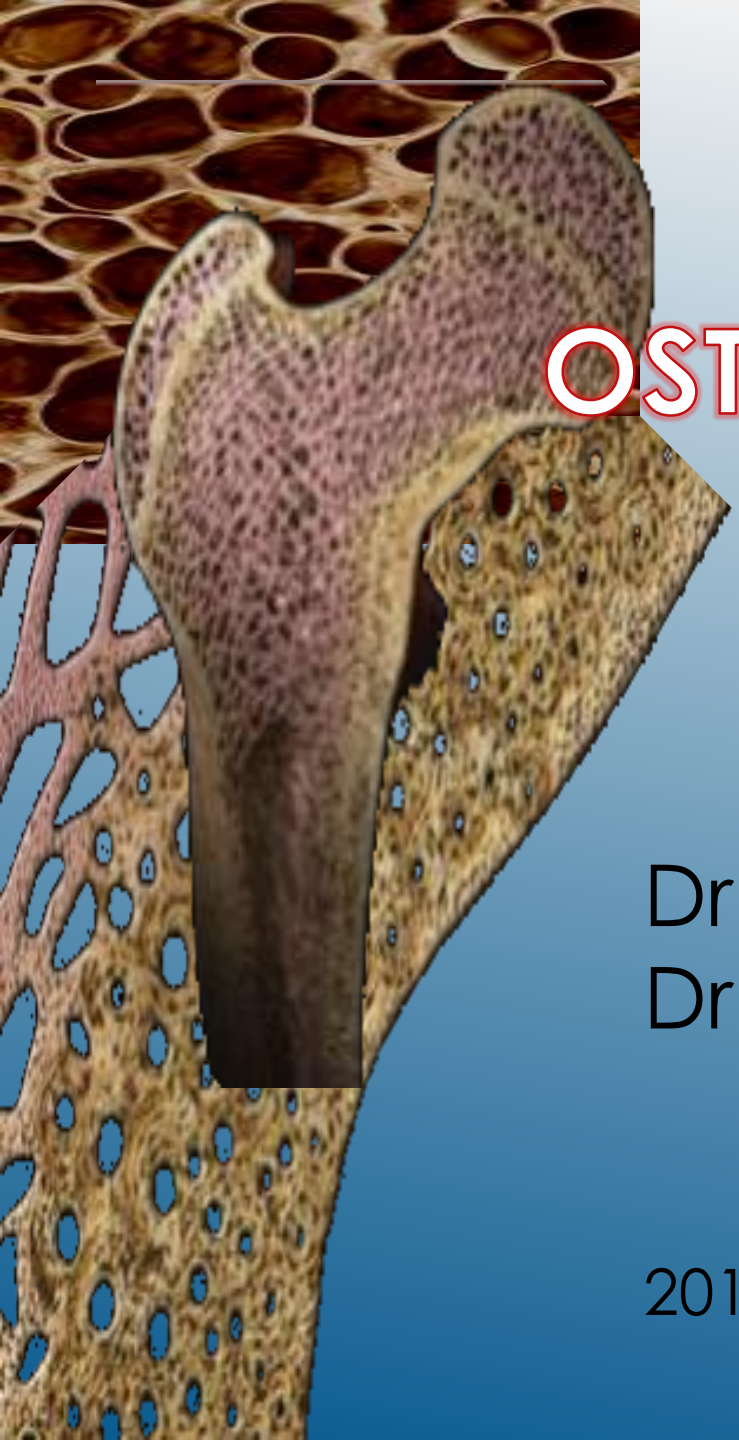

# OSTEOPOROSIS and drugs used

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Dr. Aliah Alshanwani

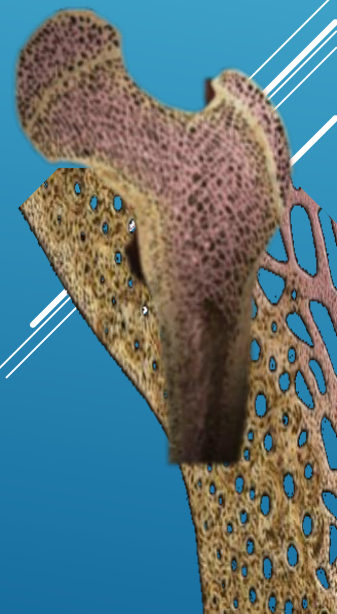
2019

# OSTEOPOROSIS

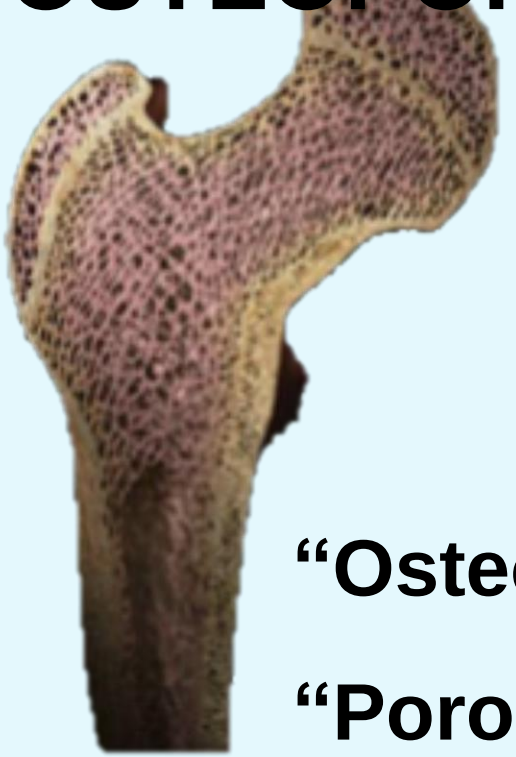
## ILOs

**By the end of this lecture you will be able to:**

- Revise the composition, regulation & the remodeling stages of bone turnover
- Recognize the interlinks of osteoblastic & osteoclastic function
- Relate changes to the development of osteoporosis
- Classify drugs according to their replacement, antiresorptive or anabolic mechanism of action
- Detail the pharmacology of such group of drugs & their clinical utility in combating osteoporosis.



# OSTEOPOROSIS: “The Silent Disease”



## OSTEOPOROSIS; Key points

**“Osteo” is Latin for “bone”**

**“Porosis” means “porous or full of holes”**

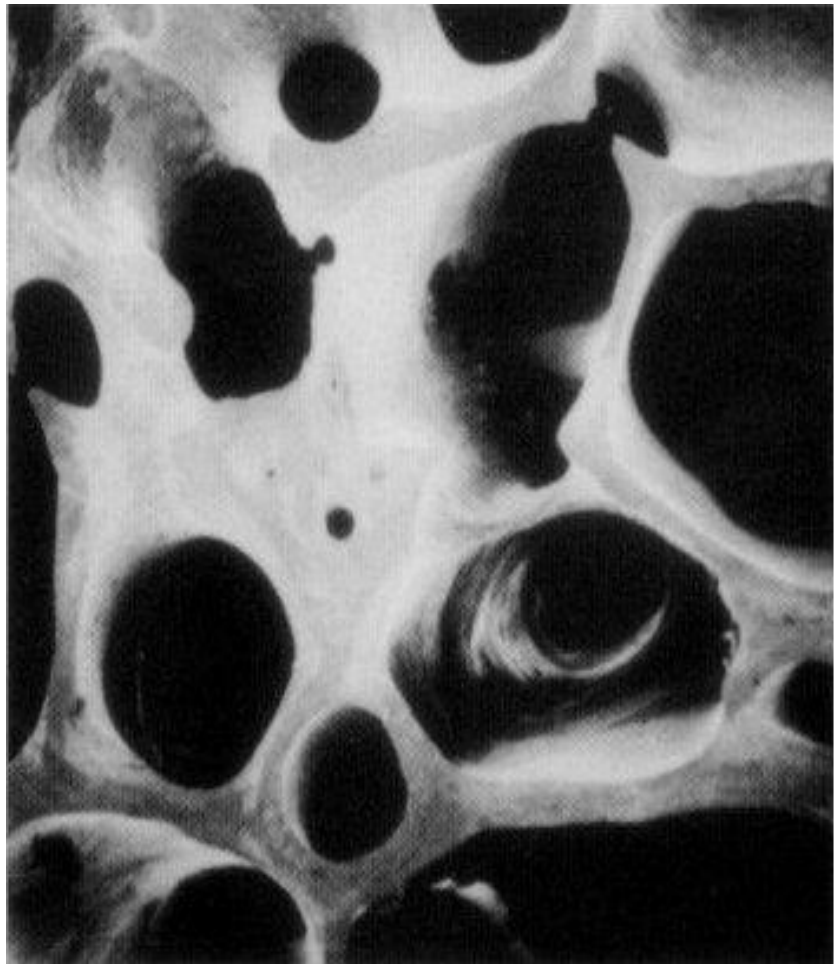
**“Osteoporosis” means “bones that are full of holes”.**

# TYPES OF BONE

(1) Cortical – is hard, compact, dense bone (e.g., long-bones of arms & legs)

(2) Trabecular – is spongy, porous & flexible bone (example: end of the wrist, hip & the spine).

# HEALTHY BONE

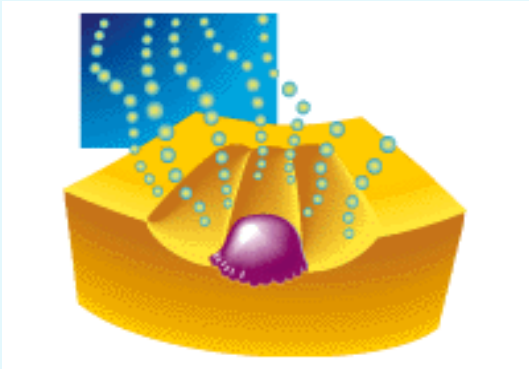


Bone is living tissue, which is constantly being broken down & rebuilt, a process called remodeling

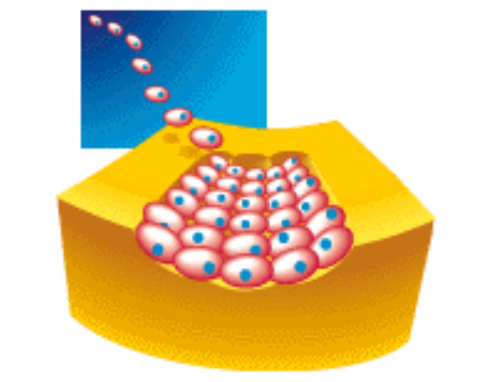
Bone is renewed like skin, hair & nails.

# BONE "REMODELING"

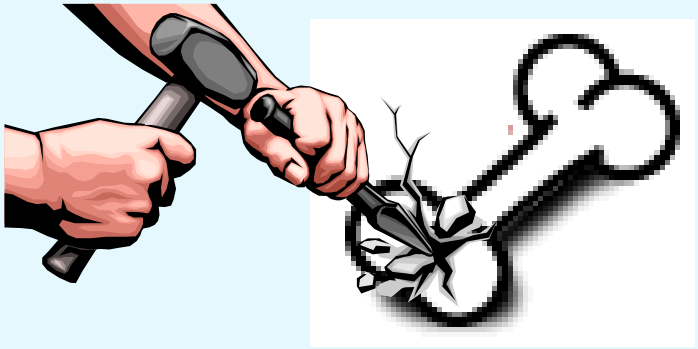
**Resorption: removes old bone cells**



**Formation: replaces old bone with new bone cells.**



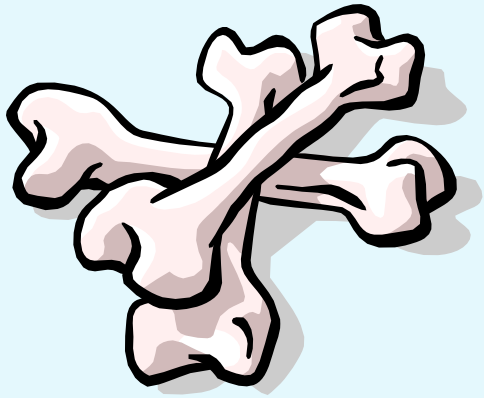
# BONE “REMODELING” OSTEOCLASTS-PHASE 1



Cells called osteoclasts (think “C” for cutting of bone) seek out old bone or damaged bone tissue & destroy it, leaving small spaces (resorption).

# BONE "REMODELING"

# OSTEOBLASTS – PHASE 2



Cells called osteoblasts (think "B" for builder) use minerals like calcium, phosphorus, & vitamin D to fill in the spaces with new bone cells (formation).

# BUILD YOUR BONE BANK

You build bone until about age 30

Steps to building healthy bones include:

Calcium & vitamin D

Limit Caffeine & Alcohol

Exercise

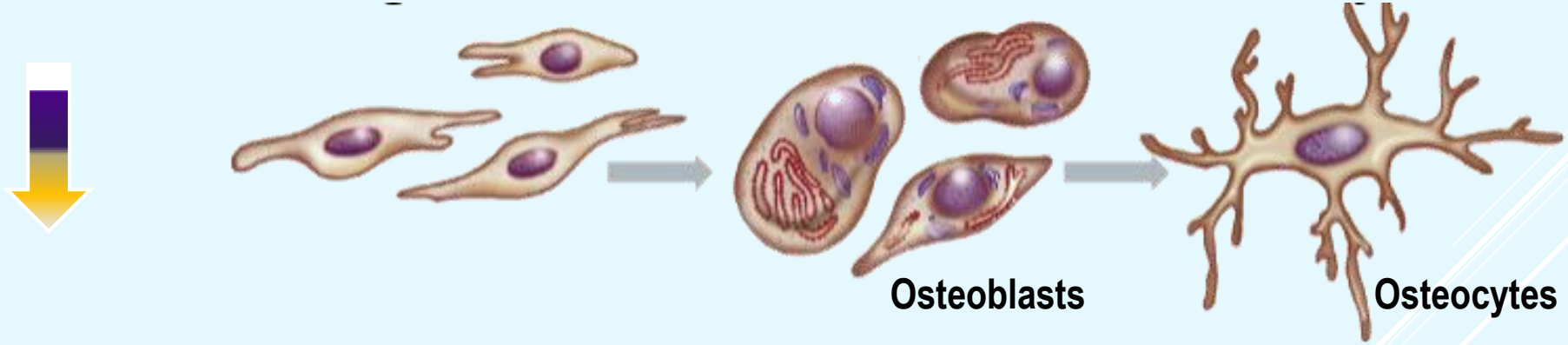
Don’t Smoke.

Bone is basically composed of 2 types of tissues

**INORGANIC** ➜65% of mass ➜ Consists of crystalline calcium phosphate salts (hydroxyapatite)

**Organic** ➜ 35% of mass ➜ Consists of; osteoblasts, osteoclasts & osteocytes)

♦ Bone cells are either; **Bone Forming** or **Bone Resorptive**




## A. Bone Forming Cells:

Osteogenic cells ➜ mesenchymal in origin ➜ are found on all bone surfaces

Osteoblasts ➜ forms osteoid framework & help in its mineralization.

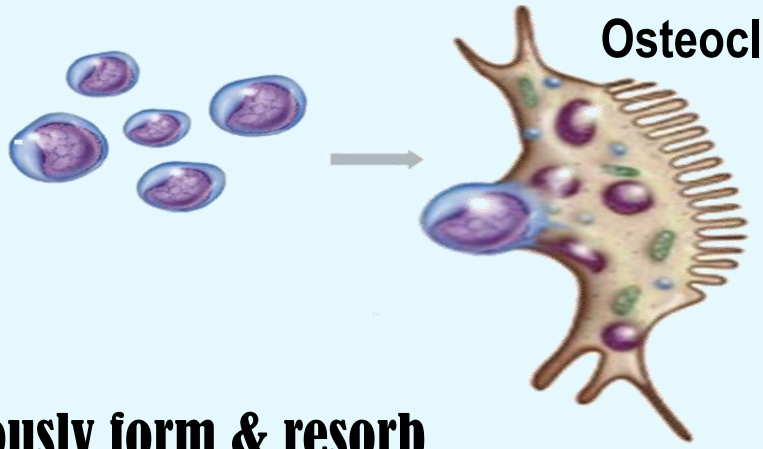
## B. Bone Resorptive Cell:

Osteoclasts ➜

Reside in pits (resorption bays) that form by eaten bone surface.

Secretes lysosomal enzymes (collagenase & metalloproteinase) +

hydrochloric a. ➜ dissolve bone matrix




**NORMALLY**

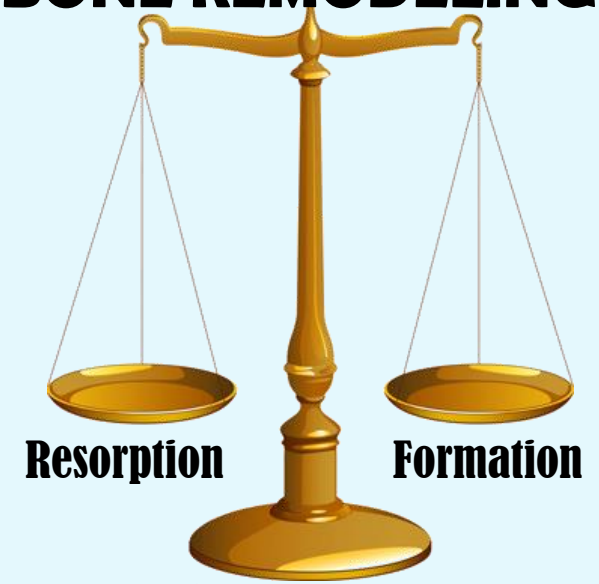
**bones continuously form & resorb**

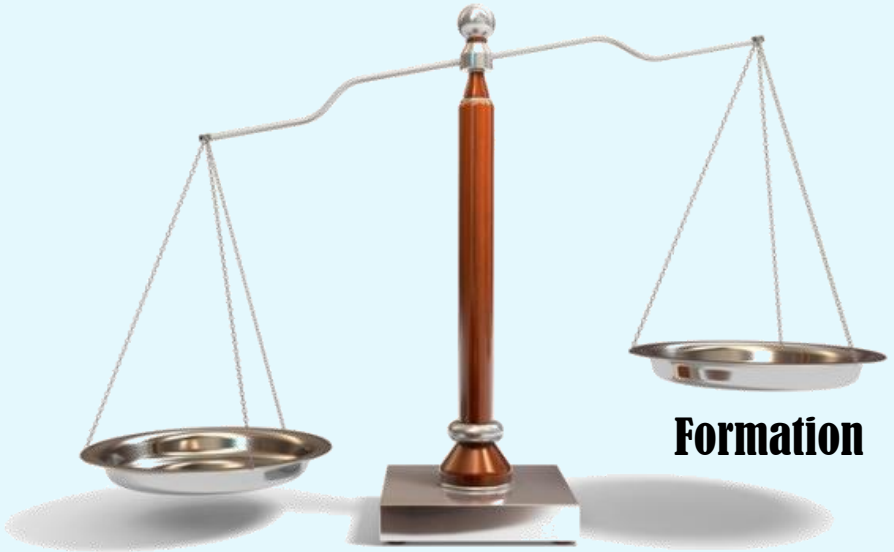
➜ **BONE REMODELING**

Under control of systemic hormones, body mineral contents & local autocrine-paracrine secretions (Cytokines, Growth Factors, PGs)

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

# BONE REMODELING



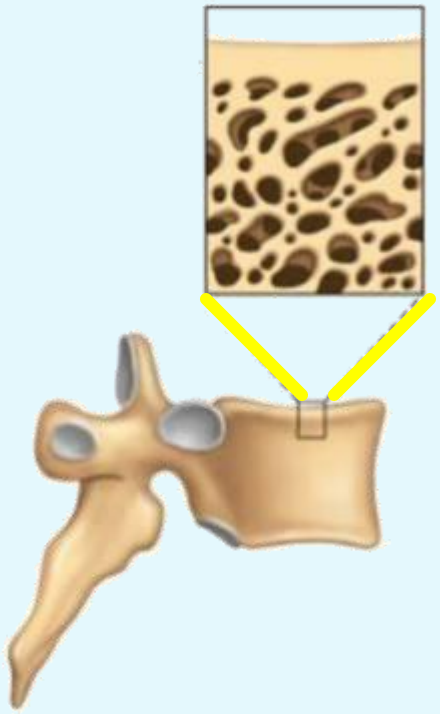



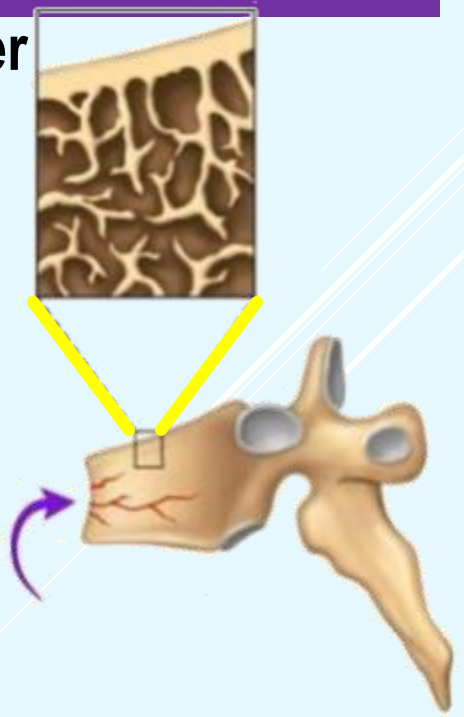

## OSTEOPOROSIS

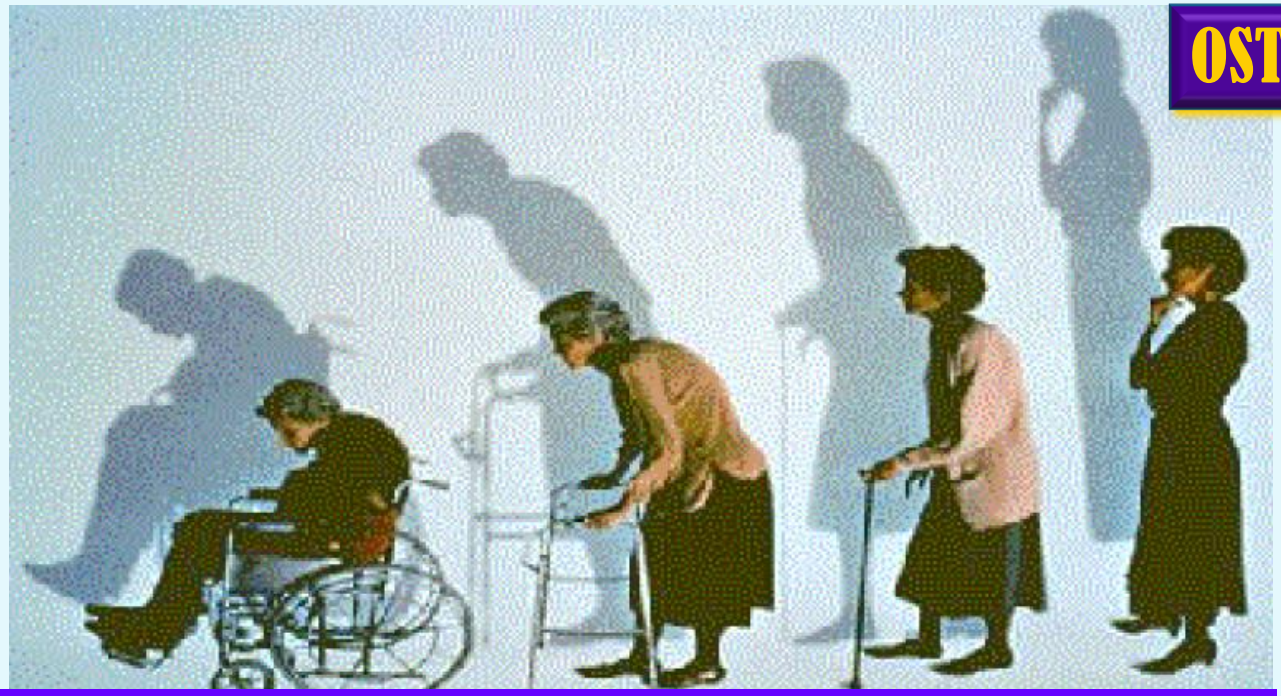
A complex endocrinologic disorder
of bone & mineral metabolism
(bone resorption > formation)

Low bone mass
Disruption of bone architecture

Reduced bone strength
Risk of fractures







# OSTEOPOROSIS

PREVENTION

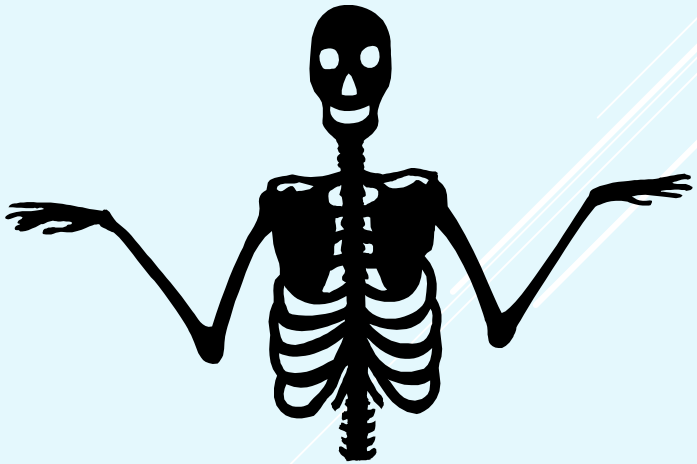
TREATMENT

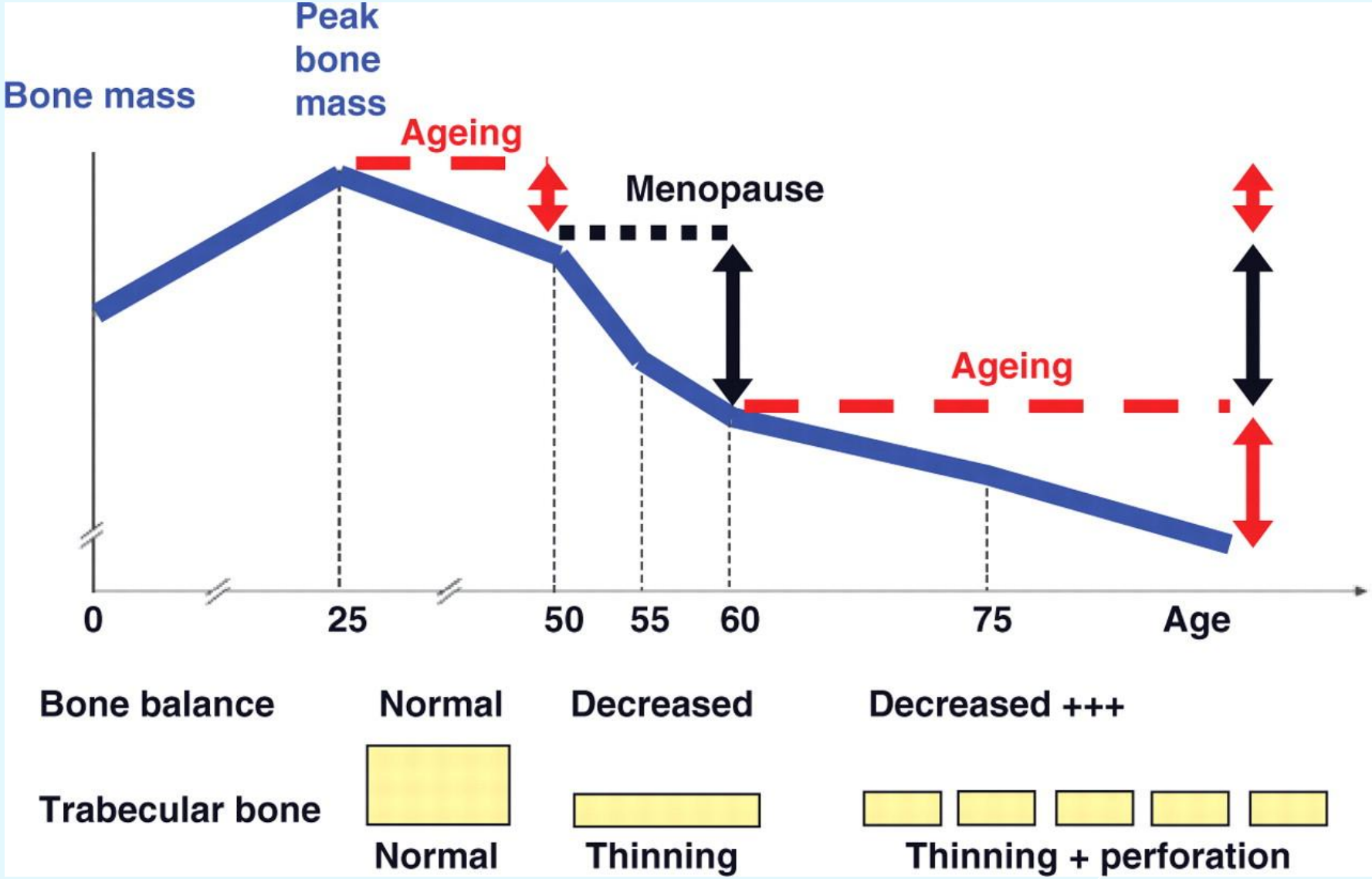
| Potentially Modifiable | Non-modifiable |
|---|---|
| Current cigarette smoking | Personal history of fracture |
| Diet low in calcium/vitamin D | 1st degree relative has fracture |
| Glucocorticoids, anticonvulsants | Race (Caucasian or Asian) |
| Excessive alcohol intake | Elderly age |
| Sedentary lifestyle | Poor health |
| Body weight | Dementia |
| | Hormonal disorders |
| Environnemental risks | Neoplastic disorders |
| | Metabolic abnormalities |

# BONE LOSS & AGING

The first 5-15 years after menopause a woman can lose approximately 25 - 30% of trabecular bone & approximately 10 – 15% of cortical bone

Bone loss often occurs without symptoms or warning signs.

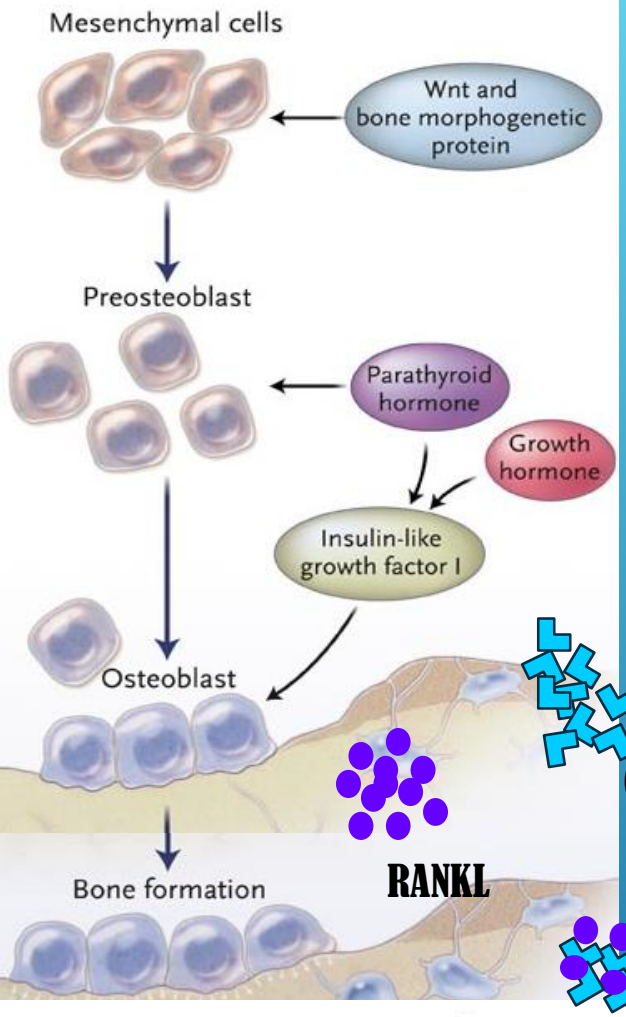


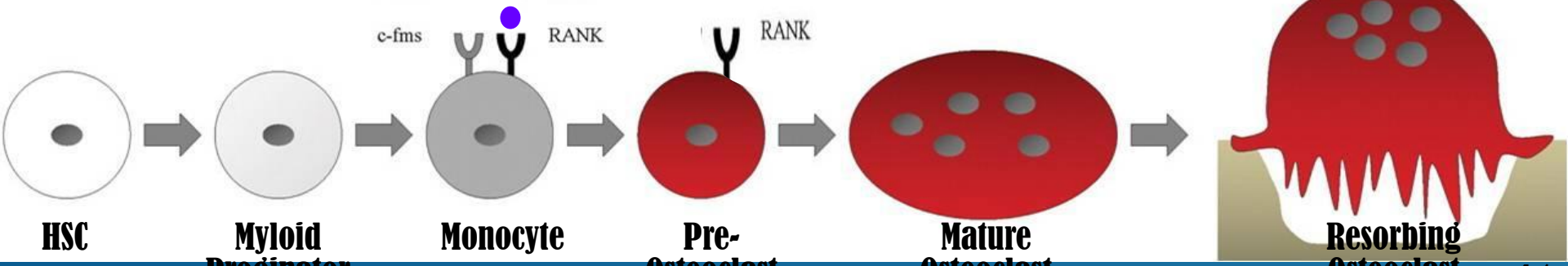

Bone mass
Peak bone mass
Ageing
Menopause
Ageing
0
25
50
55
60
75
Age
Bone balance
Normal
Decreased
Decreased +++
Trabecular bone
Normal
Thinning
Thinning + perforation

# OPG and bone

RANKL: Receptor activator of nuclear factor kappa-B ligand. It's a family member of TNF cytokine. (high in osteoporosis)

OPG: Antiosteoclast



# TREATMENT OF OSTEOPOROSIS

**Replace what is missing….Ca, Vit D, Na fluoride**
**Reset back the balance of remodeling**

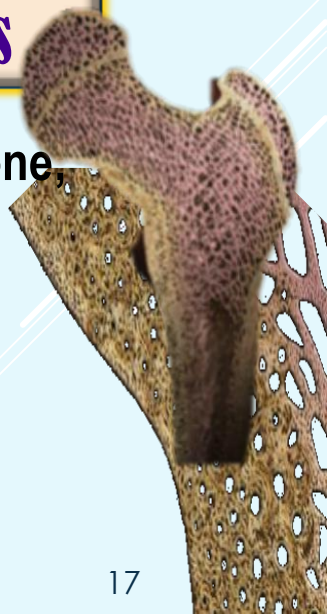
***Used to enhance the strength by the formation of fluorapatite***
***Is considered only when trabecular bone is ↓ in presence of normal cortical bones.***

## ANTIRESORPTIVE AGENTS

- BISPHOSPHONATES
- ESTROGEN ANALOGES
- ANDROGEN ANALOGES
- SERMS
- CALCITONIN
- RANKL INHIBITORS

## BONE ANABOLIC (building) AGENTS

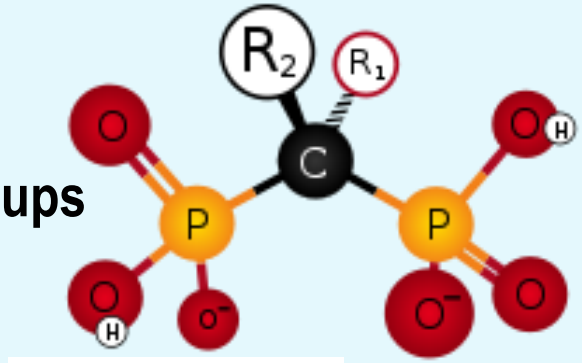
- (Parathyroid hormone, TERIPARATIDE
- STRONTIUM



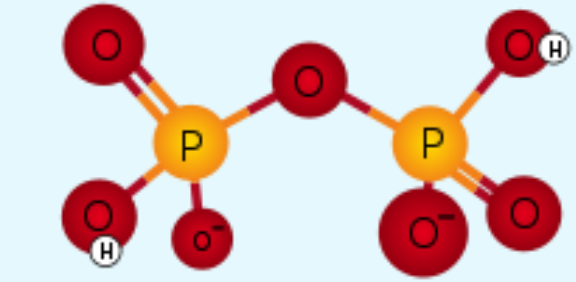
# BISPHOSPHONATES

**Are compounds that have two phosphonate ($PO_3$) groups**

| Non-Nitrogenous | Nitrogenous |
|---|---|
| Etidronate | Alendronate po |
| Clodronate | Ibandronate po |
| Tildronate | Risedronate po |
| | Zoledronate IV |



Bisphosphonate



Pyrophosphate

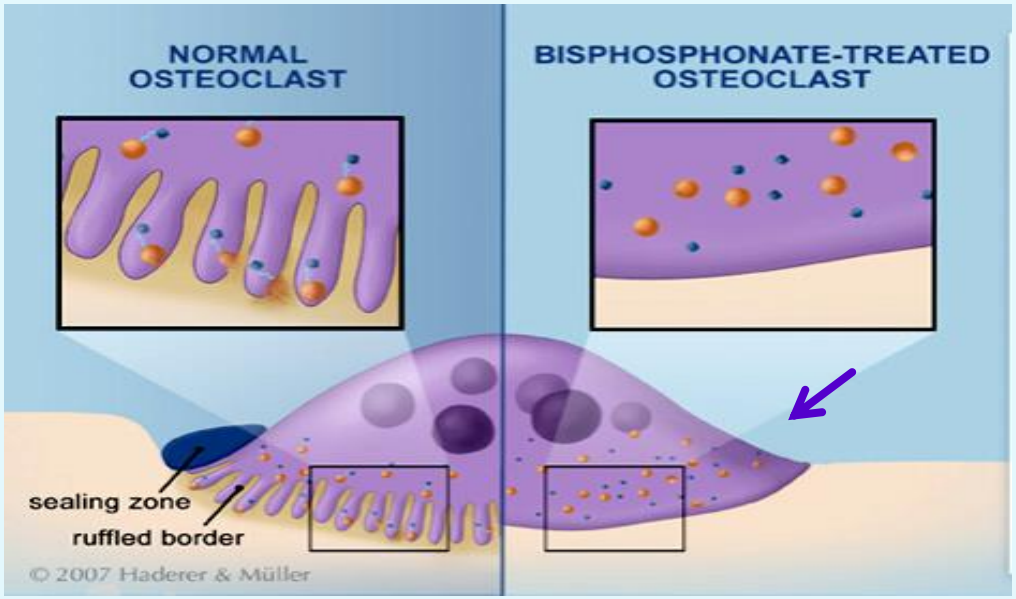
## Mechanism

- Are structurally similar to pyrophosphate
- They preferentially "stick" to calcium ➔ concentrate in bones, bound to hydroxyapatite, decreasing its solubility & making it more resistant to osteoclastic activity
- They prevent bone resorption by inhibiting osteoclast function
- Their relative potencies for osteoclast inhibition is the most with 3rd generation Zoledronate.

**BLOCK** STEPS IN CHOLESTROL SYNTHETIC PATHWAY IN OSTEOCLAST

**that act as signaling molecules responsible for the osteoclastic hydrolytic & phagocytic activity**

**Stop function ➔ apoptosis (increased death of osteoclast)**




It is also taken up by osteoclast ➔ blocks steps in cholesterol synthetic pathway within osteoclast ➔ end up by osteoclast **apoptosis**.

# BISPHOSPHONATES

## Kinetics

- Poorly abs (< 10%), food impair absorption more ➔ must be given on an empty stomach / 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, 2ndry to menopause, glucocorticoids, ….
- Paget's Disease
- Malignancy- associated hypercalcaemia

## Dosing

- Once weekly, or on two consecutive days each month
- Should be taken in upright position (to avoid esophagitis)
- Separate 4 hrs before giving Ca, Mg, Al containing drugs

Note : calcium & vit D supplementation given during bisphosphonate therapy don't ingest it along with bisphosphonate, give a gap as mentioned above…?

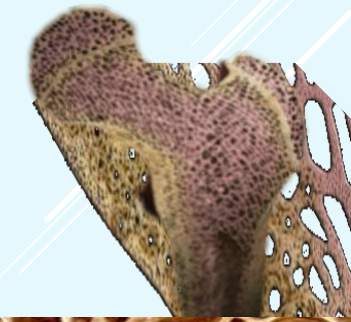
# BISPHOSPHONATES

## ADRs

- GIT irritation; nausea, vomiting, gastritis, ulceration ➜ give large amount of water **to avoid** risk of the tablet getting stuck in the esophagus
- Gastro-esophageal reflux ± ulcerations ➜ to avoid give on empty stomach while sitting in upright for 30 min
- Flue-like manifestations (fever, chills) upon IV infusion
- Osteo-necrosis of the mandible bone of jaw upon long use with IV infusion preparation usually after dental surgical procedures

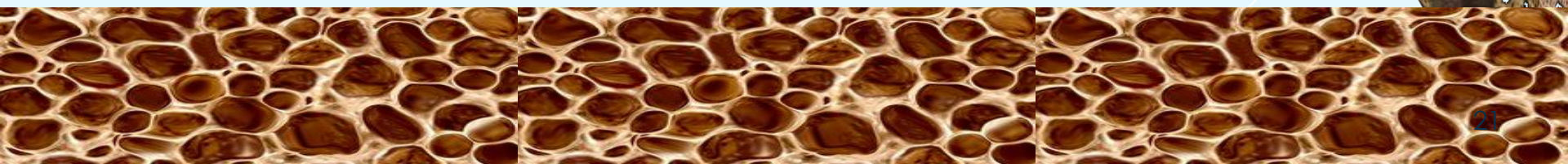
If a dental implant or extraction is already planned, delay bisphosphonate therapy for a few months until healing of the jaw is complete

- Atrial fibrillation > women with alendronate & zoledronate.



## Contraindications

- Decreased renal function and Peptic ulcer / esophageal reflux.



## RANKL INHIBITORS → DENOSUMAB (still under investigation)

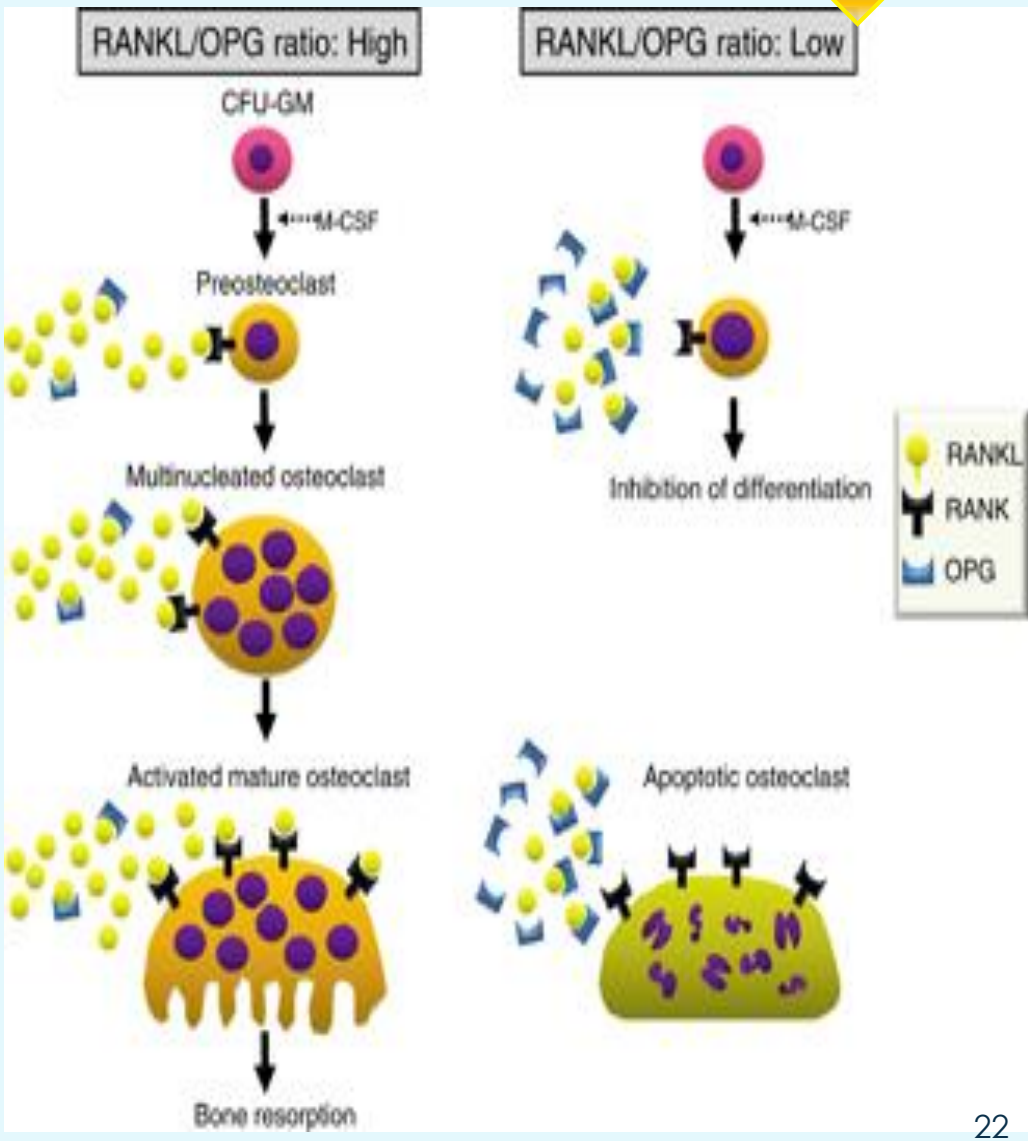
It is a fully human MOA that mimics the activity of osteoprotegerin

### Mechanism

Blocks RANKL from interacting with RANK expressed on preosteoclasts → ↓ osteoclastogenesis (no mature osteoclasts)

It binds also to mature osteoclast → its apoptosis

So net effect → ↓ bone resorption.




### Administration

Subcutaneous every 6 month

### Contraindications

In patients with hypocalcemia Correct Ca & Vit D levels before starting denosumab.

## Mechanism of action of Denosumab:

-RANKL binds to its receptor RANK on the surface of precursor & mature osteoclasts & stimulates these cells to mature & resorb bone.
-OPG, which competes with RANKL for binding to RANK, is the physiological inhibitor of RANKL
**-Denosumab** binds with high affinity to RANKL, mimicking the effect of OPG.

**Note: Densosumab decreases serum calcium conc, should not be given to patients with hypocalcemia.**

**Its extremely expensive & reserved for patients who can not tolerate or respond to bisphosphonate.**

**ADRs**

- **Infections; urinary & respiratory**
- **Eczema & skin rash**
- **pancreatitis.**

# STRONTIUM

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

## Mechanism

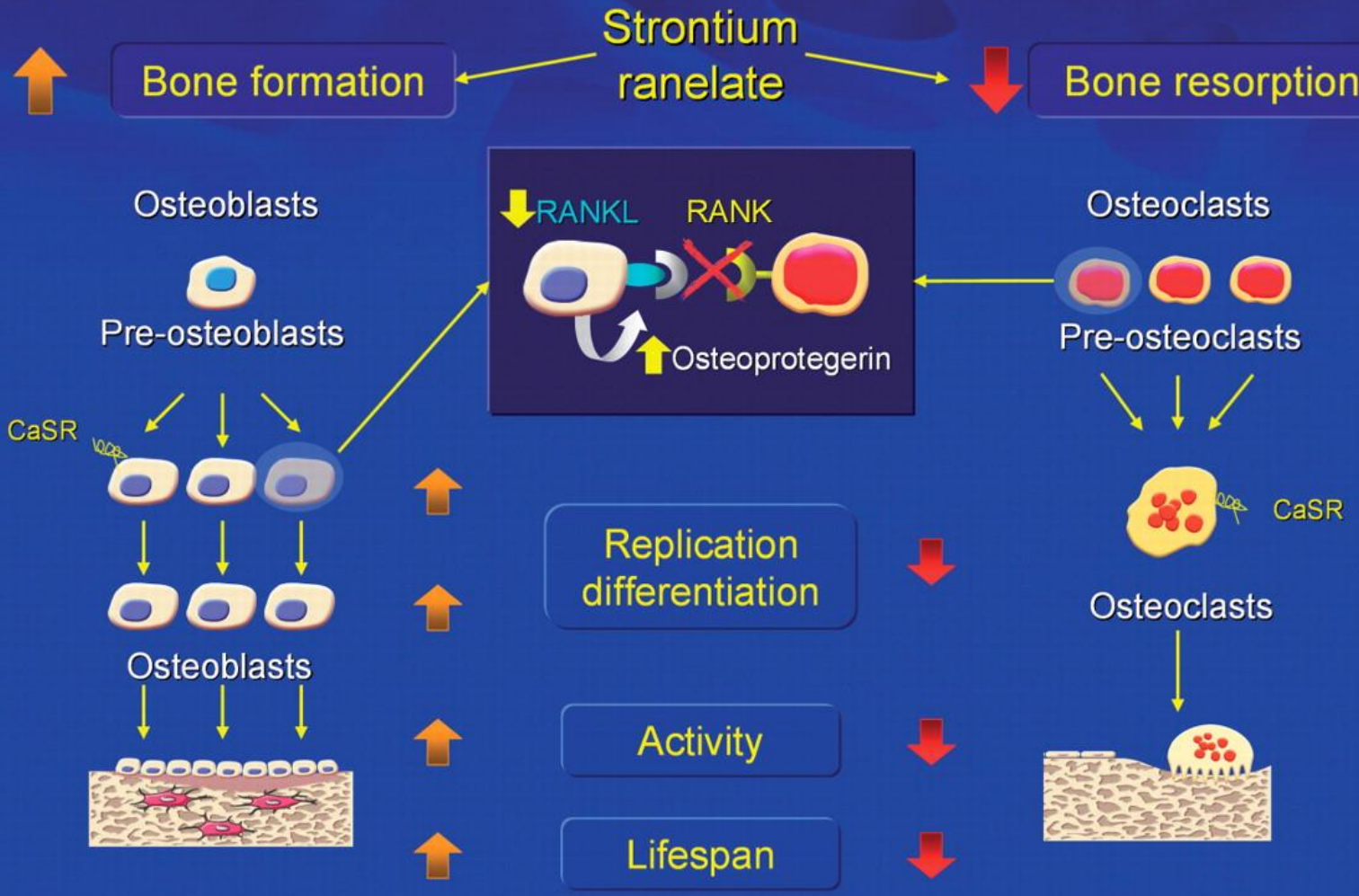
1st drug to possess " dual action " i.e has both anabolic & antiresorptive effects, resulting in a rebalance of bone turnover in favor of bone formation

**On Osteoblast**;
1- Since it is like Ca, it acts as agonist on **Ca Sensing Receptor** [CaSR]; which is a GP coupled receptor that enhances differentiation of pre-oteoblast to osteoblast → ↑ bone formation

2- It stimulates the expression of OPG → ↑RANKL binding → -ve of osteo-clustogenesis → ↓ bone resorption

**On Osteoclast**;
Acts as agonist on CaSR → suppress differentiation of pre-osteoclast to osteoclast → ↑ osteoclast apoptosis → ↓ bone resorption.

# Strontium ranelate: unique treatment with a dual effect on bone turnover



# STRONTIUM

## Pharmacokinetics

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

## Indications

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

## Contraindications

- In severe renal disease
- In hypersensitivity to it
- In increased risk of venous thromboembolism
- In phenylketonuria

## Interactions

- Food specially containing milk± its products ➔
- Antacids ➔
- Oral tetracycline & quinolones chelate it

## Precautions

2 hrs spacing

## ADRs

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

**ESTROGENS** If hystrectomy + progestins if uterus present

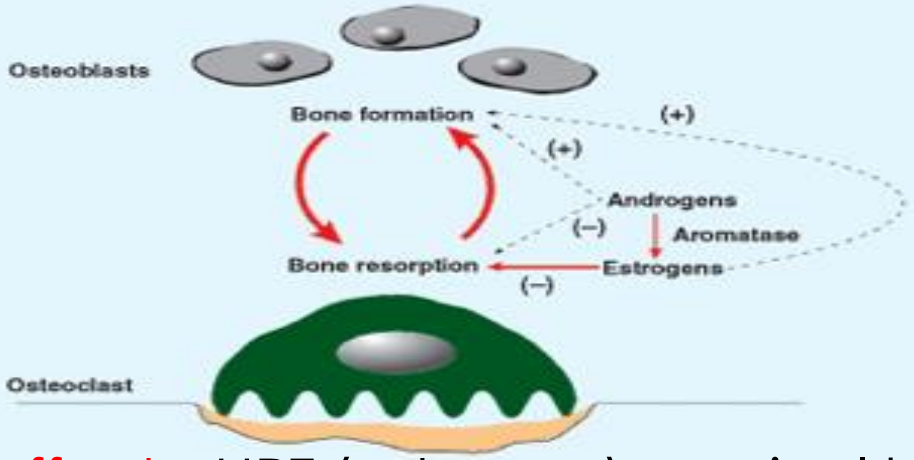
**HRT** Menopausal Symptoms

**SERMs** Menopause / Elderly

**ANDROGENS** Elderly men

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

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




Adverse effects: HRT (estrogen): vaginal bleeding, risk of breast cancer & venous thromboembolism.

# SERMs → RALOXIFENE

1st selective estrogen Receptor modulator (SERM) for prevention & treatment of osteoporosis

## Mechanism

Anti-estrogens that exhibits partial agonistic action; acting as an agonist in bone & an antagonist in some female sex organs

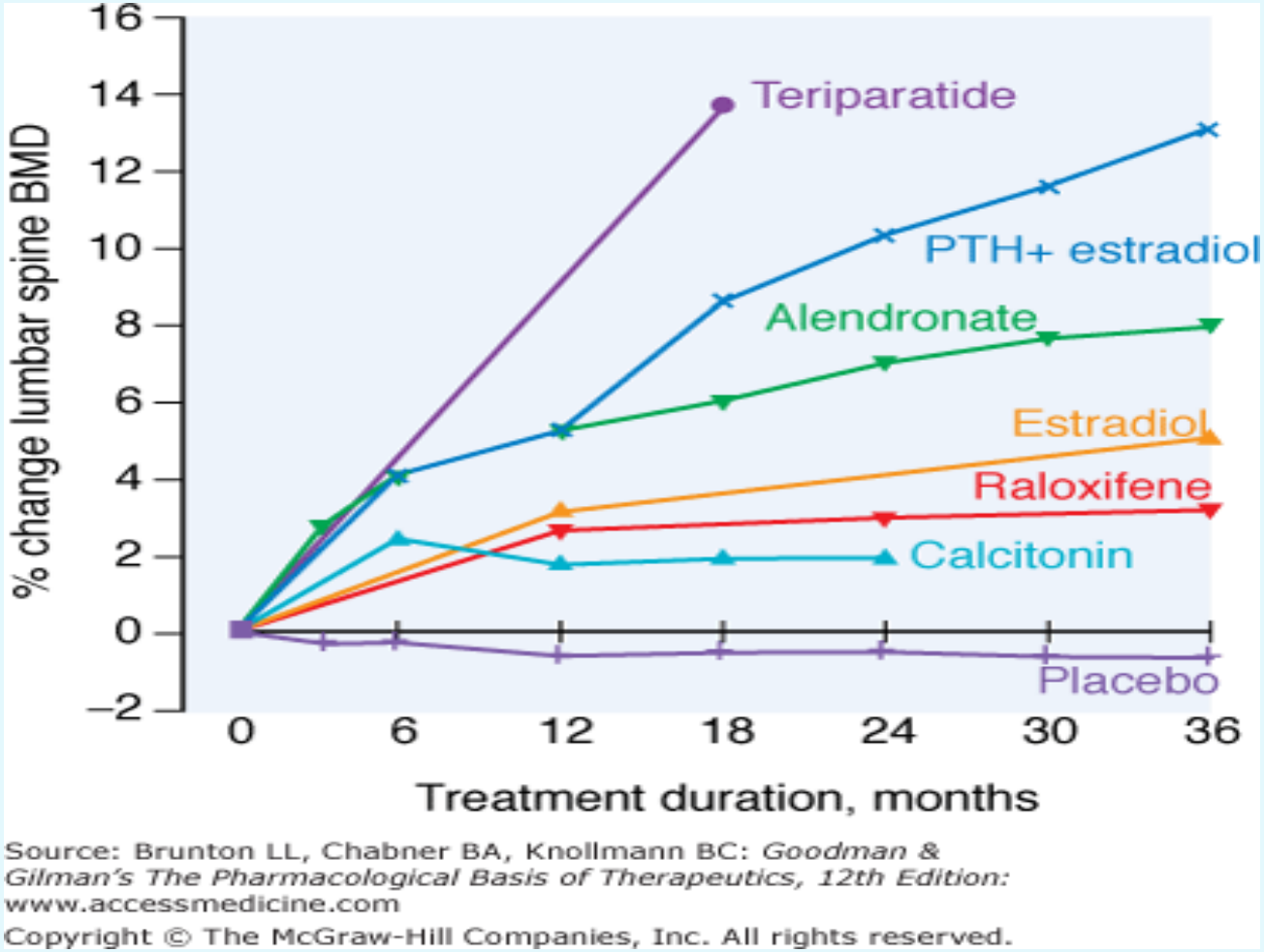
| | Brain | Uterus | Vagina | Breast | Bone | CVS |
|---|---|---|---|---|---|---|
| Estradiol | ++ | ++ | ++ | ++ | ++ | ++ |
| Raloxifene | — | — | — | — | + | + |

### Advantages

- ↑ bone density (2%) & ↓ fracture risk (30%)
- No stimulation of breast or endometrial tissue
- No need for progestin in women with uterus
- ↓ LDL
- Good for women with risk of uterine & breast cancer
- Lower risk of thromboembolism compared to estrogen

### Disadvantages

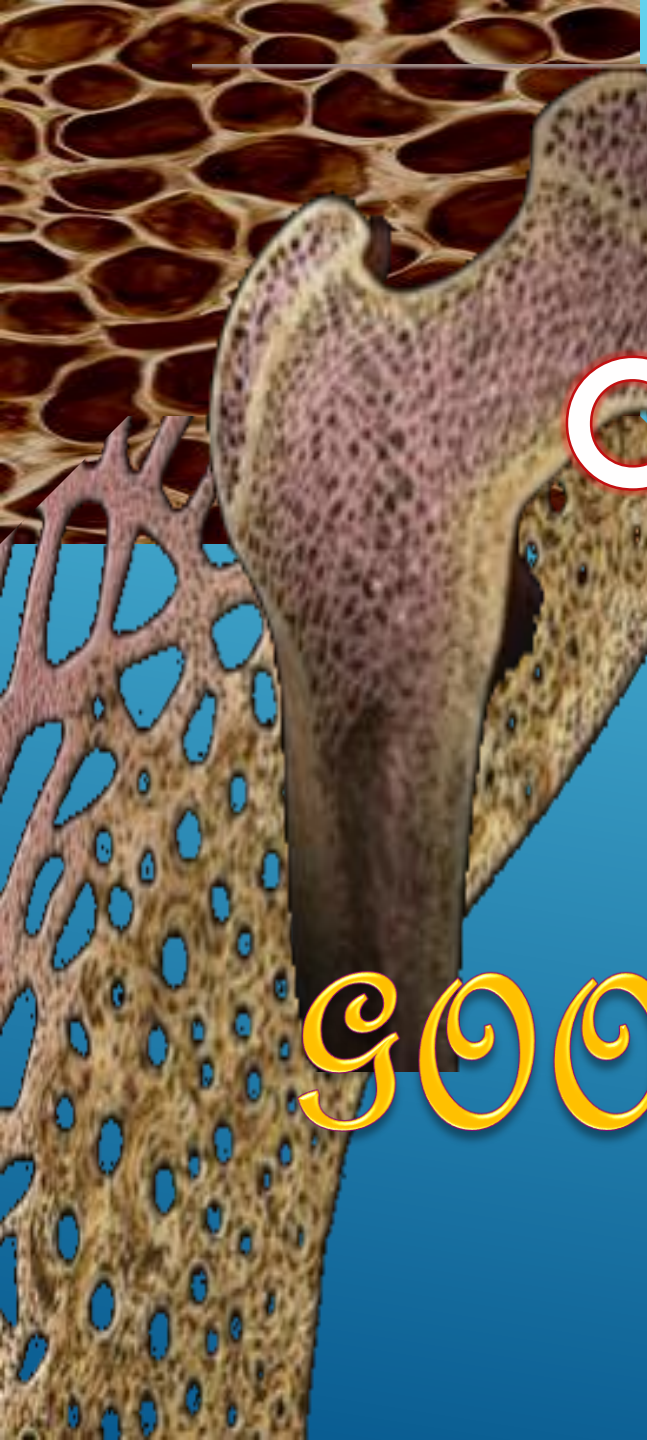
- May ↑ hot flushes
- No effect on HDL.




Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com



**Relative efficacy of different therapeutic interventions on bone mineral density of the lumbar spine**



# OSTEOPOROSIS

GOOD LUCK