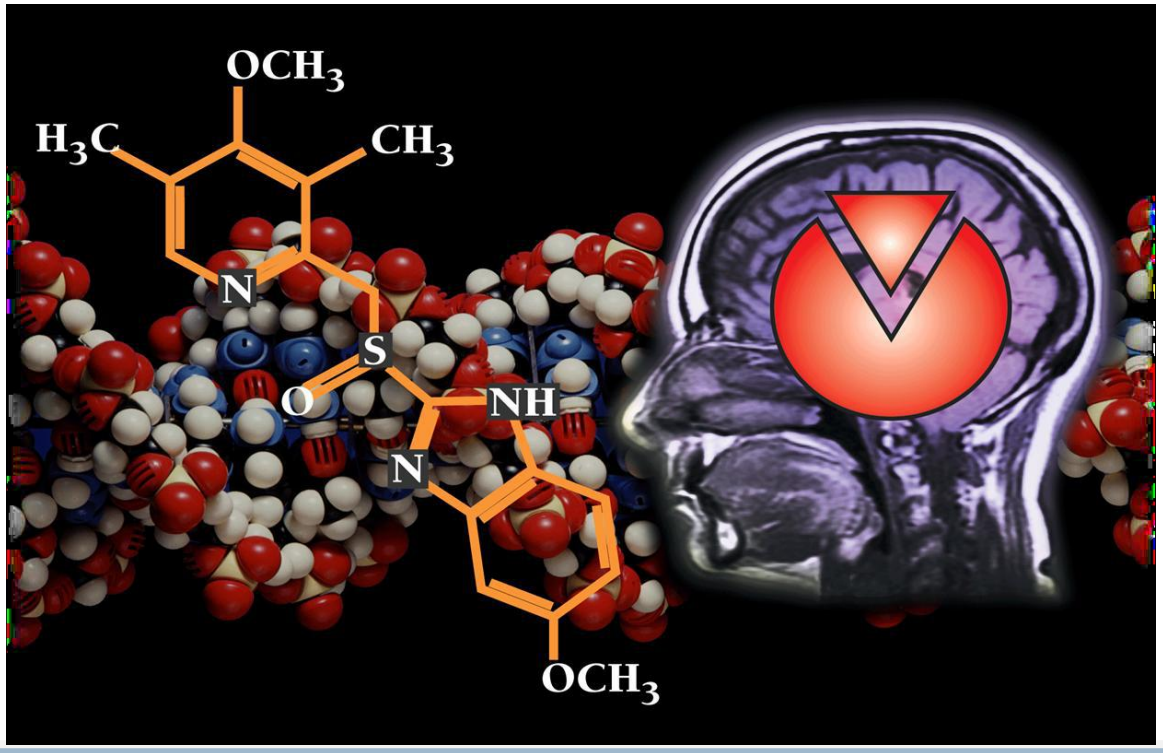
King Saud University
College Of Medicine
Pharmacology Team 430
Endocrine Block

OSTEOPOROSIS



Note: Text in red are important information, and textboxes in thick blue margins are additional info or for explanation.

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Introduction

Bone is basically composed of 2 types of tissues:

Inorganic ➜65% of mass ➜ consists of **hydroxyapatite**, **calcium & phosphorus salts**

Formed during **OSTEOGENESIS** by **MINERALIZATION** of the **organic matrix** (osteoid Frame work) & is mediated by **alkaline phosphatase** `

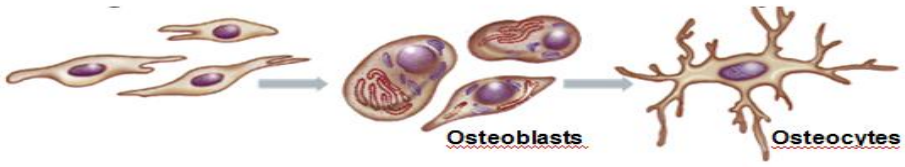
Organic ➜ 35% of mass ➜ Consists of;

♦ **Organic matrix [OSTEOID]** ➜ produced by **osteoblasts** ➜Bone Framework

♦ **Bone cells** are either; **Bone Forming (osteoblasts)** or **Bone Resorptive (osteclasts)**

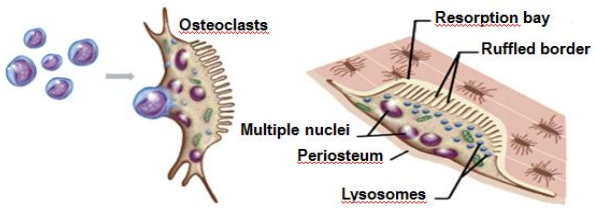
A. Bone Forming Cells:

- **Osteogenic cells** ➜ mesenchymal in origin ➜ are progenitor of **blasts & cytes** ➜ are found on all bone surfaces
- **Osteoblasts** ➜ forms **osteoid framework** & help in **its mineralization**. **Then it will convert to osteocytes**
- **Osteocytes** ➜ sense mechanical stress ➜ signals to both **blasts & clasts**



B. Bone Resorptive Cell:

Osteoclastes ➜ myloid in origin ➜ made by fusion of multiple progenitors of **monocytes.**

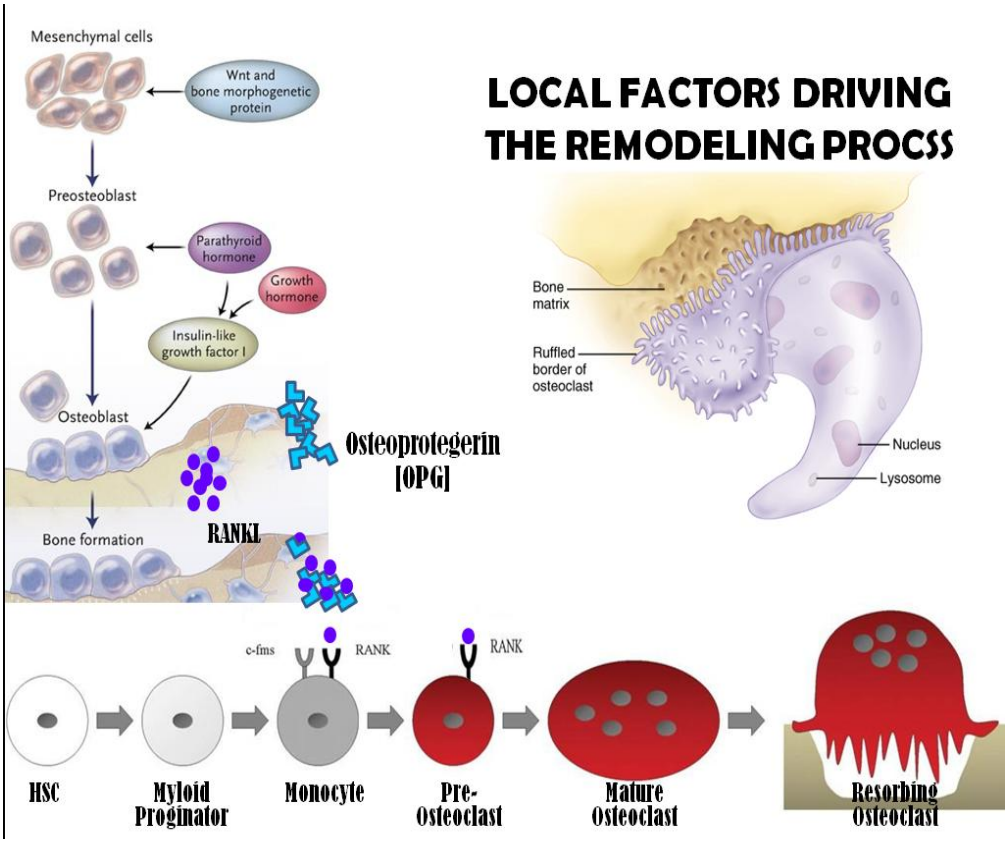


- Reside in pits **(resorption bays)** that form by eaten bone surface.
- Secretes **lysosomal enzymes** (collagenase & metalloproteinase) + **hydrochloric a**. which will lead to **dissolving of bone matrix**

Normally

Bones continuously form & resorb (**BONE** REMODELING). Under control of **systemic hormones**, body mineral contents & l**ocal** autocrine-paracrine secretions (Cytokines, Growth Factors, PGs)

It is meant to maintain calcium homeostasis & to renew bone in repair of microdamage & microcracks



RANKL or RANK ligand: An **osteoblast-derived growth factor** that stimulates **osteoclast** activity and **osteoclast** precursor differentiation. It does that by binding to **RANK receptors** in the **osteoclast precursors** forming a **RANKL-RANK ligand** interaction, which will **stimulate osteoclast differentiation**.

Osteoprotegerin (OPG), also known as **osteoclastogenesis inhibitory factor** (OCIF): is a glycoprotein functions as a decoy receptor for RANKL. By binding to RANKL, it will prevent forming a **RANKL-RANK ligand** interaction. This will inhibit osteoclasts formation.

Normally while the **osteoblast** synthesizes the bone it will produce**: RANKL** and **OPG**. These two will bind to each other after synthesis; however, RANKL is synthesized more in number, thus it will bind to monocyte and pre-osteoclast leading to the formation of the **osteoclast.**

Systemic hormones Controlling Remodeling:

1. Parathyroid hormone → Maintains calcium homeostasis via

- ↑ **bone formation (if given intermittently) While↑ bone resorption (if given continuous)**
- ↑renal tubular **calcium reabsorption**
- ↑ renal calcitriol (Vitamin D) production **(By stimulating the conversion(in the kidneys) of the inactive form of vitamin D to its active form)**

2. CALCITROL (Vitamin D)

- ↑ intestinal Ca & phosphorus absorption→ ↑ bone mineralization
- ↑ bone resorption when the body is deficient calcium.

3. ESTROGEN & ANDROGEN ↓ rate of bone loss by acting on many local factors

- **Increase osteoclast** apoptosis & growth factors from osteoblasts
- Decrease No. & depth of resorption cavities & release of cytokines (such as RANKL) .

4. CALCITONIN

Not much physiological role

Pharmacologically → ↓ osteoclasts & bone resorption

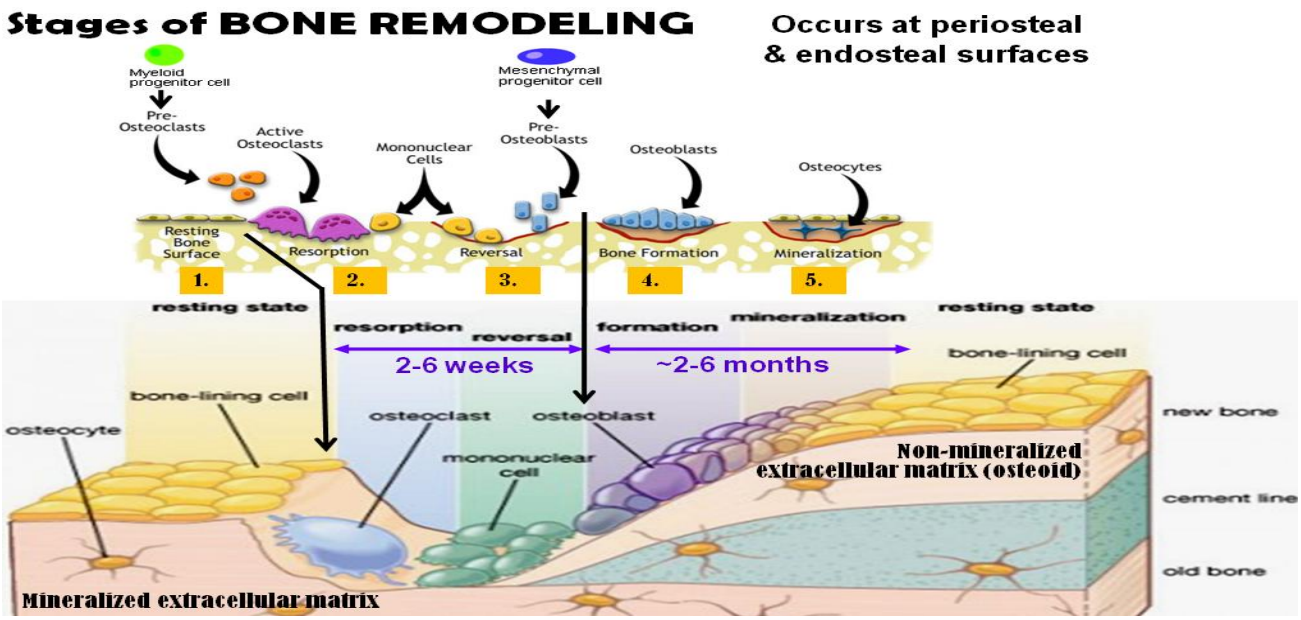
5. GLUCOCORTICOIDS

↑ apoptosis of osteoblasts & osteocytes → ↑ resorption

Note: Glucocorticoids alter bone mineral homeostasis by **antagonizing vitamin D**-stimulated intestinal calcium transport, by stimulating renal calcium excretion, and by blocking bone formation.

6. THYROID HORMONE ↑ Bone turn-over i.e. resorption & formation

7. Growth hormone & IGFs ↑ skeletal growth & endochondral bone formation.



Healing of bone is different than other tissues; It takes a long time. So, if we want to give a therapy, we give it for 6 months minimally.

OSTEOPOROSIS :

- A complex endocrinologic disorder of bone & mineral metabolism (**bone resorption > formation**) → Low bone mass
- **Disruption of bone architecture** → Reduced bone strength
- **Risk of fractures**

Potentially Modifiable	Non-modifiable
Current cigarette smoking	Personal history of fracture
Diet low in calcium/vitamin D	1st-degree relative has fracture
Glucocorticoids, anticonvulsants	Race (Caucasian or Asian)
Excessive alcohol intake	Elderly age
Sedentary lifestyle	Poor health
Body weight less than 127 lb	Dementia
Lack of estrogen	Hormonal disorders
Environmental risks	Neoplastic disorders
Poor eyesight	Metabolic abnormalities
History of organ transplants	Connective tissue disorders

Osteoporosis is defined as abnormal loss of bone predisposing to fractures. It is most common in **postmenopausal women** but also occurs in men.

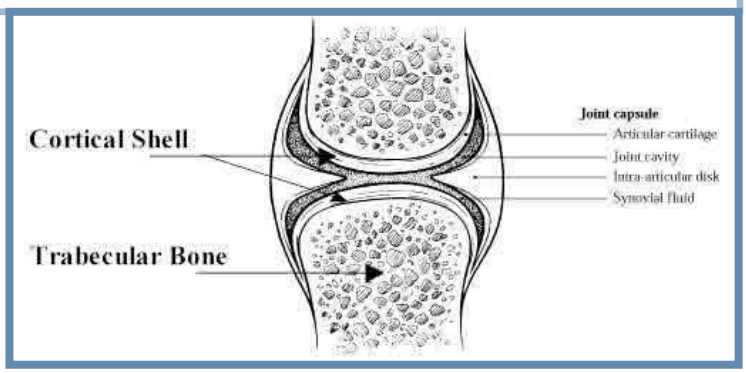
Treatment of osteoporosis

1- Replace what is missing….Ca, Vit D, Na fluoride:

Used to enhance the strength by the formation of **fluorapatite**.

Is considered only when trabecular bone is ↓ in presence of normal cortical bones

Note: Bone in human and other mammal bodies is generally classified into two types 1: Cortical bone, also known as compact bone and 2) Trabecular bone, also known as cancellous or spongy bone. These two types are classified as on the basis of porosity and the unit microstructure. Cortical bone is much denser with a porosity ranging between 5% and 10%. Cortical bone is found primary is found in the shaft of long bones and forms the outer shell around chancellors bone at the end of joints and the vertebrae. A schematic showing a cortical shell around a generic long bone joint is shown below.



2- Reset back the balance of remodeling:

Antiresorptive agents :

- **Bisphosphonates**
- **Estrogen analoges**
- **Androgen analoges**
- **SERMs (Selective Estrogen Receptors Modulator)**
- **Calcitonin**
- **Rankl inhibitors**

- Bone anabolic agents: Teriparatide

- Dual effect: Strontium (new drug)

- **Others:** Thiazide diuretics (**increase Ca reabsorbtion**), statins (they are not that effective in the treatment)

1-BISPHOSPHONATES :

Are compounds that have two phosphonate (PO_3) groups

* Non-Nitrogenous :	* Nitrogenous
Etidronate	Alendronate ➔ 500
Clodronate ➔10	Ibandronate ➔1000
Tildronate ➔10	Risedronate ➔2000
	Zoledronate ➔**10000**

We grade these drugs according to their potency out of 10000.

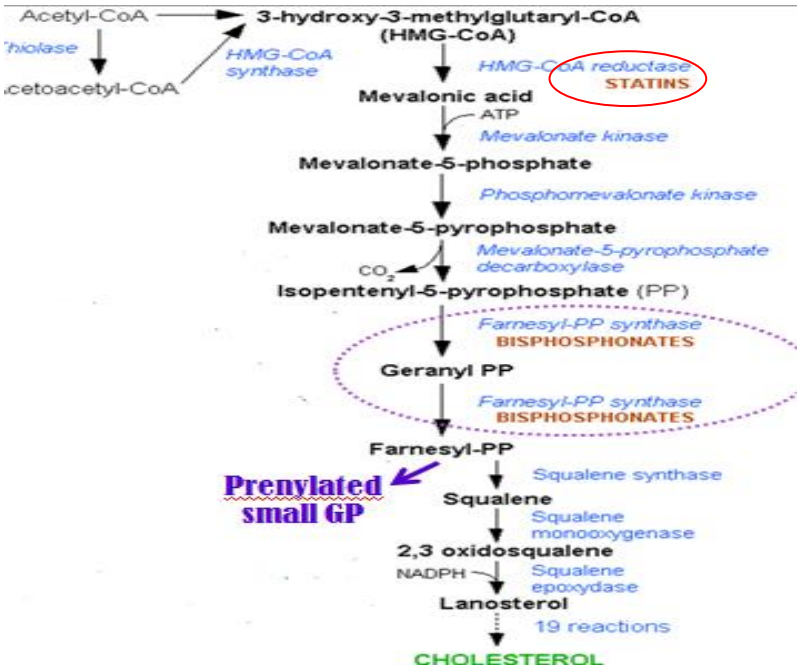
Nitrogenous drugs are more potent.

Mechanism :

- Are structurally similar to pyrophosphate (which is essential for a lot of enzyme functions), thereby inhibiting activation of these enzymes that utilize it.
- They preferentially "stick" to calcium ➔ concentrate in bones, bound **to hydroxapatite**.
- They prevent bone **resorption** by **inhibiting osteoclast function**.
- Their relative potencies for **osteoclast** inhibition is the most with 3rd generation "**Zoledronate**"

How do they inhibit osteoclasts???

It is taken up during osteoclast resorptive activity ➔ blocks **steps in cholestrol synthetic pathway within osteoclast ➔ end up by osteoclast apoptosis**



BLOCK STEPS IN CHOLESTROL SYNTHETIC PATHWAY IN OSTEOCLAST

that act as signaling molecules responsible for the osteoclastic hydrolytic & phagocytic activity. → Stop function ➔ apoptosis

Note : statins can help in case of osteoporosis , because it works on this pathway. (HMG-CoA reductase inhibitors)

In short they lead to :

1) **decrease in osteoclastic** formation/activation

2) inhibition of the cholesterol biosynthetic pathway important for **osteoclast function.**

3) increase in osteoclastic apoptosis (programmed cell death).

Kinetics (important)

- Poorly absorbed (< 10%), food impair absorption more ➔ must be given on an empty stomach or given as infused IV.
- $t_{1/2}$ 1 hr.
- Half of absorbed drug accumulates in bones, remainder ➔ excreted unchanged in urine.
- In bone it is retained for months, depending on bone turnover.

Indications

- Osteoporosis, secondary to menopause, glucocorticoids, …. etc
- Paget's Disease
- Malignancy- associated hypercalcaemia (Malignancy when metastasize to bone)

Dosing (important)

- Once weekly, or on two consecutive days each month
- Taken 1st thing am / early morning with glass of water, on empty stomach then nothing taken after for ½ hr.
- Should be taken in upright position.
- Separate 4 hrs before giving Ca, Mg, Al containing drugs
- Newer preparations can be given as 2 hrs IV infusion (or better over a lesser time), monthly in 1st year then every 3 months after.

Note: The bisphosphonates are rapidly cleared from the plasma, primarily because they avidly bind to the **hydroxyapatite mineral of bone**. Once bound to bone,they are cleared over a period of **hours to years**. Elimination from the body is **primarily through renal clearance**, and the **bisphosphonates** should not be given to individuals **with severe renal impairment.**

ADRs

- GIT irritation; nausea, vomiting, gastritis , ulceration ➔ to avoid give large amount of water
- **Gastro-esophageal reflux ± ulcerations** ➔ to avoid give on empty stomach while sitting in upright postion
- Flue like manifestations **upon IV infusion**
- **Osteo-necrosis of the jaw** [mandible > jaw] more upon long use with IV infusion preparation usually after dental surgical procedures. It is due to activation of matrix metalloproteinase that cause lysis of the bone
- Atrial fibrillation occur more in women who use **alendronate & zolidronate**

Contraindications

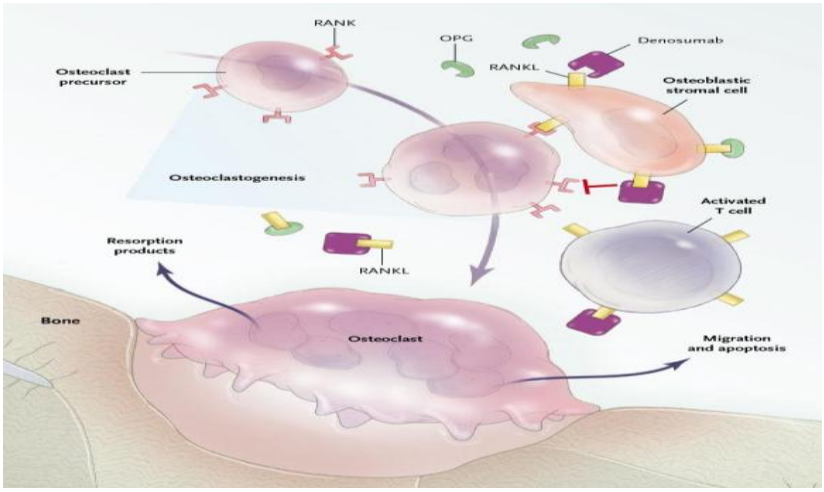
- **Decreased renal function**
- **Peptic ulcer / esophageal reflux**

2-RANKL Inhibitors (Denosumab)

It is a fully human **monoclonal antibodies** that mimics the activity of **osteoprotegrin(OPG)**

Mechanism :

- It binds to **RANKL**, expressed by osteoblasts ➔ prvents RANKL from interacting with RANK receptor expressed on preosteoclasts ➔ ↓ osteoclastogenesis (no mature osteoclasts).
- It binds also to mature osteoclast lead to its apoptosis
- So net effect ➔ ↓ bone resorption.



Administration

Subcutaneous **every 6 month**

Contraindications

In patients with hypocalcemia (because it is antiresorptive so it will decrease Ca levels in the blood) . Correct Ca & Vit D levels before starting denosumab

ADRs

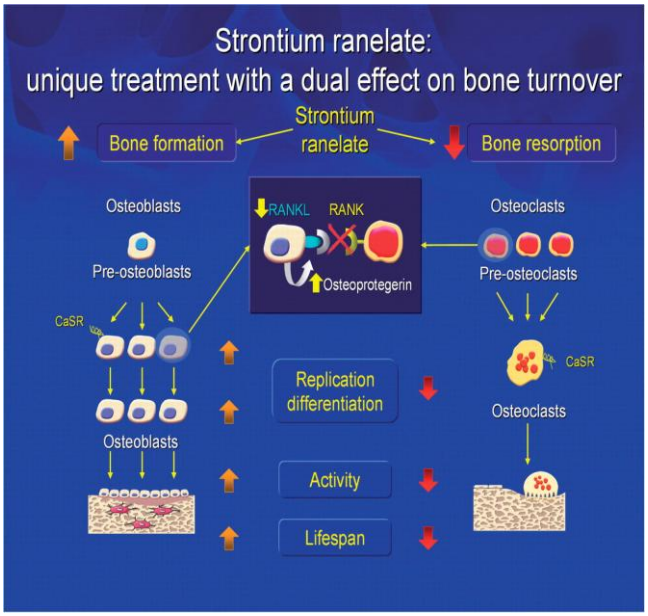
- Infections; urinary & respiratory
- Eczema & skin rash
- Constipation (As they reduce Ca levels leading to decreased motility of the bowls)
- Cataract
- Joint pains

3-Strontium:

- Sr^{2+}, is a divalent cation, **resembling Ca^{2+}** in atomic & ionic properties.
- It is orally active as **distrontium.**

Mechanism

1st drug to possess " **dual action** " i.e has **both anabolic & antiresorptive** effects resulting in a rebalance of bone turnover in favor of **bone formation.**



On Osteoblast;

- Since it is like Ca, it acts as **agonist on Ca Sensing Receptor [CaSP]** ; which is a **G-protein coupled receptor** that enhances differentiation of preosteoblast to osteoblast ➔↑ bone formation
- It **stimulate the expression of OPG (osteoprotogerin) ➔↑RANKL binding ➔** inhibition of osteo-clustogenesis ➔↓ bone resorption

On Osteoclast;

Acts as agonist **on Ca Sensing Receptor [CaSP]** ➔suppress differentiation of preoteoclast to osteoclast ➔↑ osteoclast apoptosis ➔↓ bone resorption

Pharmacokinetics

- Orally with a modest bioavailability ➔25%
- Binds partially to plasma proteins and strongly to bones
- t ½ ➔ 60 hrs
- Excreted mainly **by the kidney**

Indications

- **Osteoporosis, 2ndry to menopause, glucocorticoids, ….**
- **Malignancy- associated hypercalcaemia**

Contraindications

- **In severe renal disease.**
- In hypersensitivity to it
- In increased risk of venous thromboembolism (Calcium is necessary for some clotting factors, Strontium resembles calcium.)
- In phenylketonuria (since the drug contains phenylalanine)
- Food specially containing milk± its products — Precautions
- Antacids — 2hrs spacing
- Oral tetracycline & quinolones **chelate the active** Strontium, thus impairs their effect.

Note: **chelation** is The combination of a metal ion with a chemical compound to form a ring. Chelation is used to treat metal poisoning.

ADRs

- GIT irritation; nausea, vomiting, headache, eczema
- All resolve in 1st 3 months

Sometimes we give hormone replacement therapy in the treatment of osteoporosis:

Estrogens

In menopausal female we give it:

- If she has undergone hysterectomy (excision of the uterus)
- If the uterus is present we give estrogen + progestins . Because estrogen if given alone exogenously it may cause endometrial (uterine) cancer.

Note: The risk of throboembolic effects , myocardial infarction, and breast and endometrial cancer is increased with use of estrogen. The increased risk of endometrial cancer can be prevented by including **progestins** along with the treatment.

Estorogen is used as a HRT (Hormonal replacement therapy) for treatment Menopausal Symptoms

SERMs (Selective estrogen-receptor modulator) are used in Menopause / Elderly (They are safest and best choice in this case)

ANDROGENS in Elderly men

Estrogen in females & Androgen in males is essential for normal bone remodeling :

- ↑ osteoclast apoptosis
- ↑ release of growth factors from osteoblasts
- ↓ No. & depth of resorption cavities
- ↓ release of inflammatory cytokines causing resorption

SERMs: Raloxifene

1st selective estrogen receptor modulator for prevention of osteoporosis

Mechanism

Antiestrogens that exhibits **partial agonistic** action; acting as an agonist in bone and heart & an **antagonist in some female sex organs**

	Brain	Uterus	Vagina	Breast	Bone	CVS
Estradiol	++	++	++	++	++	++
Raloxifene	—	—	—	—	+	+

Advantages

- ↑ bone density (2%) & ↓ fracture risk (30%)
- No stimulation of breast or endometrial tissue
- No need for progestin in women with uterus
- ↓ LDL

Disadvantages

- ↑ risk of thromboembolic events
- Doesn't treat well Post-menopausal Symptoms
- May ↑ hot flushes
- No effect on HDL

Tibolone

- **Synthetic steroid ➔having estrogen, androgen & progestin properties** (because of this balance it doesn't cause thromboembolic risks)
- **Can be used without CVS risks.**

Summary:

- Osteoporosis is defined as **abnormal loss of bone** predisposing to fractures. (where there is more osteoclastic activity than osteoblastic)
- **In treatment 1- we replace the deficiency of Calcium or Vitamin D by providing them as supplements**
- **Na fluoride** Used to enhance the strength by the formation of **fluorapatite**, and it's **only when the trabecular bone is abnormal in presence of normal cortical bones**
- **BISPHOSPHONATES :**
  - **MOA :** Are structurally similar to pyrophosphate **. They prevent bone resorption** by inhibiting osteoclast function. It is taken up during osteoclast resorptive activity ➔ blocks **steps in cholestrol synthetic pathway within osteoclast ➔ end up by osteoclast apoptosis**
  - **Kinetics** : Poorly absorbed , food impair absorption more(given on an empty stomach / infused IV) . Half of absorbed drug accumulates in bones, remainder ➔ excreted unchanged in urine. In bone it is retained for months, depending on bone turnover.
  - **Indications:** Osteoporosis, 2ndry to menopause, glucocorticoids, …. Etc. Paget's Disease **.** Malignancy-associated hypercalcaemia
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- **RANKL Inhibitors (Denosumab)**
  - **MOA :** It binds to RANKL, expressed by osteoblasts →↓ osteoclastogenesis (no mature osteoclasts). It binds also to mature osteoclast enhance its apoptosis **.** So net effect ➔ ↓ bone resorption.
  - **Administration :** Subcutaneous **every 6 month**
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  - **Indications :** Osteoporosis, 2ndry to menopause, glucocorticoids, ….**, and** Malignancy- associated hypercalcaemia
  - **Contraindications :** In severe renal disease. In hypersensitivity to it **.** In increased risk of venous thromboembolism **.** In phenylketonuria, Food specially containing milk± its products **and** Antacids Oral **tetracycline & quinolones chelate it**
  - **ADRs :** GIT irritation; nausea, vomiting, headache, eczema **(**All resolve in 1st 3 months**)**
- Estrogen in females & Androgen in males is essential for normal bone remodeling .
- **Estrogens** : In under menopausal female we give it: If hysterectomy, and if If uterus present we give **estrogen + progestins.**
- **SERMs: Raloxifene :** 1st selective estrogen R modulator for prevention of osteoporosis
- **Mechanism :** Antiestrogens that exhibits **partial agonistic** action; acting as an agonist in bone and heart & an **antagonist in some female sex organs** .
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