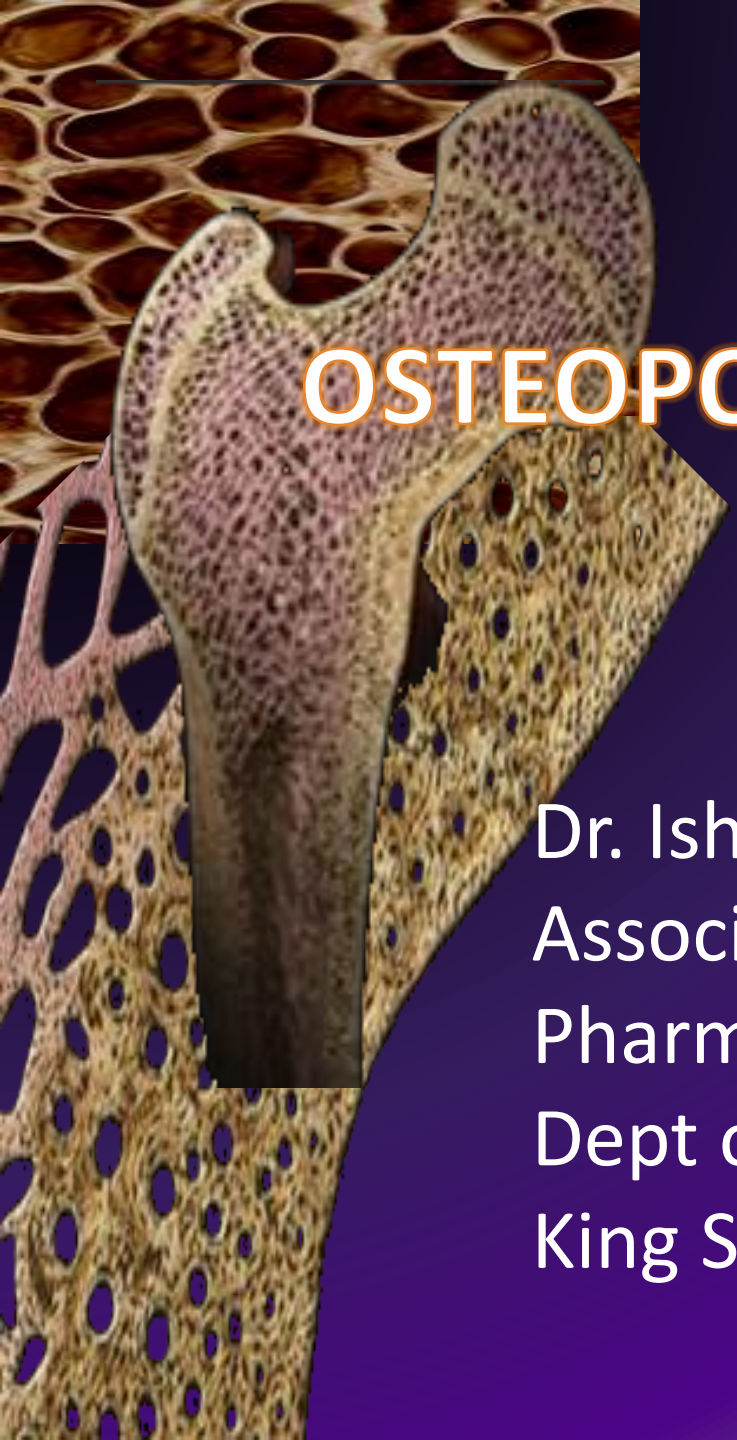

OSTEOPOROSIS and drugs used

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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 ;Key points

OSTEOPOROSIS: “The Silent Disease”

“Osteo” is Latin for “bone”

“Porosis” means “porous or full of holes”

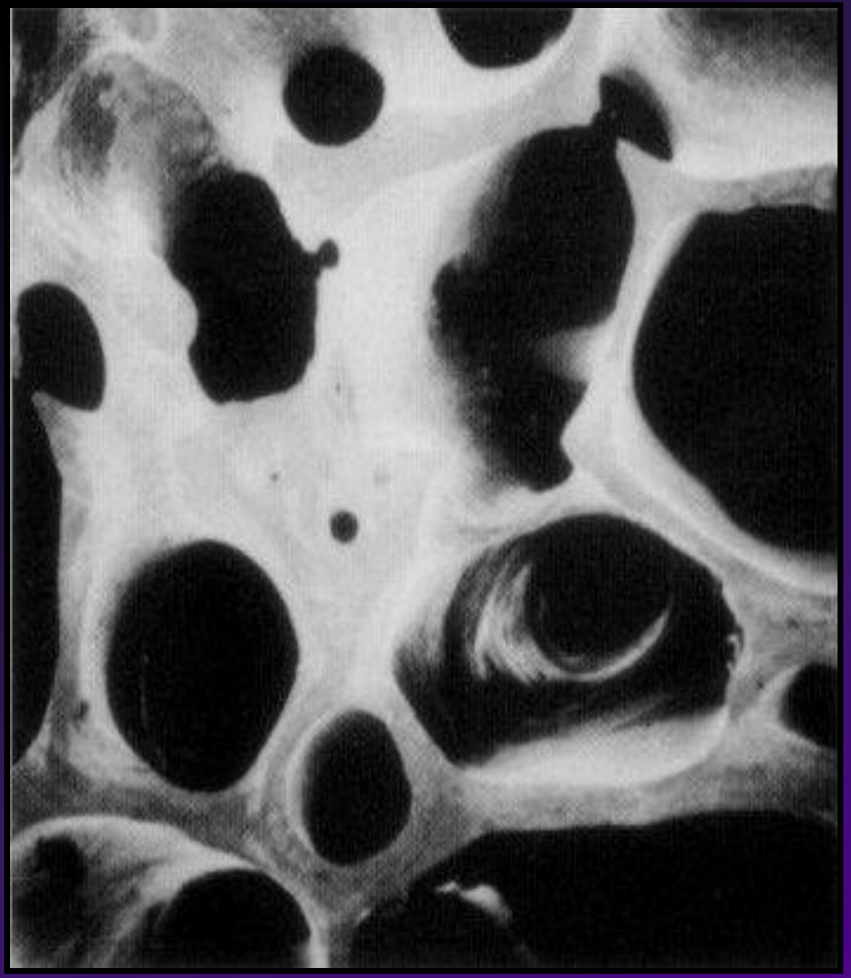
“Osteoporosis” means “bones that are full of holes”

TYPES OF BONE

(1) Cortical – is hard, compact, dense bone (eg long-bones of arms and legs)

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

HEALTHY BONE

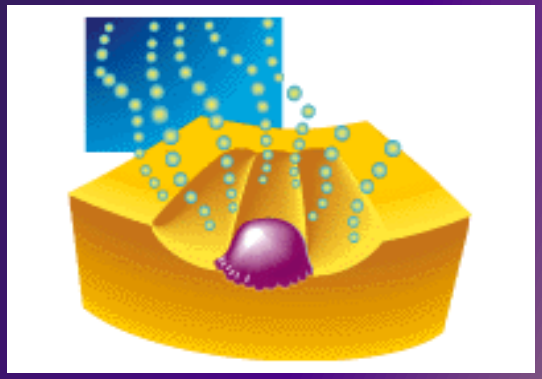


Bone is living tissue, which is constantly being broken down and rebuilt, a process called remodeling

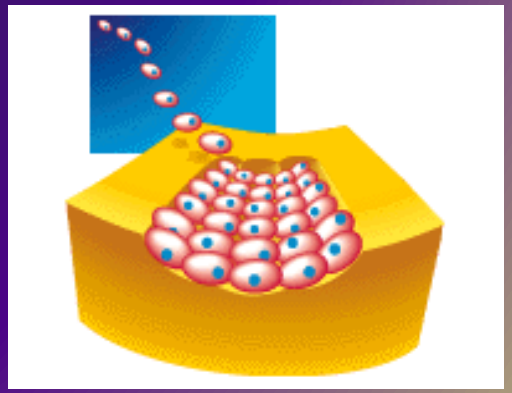
Bone is renewed like skin, hair and nails

BONE “REMODELING”

Resorption- removes old bone



Formation- replaces old bone with new bone



BONE "REMODELING" OSTEOCLASTS-PHASE 1

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

BONE “REMODELING” OSTEOBLASTS – PHASE 2

Cells called osteoblasts (think “B” for builder) use minerals like calcium, phosphorus, and vitamin D to fill in the spaces with new bone (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 crystaline calcium phosphate salts(hydroxyapatite)

Organic ➜ 35% of mass ➜ Consists of ;osteoblasts, osteoclasts and osteocytes).

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

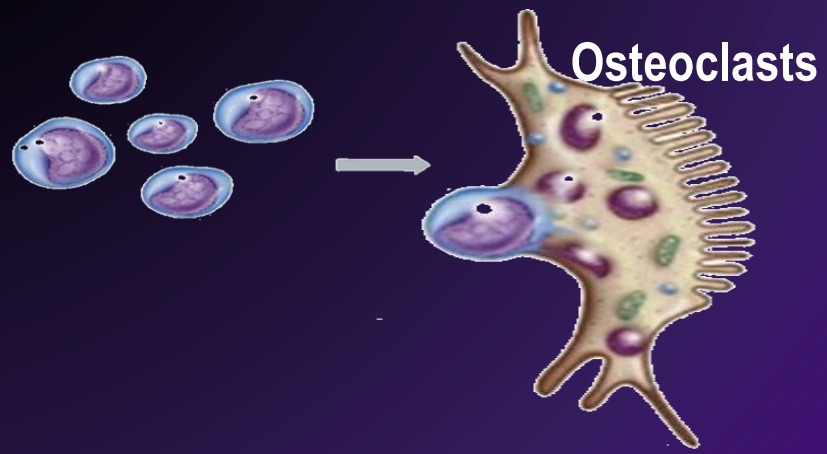
A. Bone Forming Cells:

- Osteogenic cells ➜ mesenchymal in origin ➜ are found on all bone surfaces
- Osteoblasts ➜ forms osteoid framework & help in its mineralization

B. Bone Resorptive Cell:

Osteoclastes ➜

Reside in pits (resorption bays) that form by eaten bone surface. Secretes lysosomal enzymes (collagenase & metalloproteinase) + hydrochloric a. ➜ dissolve bone matrix



NORMALLY

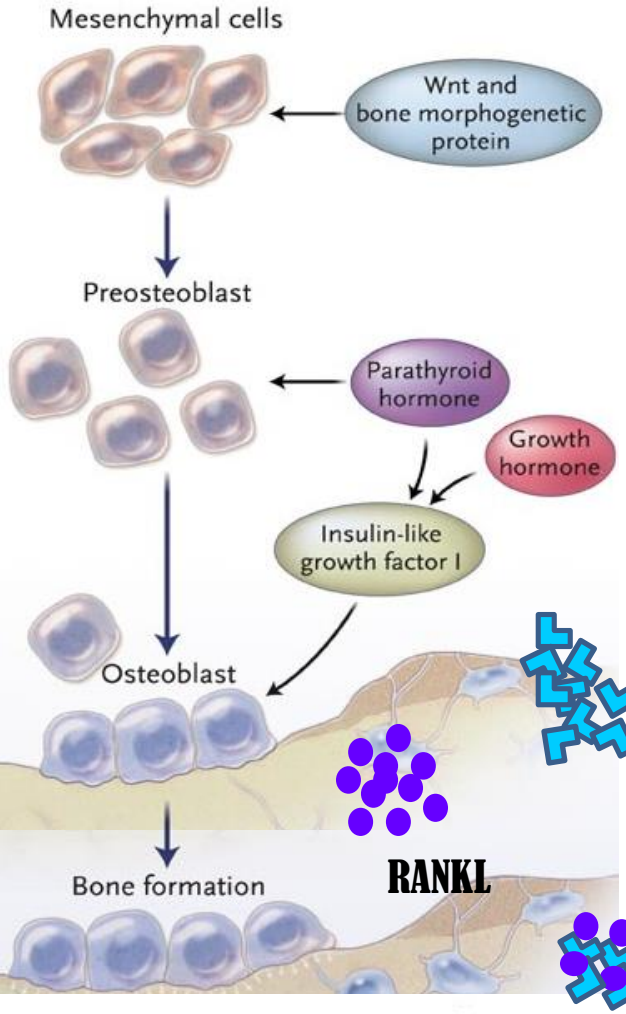
bones continuously form & resorb

➜ **BONE REMODELING**

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

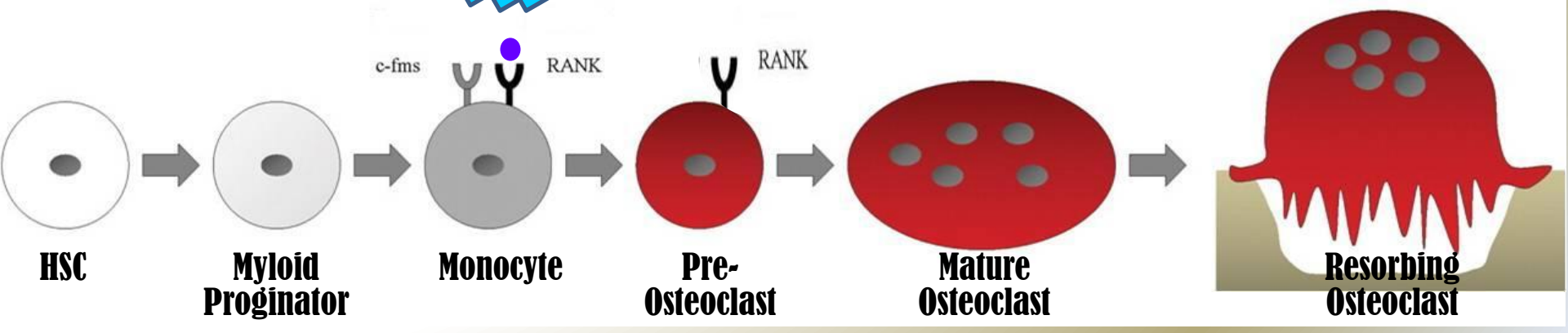
It is meant to maintain calcium homeostasis & to renew bone in repair of microdamage & microcracks

OPG and bone



Osteoprotegerin [OPG]

RANKL



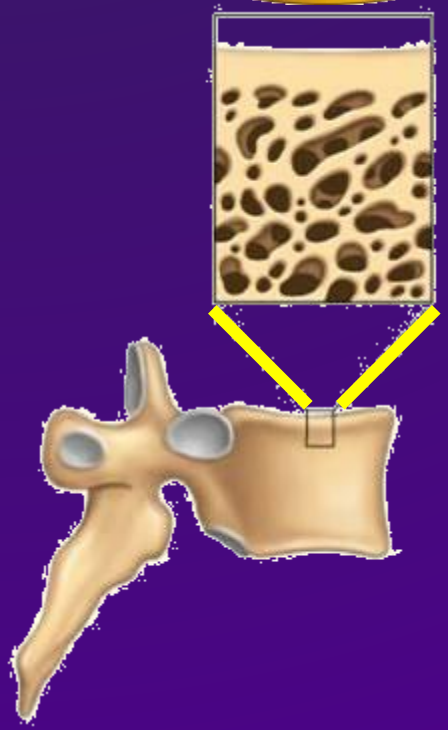
BONE REMODELING

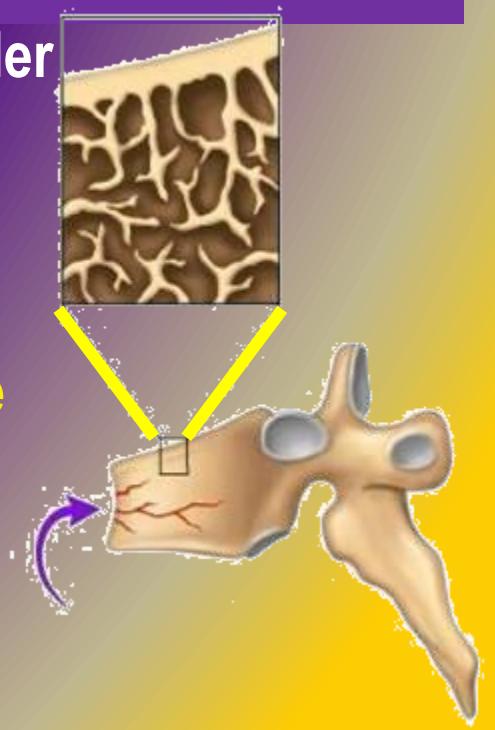
OSTEOPOROSIS

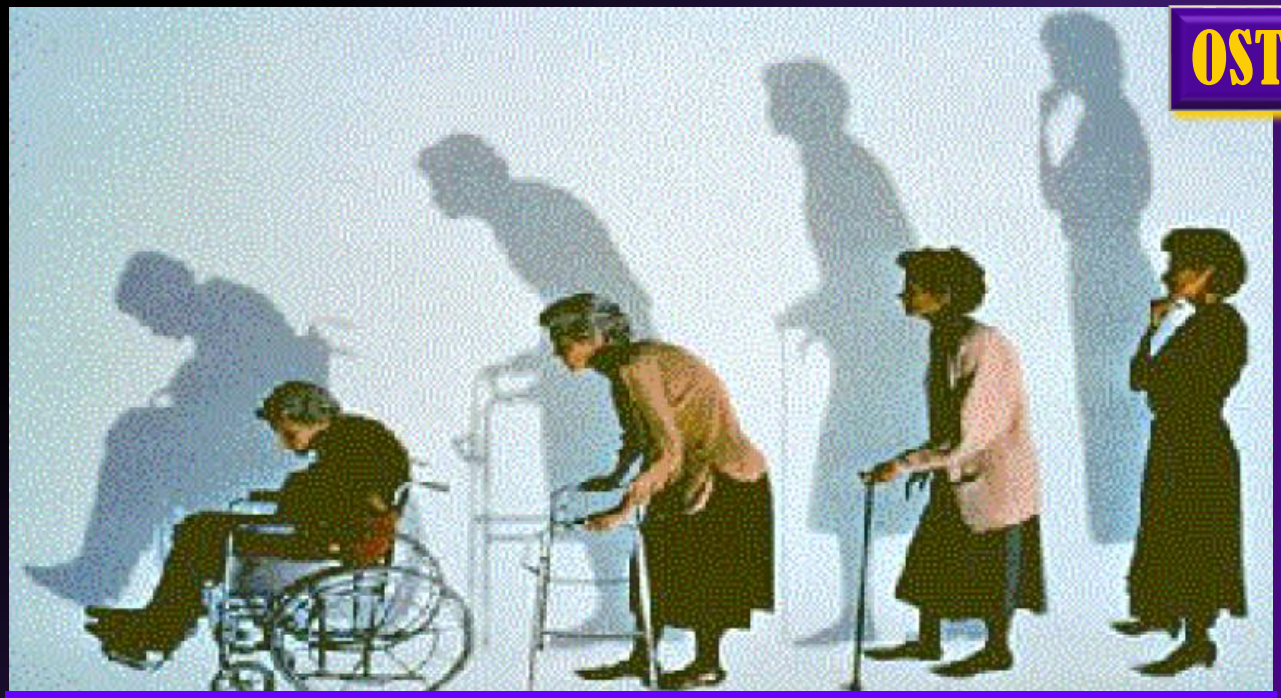
A complex endocrinologic disorder of bone & mineral metabolism (bone resorption > formation)

Low bone mass
Disruption of bone architecture

Reduced bone strength
Risk of fractures





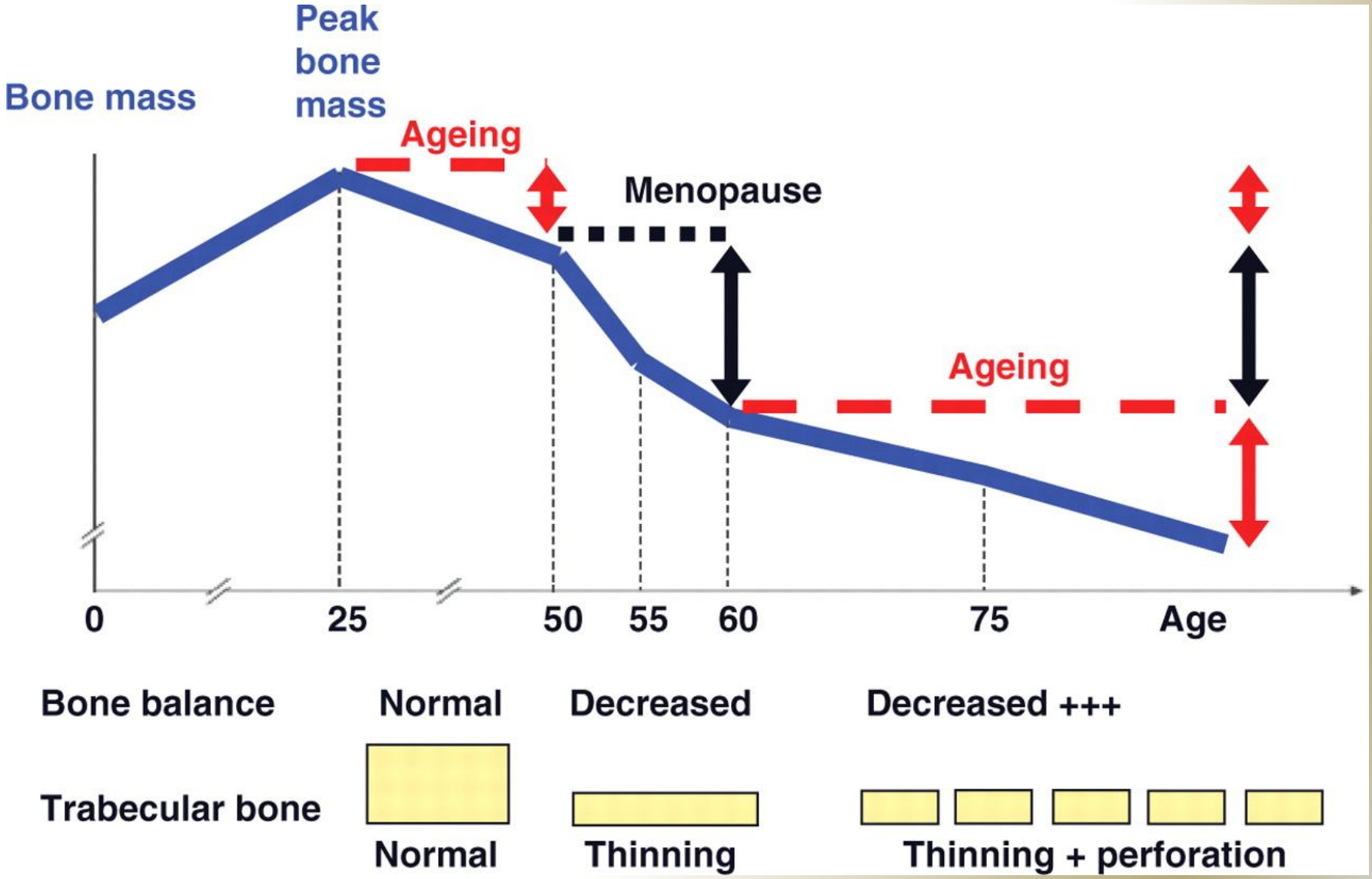


OSTEOPOROSIS

PREVENTION

TREATMENT

Potentially Modifiable	Nonmodifiable
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
Environmental risks	Neoplastic disorders
	Metabolic abnormalities


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

TREATMENT OF OSTEOPOROSIS

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

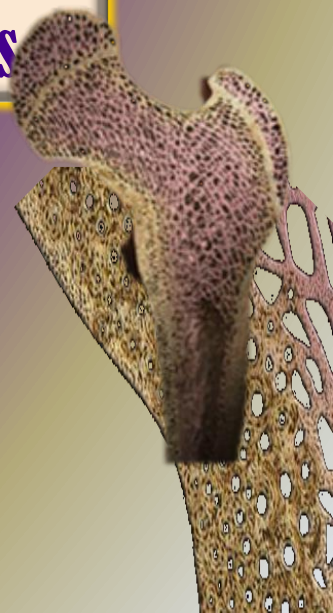
Used to enhance the strength by the formation of fluorapatite. Is considered only when trabecular bone is ↓ in presence of normal cortical bones

ANTIRESORPTIVE AGENTS

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

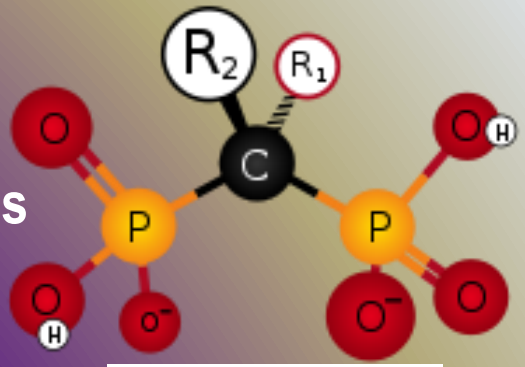
BONE ANABOLIC (building) AGENTS

- (Parathyroid hormone; TERIPARATIDE
- ☑ STRONTIUM



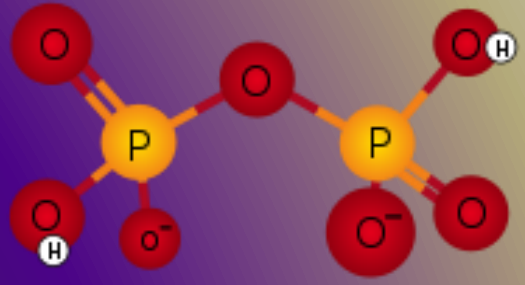
BISPHOSPHONATES

Are compounds that have two phosphonate (PO_3) groups



Bisphosphonate

Non-Nitrogenous	Nitrogenous
Etidronate	Alendronate p.o
Clodronate	Ibandronate p.o
Tildronate	Risedronate p.o
	Zoledronate i.v



Pyrophosphate

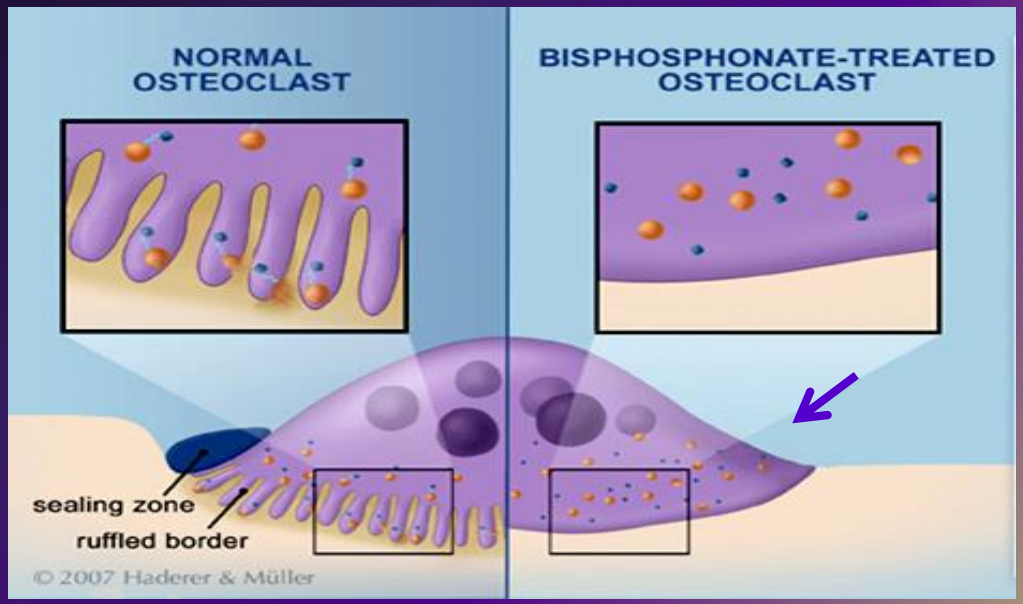
Mechanism

Are structurally similar to pyrophosphate,
They preferentially "stick" to calcium ➔ concentrate in bones, bound to hydroxapatite, decreasing its solubility and 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)



How do they inhibit osteoclasts??? ➔ It is also taken up by osteoclast ➔ blocks steps in cholestrol 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 and vit D supplementation given during bisphosphante theray don't ingest it along with bisphosphonate, give a gap as mentioned above…?

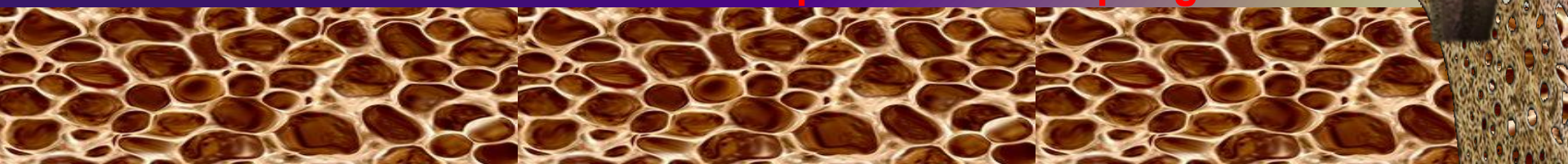
BISPHOSPHONATES

ADRs

- GIT irritation; nausea, vomiting, gastritis , ulceration ➜ to avoid 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 jaw [mandible > jaw] more 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 & zolidronate

Contraindications

- Decreased renal function and Peptic ulcer / esophageal reflux

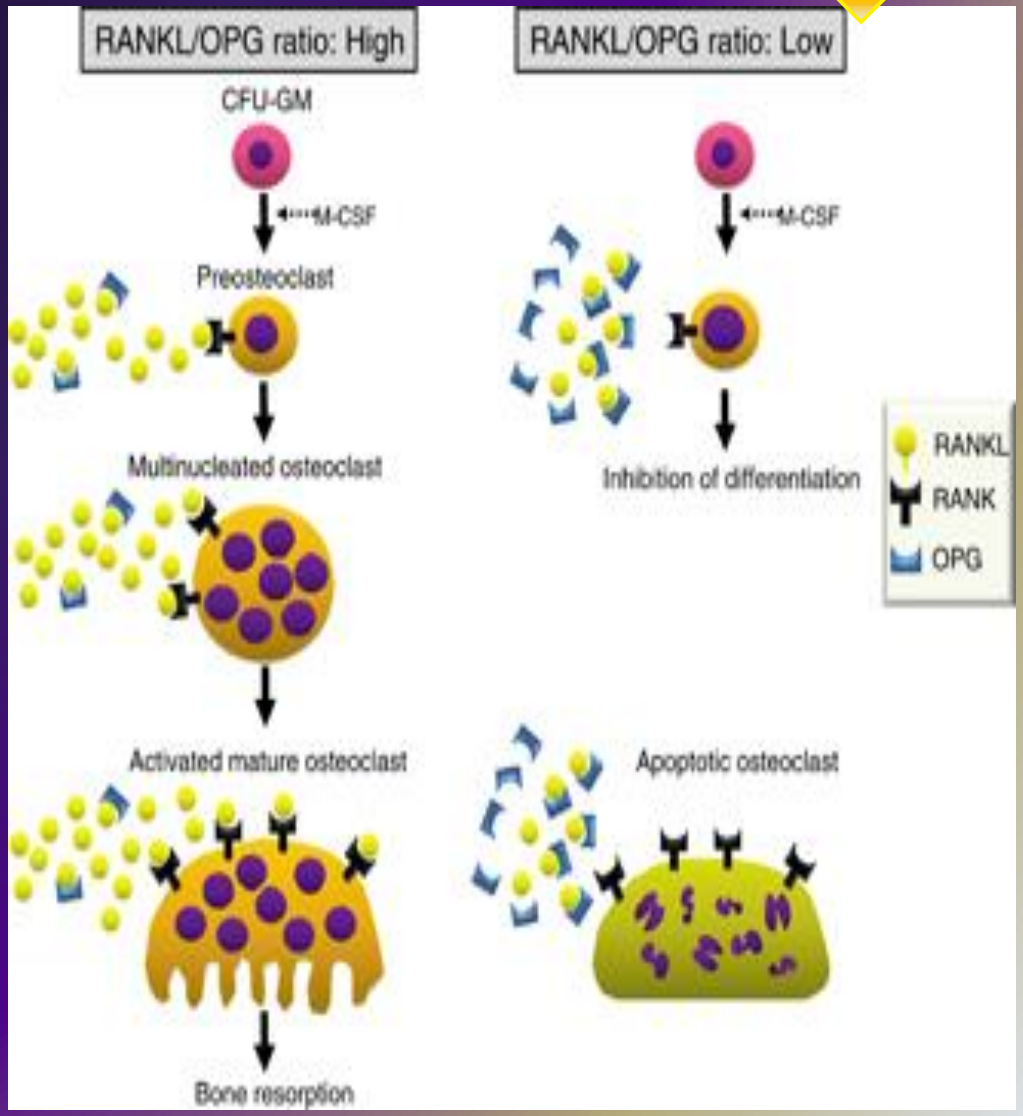


RANKL INHIBITORS ➔ DENOSUMAB (still under investigation)

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

Mechanism

It binds to RANKL, expressed by osteoblasts ➔
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 and mature osteoclasts, and stimulates these cells to mature and resorb bone. OPG, which competes with RANK for binding to RANKL, 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 extremr;ly expensive and reserved for patients who can not totllarate 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.

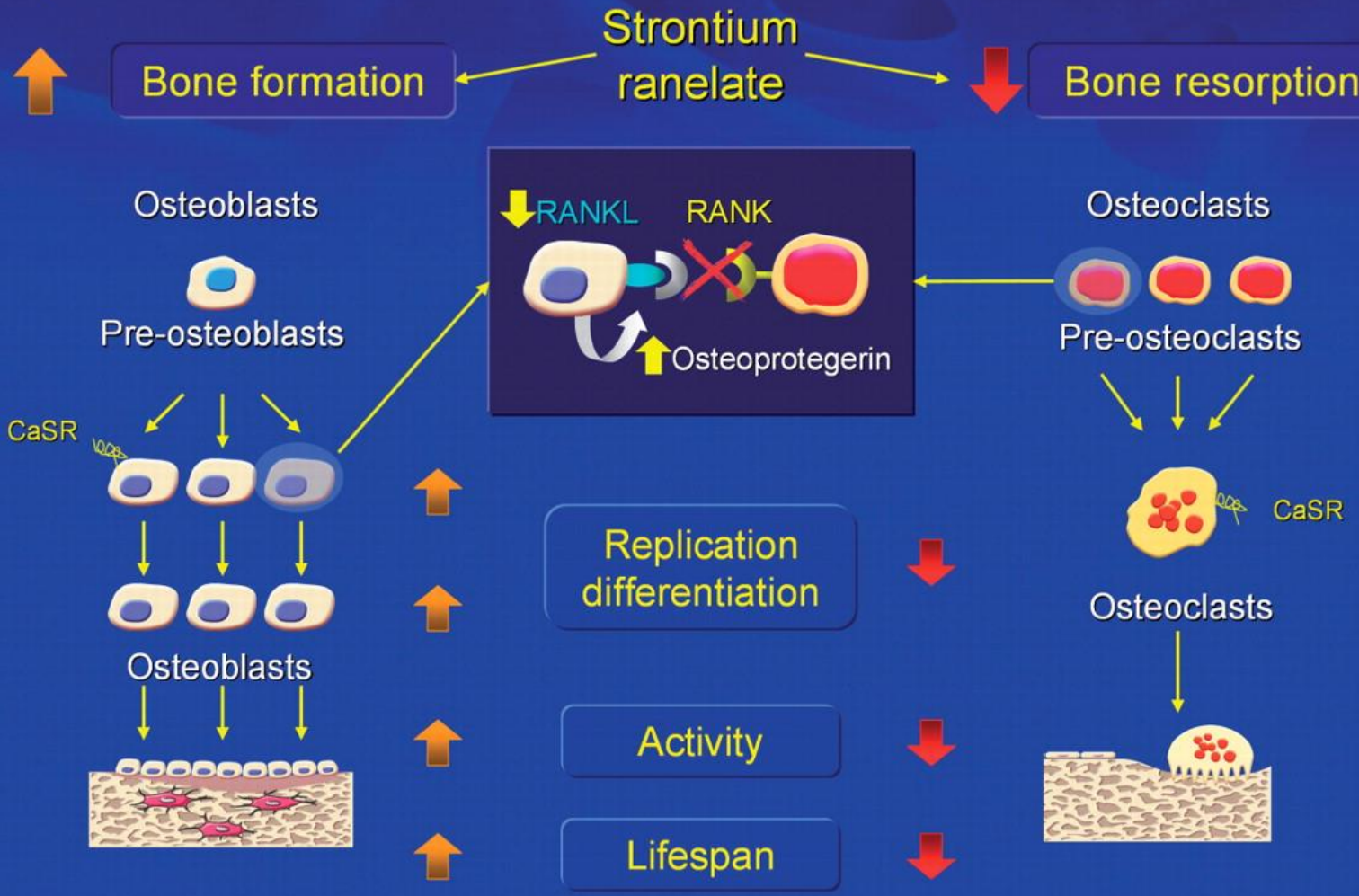
On Osteoblast;

Since it is like Ca, it acts as agonist on Ca Sensing Receptor [CaSR] ; which is a GP coupled receptor that enhances differentiation of preoteoblast to osteoblast → ↑ bone formation
It stimulate the expression of OPG → ↑RANKL binding → -ve 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

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



STRONTIUM

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
- In phenylketonuria

Interactions

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

Precautions

2hrs spacing

ADRs

GIT irritation; nausea, vomiting, headache, eczema

All resolve in 1st 3 months

ESTROGENS If hystrectomy + progestins if uterus present

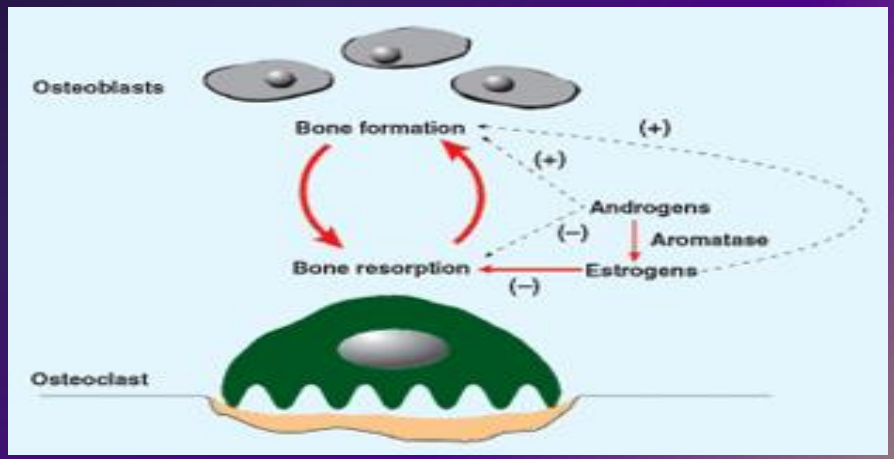
HRT Menopausal Symptoms

SERMs Menopause / Elderly

ANDROGENS Elderly men

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

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



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

SERMs → RALOXIFENE

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

Mechanism

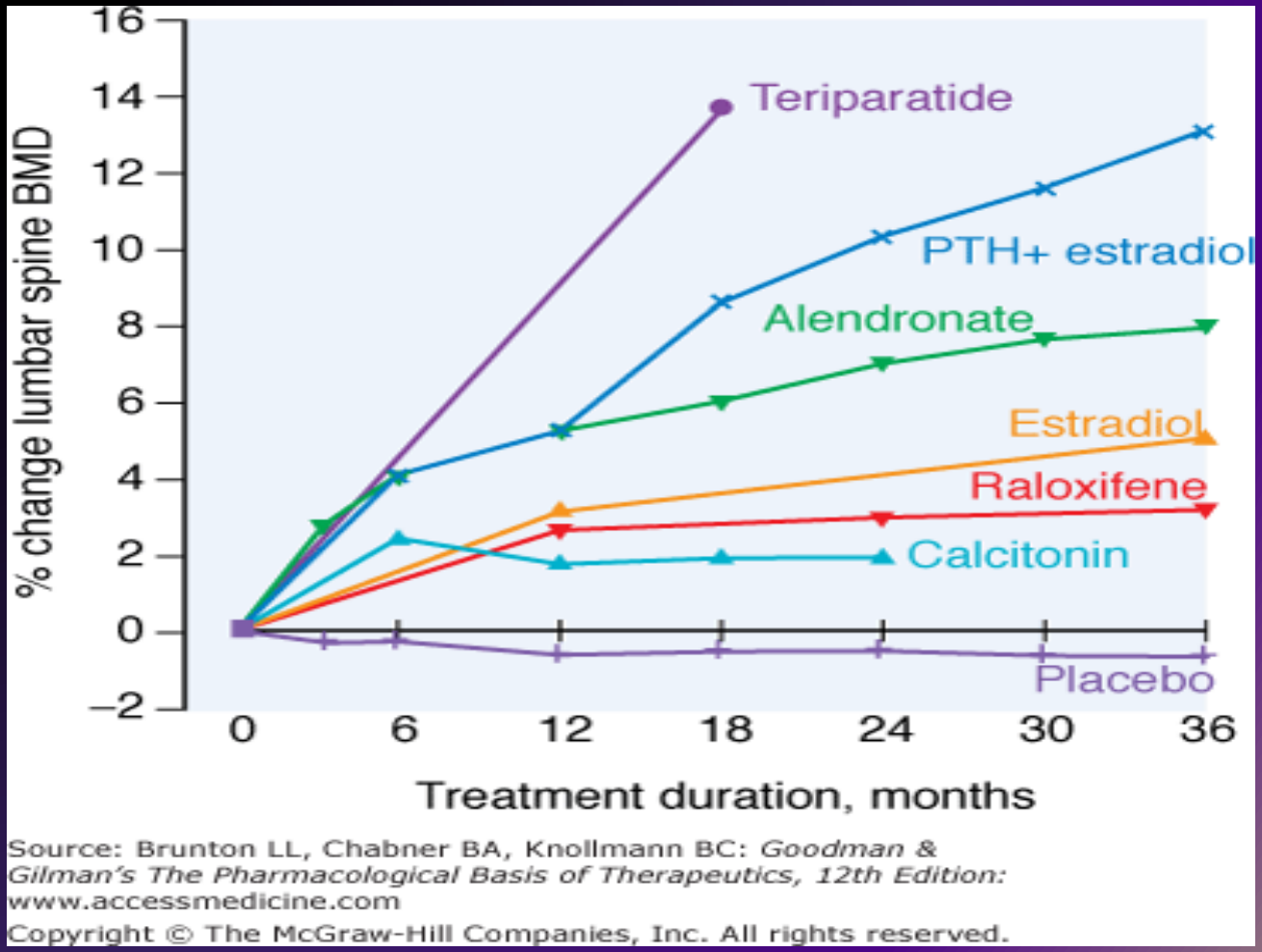
Antiestrogens that exhibits partial agonistic action; acting as an agonist in bone & an antagonist in some female sex organs

	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 and breast cancer.

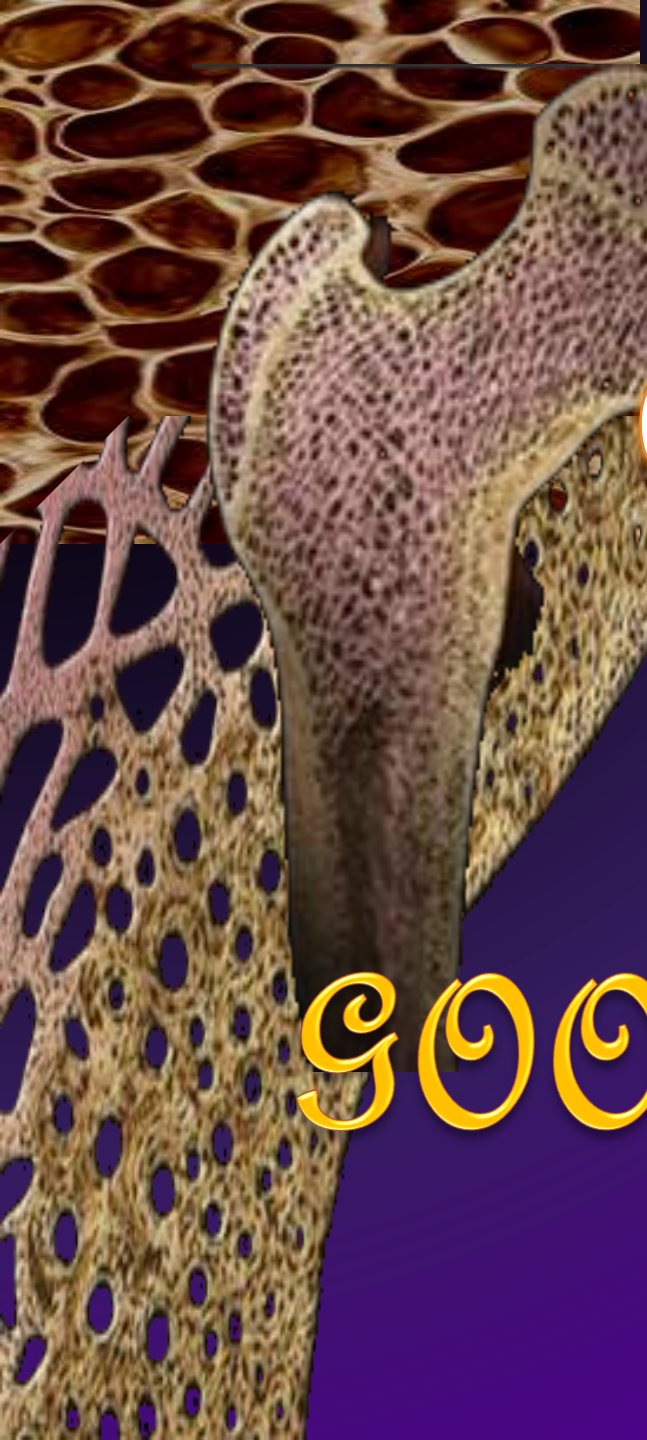
  Lower risk of thromboembolism comopared to estrogen

- **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