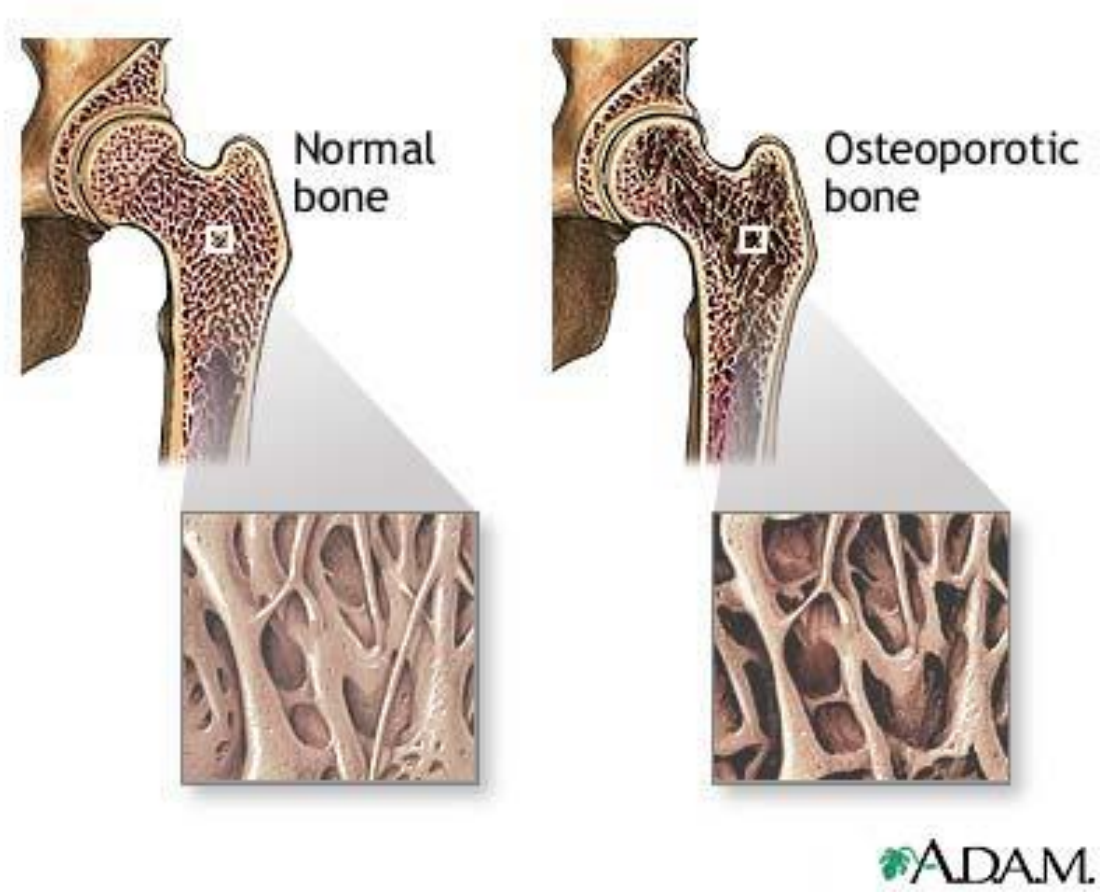
- Is a softening of bones in children, potentially leading to fractures & deformity
- It can occur in adults
- Causes: vitamin D deficiency, lack of adequate Ca in diet
- **Treatment:**

- Daily intake of 400 units of vitamin D
- Diet should contain Ca & P

4. Osteoporosis

- Is **abnormal loss of bone predisposing to fractures**
- **bone mineral density is reduced**, bone microarchitecture is disrupted
- It is **common in women after menopause** (post-menopausal osteoporosis) but may develop in men & premenopausal women
- **1 in 3 women & 1 in 12 men** over age of 50 have osteoporosis

7. Osteoporosis



Causes of Osteoporosis

- Side effect of chronic administration of glucocorticoids
- Manifestation of endocrine disease such as hyperparathyroidism
- Feature of malasbsorption syndrome
- Alcohol abuse
- Idiopathic (without obvious cause)

Treatment of Osteoporosis

- Estrogen replacement therapy

- Postmenopausal osteoporosis is due to estrogen deficiency & is treated with estrogen

- Bisphosphonates: alendronate & more recently risedronate
- Calcitonin: reduces bone resorption acutely
- Dietary Ca supplements & vitamin D

Thank you