OSTEOPOROSIS

Eman Alrashidi , Sara Bin Husain

Ismail Raslan , Mohammad Almumi

Imp. Points = red
Our notes = green

Introduction :

Bone is basically composed of 2 types of tissue:

1. **Inorganic tissue:**
   - **65% of the mass**
   - **Consists of :**

   i. **Hydroxyapatite & calcium & phosphorus salts**
   - **formed by MINERALIZATION of the organic matrix (osteoid Frame work) & is mediated by the enzyme alkaline phosphatise ((this process is called OSTEOGENESIS))**

2. **organic tissue:**
   - **35% of the mass**
   - **Consists of:**

   i. **Organic matrix : which are produced by osteoblasts**

   ii. **Bone cells : are of two types**

      1. **Bone forming cells :**
         a. **Osteogenic cells : mesenchymal in origin , progenitor of blasts & cytes are found on all bone surfaces**
         b. **Osteoblasts : forms osteoid framework & help in its mineralization**
         c. **Osteocytes : sense mechanical stress then signals to both blasts & clasts**
      2. **Bone resorptive cell : the osteoclasts : Myeloid in origin : made by the fusion of many early monocytes , Found in pits (reorption bays) , Secrete lysosomal enzymes ((collagenase & metalloproteinase) +& hydrochloric acid that dissolve the bone matrix**

In normal conditions,

- bone is continuously formed and resorped in a mechanism called bone remodelling. This works under the control of systemic hormones, body mineral content and local paracrine secretions. (bone remodling is a cycle that take 4 to 6 weeks up to months so any expected therapy should be long term)

- Calcium homeostasis in particular is very important because it's used in the repair of microfractions and microcracks.

The systemic hormones that control remodelling are:

The imp. Point : know that One of the ADRs effects of Glucocorticoids is osteoporosis

1. **Parathormone: which maintains calcium homeostasis by :**

a. **Increase bone resorption continuously and increasing bone formation intermittently**
b. **Increase calcium absorption from the kidney**
c. **Increase the production of calcitriol from the kidney**

2. **Calcitrol**

a. **Increases absorption of calcium and phosphorus from the intestine : this leads to bone mineralization**
b. **When deficient increases bone resorption**

3. **Estrogens and androgens : Decrease rate of bone loss by :**

a. **Decrease the number and depth of resorption pits and the release of cytokines**
b. **Increase osteoclast apoptosis**
c. **Increase growth factors of osteoblasts**

4. **Calcitonin**

a. **Does not have a clear physiological action in humans**
b. **Pharmacologically is used to : decrease osteoclasts and bone resoprtion**

5. **Glucocorticoids**

a. **Increase the apoptosis of osteoblasts and osteocytes : this leads to increase resorption**

b. **Increase the differentiation of osteoblasts : this leads to increase formation**

6. **Thyroid hormone**

a. **Increases bone turnover : resorption and formation**

7. **Growth hormone and IGF's:**

a. **Increase in skeletal growth & endochondral bone formation**

In normal conditions bone remodelling should happen in equilibrium between formation and resoprtion. In osteoporosis the bone resorption is much more than bone formation so you end up with:

- **Low bone mass**
- **Disruption of bone architecture**
- **Reduced bone strength**
- **Risk of fractures**

The causes of osteoporosis can be classified into:

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

STAR to START memorization

In the treatment of osteoporosis the aim is:

1- **to replace what is missing** : Like vitamin D or calcium or Na fluoride

2- Or reset the balance of bone remodelling: by 2 types of drugs :

A. ***Antiresorptive agents :*** (Because in osteoporosis you have more resorption than bone formation) :

a. **BISPHOSPHONATES ****
b. **ESTROGEN ANALOGES**
c. **ANDROGEN ANALOGES**
d. **SERMS**
e. **CALCITONIN**
f. **RANKL INHIBITORS ** (**DENOSUMAB)

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

B. ***Bone anabolic agents :***

a. **TERIPARATIDE**

C. **Some drugs act in both ways** (antiresorptive and bone anabolic) like: **STRONTIUM** **

D. ***Others; Thiazide diuretics, statins***

3 major drugs in this lect . :
1- BISPHOSPHONATES
2- DENOSUMAB
3- STRONTIUM

First : BISPHOSPHONATES

- These are Are compounds that have two phosphonate (PO3) groups.
- They are 2 types : **Non-Nitrogenous** (eg. Etidronate & Clodronate & Tildronate)
  & **Nitrogenous - most potent –** (eg. Alendronate& Ibandronate & Risedronate & Zoledronate)

• MoA:

BLOCK STEPS IN CHOLESTROL SYNTHETIC PATHWAY IN OSTEOCLAST
that act as signaling molecules responsible for the osteoclastic hydrolytic & phagocytic activity >>> **Stop function of osteoclast ➔ apoptosis**

How?

First of all , The structure of **BISPHOSPHONATES** is similar to pyrophosphate. So it can bind to the same site of pyrophosphate on the enzymes that utilize it and then it can block that enzyme.

1- Bisphosphonates stick to calcium and concentrate in the bone and bound to hydroxapatite.

2-Then during resorptive activity the osteoclasts take these molecules up..

3- So after the molecule is in the osteoclasts it inhibits the **farnesyl pyrophosphate synthase enzyme** which blocks cholesterol synthetic pathways that osteoclast needs for signaling and their phagocytic function
4- So no function will lead to apoptosis. And apoptosis of osteoclasts will lead to less resorption.

***** Their relative potencies for osteoclast inhibition is the most with 3rd generation "Zoledronate "((most potent drug))**

- **Kinetics** :
  - It is poorly absorbed , and food makes it worse so given on empty stomach
  - T1/2 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
- **Indication** :
  - Osteoporosis, secondary to
    - menopause,
    - glucocorticoids
  - Paget's Disease
  - Malignancy- associated hypercalcaemia (Some of malignancy have tendency to break down the bones especially in metastatic → ↑ Ca in circulation → "hypercalcemia ADRs !)
- **Dose**:
  - 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** (After taking the drug, the pt should not lie down otherwise he will develop reflux gastritis, ulceration…etc !)
  - 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
- **ADR's**:
  - GIT irritation; nausea, vomiting
  - **Gastric & esophageal ulcerations**
  - Flue like manifestations upon IV infusion
  - **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 . (There must be no history of nearly teeth extraction.)
  - Atrial fibrillation > women with alendronate & zolidronate (drugs from nitrogenous group)
- **Contraindications**:
  - Decreased renal function
  - Peptic ulcer / esophageal reflux

Second: Rankl inhibitors (DENOSUMAB):

Osteoprogestrin is a molecule that binds to RANKL and stops it from binding to the osteoclast.

It is a fully human MOA that mimics the activity of osteoprotegrin. (OPG)

- **MOA**: **imp !!**

- Osteoblasts express the molecule RANKL and RANKL inhibitors bind to it.
  - So RANKL cannot interact with RANK receptors on the osteoclast → this decreases osteoclastogenesis (formation of osteoclasts).
- **It binds also to mature** osteoclasts and cause apoptosis

So in overall it decreases bone resorption

- **Administration :**

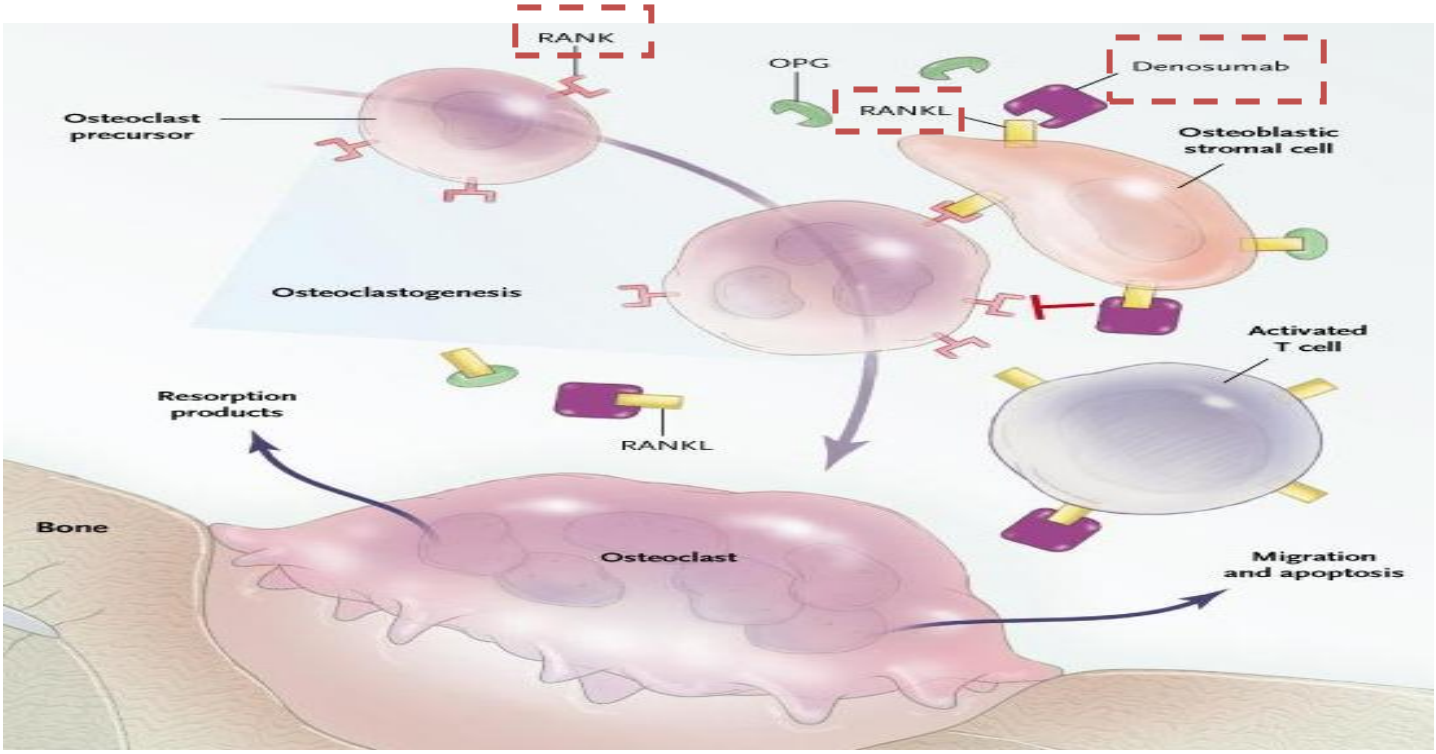
- Subcutaneous every 6 months

- **Contraindications**

- Patients with hypocalcaemia
- Correct Ca & Vit D levels before starting denosumab

- **ADR's**:

- Infections;
- urinary & respiratory
- Eczema & skin rash
- Constipation
- Cataract
- Joint pains



RANKL = receptors found on osteoblasts serves to activate osteoclasts .

RANK = the site of RANKL attachment, expressed on the surface of osteoclasts

DENOSUMAB = drug binds to RANKL which prevent osteoclast activation

Third: STRONTIUM:

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

- **MoA**:

  this drug has **two actions** which are

  1. Anabolic (bone formation)

  2.antiresorptive effects

  CaSR agonist :
  - On osteoblast >> **enhance** differentiation
  - On osteoclast >> **suppress** differentiation

  - **Effect on osteoblast:**
    - It's an **agonist on the calcium sensing receptor [CaSR]** (because we said it's like calcium). → this receptor **enhances the differentiation** of preosteoblast to osteoblast → more osteoblasts → more bone formation
    - **Stimulates the expression of osteoprogsetrin(OPG)** → OPG binds to RANKL → no osteoclastogenesis → decrease bone resorption
  - **Effect On osteoclasts:**
    - Its an **agonist on the calcium sensing receptor [CaSP]**→ **suppress differentiation** of preosteoclast to osteoclast → increase in osteoclast apoptosis → decrease bone resorption
- **Kienetics** :
  - 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, secondary to
    - Menopause
    - Glucocorticoids
  - Malignancy- associated hypercalcaemia

  The same indication of **BISPHOSPHONATES** **except Paget`s disease**
- **Contraindications**:
  - In severe renal disease.
  - In hypersensitivity to it
  - In increased risk of venous thromboembolism
  - In phenylketonuria
- **Interactions** :
  - Oral tetracycline & quinolones chelate
  - Food , specially containing milk and its products
  - Antacids

  should be given 2 hours before or after the administration of STRONTIUM
- **ADR's**:
  - GIT irritation; nausea, vomiting, headache, eczema ((All resolve in 1st 3 months))

Fourth: estrogens and androgens:

- **Estrogens**:
  - Given alone if patients has undergone hysterectomy
    - If no hysterectomy combined with progestins
- **Andorgens**
  - Given to elderly men
- **Actions of estrogens and androgens:** **imp!!!**
  - Increase osteoclast apoptosis
  - Increase release of growth factors from osteoblasts
  - Decrease number and depth of resorptive cavities
  - Decrease in the inflammatory cytokines that cause resorption

Fifth: SERM: raloxifen

- Given to elderly women (menopause)
- **It is the 1st selective estrogen receptor modulator in the treatment of osteoporosis**
- **MoA**
  - Agonist on Bone
  - Antagonist on other female sex organs
- **Advantages**:
  - Increase bone density (2%) & decrease fracture risk (30%)
  - No stimulation of breast or endometrial tissue
  - No need for progestin in women with uterus
  - ↓ LDL
- **Disadvantages**
  - ↑ risk of thromboembolic events
  - Doesn't treat well Post-menopausal Symptoms
  - May ↑ hot flushes
  - No effect on HDL

Sixth: tibilone:

Synthetic steroid that is metabolized into : estrogen, androgen & progestin properties

Can be used without CVS risks

The imp. Thing you need To remember from this page is **highlighted 2 points**

AS dr. Omnia said ((we already took these categories SO No need to ask u about them))