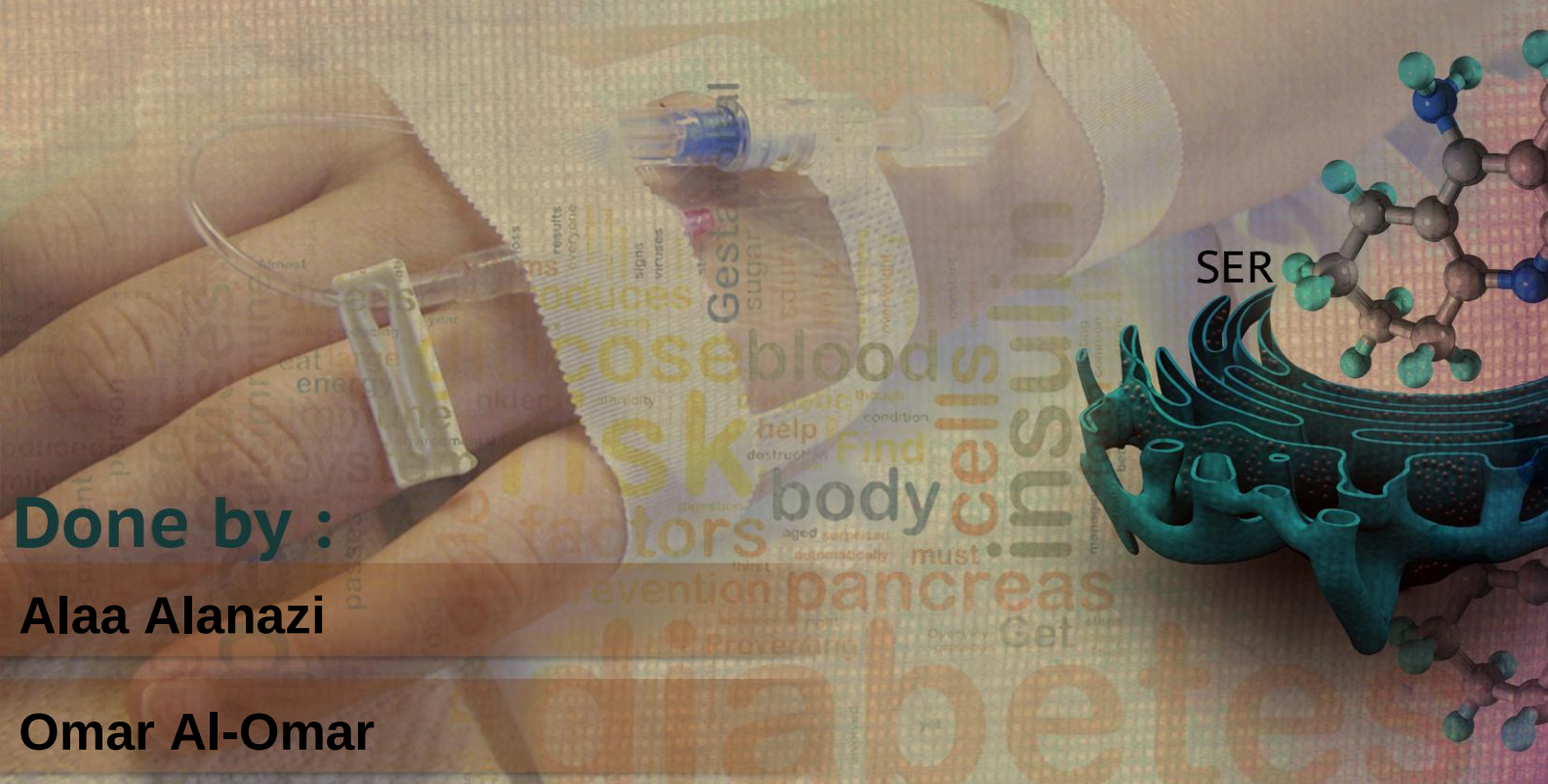
431 Teams
medical students

DT431 Team Pharmacology

Endocrine block

Lecture 4

Treatment of Osteoporosis



Done by :

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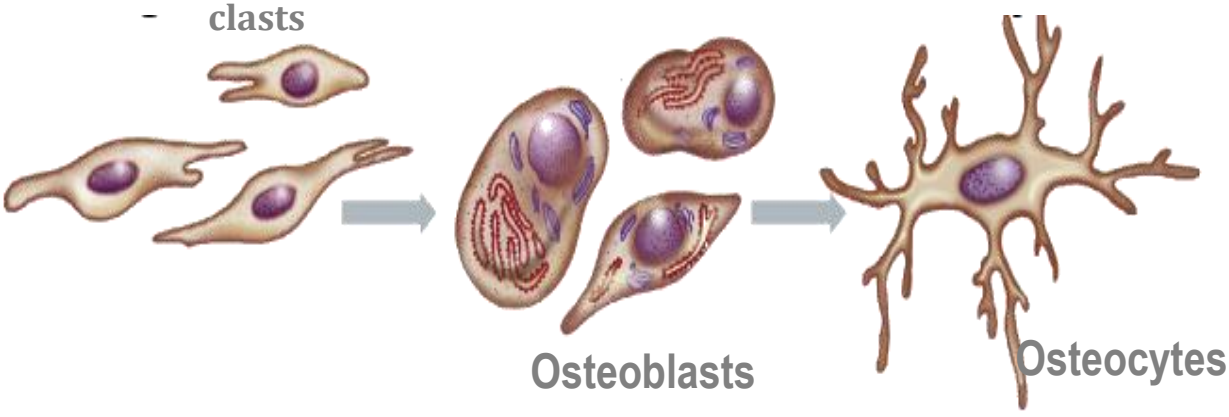
Red = Important
Gray= not important
Blue = Dr said
Green= team notes

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**

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 **or** Bone Resorptive
A. Bone Forming Cells:

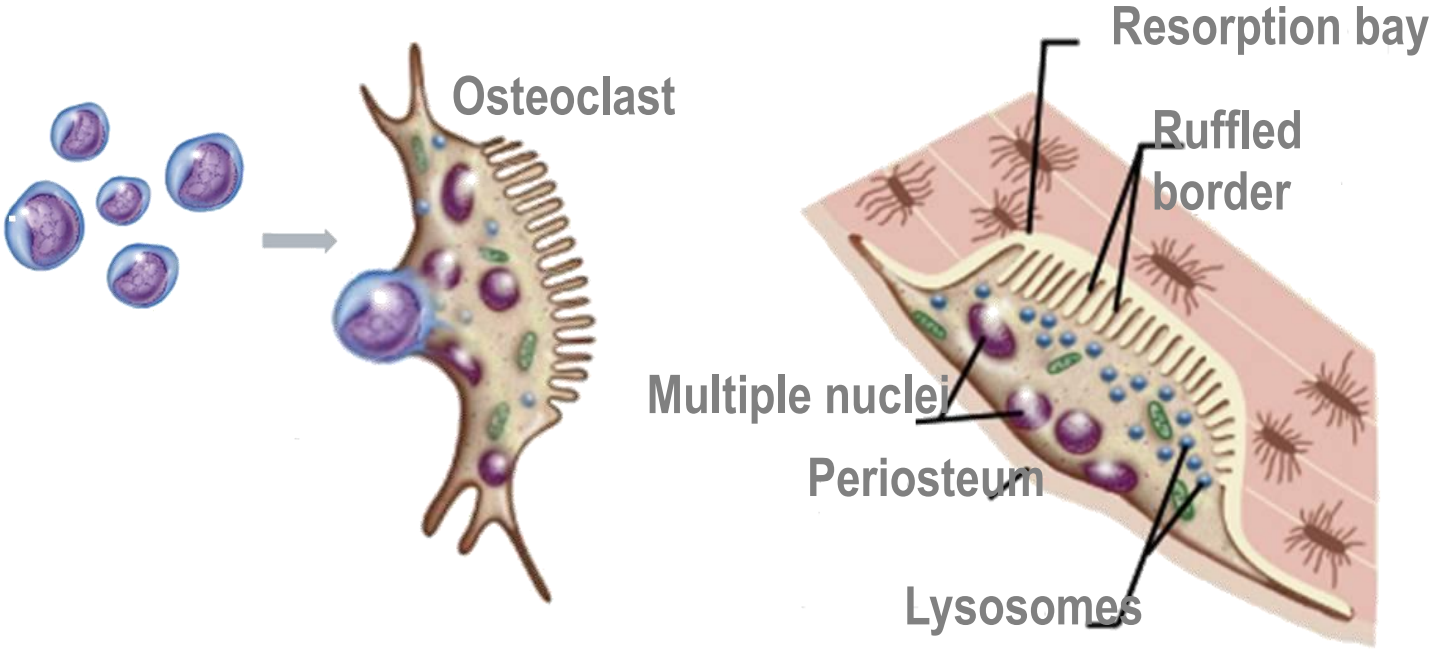
- **Osteogenic cells ➜ mesenchymal in origin ➜ are progenitor of blasts & cytes ➜ are found on all bone surfaces**
- **Osteoblasts ➜ forms osteoid framework & help in its mineralization**
- **Osteocytes ➜ sense mechanical stress ➜ signals to both blasts & clasts**



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. ➜ dissolve bone matrix



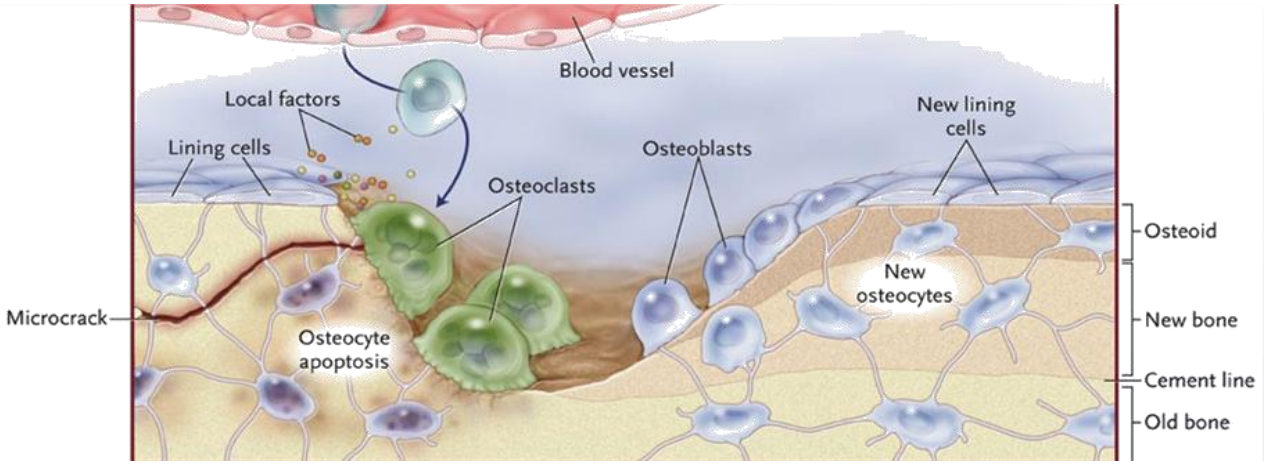
NORMALLY

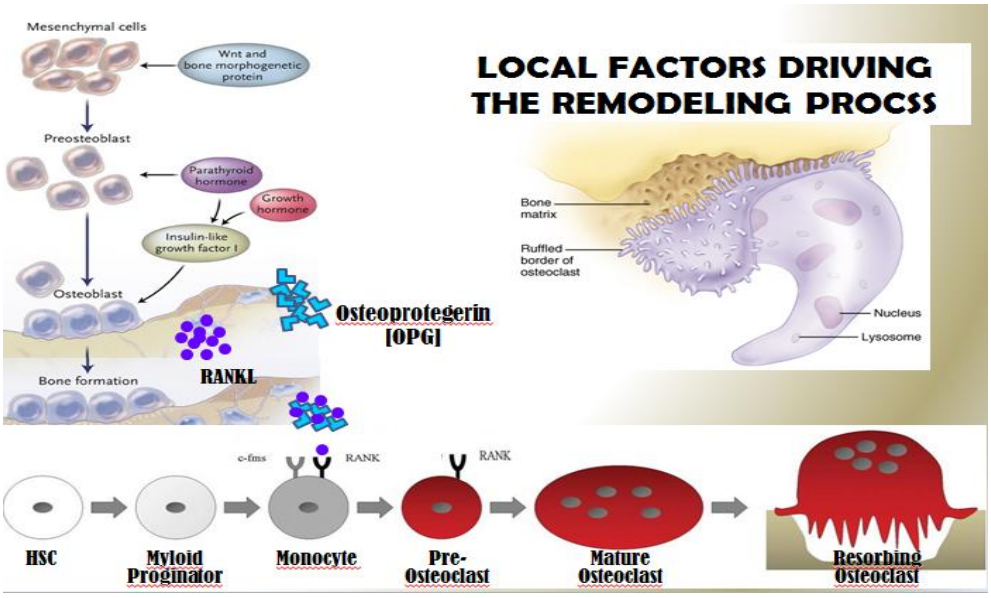
bones continuously form & resorb

➜ 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





Dr Omnia said this pic important to understand not for our exam.
Normally, the osteoblasts secrete RANKL & OPG in equal amount, then the RANKL bind to OPG.
In some case like osteoporosis , the RANKL produce more than OPG, so the extra amount don't have enough OPG to bind to them , as a result they bind to receptors in the Monocytes , that leading to form more Osteoclast.
So when we want to treat osteoporosis, we can make drug that inhibit the RANKL, and that what will see in some mechanism of action of osteoporosis drugs.

SYSTEMIC HORMONES Controlling Remodeling:

1. PARATHORMONE → **Maintains calcium homeostasis via**
   - ↑ **bone formation (intermittent) /↑ bone resorption (continuous)**
   - ↑**renal tubular calcium reabsorption**
   - ↑ **renal calcitriol production**

2. CALCITROL

↑ intestinal Ca & phosphorus absorption → ↑ bone mineralization
↑ bone resorption when they are deficient

3. ESTROGEN & ANDROGEN

↑ rate of bone loss by acting on many local factors
   - ↑ **osteoclast apoptosis & growth factors from osteoblasts**
   - ↓**No. & depth of resorption cavities & release of cytokines**

4. CALCITONIN

Not much physiological role in man
Pharmacologically → ↓ osteoclasts & bone resorption

5. CLUCOCORTICOIDS

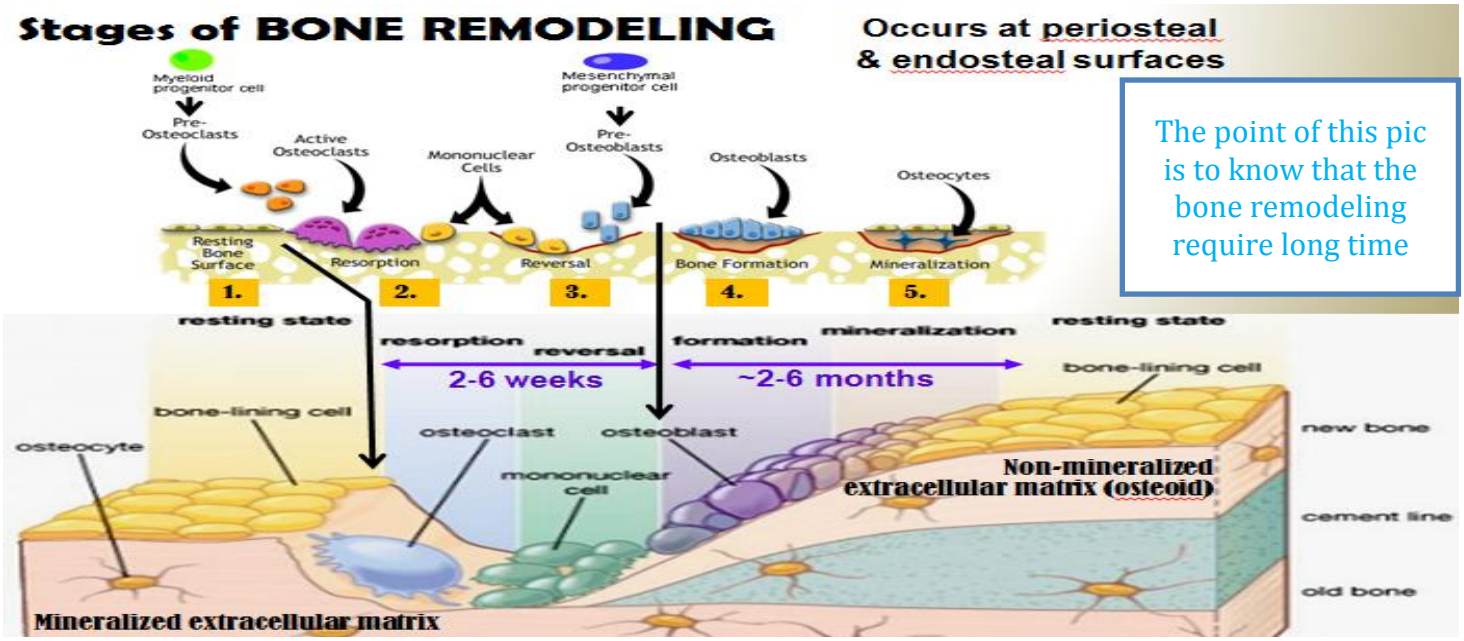
↑ apoptosis of osteoblasts & osteocytes → ↑ resorption ↑ differentiation of osteoblasts → ↑ formation

6. THYROID HORMONE

↑ Bone turn-over i.e. resorption & formation

7. Growth hormone & IGFs

↑ skeletal growth & endochondral bone formation.



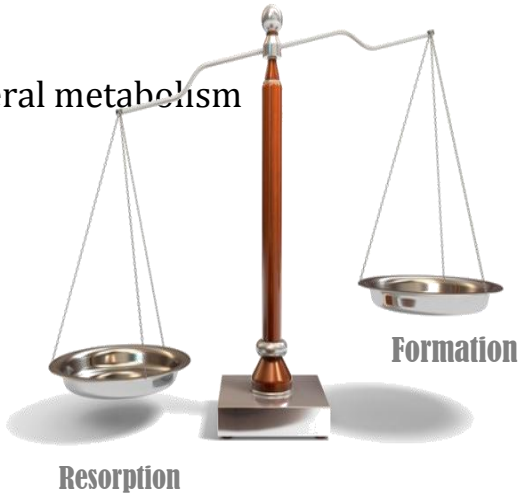
The point of this pic is to know that the bone remodeling require long time

OSTEOPOROSIS:

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

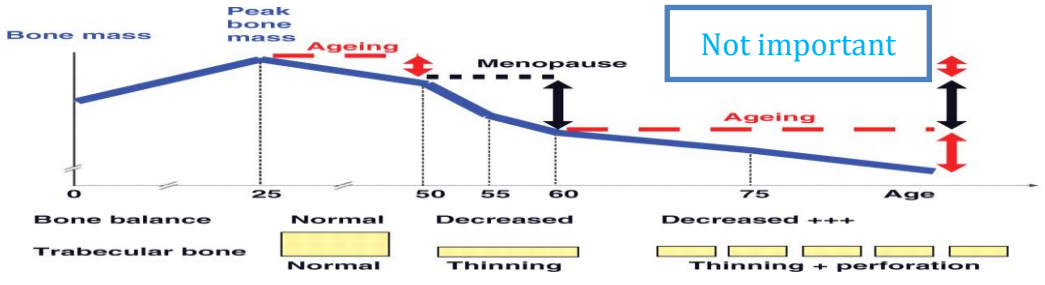
Low bone mass
Disruption of bone architecture

Reduced bone strength
Risk of fractures



PREVENTION: (Don't study it)

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 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



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

2- Reset back the balance of remodeling

ANTIRESORPTIVE AGENTS	BONE ANABOLIC AGENTS
BISPHOSPHONATES ESTROGEN ANALOGES ANDROGEN ANALOGES SERMS CALCITONIN RANKL INHIBITORS	TERIPARATIDE
STRONTIUM	

- ***Others; Thiazide diuretics, statins***
  (Decrease the incidence of Osteoporosis)

BISPHOSPHONATES

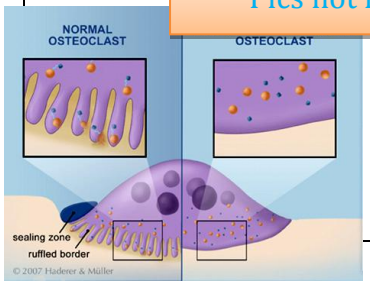
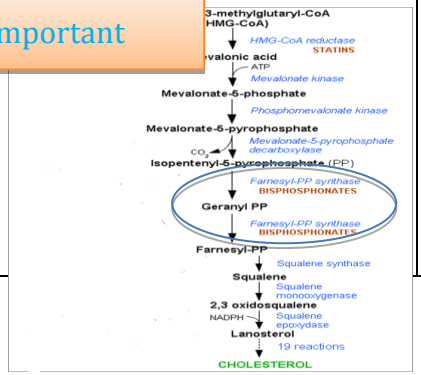
Are compounds that have two phosphonate (PO_3) groups

Non-Nitrogenous: Etidronate ,Clodronate → 10 ,Tildronate → 10

Nitrogenous: Alendronate (orally and common)→500 , Ibandronate → 1000 , Risedronate → 2000 ,

Zoledronate (injectable) → 1000

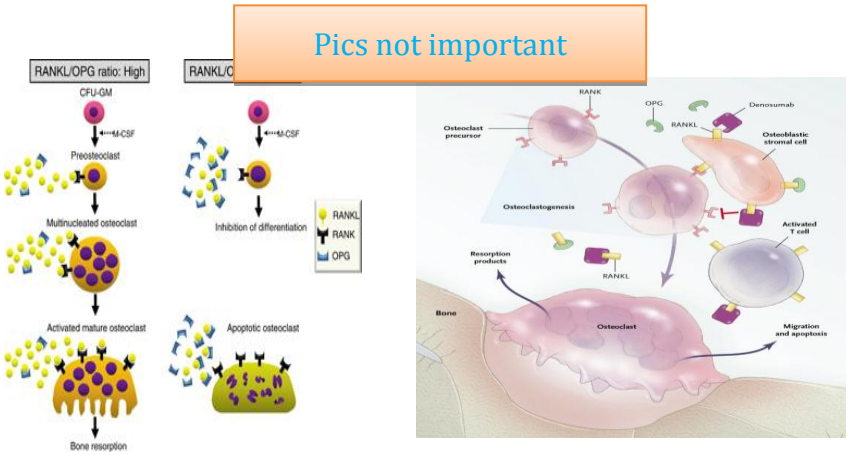
(numbers are the doses)

Mechanism	Kinetics	Indications	ADR	Contra-indications
1-Are structurally similar to pyrophosphate, thereby inhibiting activation of enzymes that utilize it. 2-They preferentially "stick" to calcium → concentrate in bones, bound to hydroxapatite. 3-They prevent bone resorption by inhibiting osteoclast function. 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 Their relative potencies for osteoclast inhibition is the most with 3rd generation "Zoledronate" Pics not important  	1-Poorly abs (< 10%), food impair absorption more → must be given on an empty stomach. / infused IV. 2-$t_{1/2}$ 1 hr. 3-Half of absorbed drug accumulates in bones, remainder → excreted unchanged in urine. 4-In bone it is retained for months, depending on bone turnover. **Dosing:** Once weekly, or on two consecutive days each month Taken 1st thing am 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.	1-Osteoporosis , 2ndry to menopause, glucocorticoids, 2-Paget's Disease 3-Malignancy-associated hyper-calcaemia	1-GIT irritation; nausea, vomiting, gastritis , ulceration → to avoid give large amount of water 2-Gastro-esophageal reflux ± ulcerations → to avoid give on empty stomach while sitting in upright 3-Flue like manifestations upon IV infusion 4-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 5-Atrial fibrillation > women with alendronate & zolidronate	1-Decreased renal function 2-Peptic ulcer / esophageal reflux

RANKL INHIBITORS (DENOSUMAB)

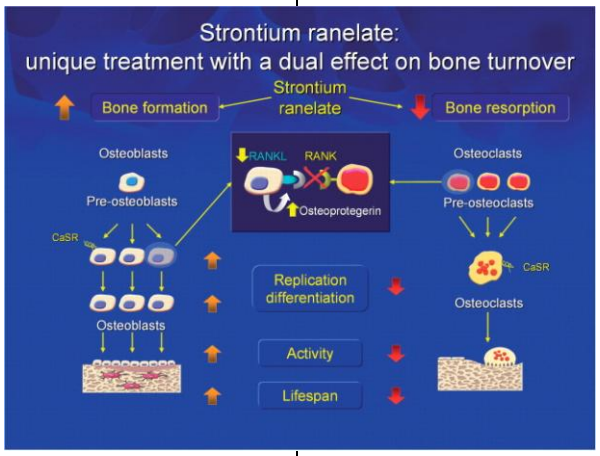
It is a fully human MOA that mimics the activity of osteoprotegrin (MOA= Monoclonal Antibody)

Administration: Subcutaneous every 6 month

Mechanism	Contraindications	ADRs
It binds to RANKL, expressed by osteoblasts ➔ -ve 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 .  Pics not important	**In patients with hypocalcemia.** **Correct Ca & Vit D levels before starting denosumab**	• **Infections; urinary & respiratory** • **Eczema & skin rash** • **Constipation** • **Cataract** • **Joint pains**

STRONTIUM

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

Mechanism	kinetics	Indications	Contraindications	Interactions	ADRs
1st drug to possess " dual action " i.e has both anabolic & antiresor-ptive 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	• Orally with a modest bioavailability →25% • Binds partially to plasma proteins and strongly to bones • t ½ → 60 hrs • Excreted mainly by the kidney 	• Osteoporosis , 2ndry to menopause, glucocorticoids. • Malignancy-associated hypercalcaemia	• In severe renal disease. • In hypersensitivity to it • In increased risk of venous thromboembolism • In phenylketonuria	• Food specially containing milk± its products → • Antacids • Oral tetracycline & quinolones chelate it Precautions **2hrs spacing**	GIT irritation; nausea, vomiting, headache, eczema All resolve in 1st 3 months

ESTROGENS: use →

1- **If hystrectomy**

2- **With progestins if uterus present**

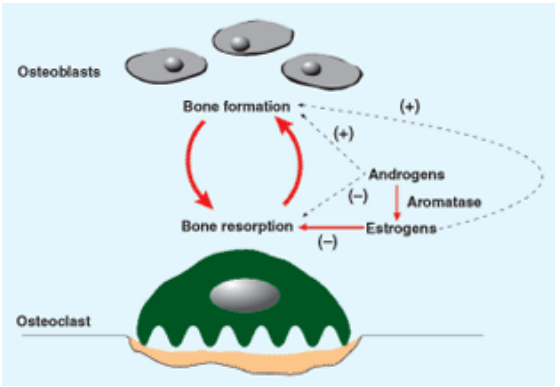
(Adding the progestin to prevent the endometrial cancer)

HRT: (Hormone replacement therapy) → **Menopausal Symptoms**

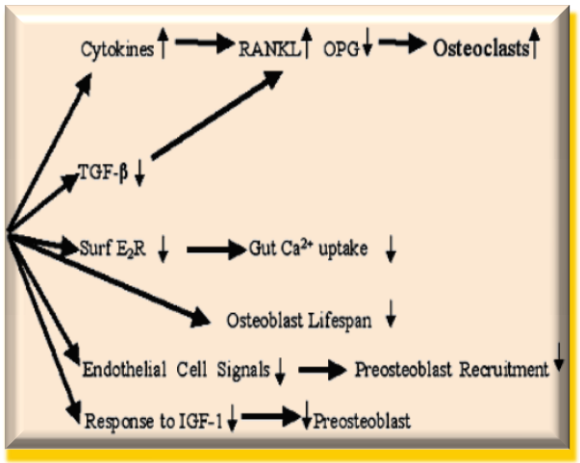
ANDROGENS →Elderly men

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

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



So when there are ↓ ANDROGENS & ↓ESTROGENS



→ **Osteoporosis → REPLACEMENT THERAPY OR OTHER THERAPY MODALITIES**

SERMs:

RALOXIFENE

Use → **Menopause /Elderly (male and female)**

1st selective estrogen R modulator for prevention of osteoporosis

Mechanism

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

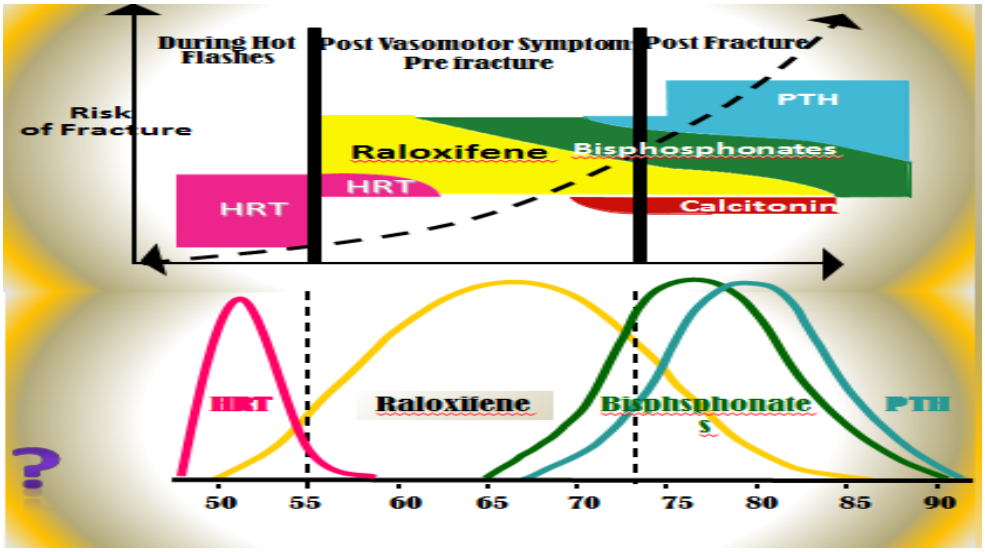
	Brain	Uterus	Vagina	Breast	Bone	CVS
Estradiol	++	++	++	++	++	++
Raloxifene	—	—	—	—	+	+

➢ Advantages	➢ Disadvantages
➢ ↑ bone density (2%) & ↓ fracture risk (30%) ➢ No stimulation of breast or endometrial tissue ➢ No need for progestin in women with uterus ➢ ↓ LDL	➢ ↑ risk of thromboembolic events ➢ Doesn't treat well Post-menopausal Symptoms ➢ May ↑ hot flushes ➢ No effect on HDL

TIBOLONE

Synthetic steroid → estrogen, androgen & progestin properties

Can be used without CVS risks



Summary

DRUG SUMMARY TABLE: Drugs Affecting Bone Mineral Metabolism

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Drug Interactions
Vitamin D, metabolites, analogs				
Cholecalciferol, ergocalciferol	Regulates gene transcription via the vitamin D receptor to produce the effects detailed in Table 42–1	Vitamin D deficiency	Oral administration	Hypercalcemia, hyperphosphatemia, hypercalciuria
Calcitriol: Used for management of secondary hyperparathyroidism in patients with chronic kidney disease and for management of hypocalcemia in patients with hypoparathyroidism Doxercalciferol (1-hydroxyvitamin D_2): Used for management of secondary hyperparathyroidism in patients with chronic kidney disease Paricalcitol: An analog of calcitriol used for management of secondary hyperparathyroidism in patients with chronic kidney disease Calcipotriene: An analog of calcitriol approved for psoriasis				
Bisphosphonates				
Alendronate	Suppresses the activity of osteoclasts and inhibits bone resorptions	Osteoporosis, Paget's disease	Oral administration daily or weekly	Adynamic bone, esophageal irritation, osteonecrosis of the jaw (rare)
Risedronate, ibandronate, pamidronate, zoledronate: Similar to alendronate				
Parathyroid hormone (PTH) analog				
Teriparatide	Acts through PTH receptors to produce a net increase in bone formation	Osteoporosis	Subcutaneous injection	Hypercalcemia, hypercalciuria; osteosarcoma in experimental animals
Calcitonin				
Calcitonin	Acts through calcitonin receptors to inhibit bone resorption	Osteoporosis	Subcutaneous injection or intranasal	Rhinitis with the nasal spray
Selective estrogen-receptor modulator (see Chapter 40)				
Raloxifene	Estrogen agonist effect in bone; estrogen antagonist effects in breast and endometrium	Osteoporosis in postmenopausal women	Oral administration	Hot flushes, thromboembolism
Calcimimetic				
Cinacalcet	Activates the calcium-sensing receptor	Hyperparathyroidism	Oral administration	Nausea, hypocalcemia, adynamic bone

Questions

1- A 58-year-old postmenopausal woman was sent for dual energy x-ray absorptiometry to evaluate the bone mineral density of her lumbar spine, femoral neck and total hip. The test results revealed significantly low bone mineral density in all sites. If she began oral therapy with alendronate, she would be advised to drink large quantities of water with tablets and remain in an upright position for at least 30 min and until eating the first meal of the day. These instructions would be given to decrease the risk of which of the following?

a- Cholelithiasis
b- Diarrhea
c- Constipation
d- Erosive esophagitis
e- Pernicious anemia

2- Which of the following conditions is an indication for the use of raloxifene ?

a- Chronic kidney failure
b- Hypoparathyrodism
c- Intestinal osteodystrophy
d- Postmenopausal osteoporosis
e- Rickets

Answers : D,D .