Lecture 3

OSTEOPOROSIS and drugs used

Objectives:

- ★ 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 o anabolic mechanism of action
- ★ Detail the pharmacology of such group of drugs & their clinical utility in combating osteoporosis

- Additional Notes
- Important
- Explanation –Extra-

before starting, please check our Endocrine block correction

For any correction, suggestion or any useful information
do not hesitate to contact us: Pharmacology434@gmail.com

INTRODUCTION

Bone is composed of 2 types of tissues:

1. Inorganic : 65% of mass. Consist of hydroxyapatite
2. Organic : 35% of mass. Consist of : osteoblasts , osteoclast and osteocyte.

- Bone cells are either ; Bone forming (osteogenic cells , osteoblast) or bone resorptive (osteoclast)

★ 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

control of bone remodeling

- control of bone remodeling is even by **local factor** produced by osteoblast or by **systemic hormones:**

Local factors:

- osteoprotegrin [OPG]
- RANKL
-

Systemic Hormones:

★ **PARATHORMONE:** Maintains calcium homeostasis via:
- ↑ bone formation (intermittent)/↑ bone resorption (continuous)
- ↑ renal tubular calcium resorption
- ↑ renal calcitriol production

★ **CALCITRIOL:**
- ↑ intestinal ca & phosphorus absorption →↑ bone mineralization
- ↑ bone resorption when they are deficient

★ **ESTROGEN & ANDROGEN :** ↓Resorption by acting on many local factors
- ↑ osteoclast apoptosis & growth factors from osteoblasts
- ↓ No. & depth of resorption cavities & release of cytokines

★ **GLUCOCORTICOIDS :** ↑apoptosis of osteoblasts & osteocytes→↓ resorption

★ **THYROID HORMONE :** ↑ bone turn-over i.e. resorption & formation

★ **Growth Hormone & IGFs :** ↑skeletal growth

Osteoporosis

Definition

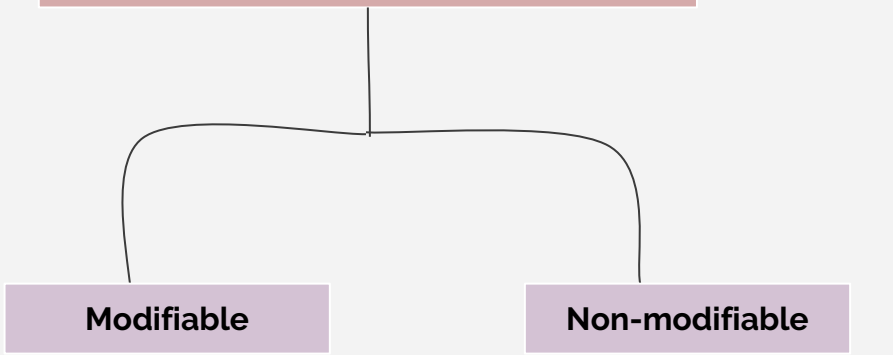
A complex endocrinologic disorder of bone & mineral metabolism

(bone resorption > formation)

Low bone mass
Disruption of bone architecture

Reduced bone strength
Risk of fractures

Osteoporosis Risk Factors



-cigarette smoking
-Diet low in ca/VD
-Glucocorticoids
-Anticonvulsants
-Excessive alcohol intake
-Sedentary lifestyle
-Low body weight
-Environmental risk

-Personal history of fracture
-1st degree relative has fracture
-Race (Caucasian or Asian)
-Elderly age
-Poor health
-Metabolic abnormalities

TREATMENT OF OSTEOPOROSIS

1. Replace what is missing (Ca , Vit D , Na fluoride)

→ Fluorapatite
considered only when trabecular bone ↓ in presence of cortical bone

2. Reset back the balance of remodeling

- Anti-resorptive Agents
  - Bisphosphonates
  - RANKL inhibitors
  - Strontium
  - Androgen Analoges
  - Estrogen Analoge
  - SERMS
  - Calcitonin
- Bone Anabolic Agents
  - Teriparatide
  - Strontium

1- BISPHOSPHONATES

Are compounds that have 2 phosphonate (PO3) groups.

- **Non- Nitrogenous :**

Etidronte , Clodronate (10) , Tildronate (10)

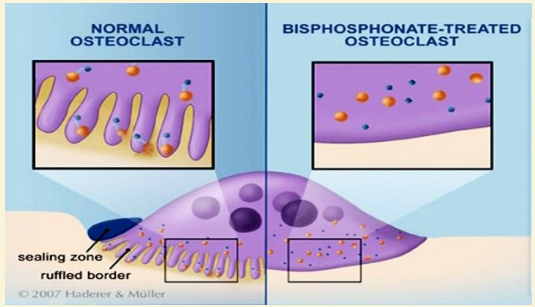
- **Nitrogenous :**

Alendronate (500) , Ibandronate (1000) , Risedronate (2000) , Zoledronate (10000)

★ **Mechanism of Action :** prevent the action of pyrophosphate

- structurally similar to pyrophosphate*. thereby inhibiting activation of enzymes that utilize pyrophosphate
- They preferentially " stick " to calcium → concentrate in bones , bound to hydroxyapatite decreasing its solubility and making it more resistant to osteoclastic activity.
- They prevent bone resorption by inhibiting osteoclast function.
- Their relative potencies for osteoclastic inhibition is the most with 3rd generation " Zoledronate"
- Block steps in cholesterol synthetic pathway in osteoclast that act as signaling molecules responsible osteoclastic hydrolytic & phagocytic activity →(stop function→apoptosis)

*Pyrophosphate is a natural circulating inhibitor of mineralization in the blood and urine which can't get inside the bones because the lining cells destroy it with alkaline phosphatase. People with genetic problems of alkaline phosphatase have osteomalacia, because the pyrophosphate can get into the bone and it prevents mineralization



1- BISPHOSPHONATES

kinetics	- poorly absorbed (<10%), food impair absorption more >> must be given on an empty stomach / or infused IV. - t1/2 1 hr. - half of absorbed drug accumulates in bones , remainder →excreted unchanged in urine - in bone it's retained for months , depending on bone turnover
indication	• osteoporosis , 2ndry to menopause , glucocorticoids • Paget's disease • Malignancy - associated hypercalcemia
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
ADRs	1- **GIT irritation**, nausea , vomiting , gastritis , ulceration >> to avoid give large amount of water 2- **Gastro-esophageal reflux + ulceration**>> to avoid give on empty stomach while sitting in upright for 30 min 3- **flu like manifestation** upon IV infusion **4- 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. 5- **Atrial fibrillation** > women with alendronate & zolidronate
C/I	- decreased renal function - peptic ulcer / esophageal reflux

2- RANKL INHIBITORS (DENOSUMAB)

" still under investigation"

MOA	it's fully human MOA the mimics the activity of osteoprotegrin (OPG)>> the physiological inhibitor of RANKL - it binds to RANKL , expressed by osteoblast >> block RANKL from interacting with RANK expressed on preosteoclasts → inhibit osteoclastogenesis (no mature osteoclasts) - it binds also to mature osteoclast promote its apoptosis Net effect : prevent bone resorption .
C/I	in patients with hypocalcemia. (correct ca & vit D levels before starting denosumab)
ADRs	• Infections : urinary & respiratory • Eczema & skin rash • Constipation • Cataract • Joint pain

Explanation:

RANKL is substance released by osteoblast and it's imp in osteoclastogenesis process , it binds to its receptor (RANK) which expressed
on preosteoclasts >> stimulate its maturation into osteoclast
OPG bind to RANKL >> inhibit its interaction with its receptor >> block the osteoclastogenesis process >> ↓ bone resorption. Which it's the same mechanism of Denosumab

3-STRONTIUM

Sr2+ (like Calcium), is a divalent cation, resembling Ca2+ in atomic & ionic properties.
It is orally active as **distrontium**

Mechanism

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** > **increase 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

Pharmaco-kinetics

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

3-STRONTIUM

Indication	• Osteoporosis, 2ndry to menopause, glucocorticoid • Malignancy, associated hypercalcaemia
Contraindication	• In severe renal disease. • In hypersensitivity to it • In increased risk of venous thromboembolism • In phenylketonuria
Interaction	Food specially containing milk + its products Antacids Oral tetracycline & quinolones chelate it } 2 hour space
ADRs	GIT irritation; nausea, vomiting, headache, eczema All resolve in 1st 3

Estrogen and androgen

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

Mechanism	• **Increase** osteoclast apoptosis & inhibit osteobalst apoptosis • **Decrease** No. & depth of resorption cavities • **Increase** release of growth factors from osteoblasts • **Decrease** release of inflammatory cytokines causing resorption

Estrogen: If hystrectomy (the surgical removal of the uterus) + **progestins** if uterus present
Hormonal replacement therapy (HRT): menopausal symptoms

ADRs	HRT (estrogen): vaginal bleeding, risk of breast cancer, and venous thromboembolism.

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

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

Disadvantages

May **increase** hot flushes
No effect on HDL

MCQs

Q1: A 54 year-old peptic ulcer patient came to clinic with pain in his knee,lap investigations confirm an osteoporosis condition , which drug we should avoid?
A-Strontium
B-Bisphosphonates
C-denosumab

Q2: patient came with hypocalcemia , which develop osteoporosis , which one is avoiding to start immediately?
A-Denosumab
B-Androgens
C-Strontium

Q3: An elderly female came to ER with severe osteoporosis , which one best choice ?
A- androgens
B- denosumab
C- strontium

Q4- Patient came with vitamin d deficiency, that resulting of hypocalcemia , which develop osteoporosis , which one is avoiding to start immediately ?
A- androgens
b- denosumab
C- strontiu

Q 5-In previous question , what the doctor should do to manage his status ?
A- correct vit D and ca level then start DENOSUMAB
B- start with very low dose .
C- start with a another adjunctive therapy

1: B
2 : A
3: C
4: B
5: A

Good luck!

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