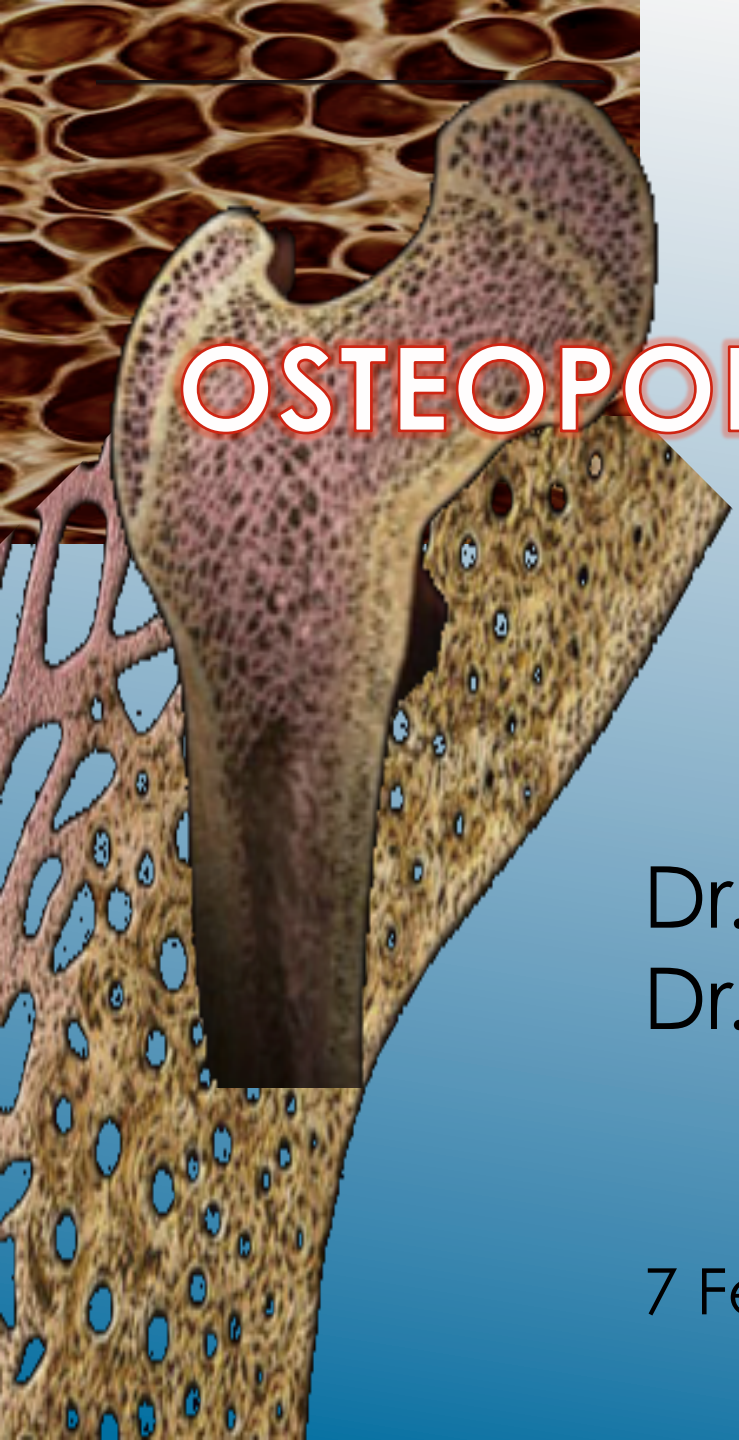

OSTEOPOROSIS and drugs used

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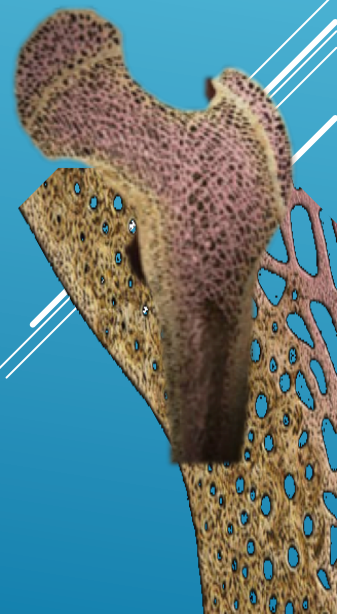
7 Feb 2018

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”

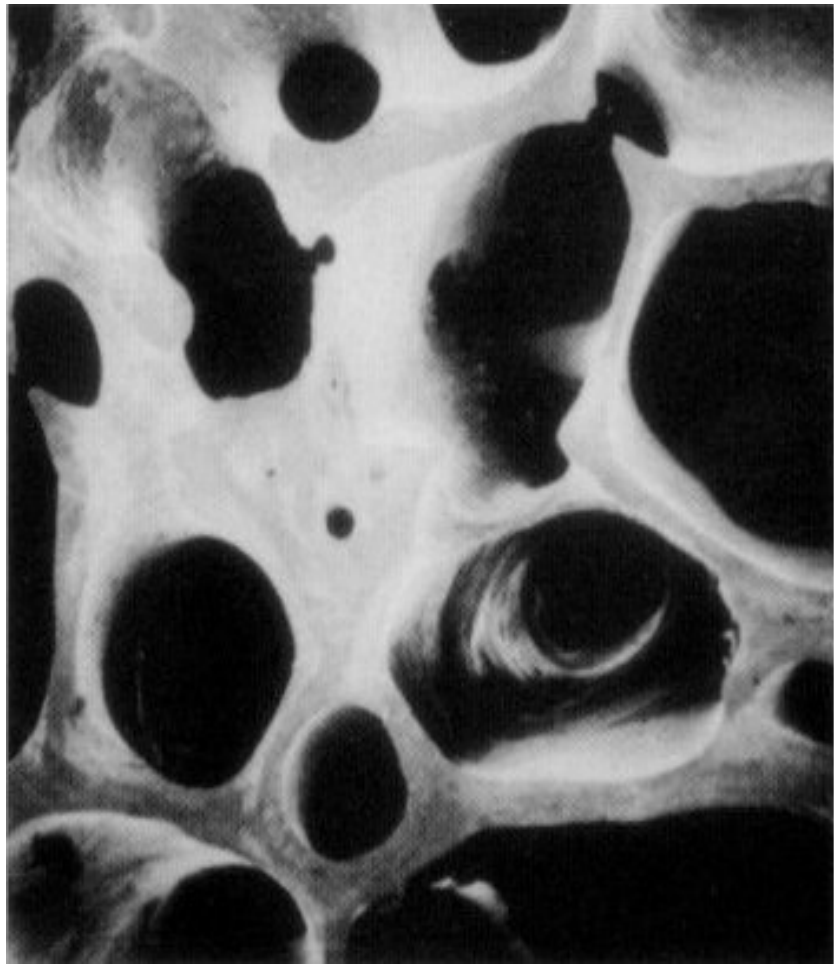
“Osteoporosis” means “bones that are full of holes”.

TYPES OF BONE

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

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

HEALTHY BONE

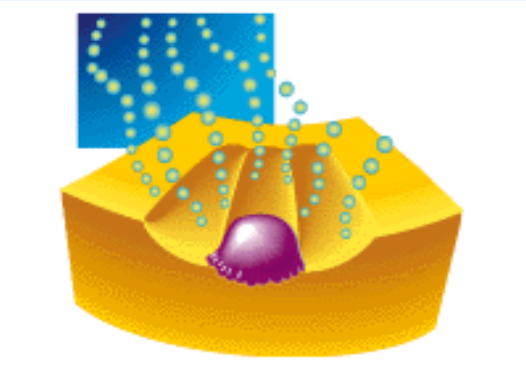


Bone is living tissue, which is constantly being broken down and rebuilt, a process called remodeling

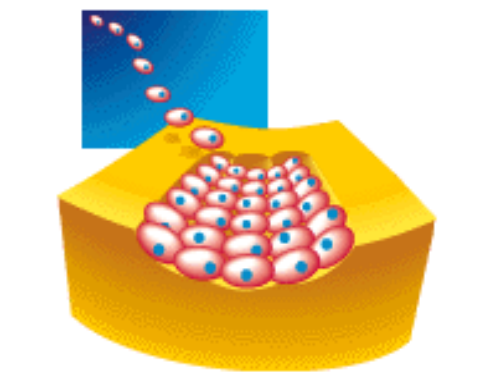
Bone is renewed like skin, hair and nails.

BONE "REMODELING"

Resorption: removes old bone



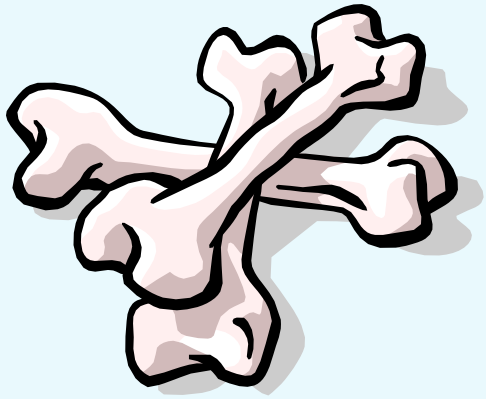
Formation: replaces old bone with new bone.



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

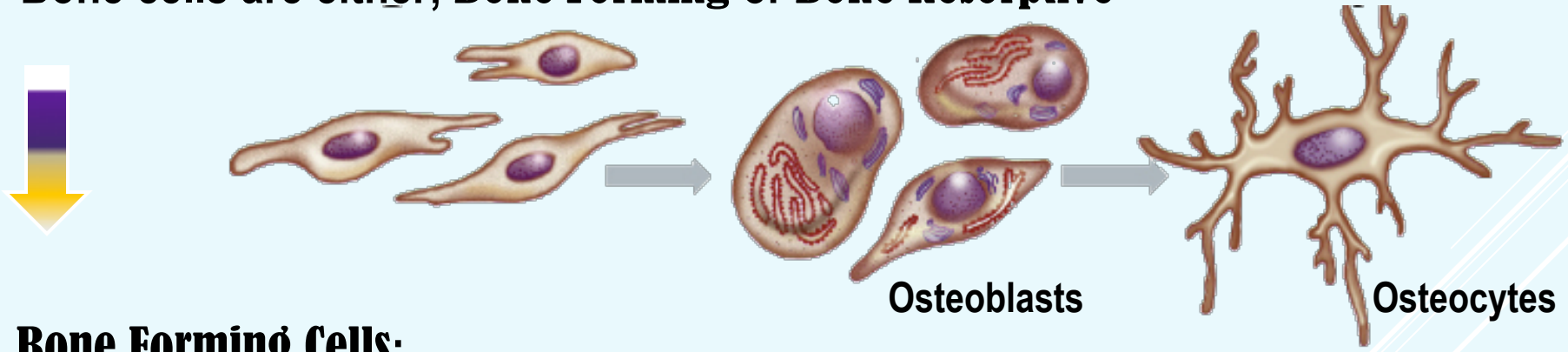
Don’t Smoke.

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**



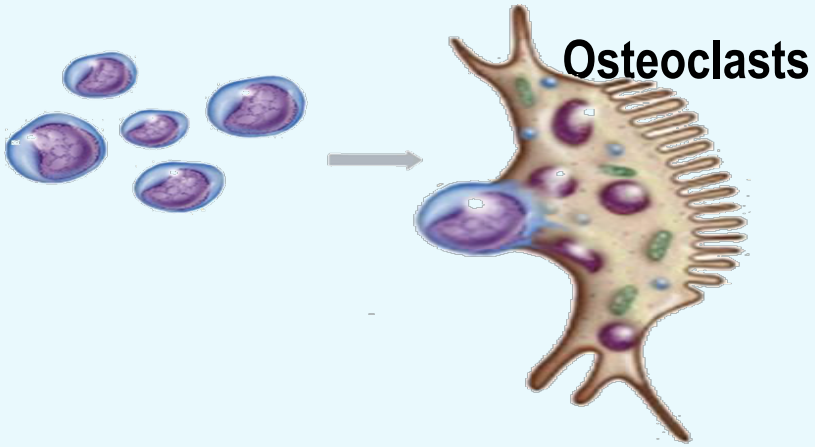
A. Bone Forming Cells:

- 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

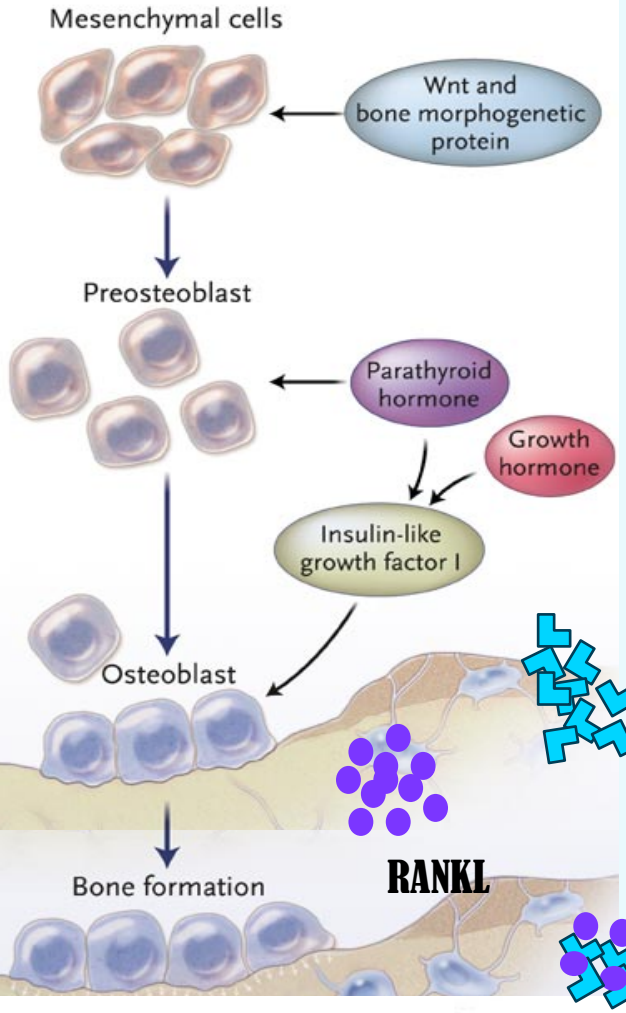
bones continuously form & resorb

➜ BONE REMODELING

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

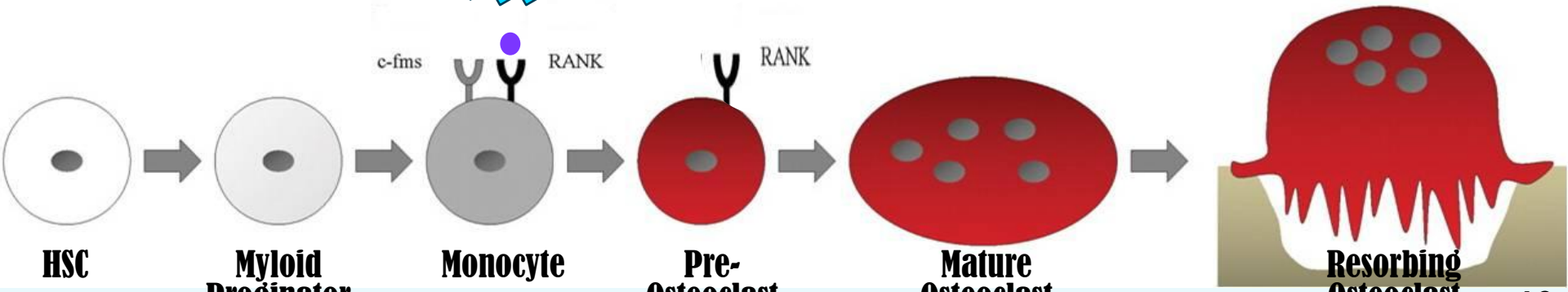
It is meant to maintain calcium homeostasis & to renew bone in repair of microdamage & microcracks.

OPG and bone

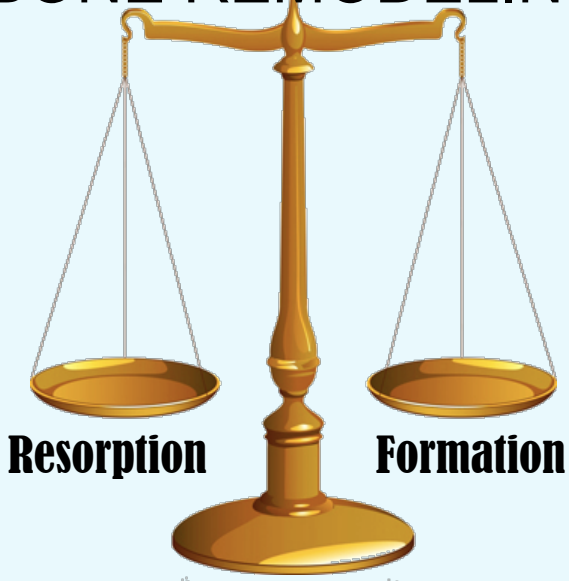


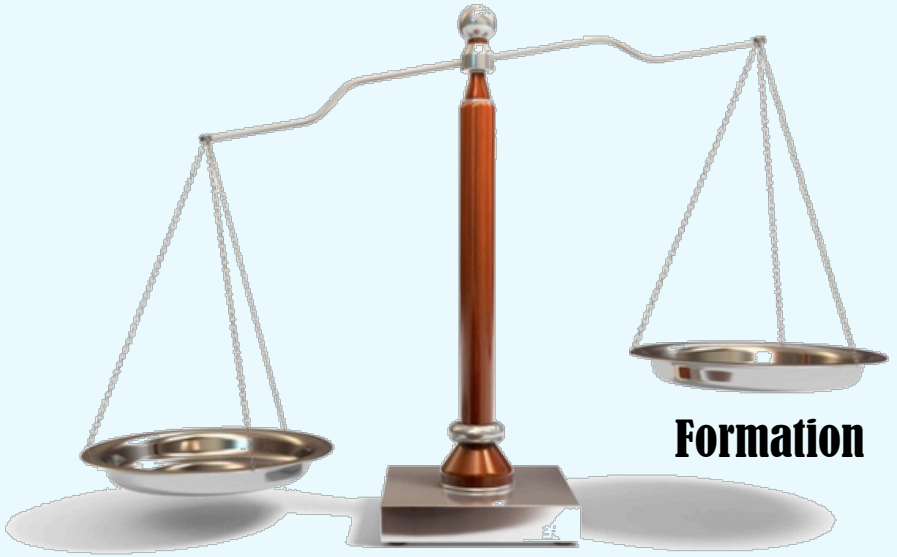
Osteoprotegerin [OPG]

RANKL



BONE REMODELING



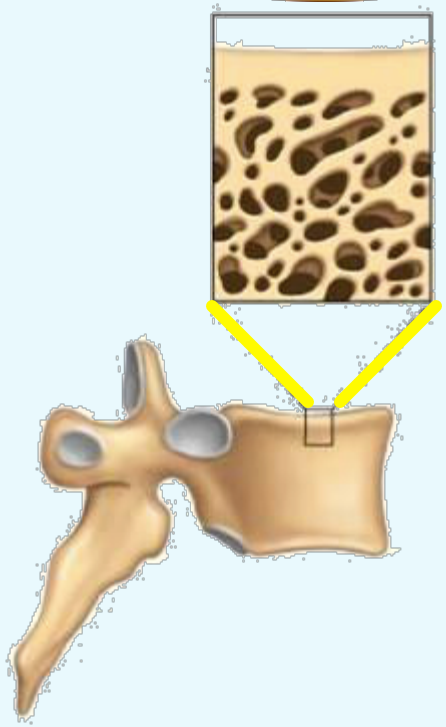


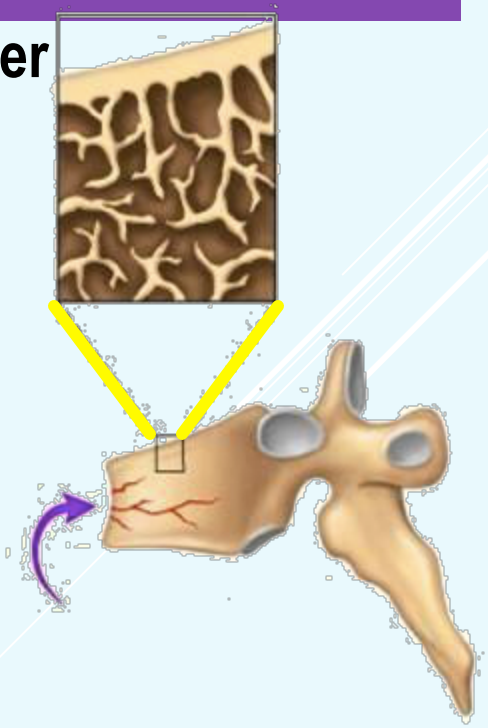
OSTEOPOROSIS

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

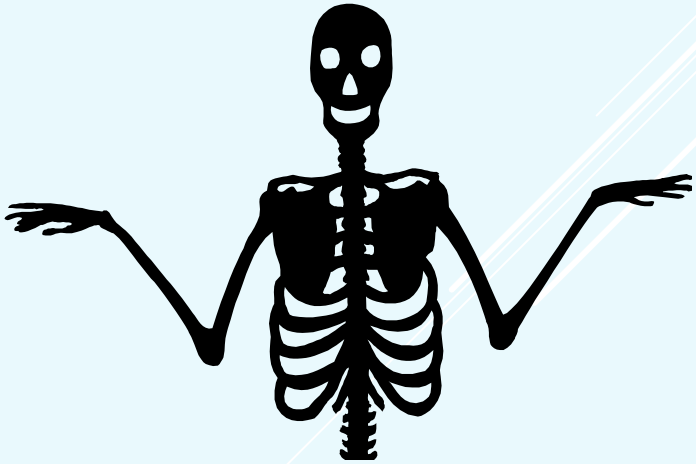
- PREVENTION
- TREATMENT

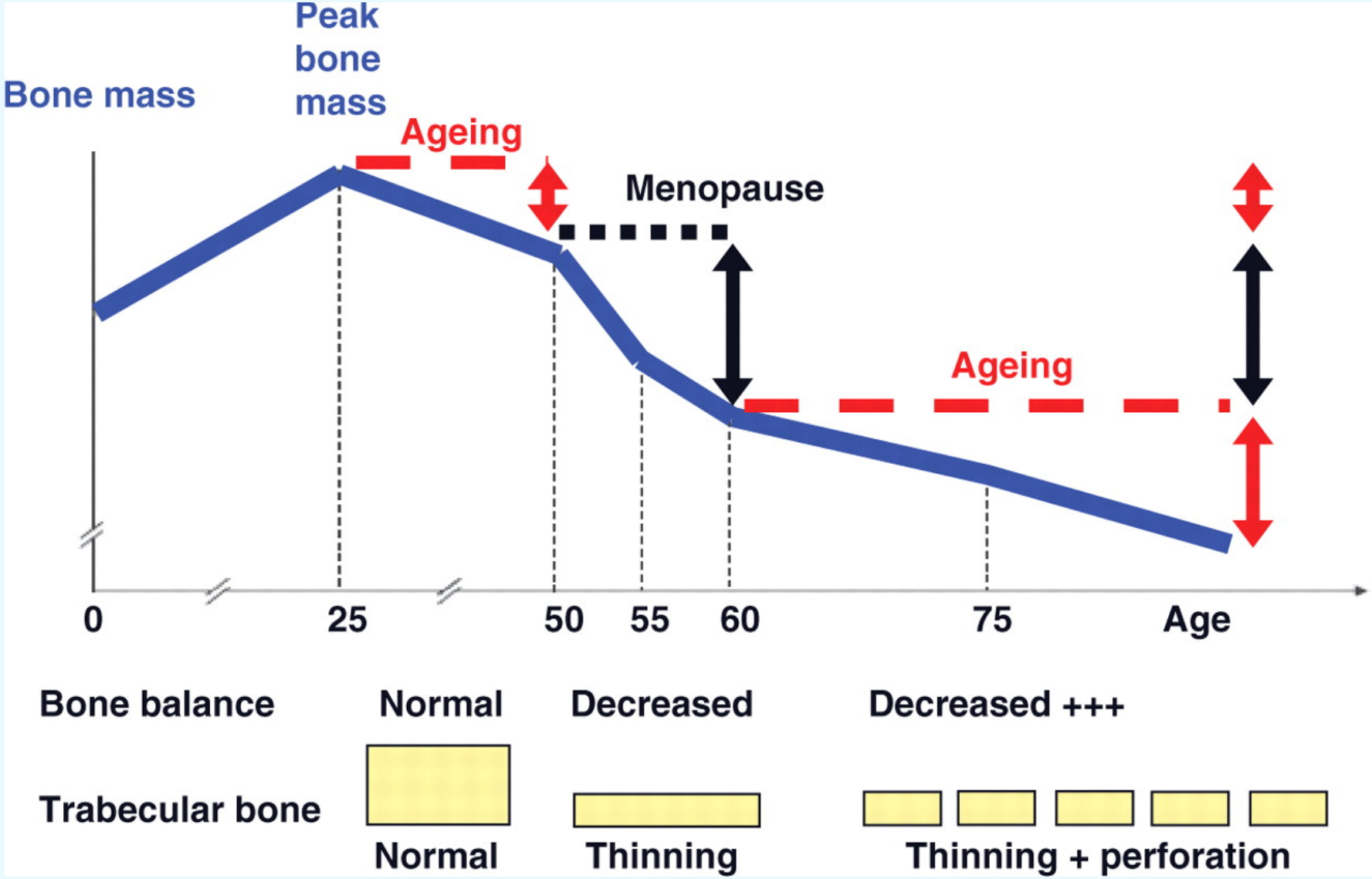
Potentially Modifiable	Non-modifiable
Current cigarette smoking	Personal history of fracture
Diet low in calcium/vitamin D	1st degree relative has fracture
Glucocorticoids, anticonvulsants	Race (Caucasian or Asian)
Excessive alcohol intake	Elderly age
Sedentary lifestyle	Poor health
Body weight	Dementia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

TREATMENT OF OSTEOPOROSIS

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

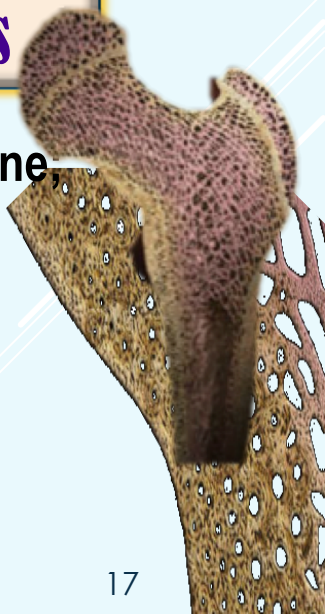
Used to enhance the strength by the formation of fluorapatite
Is considered only when trabecular bone is ↓ in presence of normal cortical bones.

ANTIRESORPTIVE AGENTS

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

BONE ANABOLIC (building) AGENTS

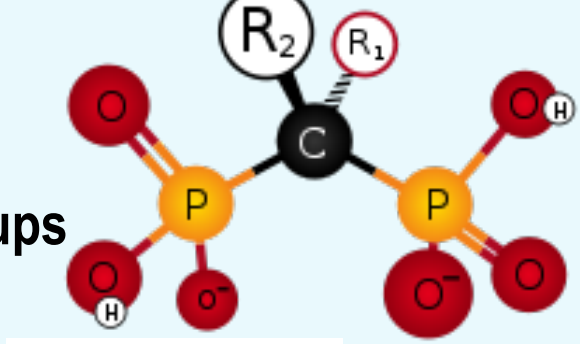
- (Parathyroid hormone, TERIPARATIDE
- STRONTIUM



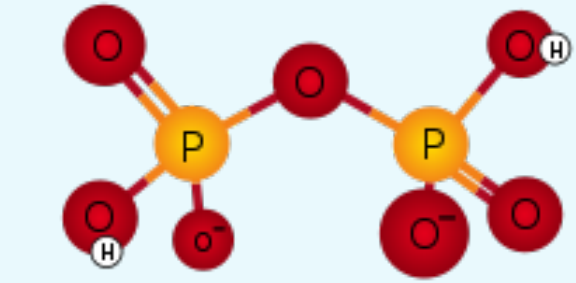
BISPHOSPHONATES

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

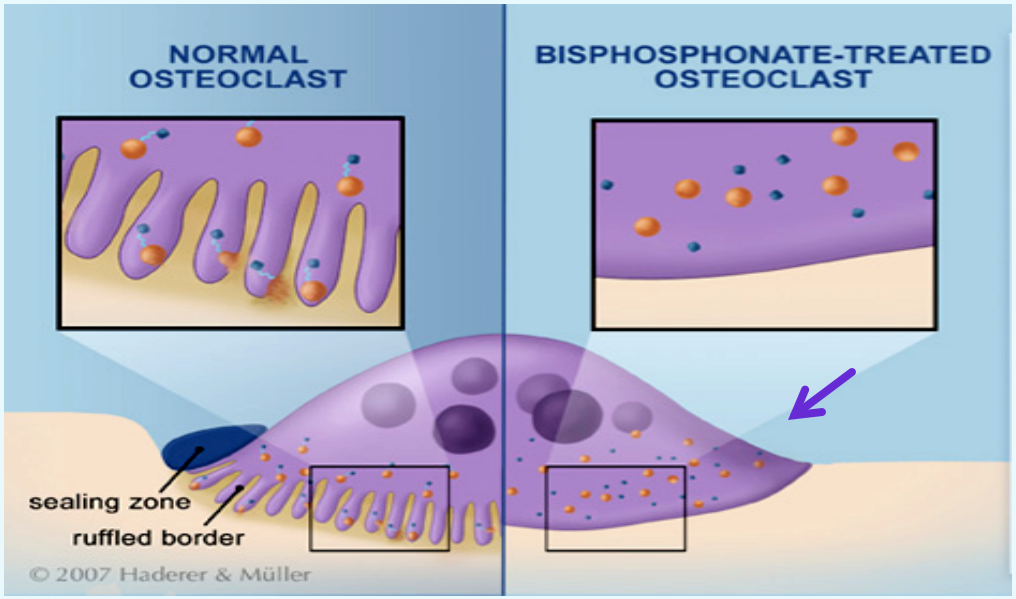
Mechanism

- 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

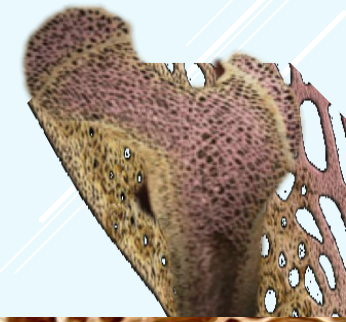
Note : calcium & vit D supplementation given during bisphosphonate therapy don't ingest it along with bisphosphonate, give a gap as mentioned above…?

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

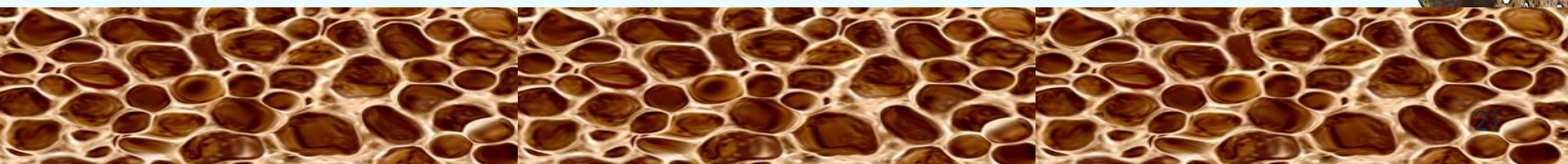
If a dental implant or extraction is already planned, delay bisphosphonate therapy for a few months until healing of the jaw is complete

- Atrial fibrillation > women with alendronate & zolidronate.



Contraindications

- Decreased renal function and Peptic ulcer / esophageal reflux.



RANKL INHIBITORS → DENOSUMAB (still under investigation)

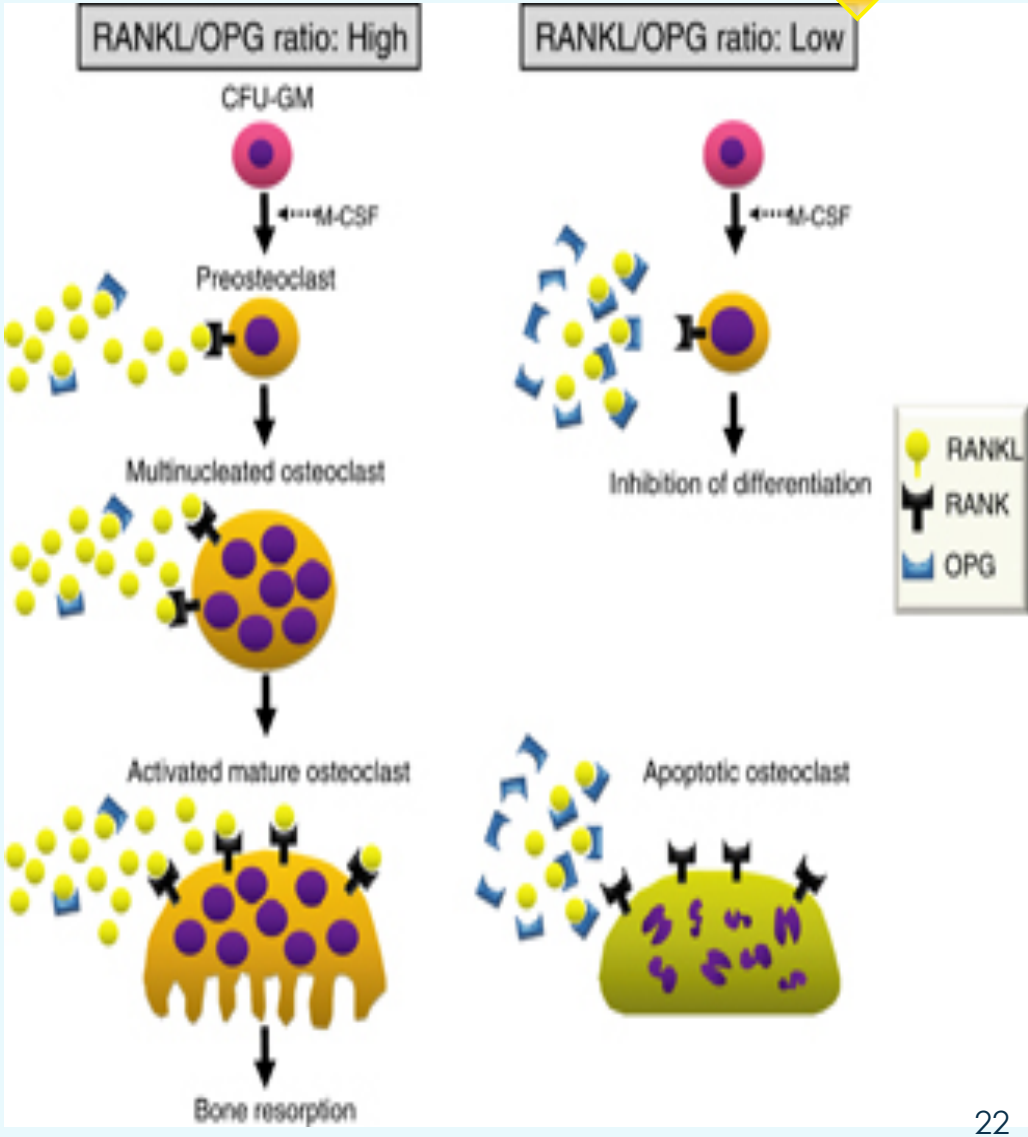
It is a fully human MOA that mimics the activity of osteoprotegerin

Mechanism

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

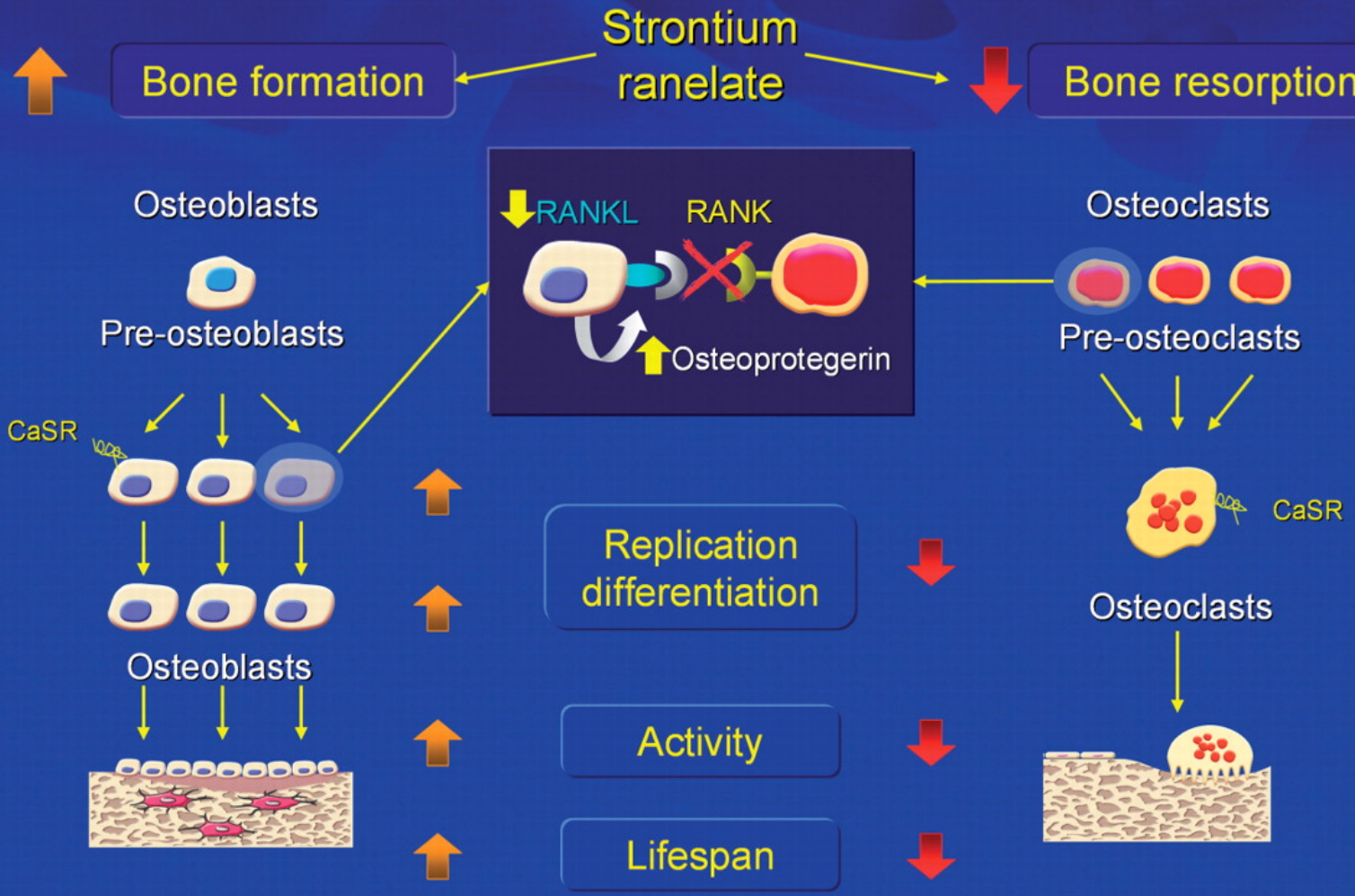
1st drug to possess " dual action " i.e has both anabolic & antiresorptive effects, resulting in a rebalance of bone turnover in favor of bone formation

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

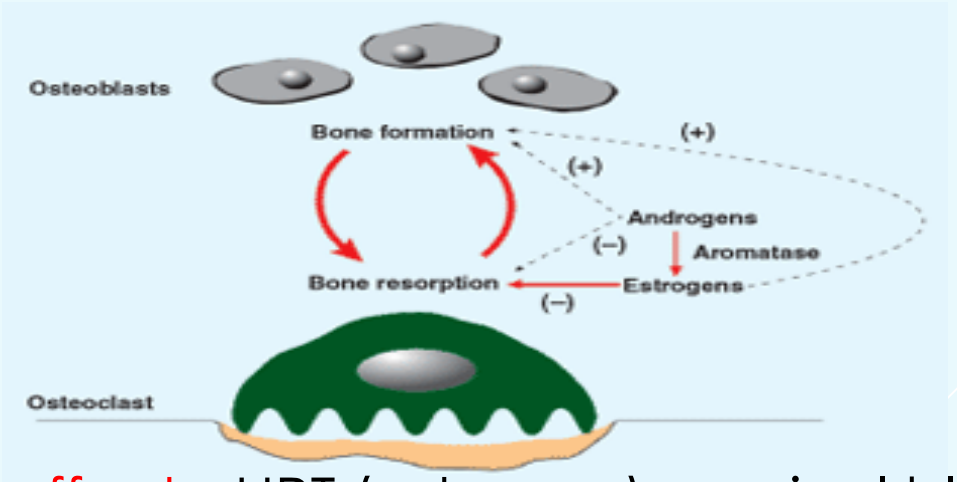
HRT Menopausal Symptoms

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

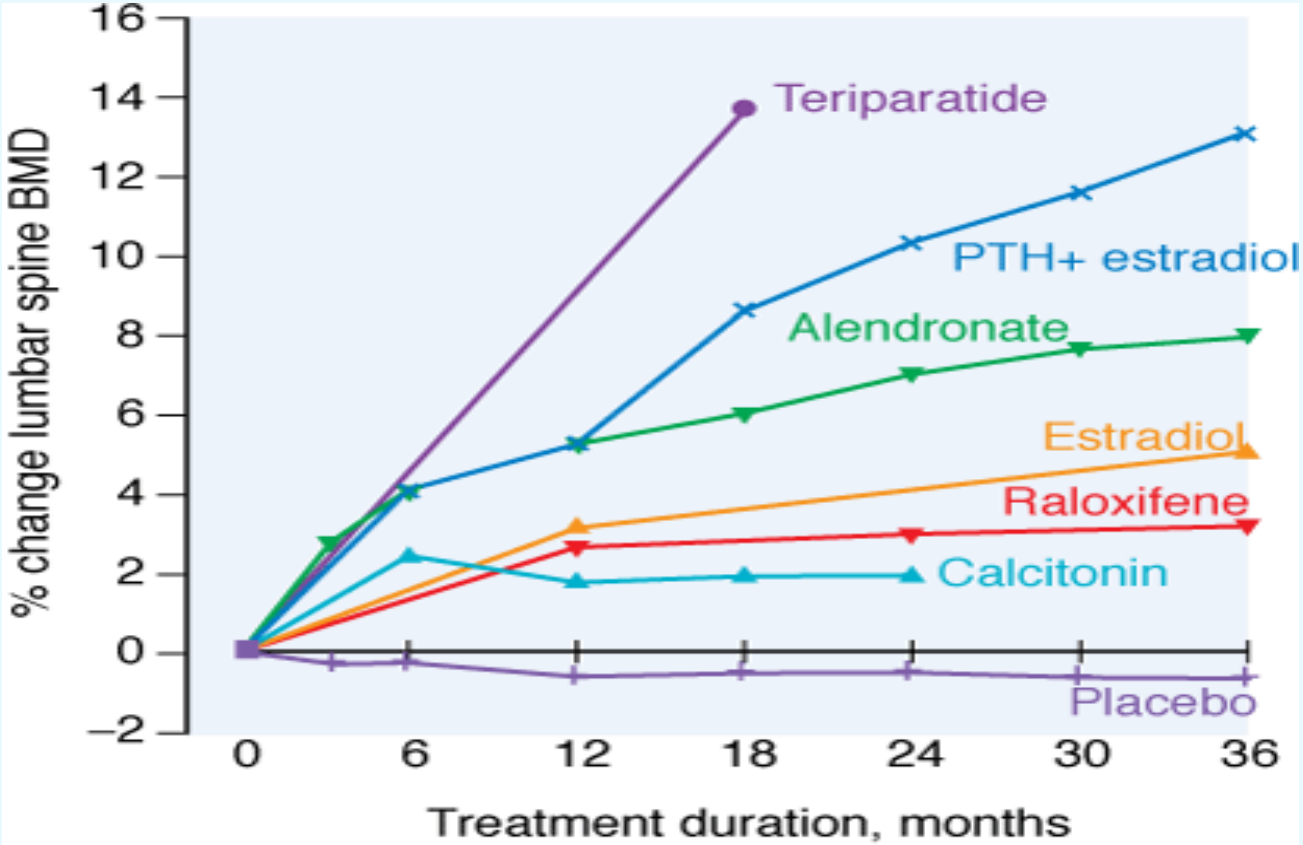
	Brain	Uterus	Vagina	Breast	Bone	CVS
Estradiol	++	++	++	++	++	++
Raloxifene	—	—	—	—	+	+

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