بسم الله الرحمن الرحيم

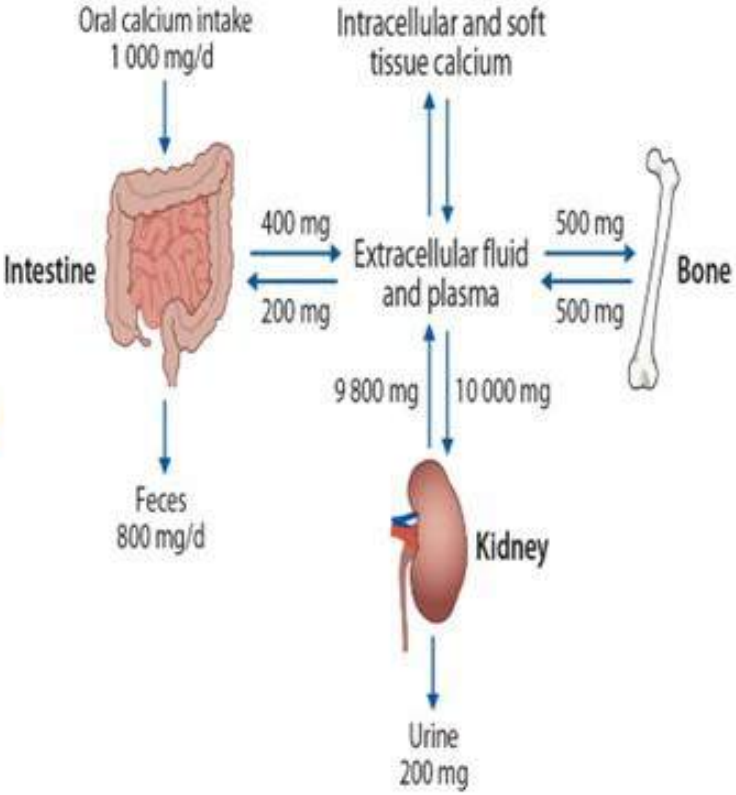
Pharmacology of parathyroid hormone, Vitamin D & calcium hemostasis

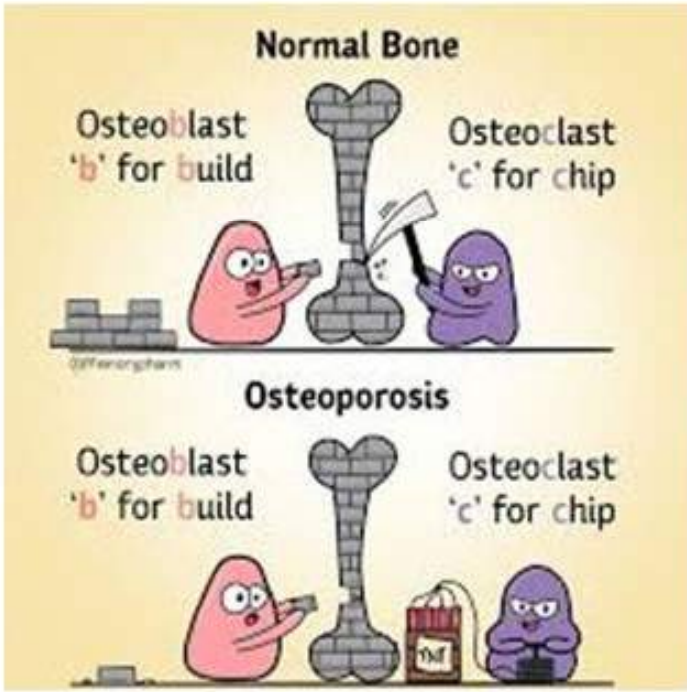
by
Dr Mohmmad Salem Hareedy

2025

Introduction to Calcium regulation

- Calcium (the 5th abundant element in the body), exist in **bones** & **teeth**.
- Calcium is essential for **muscle contraction**, **cardiac function**, **depolarization**, **secretions**, **blood coagulation** & **intracellular signaling**.
- Three organs maintain serum Ca^{2+} level: **kidneys**, **intestine** and **bone**.
- **Intestine** absorbs calcium under Vitamin D effects.
- **Kidneys** reabsorb calcium under PTH effects.
- Normally **bone** undergoes constant turnover through osteoblasts "creating bone" & osteoclasts "destroying bone".
- Osteoclasts can resorp bone to release calcium into the circulation when calcium levels drops.





Disorders related to calcium abnormalities

1-Hypocalcemia: may lead to neuromuscular tetany, muscle cramps, convulsions and laryngospasm.

2-Rickets: It is inadequate bones mineralization during development (childhood).

3-Osteomalacia: it is inadequate bone mineralization in adult.

4-Osteoprosis: due to enhanced bone resorption; it is common after menopause in women.

5- Hypercalcemia: It is a dangerous disorder which can cause cardiac arrhythmias (life threatening), renal damage (stone), and soft tissue calcification including CNS.

Causes of hypocalcaemia, rickets, osteomalacia and osteoporosis

1. Inadequate dietary Ca^{++} &/or vitamin D.
2. Malabsorption of Ca^{++} &/or vitamin D.
3. Defective vitamin D activation.
4. Hypoparathyroidism.
5. Renal failure.
6. Estrogen deficiency in women (e.g., menopause)
7. Drugs like corticosteroids.

Causes of hypercalcemia

Hyperparathyroidism, hypervitaminosis D, sarcoidosis, malignancy, etc.).

- The treatment of hypercalcemia include treating the cause, plenty fluids & low Ca2+ diets and the use of:

- **loop diuretics**
- **Glucocorticoids**
- **Calcitonin**

Vitamin D

➢It can be considered as a **hormone**; it is synthesized in skin under ideal conditions, (not required in diet), transported by blood to target tissues where it is **activated**, and binds to specific intracellular receptors.

➢Both vitamin **D2** & **D3** are not biologically active (**pro-hormones).**

➢Vitamin D2/D3 in the **liver** are activated to calcifediol (25-hydroxy vit. D) which is further hydroxylated in the **kidney** (under the effects of **parathyroid hormone)** to **Calcitriol** (1,25-dihydroxy vit. D) which is the most potent form of vit. D

➢ Potency: Vitamin D3< 25-hydroxy D< 1,25 di-hydroxy D.

➢ Negative feed-back control: **High Ca^{2+}** directly inhibits 1 hydroxylase & decrease PTH secretion, Also, **Calcitriol** inhibits transcription of PTH.

Cholecalciferol

Vitamin D

LIVER

Calcifediol

25-hydroxy Vitamin D

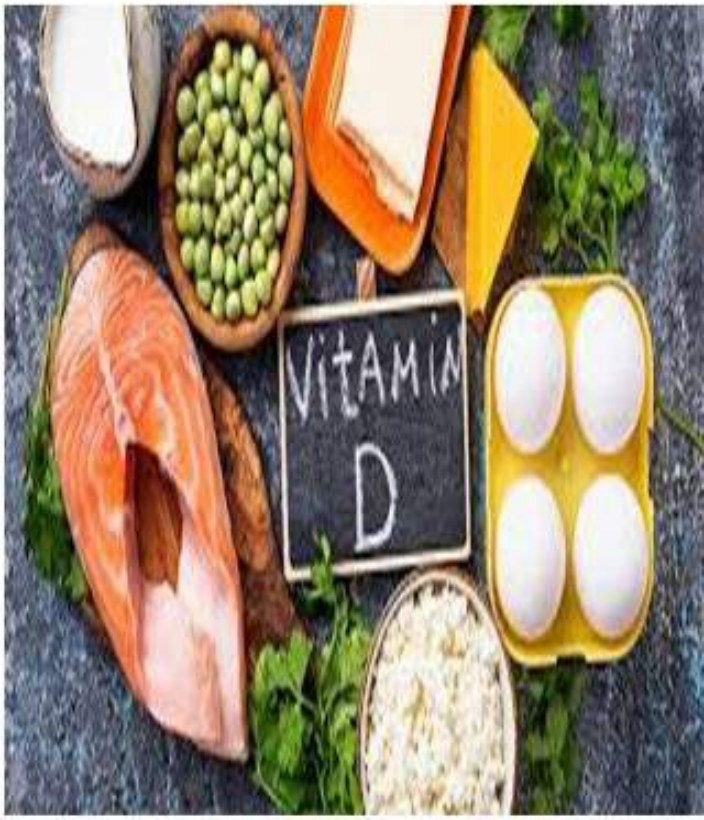
High Ca^{2+} & PO_4^-

KIDNEY

PTH or Low
Serum phosphate

Calcitriol

1, 25-dihydroxy Vitamin D



Calcitriol binds to intracellular receptors which then alter transcriptional regulation of genes leading to:

1. ↑ absorption of Ca^{2+} & phosphate from the intestine → ↑ serum Ca^{2+} → ↑ bone mineralization & Stimulates **osteoblasts**
2. If dietary supplement of Ca^{2+} is inadequate: **Calcitriol** will stimulate bone resorption "Ca^{2+} mobilization from the bone to the blood" by activating **osteoclasts**.

- Excess vitamin D (**hypervitaminosis D**) leads to hypercalcemia.
- Vitamin D toxicity is usually not life-threatening, but it can cause **kidney failure**, arrhythmias, unsteady gait and **confusion**.

Therapeutic Uses of vitamin D (oral or injectable):

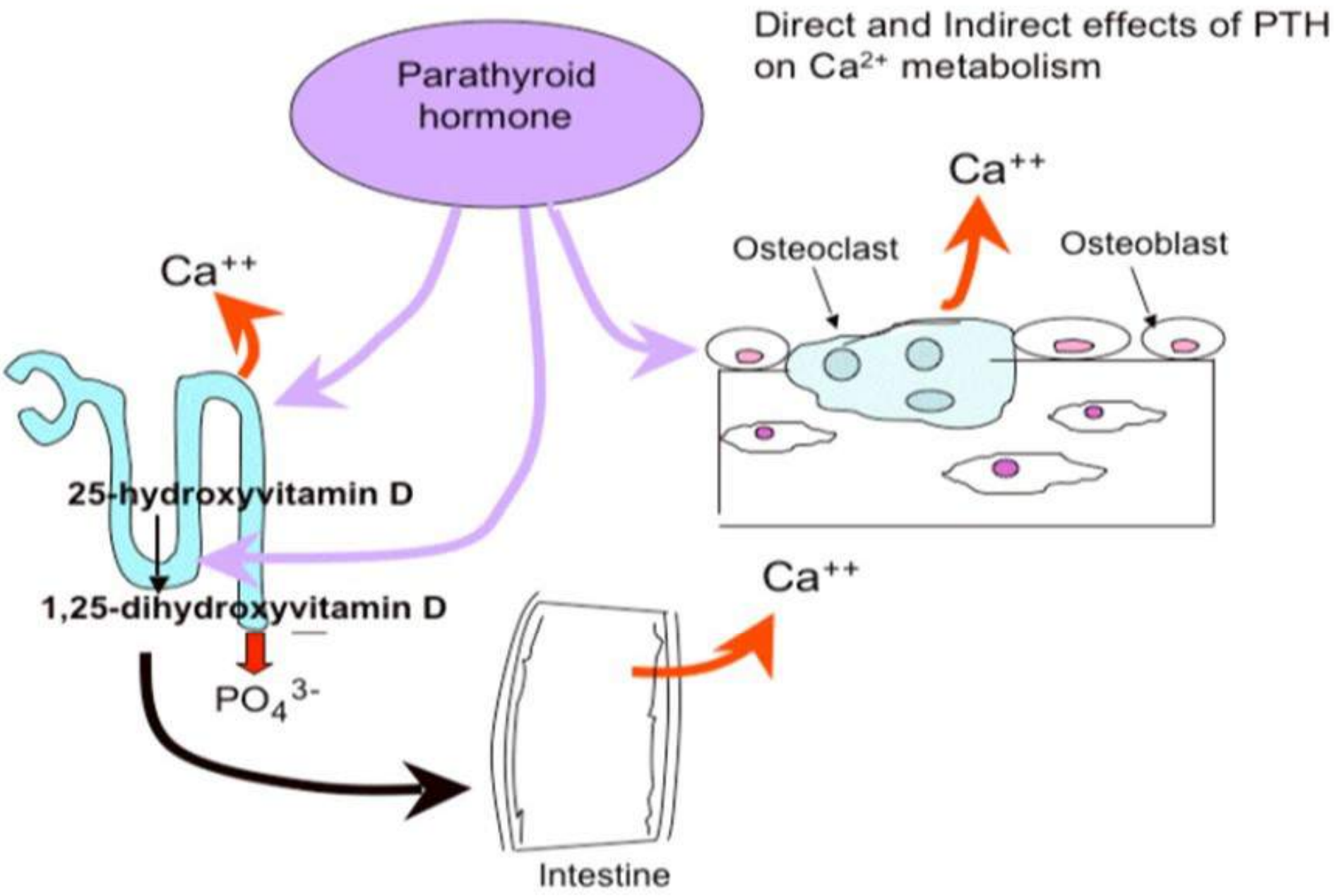
1. Prophylaxis and cure of **nutritional rickets** (vitamin D deficiency due to inadequate sunlight or deficient diet).
2. Treating **metabolic rickets** & **osteomalacia** in chronic renal failure.
3. Treatment of **hypoparathyroidism**.
4. Prevention and treatment of **osteoporosis**.
5. Calcipotiol is used topically for **psoriasis**.

Drug Interactions:

1. Estrogen, isoniazid, thiazide diuretics increase vit D levels .
2. Calcium Channel blockers (verapamil) decrease vit D synthesis.
3. Cholestyramine decreases vit D. absorption.
4. Phenobarbital, Phenytoin, increase vit D metabolism.
5. Antacids (over long term) alter vit D. metabolism/bioavailability.

Parathyroid Hormone (PTH)

- PTH is synthesized in the parathyroid glands.
- It binds to specific plasma membrane receptors & **activates adenylyl cyclase (Gs signaling).**
- PTH acts directly on the **kidneys** to stimulate renal tubular reabsorption of **Ca^{2+}** and **increases formation** of **1,25-dihydroxy vit. D**.
- PTH indirectly (through 1,25dihydroxy vit.D.) enhances dietary Ca^{2+} absorption.
- PTH stimulates Ca2+ resorption from the **bone** to correct hypocalcaemia.
- **The production and release of PTH is dependent on serum calcium levels.**


Direct and Indirect effects of PTH on Ca^{2+} metabolism
Parathyroid hormone
Ca^{++}
Osteoclast
Osteoblast
Ca^{++}
25-hydroxyvitamin D
1,25-dihydroxyvitamin D
PO_4^{3-}
Ca^{++}
Intestine

Uses of PTH:

- PTH has **very short half-life:** used mainly as **diagnostic** tool.
- However intermittent administration of **PTH** has been shown to increase bone deposition.
- Injectable Recombinant Human PTH (**Teriparatide**) is used for treatment of severe osteoporosis.
- Combination of **teriparatide & alendronate** may **synergistically** increase efficacy.
- PTH is not useful in treatment of hypoparathyroidism due to its short half-life.

Adverse Effects and Contraindications

1. **Osteosarcoma** occurred in animal model; however, no human data are confirmatory.
2. Patients with increased risk of osteosarcoma (e.g., **Paget's disease** with elevated Alkaline Phosphatase, open epiphyses) should not receive **teriparatide**
3. Not approved for use in **children.**

N.B. Hypoparathyroidism is best treated by **vitamin D & dietary Ca^{2+}**

➢Hyperparathyroidism is usually treated by **surgical resection** of the parathyroid glands or by calcimimetics if surgery is contraindicated.

Calcimimetics

Cinacalcet activates the Ca^{2+} sensing receptor (CaR) in the parathyroid gland. Activation of CaR **inhibits PTH release.**

It is indicated for treatment of **parathyroid carcinoma, 2ry hyperparathyroidism**, **Hypercalcemia** & **chronic kidney disease.**

Drug Interactions: Metabolized by CYP450 therefore, certain drugs (ketoconazole, itraconazole, erythromycin and others) increase cinacalcet concentration.

Adverse reactions: Hypocalcaemia (It is advised to check serum calcium closely).

Calcitonin

It is synthesized by the para-follicular cells of the thyroid gland. Its secretion is regulated by plasma Ca^{2+}levels; **high Ca^{2+} stimulates release of calcitonin**.

Actions: (generally opposite of those of PTH)

- Decreases absorption of Ca^{2+} from intestine.
- Increases urinary excretion of Ca^{2+}, Na+, Mg2+, Cl-, & PO43+.
- Inhibits osteoclast activity resulting in decreased bone resorption and therefore, increased calcium deposition in bone, this leads to **decreased plasma Ca^{2+} concentration.**

Therapeutic use

Human synthetic calcitonin (**Cibacalcin**) or salmon calcitonin (**Calcimar** or **Miacalcin**) can be administered IM, SC., or by nasal spray to treat the following conditions.

1. **Paget's Disease** (abnormal bone turnover).
2. **Osteoporosis**
3. Useful in **vit. D intoxication**.
4. **Hypercalcemia** associated with malignancy (osteolytic bone metastasis).

Adverse Effects of calcitonin:

1-Hypersensitivity reactions & GIT upset like nausea.

2-Escape or resistance a major problem: **loss of effectiveness** especially of actions at the bone tissue.

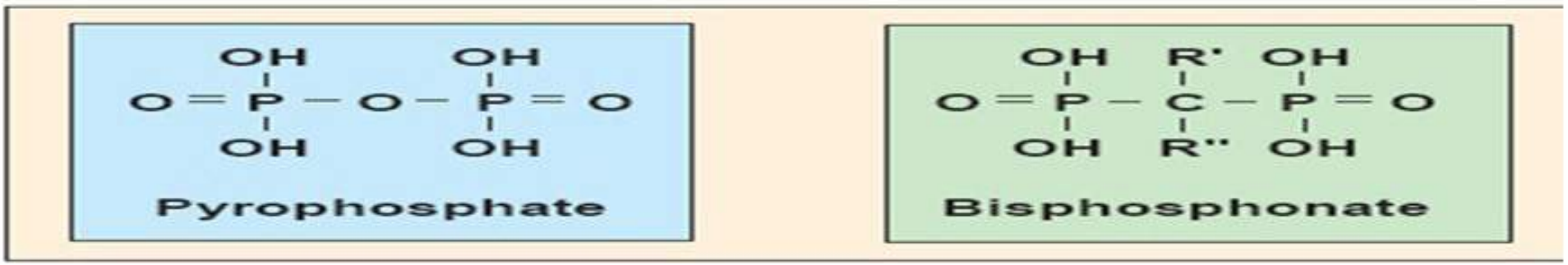
Bisphosphonates (BP)

Drugs like pyrophosphate. They have **very high affinity for calcium →concentrated in bone**.

There are two classes BP work differently in killing osteoclasts.

1-The non-nitrogenous bisphosphonates (disphosphonates) like **Etidronate**, **Clodronate** and **Tiludronate**

2-Nitrogenous bisphosphonates like **Alendronate**, **Pamidronate**, Neridronate,Olpadronate, Ibandronate, Zoledronate.



Mechanisms of action of BP:

Promote bone formation and **prevent bone loss:**

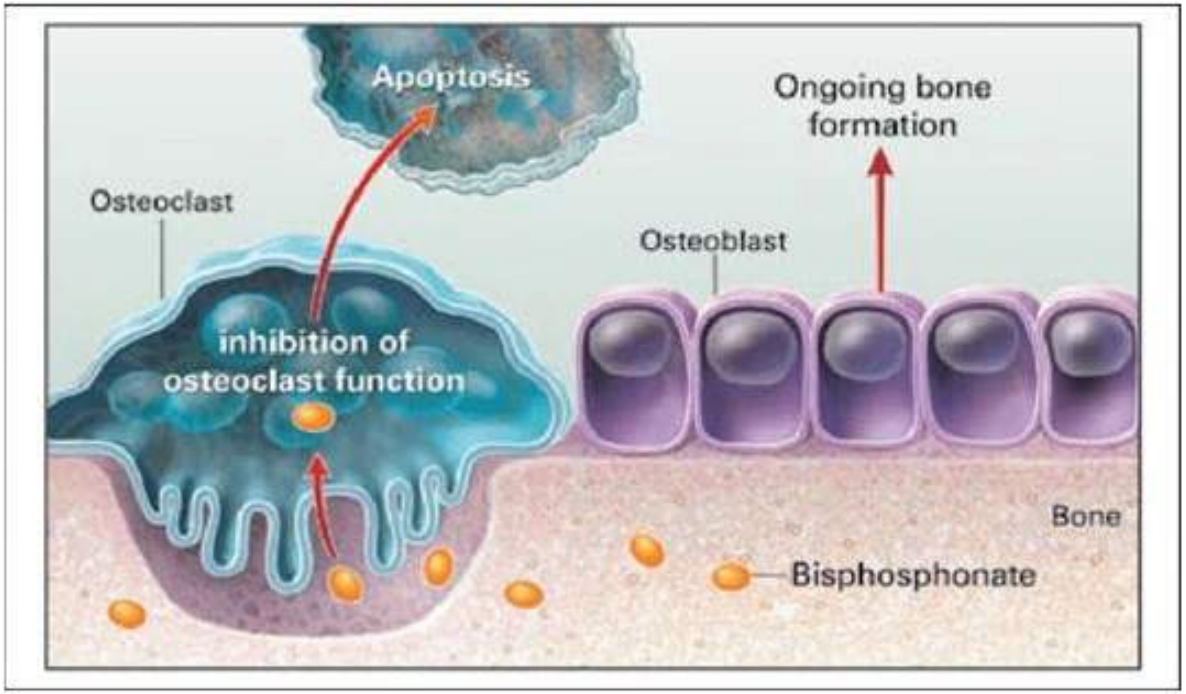
- BP inhibits osteoclasts activity and decreases their numbers and encourages apoptosis (cell death) of osteoclasts. Thereby BP slow the bone loss.
- BP is **incorporated in bone** and when **ingested by osteoclasts** they **inhibit their activity** & induce their **apoptosis**; this wills shift the balance in favor to **osteoblasts** (bone formation).
- BP also down **regulate receptor activator of nuclear factor kappa-B ligand** expression, and this **inhibit the transformation of osteoblasts to osteoclasts** (leading to decreased number of osteoclasts).

- BP also **inhibit production of 1,25-di-OH vit D**; this add advantage in treatment of hypercalcemia due to Paget's disease but could lead to osteomalacia.

❑The non-nitrogenous bisphosphonates are metabolized in osteoclasts to compounds **competes with adenosine triphosphate (ATP)** in the cellular energy metabolism → apoptosis.

- ➢ These drugs are now less prescribed due to more adverse effects than the nitrogen containing group.

❑ Nitrogenous bisphosphonates **disrupts HMG-CoA reductase enzyme** →prevents the connecting small proteins to the cell membrane (prenylation) → inhibition of osteoclast functions and dynamics → death.



Pharmacokinetics of BP:

Administration

- oral (for Paget's disease)
- i.v. (for hypercalcemia).
  - BP are Poorly absorbed orally.

Aluminum hydroxide, antacids, calcium salts, magnesium salts and iron salts may inhibit the BP absorption.

  - Distributes readily and concentrates in bone.
  - Excreted by kidneys; not metabolized.
  - Plasma elimination half-life about 6 hr.
  - Retention half-life in bone may reach 3-6 months.

Therapeutic uses:

BP are used in the treatment of bone diseases involving excessive bone destruction or resorption, e.g.

1. Paget's disease
2. Tumor-associated osteolysis
3. Post-menopausal osteoporosis
4. Multiple myeloma
5. Primary hyperparathyroidism
6. Fibrous dysplasia
7. Other conditions that exhibit bone fragility.

Adverse effects of BP

1. Bone, joint, or musculoskeletal pain have been reported.
2. Metallic taste is common.
3. GIT side effects like dysphagia, pain, gastritis & esophagitis. esophageal carcinoma (not confirmed yet).

The GIT side effects can be prevented by remaining seated upright for 30 to 60 minutes after taking the medication.

4. Intravenous BP may cause fever and flu-like symptoms after the first infusion, due to activation of T cells.
5. Glomerulopathy and nephrotic syndrome (with alendronate).

4.When administered intravenously for the treatment of cancer, have been associated with osteonecrosis of the jaw.

5.Hypocalcaemia or fluctuation of calcium levels which may cause atrial fibrillations.

6.Osteomalacia (due to decrease vit D).

Contraindications or precautions

Children, pregnancy, breast-feeding, colitis and renal impairment.

Fluoride

Mechanism of Action: it is a **mitogen for osteoblasts** to stimulate bone formation. It is Stored in bones and teeth.

Indications: **Prophylaxis of dental caries.**

Administration:

1. Oral (Absorption from GI tract is rapid and complete).
2. Topical to oral cavity preferably during teething in children.

Other drugs in treatment of osteoporosis

- ❑ Estrogen Specific Estrogen Receptor Modulators (Raloxifene)
- ❑ Androgen


Thank
You