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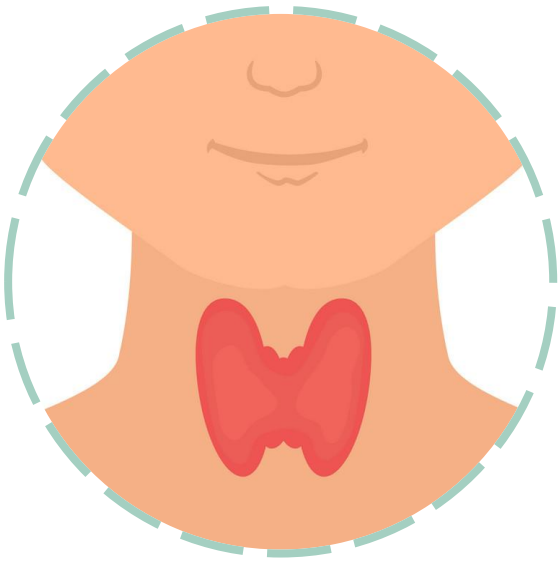


Endocrine Block

Pharmacology team 438

Drugs used in Osteoporosis

Objectives:

By the end of the lecture , you should know:

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

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Purple: Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Healthy Bones

- Bones are living tissues which are constantly being broken down and rebuilt in a process called **remodeling**

Types of bones

Cortical

- Hard, compact, & dense bone

Ex:

- Long bones of arms and legs

Trabecular

- Spongy, porous & flexible bone

Ex:

- End of the wrist, hip and spine

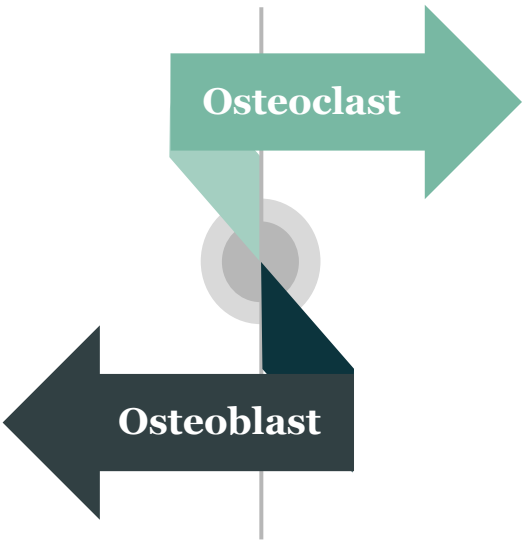
Components of bones

- Bones are basically composed of two types of tissue:

1. **Inorganic** (65% of mass)
   - Consists of crystalline calcium phosphate salts called hydroxyapatite[1]
2. **Organic** (35% of mass)
   - Consists of living cells which are: osteocytes, osteoclasts and osteoblasts
   - Bone cells are either **bone forming** or **bone resorptive** cell

Bone forming cells

- Osteogenic cells
- Mesenchymal in origin
- Found on all bone surface
- Forms osteoid framework and helps in its mineralization



Bone resorptive cells

- Phagocytic cells
- Hematopoietic in origin
- Reside in pits (resorption bay)
- Secrete lysosomal enzyme (e.g.collagenase , metalloproteinase) and HCl to dissolve bone matrix

Bone Remodeling

- **Normally,** bones are continuously formed and absorbed under the control of systemic hormones, body mineral contents and local autocrine/paracrine such as: cytokines, Growth Factors and PGs.
- It is meant to maintain calcium homeostasis and to renew bone in case of micro damages

01

Phase 1: Resorption

Osteoclasts seek out old bone or damaged ones and destroy it, leaving a small empty space

02

Phase 2: Formation

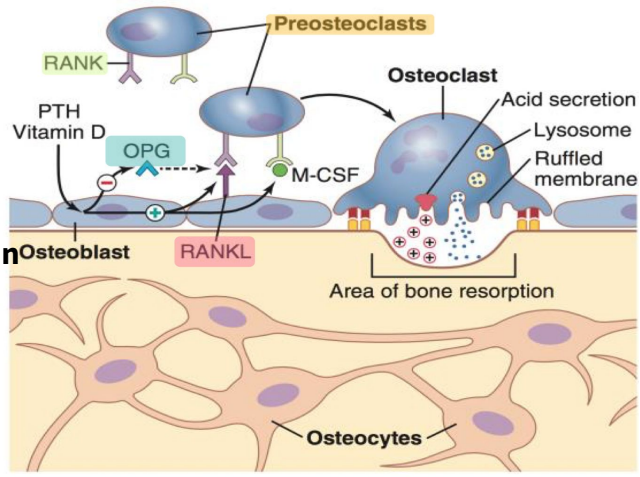
Osteoblasts use minerals like calcium, phosphorus and Vit D to fill in this space with new bone cells

1: required for bone mineralization, giving the bone its strength.

Balance of Bone Remodeling

Doctor explanation (important to understand as it has pharmacological application):

- Osteoblasts express a ligand **called RANKL**[1] (Receptor Activator of Nuclear factor Kappa-B Ligand). It's a family member of TNF cytokine.
- RANKL binds to a receptor located on the surface of **preosteoclasts** called RANK.
- This will convert the preosteoclast into a mature osteoclast (osteoclastogenesis). **As RANKL is high in osteoporosis**, maturation of preosteoclast and resorption of the bone are increased.
- ★ RANKL can be inhibited physiologically by an endogenous inhibitor called **osteoprotegerin (OPG)**[2], OPG binds to RANK receptor



Osteoporosis

- A complex endocrinological disorder of bone and mineral metabolism leading to a decrease in bone mass, disruption of its architecture, density reducing its strength and increase the risk for fractures **"Bone resorption > Bone formation"**

Risk Factors

1 Potentially modifiable[3]

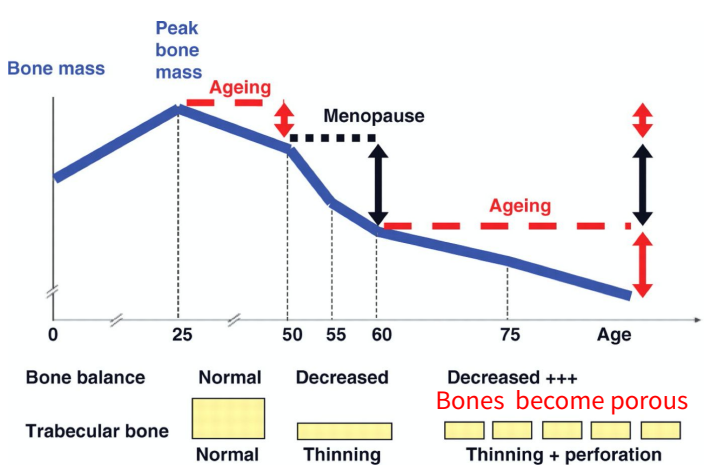
- **Cigarette smoking**
- **Low calcium/ Vit D[4] in diet**
- **Glucocorticoids**
- **Anticonvulsants**
- **Excessive alcohol intake**
- **Obesity**
- **Sedentary lifestyle**
- **Environmental risks**

2 Non-modifiable

- **History of fractures (personal\1st degree relative)**
- **Elderly**
- **Poor health**
- **Dementia**
- **Hormonal disorders**
- **Neoplastic disorders**
- **Metabolic abnormalities**
- **Rase(Caucasian or Asian)**

Bone Loss and Aging

- The first 5-15 years after menopause, a woman can lose approximately 25-30% of her trabecular bone and 10-15% of her cortical bone
- Bone loss often occurs without symptoms or warning signs
- Most common symptom is bone fracture after minor trauma
- This loss is due to loss of estrogen levels after menopause



1: ensures maturation of osteoclasts by binding to pre-osteoclasts
2: prevents the maturation of osteoclasts = decrease bone resorption (some osteoporosis drugs work in the same mechanism).
3: can be changed, to minimize bone damage.
4: required for calcium absorption.

Treatment for Osteoporosis

1. Replace the missing components such as: Ca, Vit D, Na fluoride
   - Used to enhance the strength of the bone by the formation of fluorapatite
   - Considered when there is a decrease in the trabecular bone density with **<u>normal</u>** cortical bone.
2. **Restore the balance of remodeling by using:**

Antiresorptive	Bone Anabolic	Dual effect
- Bisphosphonates[1] - Estrogen analogues - Androgen analogues - SERMS[2] - Calcitonin - RANKL inhibitors	- Parathyroid hormone (PTH) - Teriparatide[3] (PTH analogue)	- Strontium
Mainly inhibit osteoclasts	Mainly activate osteoblasts	Both effects

(1) Antiresorptive: Bisphosphonates[4]

Class	Nitrogenous	Non-Nitrogenous
Drugs	• Alendronate (oral) • Ibandronate (oral) • Risedronate (oral) • Zoledronate (I.V.)	• Etidronate • Clodronate • Tiludronate
MOA **Both are important**	• Bisphosphonates are compounds made of two phosphate groups (PO_3) • They are structurally similar to **pyrophosphate**[5] and works as: 1. **Bind to calcium** and concentrate in bones, **bound to hydroxyapatite decreasing its solubility** and make it more resistance to osteoclastic activity since osteoclasts mainly dissolve and break pyrophosphate not bisphosphonates 2. **Prevent bone resorption by Inhibit osteoclast function** a. Block steps in cholesterol synthetic pathway[6] in osteoclast that act as signaling molecules responsible for the osteoclastic hydrolytic & phagocytic activity → osteoclast stops functioning leading to apoptosis.	
P.K	• Zoledronate (3rd generation) has the highest potency for osteoclast inhibition • Poorly absorbed (<10%), food impair absorption more so must be given on an empty stomach / infused IV • T½ = 1 hr • ½ of absorbed drug accumulates in bones[7], remainder is excreted in urine • **In bones it is retained for months[8], depending on bone turnover**	
Dosing	• Once weekly or on two consecutive days each month ★ **Should be taken in upright position to prevent esophagitis** ★ **Should be taken with a large amount of water to prevent esophagitis** • Should be given 4 hrs before having any Ca, Mg, Al containing drugs **<u>Note:</u>** Calcium and Vit D supplementation should be given after a gap from ingestion of bisphosphonates because it can inhibit their absorption	
Uses	• Osteoporosis; secondary to menopause or glucocorticoids..etc • Paget's Disease[9] • Malignancy associated with hypercalcemia[10]	

1: most used drug in osteoporosis.
2: selective estrogen receptor modulators.
3: Recombinant DNA derivative of PTH.
4: if asked about MOA write both
5: involved in normal bone mineralization.
6: leads to destruction of normal osteoclastic brush border = dysfunctional osteoclasts
7: the therapeutic site of action.
8: long duration of action.
9: diseases of excessive breakdown of bone.
10: helps by storing calcium in the bone = decrease serum calcium.

(1) Antiresorptive: Bisphosphonates cont...

Drug	Nitrogenous	Non-Nitrogenous
ADR	• GIT irritation: nausea, vomiting, gastritis, ulceration→ **Drinking large amount of water to prevent the risk of tablet from getting stuck in esophagus.** • Gastroesophageal reflux ± ulceration→ **Avoiding this by giving it on empty stomach and sitting while sitting in upright for 30 min.** • Flu like manifestation: fever, chills when given I.V. infusion • Osteonecrosis of the 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 the jaw heals completely** • Atrial fibrillation → more in women with alendronate and zoledronate	
C.I	• Decreased renal function • Peptic Ulcer • Esophageal reflux	

(2) Antiresorptive: RANKL inhibitors

Drug	Denosumab (Still under investigation)
	• It is a fully humanized monoclonal antibody that **mimics the activity of osteoprotegerin (OPG)**
MOA	• **Normally:** RANKL binds to its receptor RANK on the surface of precursor (preosteoclast)& 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:** ★ **Blocks RANKL from interacting with RANK receptor** expressed on preosteoclast→↓osteoclastogenesis→ no mature osteoclasts • Binds also to mature osteoclasts → increase their apoptosis • Net effect is decreasing bone resorption
P.K	• Administered subcutaneously every 6 months
Uses	• Extremely expensive treatment **reserved for patients who cant tolerate nor respond to bisphosphonates**
ADR	• Respiratory and urinary infections[1] • Eczema and skin rash • Pancreatitis
C.I	• Patients with **hypocalcemia** as **denosumab decreases serum calcium conc.** ○ correct Ca and Vit D levels before starting the treatment

1: because RANKL is a cytokines, inhibiting cytokines will compromise immunity.

(3) Antiresorptive + Bone Anabolic Agents (Dual effect)

	Strontium
Drug	• Sr^{2+} is a divalent cation resembling Ca^{2+} in atomic and ionic properties • 1st drug to possess a dual effect has both anabolic & antiresorptive effects, **resulting in rebalance of bone turnover in favor of bone formation**
MOA	**Effects on Osteoblasts:** 1. **Acts as an agonist on Ca Sensing Receptor [CaSR]** a GP coupled receptor → **enhances** differentiation of preosteoblast **to osteoblast** → increase bone formation 2. **Stimulate the expression of OPG** → increase RANKL binding →↓bone resorption **Effects on Osteoclasts:** 1. Acts as an agonist on CaSR → **suppress** differentiation of preosteoclast **to osteoclast** → decrease bone resorption
P.K	• Orally active as distrontium with a modest bioavailability of 25% • Binds partially to plasma proteins and strongly to bones • T½ = 60 hrs • Excreted mainly by the kidney
Uses	• Osteoporosis; secondary to menopause or glucocorticoids..etc • Malignancy associated hypercalcemia
ADR	• GIT irritation: nausea, vomiting, headache & eczema - All resolve within the first 3 months
C.I	• Severe renal disease • Hypersensitivity to the drug • Risk of venous thromboembolism ★ **Phenylketonuria**[1]
inter-action	• Food containing milk or its products • Antacids • Oral Tetracycline and quinolones chelates[2] it - They can be prevented by having a 2 hrs spacing between them

(4) Sex Hormones

Drugs	Estrogen	Androgen
MOA	• Estrogen in females and Androgens in males **are essential for normal bone remodeling:** ○ ↑ osteoclast apoptosis and Inhibit osteoblast apoptosis ○ ↑ release of growth factors from osteoblasts ○ ↓ number and depth of resorption cavities ○ ↓ release of inflammatory cytokines causing resorption	
Uses	• Hysterectomy[3]: use estrogen only • If uterus is present: Estrogen + Progestin • Hormonal Replacement therapy (HRT): menopausal symptoms • SERMs: Menopause\ elderly	• For elderly men only
ADR[4]	• Risk for breast cancer • Vaginal bleeding • Venous thromboembolism	-

1: inborn disorder of phenylalanine metabolism, and since strontium contain phenylalanine, it will accumulate leading to complications.
2: bind to it = decrease its activity.
3: uterus is resected.
4: most common in females taking HRT.

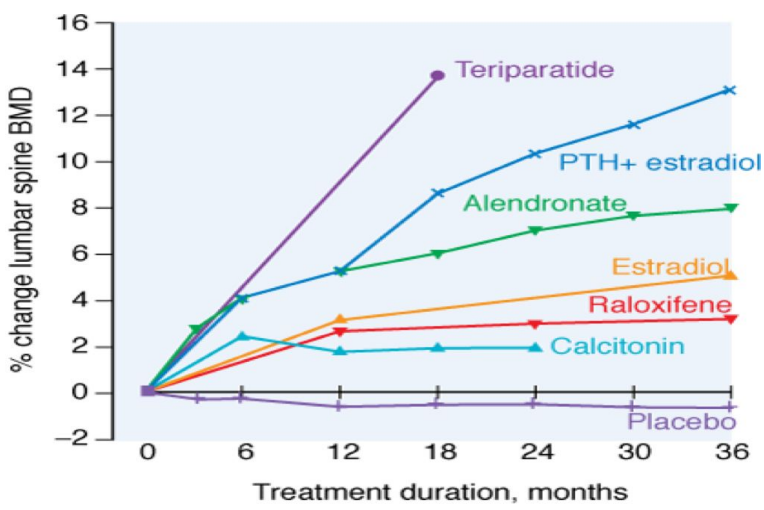
(5) Selective Estrogen Receptor Modulators (SERMs)

Drug	Raloxifene
	• Raloxifene is the 1st SERM for prevention and treatment of osteoporosis
MOA	• Antiestrogens that exhibit partial agonistic action • Acting as an agonist in bones and an antagonist in female sex organs • Works only on women especially post-menopausal women
Selectivity	

	Brain	Uterus	Vagina	Breast	Bone	CVS
Estradiol[1]	++	++	++	++	++	++
Raloxifene	-	-	-[2]	-[2]	+	+

- Raloxifene has a partial agonism on bones and heart only. It doesn't work as estrogen on the sex organs, thus decreasing its risk for uterine and breast cancer. "MALE doctor note"

Advantages	• Increase bone density by 2% and decrease fracture risk by 30% • No stimulation of breasts nor endometrial tissue • No need for progestin in women with a uterus • Decrease LDL • Good for women with a risk of uterine and breast cancer • Lower risk for thromboembolism compared to estrogen
Dis-advantages	• May increase hot flashes • No effect on HDL



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

1: = estrogen.
2: no risk of vaginal bleeding or breast cancer.

Quiz

MCQ

Q1- Which of the following drugs exhibits its therapeutic effect for osteoporosis by agonizing CaSR to enhance osteoblasts and suppress osteoclasts?

A- Alendronate B- Strontium C- Raloxifene D- Denosumab

Q2- A 68-year-old woman came to the clinic for pain around her pelvis. The doctor suspected an osteoporotic microfracture, so he ordered a DEXA scan. The scan showed diminished bone density. The doctor gave the patient a drug and asked her to take it in an upright position and drink a full glass of water with it. Which of the following is the most likely prescribed drug?

A- Estrogen HRT B- Strontium C- Risedronate D- Denosumab

Q3- Which of the following is one benefit of Raloxifene over Estrogen in treating post-menopausal osteoporosis?

A- Estrogen causes increase HDL in blood
B- Raloxifene antagonizes some estrogen receptors
C- Estrogen exerts unwanted effects on the brain
D- Raloxifene increases osteoclast apoptosis and Inhibits osteoblast apoptosis

Q4- Which of the following mimics OPG activity in inhibiting RANKL

A- Raloxifene B- Teriparatide C- Denosumab D- Strontium Ranelate

SAQ

A 59-year-old post-menopause lady came to the clinic for her periodic health examination. She has an excellent health and no past medical or surgical history. The doctor ordered a bone-density test and found out that her bone density decreased by at least 40%. She was diagnosed with postmenopausal osteoporosis.

Q1) What is the drug of choice in her case?

Q2) What is the M.O.A of that drug?

Q3) What are 2 non-pharmacological approaches the doctor can recommend?

Answers:

MCQ

Q1	B
Q2	C
Q3	B
Q4	c

SAQ

Q1	Bisphosphonates such as: Alendronate, Risedronate...
Q2	Increase resistance to osteoclasts and inhibit osteoclasts signaling
Q3	Increase Calcium and Vit D in diet, increase physical activity, & reduce weight

pharmacology

Team 438

Thank you for all your love and support.

Good luck future doctors!

Team Leaders:

May Babaeer Zyad Aldosari

This Magnificent Work was Done By:

Mohammed Alhuqbani

Note writers

Raghad AlKhashan

Quiz writers

Mohammed Alhuqbani