Drugs used in Osteoporosis

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 or anabolic mechanism of action.
- **Detail** the pharmacology of such group of drugs& their clinical utility in combating osteoporosis.

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Drug's name | Doctors' notes | Important | Extra

« لو أن الناس كلما استصعبوا أمرًا تركوه؛ ما قام للناس دنيا ولا دين! »
عمر بن عبدالعزيز

Mind Map

Treatment of osteoporosis

Reset back the balance of remodeling

- **Anti-Resorptive Agents**
  - Bisphosphonates
  - RANKL inhibitors
  - Strontium
  - Androgen Analogues
  - Estrogen Analogues
  - SERMS
  - Calcitonin
- **Bone Anabolic Agents**
  - PTH, Teriparatide
  - Strontium

Strontium: Have a dual effect

PTH: Natural
Teriparatide: synthetic form. Common to cause malignancy

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

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

Others: Thiazide diuretics, statins (Decrease the incidence of Osteoporosis)

A very important mind map!

If you do not have time, studying slides: 8-13 is enough إن شاء الله

To Understand Better

OSTEOPOROSIS: "The Silent Disease"

Osteo: is Latin for "bone"
Porosis: means "porous or full of holes"
"**Osteoporosis**" means bones that are full of holes"
Osteoporosis can develop without symptoms

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

It includes:
1) Resorption-removes old bone which done by osteoclast cells.
2) Formation-replaces old bone with new bone which done by osteoblast cells.

TYPES OF BONE

- **Cortical** — is hard, compact, dense bone (example: mid-section of larger, long-bones of arms and legs)
- **Trabecular** — is spongy, porous and flexible bone (example: end of the wrist, hip and the spine)

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)
- **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)

To Understand Better

You build bone until about age 30
Steps to building healthy bones include:

1. Calcium & vitamin D
2. Limit Caffeine & Alcohol
3. Exercise
4. Don't Smoke

Bone components:

Bone is basically composed of 2 types of tissues

Inorganic components → 65% of mass + consists of crystalline calcium phosphate salts (hydroxyapatite, HAp).

Organic components → 35% of mass + consists of osteoblasts, osteoclasts and osteocytes.

Bone cells:

Bone forming cells	Bone rebsorbtive cells
Osteogenic cells → mesenchymal in origin + found on all bone surfaces **Osteoblasts** → forms osteoid frame work and help in its mineralization	**Osteoclasts** → reside in pits (resorption bays) that form by eaten bone surface. It secretes lysosomal enzymes (collagenase & metalloproteinase) + hydrochloric acid that dissolve bone matrix

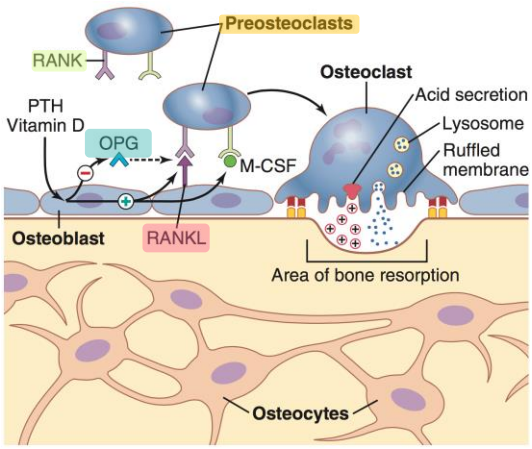
Bone remodeling

- It occurs under the 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.

Local factors driving the remodeling process:

Extra

Figure 80-5. Bone resorption by osteoclasts. Parathyroid hormone *(PTH)* binds to receptors on osteoblasts, causing them to form receptor activator for nuclear factor κ-B ligand *(RANKL)* and to release macrophage-colony stimulating factor *(M-CSF)*. RANKL binds to RANK and M-CSF binds to its receptors on preosteoclast cells, causing them to differentiate into mature osteoclasts. PTH also decreases production of osteoprotegerin *(OPG)*, which inhibits differentiation of preosteoclasts into mature osteoclasts by binding to RANKL and preventing it from interacting with its receptor on preosteoclasts. The mature osteoclasts develop a ruffled border and release enzymes from lysosomes, as well as acids that promote bone resorption. Osteocytes are osteoblasts that have become encased in bone matrix during bone tissue production; the osteocytes form a system of interconnected cells that spreads all through the bone.



بسيطة، عندما الاوستيوبلاست expressed a RANKL protein، وهذا الدور فين يساعد في الdifferentiation of osteoclasts لان الاوستيوكلاست عندها الريسبتور الخاص بهالبروتين.
طيب وش الي يمنع عمل هالبروتين عشان ما تنشط عندنا اوستيوكلاست كثير؟ وذكرنا الحظ؟ الي يعمل منه هو OPG ، بحيث انه يمسك فيه ويمنعه من الاثر ثبط بالاوستيو هقه على الاوستيوكلاست

To Understand Better

Hormones controlling remodeling:

Parathyroid hormone →
Maintains Ca^{2+} homeostasis via Increasing:
Bone **formation** (intermittent)
Bone **resorption** (continuous)
Renal tubular calcium reabsorption
Renal calcitriol production

Calcitriol (vit.D) →
↑ → intestinal Ca phosphorus absorption + bone mineralization

Estrogen and androgen →
↑ rate of bone loss by acting on many local factors including:
- ↑ osteoclast apoptosis and growth factors from osteoblasts.
- ↓ number and depth of resorption cavities and release of cytokines.

Calcitonin →
No significant physiological role in men
Pharmacologically → **decreases** osteoclasts and bone resorption.

Glucocorticoids →
↑ apoptosis of osteoblasts and osteocytes → ↑ resorption

Thyroid hormone →
↑ turn-over (i.e. resorption and formation)

Growth hormone →
↑ skeletal growth

To Understand Better

❖ **Stages of bone remodeling:**

- From birth through adolescence, new bone is built faster than old bone is removed
- In mid-life, depending on lifestyle and other factors, bone removal can achieve a balance with bone formation.
- After **menopause**, bone removal may accelerate due to a decrease in estrogen.
- So it results from the **imbalance** between resorption and formation of bones.
- → The point is to know that the bone remodeling **require long time**.

Osteoporosis:

A complex of endocrinological disorders of bone and mineral metabolism (bone resorption > formation)

⬇

It'll lead to low bone mass + disruption of bone architecture + reduced bone strength and increased risk of fractures.

osteoporosis risk factors

Potentially modifiable يمكنك التحكم بها	Non-modifiable لا يمكنك التحكم بها
- Current cigarette smoker. **- Diet low on calcium or Vit.D.** **- Glucocorticoids anticonvulsants.** **- Excessive alcohol intake.** **- Sedentary lifestyle** (lacking the physical activity and movements) **- Body weight.** **- Environmental risks** → especially in elderly. **- Poor eyesight**.	**- Personal history of fracture** **- 1st degree relative has a history of fractures** **- Race** (Caucasian or Asian) **- Elder people** **- Poor health** **- Dementia** **- Hormonal disorders** **- Neoplastic disorders** **- Metabolic abnormalities**

Relation to 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.

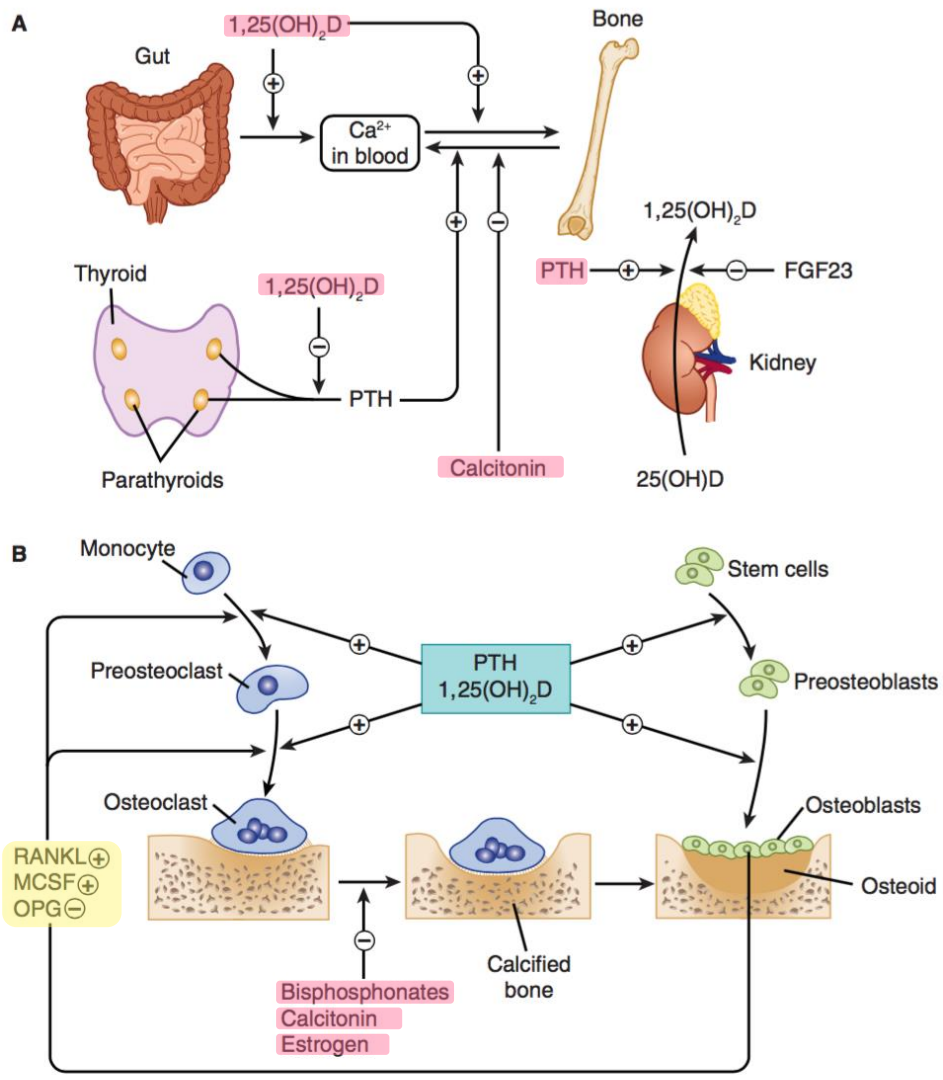


FIGURE 42–2 The hormonal interactions controlling bone mineral homeostasis. In the body **(A)**, 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) is produced by the kidney under the control of parathyroid hormone (PTH), which stimulates its production, and fibroblast growth factor 23 (FGF23), which inhibits its production. $1,25(OH)_2D$ in turn inhibits the production of PTH by the parathyroid glands and stimulates FGF23 release from bone. $1,25(OH)_2D$ is the principal regulator of intestinal calcium and phosphate absorption. At the level of the bone **(B)**, both PTH and $1,25(OH)_2D$ regulate bone formation and resorption, with each capable of stimulating both processes. This is accomplished by their stimulation of preosteoblast proliferation and differentiation into osteoblasts, the bone-forming cell. PTH and $1,25(OH)_2D$ stimulate the expression of RANKL by the osteoblast, which, with MCSF, stimulates the differentiation and subsequent activation of osteoclasts, the bone-resorbing cell. FGF23 in excess leads to osteomalacia by inhibiting $1,25(OH)_2D$ production and lowering phosphate levels. MCSF, macrophage colony-stimulating factor; OPG, osteoprotegerin; RANKL, ligand for receptor for activation of nuclear factor-κB.

Anti-Resorptive Agents

Drug: Bisphosphonates (1st line therapy)

Definition

- Are compounds that have 2 phosphonate (PO_3) groups.
- ❖ **Non- Nitrogenous:**
- Etidronate, Clodronate , Tildronate
- ❖ **Nitrogenous*:** → currently used
- Alendronate P.O, Ibandronate I.V, Risedronate P.O, Zoledronate I.V (the strongest)
- First-line osteoporosis pharmacotherapy employs **nitrogen-containing** bisphosphonates.
- **Antiresorptive activity of some bisphosphonates.**

Mech. of action

- Structurally similar to pyrophosphate (preventing its action by **inhibiting the enzymes responsible for utilizing it** -Suppress the activity of osteoclasts in part via inhibition of **farnesyl pyrophosphate synthesis-**).
  - Pyrophosphate is a natural circulating **inhibitor of mineralization** that doesn't enter bones because the lining cells destroy it with alkaline phosphatase. Deficiency of alkaline phosphatase results in pyrophosphate entering bones causing osteomalacia by preventing mineralization.
- They preferentially **"stick" to calcium → concentrate in bones**, bound to hydroxyapatite decreasing its solubility and making it **more resistant to osteoclastic activity**. (predominant mechanism)
- They prevent bone resorption by inhibiting osteoclast function
- Their relative potencies for osteoclastic inhibition is the most with 3rd generation "Zoledronate" (IV)
- **Block steps in cholesterol synthetic pathway** in osteoclast that act as signaling molecules responsible for the osteoclastic hydrolytic & phagocytic activity → (stop function → apoptosis) (some of the drugs ↓ LDL)
  - (The cholesterol-lowering statin drugs (eg, lovastatin), which **block mevalonate synthesis**, **stimulate bone formation**, at least in animal studies. Thus, the **mevalonate pathway appears to be important in bone cell function** and provides new targets for drug development. The mevalonate pathway effects vary depending on the bisphosphonate (ie, only amino bisphosphonates have this property), and may account for some of the clinical differences observed in the effects of the various bisphosphonates on bone mineral homeostasis.).
  - **Mevalonate pathway & bisphosphonate action.**

P.K

- Poorly absorbed (<10%), food impair absorption more; must be given on an **empty** stomach / or infused **IV** + with a full glass of water.
- t ½ = 1 hr (short) (rapidly cleared from the plasma, primarily because they avidly bind to the hydroxyapatite mineral of bone. Once bound to bone, they are cleared over a period of hours to years)
- Half of absorbed drug accumulates in bones, remainder → excreted unchanged in urine (dose is adjusted in patients with **renal impairment**)
- In bone it is retained for months, depending on bone turnover

Drug

Bisphosphonates (cont.)

Indications

- Osteoporosis, 2ndry to menopause, glucocorticoids → Bisphosphonates are **preferred** agents for the prevention and treatment of **postmenopausal osteoporosis**.
- Paget's disease
  - (excessive breakdown and formation of bone, followed by disorganized bone remodeling. This causes affected bone to weaken, resulting in pain, fractures and arthritis in the joints near the affected bones. Rarely, it can develop as Paget's sarcoma)
- Malignancy - associated hypercalcemia.

Dosing

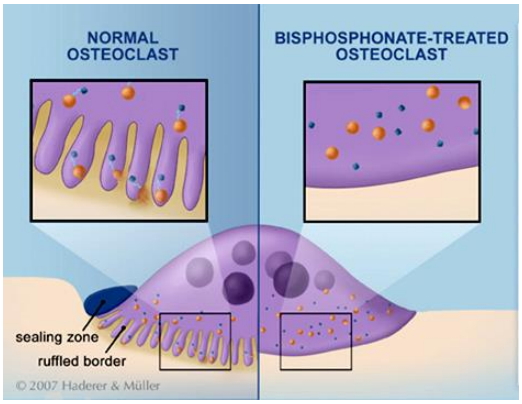
- Once weekly, or on two consecutive days each month.
- Should be taken in **upright position** (to avoid esophagitis).
- Taken after ½ hr.
- Separate 4 hrs. before giving Ca, Mg, Al containing drugs (may not be absorbed since Ca is provided by tablets and not from the bone)

ADRs

1. **GIT irritation**, nausea , vomiting , gastritis , ulceration → to avoid, give large amount of water to avoid risk of the tablet getting stuck in the esophagus (in case of orally taken)
2. **Gastro-esophageal reflux** + ulceration (with *Alendronate*, *risedronate*, and *ibandronate*) → 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.
5. If a dental implant or extraction is already planned, **delay** bisphosphonate therapy for a few months until healing of the jaw is complete.
   - This complication is more frequent when high intravenous doses of zoledronate are used to control **bone metastases** and **cancer-induced hypercalcemia**.
6. **Atrial fibrillation** → women with alendronate & zoledronate
7. Hypocalcemia (especially IV *zolidronate*)
8. *Etidronate* is the only member of the class that causes **osteomalacia**.

C.I

- **Decreased renal function**.
- Peptic ulcer / esophageal reflux.



Drug

RANKL Inhibitors (Denosumab)

"still under investigation"

Video

مهم جدًا تشوفون هذا الأنيميشن عن الRANKL & OPG ، بيساعدكم في الفهم وبيختصر عليكم وقت أكثر.
5:15 min

Mech. of action

- It's fully human MOA (a human monoclonal antibody). It mimics the activity of osteoprotegrin (OPG) but with higher affinity → the physiological inhibitor of RANKL (Receptor Activator Nuclear Kappa Ligand).
- 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.
- So, net effect → ↓ **bone resorption**
- RANKL* is substance released by osteoblast and it's important in osteoclastogenesis process , it binds to its receptor (RANK) expressed on preosteoclasts → stimulate its maturation into osteoclast. OPG competitively binds to RANKL → inhibit its interaction with its receptor >> block the osteoclastogenesis process → ↓ bone resorption. Which it's the same mechanism as Denosumab
- It is approved for treatment of postmenopausal osteoporosis in women at **high risk of fracture**, It should be reserved for women intolerant of or unresponsive to other osteoporosis therapies.

P.K

- **Subcutaneous** every 6 month.

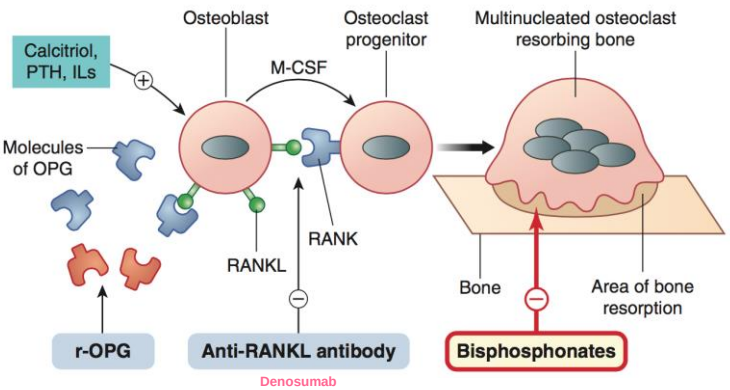
ADRs

- **Infections: urinary & respiratory**
- Eczema & skin rash
- Constipation
- Cataract
- Joint pain

Due to the immunological nature of the drug

C.I

- In patients with hypocalcemia. (correct Ca^{2+} & vit D levels before starting denosumab)



Drug	**Strontium** "strontium ranelate" **Imp!**
Definition	○ Sr^{2+} (like Calcium), is a divalent cation, resembling Ca2+ in atomic & ionic properties. It is orally active as **distrontium.** ○ Distrontium is the active form of strontium "di+strontium".
Mech. of action	○ 1st drug to possess " dual action " i.e. has both **anabolic** & **anti-resorptive** 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^{2+} Sensing Receptor** [CaSR] ; which is a GP coupled receptor that enhances differentiation of **preoteoblast to osteoblast → ↑ bone formation**. ○ It stimulates the expression of **OPG → ↑RANKL binding >** -ve of osteoclastogenesis → **↓ bone resorption** ❖ **On Osteoclast:** ○ Acts as agonist on **Ca^{2+} Sensing Receptor** [CaSP] suppress differentiation of **preosteoclast to osteoclast → ↑** osteoclast apoptosis **→↓** bone **resorption** ✓ ↑ Osteoblastic activity + ↓ Osteoclastic activity
P.K	○ Orally with a modest bioavailability 25%. ○ Binds partially to plasma proteins and strongly to bones and Ca containing products. ○ t ½ = 60 hrs. (long) ○ Excreted mainly by the kidney.
Uses	○ Osteoporosis, 2ndry to menopause, glucocorticoid,… ○ **Malignancy, associated hypercalcemia**.
ADRs	○ GIT irritation; nausea, vomiting, headache, eczema ○ All resolve in 1st 3 months → Reversible → بمجرد توقف المريض عن أخذه، يرجع كل شيء طبيعي بعد ٣ شهور.
Interactions	○ Food specially containing milk + its products ○ Antacids → in treating peptic ulcer ○ Oral tetracycline & quinolones chelate it } Precautions 2 hour space
C.I	○ In severe renal disease. ○ In hypersensitivity to Strontium. ○ In increased risk of **venous thromboembolism**. ○ In **phenylketonuria**.

Drug

Estrogen & Androgen

(use what's missing)

Definition

- Estrogen in females & Androgen in males are essential for normal bone remodeling.

❖ **How to use Estrogen?**

1. **If hysterectomy** (the surgical removal of the uterus):
   - ✓ use Estrogen only.
2. **Is uterus is present:**
   - ✓ Estrogen + Progestins (synthetic form of progesterone. Taken orally).
     - Why *progestins* with *estrogen* if uterus is present? Bc Estrogen alone causes **endometrial hyperplasia** unless given cyclically with a progestogen.
     - Estrogen-progestogen therapy is **no longer the therapy of choice** for the treatment of osteoporosis in postmenopausal women because of increased risk of **breast cancer**, stroke, venous thromboembolism, and coronary disease.
3. **As Hormonal replacement therapy (HRT):**
   - ✓ Menopausal symptoms (mild activity)
4. **SERMs** (Selective Estrogen Receptor Modulator, e.g. Raloxifene):
   - ✓ Menopause/Elderly.

- Androgen → for elderly men.
- Since they are natural hormones in the body, they can also relieve other post-menopausal symptoms. Unlike bisphosphonates that are only specific for osteoporosis.

Mech. of action

- ↑ Osteoclast apoptosis & inhibit osteoblast apoptosis (↑ age of Blast ↓ Clast activity)
- ↓ Number & depth of resorption cavities.
- ↑ Release of growth factors from osteoblasts.
- ↓ Release of inflammatory cytokines causing resorption.

ADRs

❖ **As a HRT (estrogen):**

- Vaginal bleeding.
- Risk of **breast cancer**.
- Venous thromboembolism.

SERMs

Drug

Raloxifene

(modified form of estrogen)

Definition

- 1st **selective estrogen Receptor modulator[1] (SERM)** for prevention and treatment of osteoporosis → *Raloxifene* is a first-line alternative for postmenopausal osteoporosis in women who are intolerant to bisphosphonates.

[1] means it can be agonist or antagonist.

- Estrogen on long use can cause breast cancer, that's why we use Raloxifene

MOA

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

+: Agonist, -:Antagonist

	Brain	Uterus	Vagina	Breast	Bone	CVS
❖ **Estradiol[1]**	++	++	++	++	++	++
❖ **Raloxifene**	—	—	—	—[2]	+	+

[1] not a SERM, it is like Estrogen.

[2] Raloxifene is approved for the **prophylaxis** of breast cancer in high-risk women.

Advantages

- Increases bone density without increasing the risk of endometrial cancer. In addition, *raloxifene* **reduces** the risk of invasive breast cancer in women at high risk.
- ↑ 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 and breast cancer.
- ↓ risk of thromboembolism compared to estrogen.

Disadvantages

- May ↑ hot flushes → acute symptom, mainly in female.
- No effect on HDL.
- It protects against spine fractures but **not hip fractures**—unlike bisphosphonates & denosumab, which protect against both.

Summary-1

	1- BISPHOSPHONATES Are compounds that have 2 phosphonate (PO3) groups.	2- RANKL INHIBITORS
Drug	❖ **Non- Nitrogenous:** ○ Etidronte, Clodronate , Tildronate ❖ **Nitrogenous*:** → currently used ○ Alendronate P.O, Ibandronate I.V, Risedronate P.O, Zoledronate I.V (the strongest)	Denosumab
MOA	○ Are structurally similar to pyrophosphate, ○ They preferentially "stick" to calcium ➔ concentrate in bones, bound to hydroxapatite, decreasing its solubility and making it more resistant to osteoclastic activity. ○ Inhibit osteoclast function → prevent bone resorption. 3rd generation "**Zoledronate**" the most potent osteoclast inhibitor. ○ Block steps in cholesterol synthetic pathway in osteoclast that act as signaling molecules responsible osteoclastic hydrolytic & phagocytic activity →(stop function→apoptosis)	1- binds to RANKL "expressed by osteoblast" → block RANKL from interacting with RANK "expressed on preosteoclasts" → inhibit osteoclastogenesis 2- it binds to mature osteoclast promote its apoptosis. Net effect : prevent bone resorption
P.K	○ poorly absorbed (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	-
Uses	○ osteoporosis , 2ndry to menopause , glucocorticoids ○ Paget's disease ○ Malignancy - associated hypercalcemia	-
Dose	○ 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 "avoided by large amount of water" 2- Gastro-esophageal reflux + ulceration "avoided if given on empty stomach while in upright position for 30 min." 3- flu like manifestation upon IV infusion. 4- osteonecrosis of the jaw "in 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 & zoledronate**	○ Infections : urinary & respiratory ○ Eczema & skin rash ○ Constipation ○ Cataract ○ Joint pain
C.I	○ decreased renal function. ○ peptic ulcer / esophageal reflux	in patients with hypocalcemia. (correct ca & vit D levels before starting **denosumab**)

Summary-2

3- STRONTIUM

Sr2+ : is a divalent cation, resembling Ca2+ in atomic & ionic properties.
It is orally active as distrontium

MOA	possess " dual action " resulting in a rebalance of bone turnover in favor of bone formation. ● **On Osteoblast**: it acts as agonist on Ca Sensing Receptor (CaSR) 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
P.K	○ Orally with a modest bioavailability 25% ○ Binds partially to plasma proteins and strongly to bones. ○ t ½ 60 hrs. ○ Excreted mainly by the kidney
Uses	○ Osteoporosis, 2ndry to menopause, glucocorticoid. ○ Malignancy, associated hypercalcaemia
interaction	Food specially containing milk + its products - **Antacids** - Oral **tetracycline & quinolones** chelate it "2 hour space for precaution"
ADRs	GIT irritation; nausea, vomiting, headache, eczema "resolve in 1st 3 months''
C.I	In severe renal disease - In hypersensitivity to it - In increased risk of venous thromboembolism - In phenylketonuria

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

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

Estrogen and androgen

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

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

ADRs

- For HRT (estrogen):

vaginal bleeding,
risk of breast cancer
venous thromboembolism.

Primary	Secondary
22. Drugs and bone (Ch. 35)	
parathyroid hormone (med/trnsm)	calcitonin
vitamin D	teriparatide
calcium salts	cinacalcet
oestrogen (med/trnsm)	
raloxifene	
alendronate	etidronate
risedronate	strontium ranelate

Bisphosphonates

- Orally active, stable analogues of pyrophosphate, which are incorporated into remodelling bone and remain there for months or years.
- Released when osteoclast-mediated bone resorption occurs, exposing osteoclasts to their toxic effects.
- First-generation compounds (e.g. **etidronate**) act by promoting apoptosis of osteoclasts.
- Second-generation compounds (e.g. **risedronate**) with N-containing sidechains are much more potent, and prevent osteoclast action by inhibiting prenylation reactions required for membrane anchoring of functional proteins.
- Used long term for prevention and treatment of osteoporosis.
- Main unwanted effect is gastrointestinal disturbance

Clinical uses of bisphosphonates

- *Osteoporosis*:
  - 'primary' prevention of fractures in high-risk individuals (e.g. with established osteoporosis, several risk factors for osteoporosis, treated chronically with systemic glucocorticoids)
  - 'secondary' prevention after an osteoporitic fracture
  - **alendronate** by mouth is the bisphosphonate of choice, given daily or once weekly in addition to calcium with vitamin D_3. **Risedronate** or **etidronate** are alternatives; **zoledronate** is given annually by intravenous infusion but is expensive.
- *Malignant disease* involving bone (e.g. metastatic breast cancer, multiple myeloma):
  - to reduce bone damage, pain and hypercalcaemia (e.g. **clodronate**, **ibandronate**, **zoledronate**).
- *Paget's disease* of bone (e.g. **etidronate**, **pamidronate**) administered intermittently and with monitoring of serum phosphate, alkaline phosphatase and urinary hydroxyproline (a marker of collagen turnover).

SUMMARY Major Drugs Used in Diseases of Bone Mineral Homeostasis

Subclass	Mechanism of Action	Effects	Clinical Applications	Toxicities
VITAMIN D, METABOLITES, ANALOGS				
• Cholecalciferol • Ergocalciferol • Calcitriol • Doxercalciferol • Paricalcitol • Calcipotriene	Regulate gene transcription via the vitamin D receptor	Stimulate intestinal calcium absorption, bone resorption, renal calcium and phosphate reabsorption • decrease parathyroid hormone (PTH) • promote innate immunity • inhibit adaptive immunity	Osteoporosis, osteomalacia, renal failure, malabsorption, psoriasis	Hypercalcemia, hypercalciuria • the vitamin D preparations have much longer half-life than the metabolites and analogs
BISPHOSPHONATES				
• Alendronate • Risedronate • Ibandronate • Pamidronate • Zoledronate	Suppress the activity of osteoclasts in part via inhibition of farnesyl pyrophosphate synthesis	Inhibit bone resorption and secondarily bone formation	Osteoporosis, bone metastases, hypercalcemia	Adynamic bone, possible renal failure, rare osteonecrosis of the jaw, rare subtrochanteric (femur) fractures
HORMONES				
• Teriparatide • Calcitonin	These hormones act via their cognate G protein-coupled receptors	Teriparatide stimulates bone turnover • calcitonin suppresses bone resorption	Both are used in osteoporosis • calcitonin is used for hypercalcemia	Teriparatide may cause hypercalcemia and hypercalciuria
SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)				
• Raloxifene	Interacts selectively with estrogen receptors	Inhibits bone resorption without stimulating breast or endometrial hyperplasia	Osteoporosis	Does not prevent hot flashes • increased risk of venous thromboembolism
RANK LIGAND (RANKL) INHIBITOR				
• Denosumab	Monoclonal antibody • binds to RANKL and prevents it from stimulating osteoclast differentiation and function	Blocks bone resorption	Osteoporosis	May increase risk of infections
CALCIUM RECEPTOR AGONIST				
• Cinacalcet	Activates the calcium-sensing receptor	Inhibits PTH secretion	Hyperparathyroidism	Nausea
MINERALS				
• Calcium • Phosphate • Strontium	Multiple physiologic actions through regulation of multiple enzymatic pathways	Strontium suppresses bone resorption and increases bone formation • calcium and phosphate required for bone mineralization	Osteoporosis • osteomalacia • deficiencies in calcium or phosphate	Ectopic calcification

You can find it in high resolution in L4

MCQs

1- Bone remodeling refer to which of the following:
A- Resorption-removes old bone
B- Formation-replaces old bone with new bone
C- A & B

2- Which one of the following cells that responsible for formation and replacing an old bone with a new one:
A- Osteoclast
B- Osteoblast
C- osteocytes

3- A 54 year-old patient with phenylketonuria came to a clinic with pain in his knee, lab investigations confirm an osteoporosis condition , which drug should we avoid?
A- Strontium
B- Bisphosphonates
C- Denosumab

4- Which one of the following drugs can cause osteo-necrosis of the jaw after a dental surgical procedure?
A- Strontium
B- Bisphosphonates
C- Denosumab

5- The following is true of raloxifene except:
A- It acts as an estrogen agonist in bone.
B- It exerts estrogen antagonistic action on endometrium.
C- It increases risk of developing breast cancer.
D- It can induce/aggravate menopausal hot flushes.

6- A 63-year-old woman falls at home and fractures her wrist. She has a 40 pack-year history of smoking. Her doctor recommends a DXA scan, which reveals a very low bone density and prescribes alendronate. How will alendronate help this patient?
A- Enhancing GI calcium absorption
B- Inhibiting calcium excretion in the kidneys
C- Inhibiting osteoclasts
D- Stimulating osteoblasts
E- Providing the starting material for bone mineralization

7- A 52-year-old postmenopausal patient has evidence of low bone mineral denisity. She and her physician are considering therapy with raloxifene or a combination of conjugated estrogens and medroxyprogesterone acetate. Which of the following patient characteristics is most likely to lead them to select raloxifene?
A- Previous hysterectomy
B- Recurrent vaginitis
C- Troublesome hot flushes
D- Strong family history of breast cancer

8- A 78-year-old woman with known osteoporosis presents to her primary care physician for follow-up. She is managed with alendronate. Physical examination reveals a woman with a height of 5 ft 3 in and weight of 143 lb. The most likely effects on bone would be which of the following?
A- Increased osteoblastic bone resorption
B- Inhibition of cholesterol biosynthesis
C- Inhibition of osteoclastic apoptosis
D- Inhibition of osteocyte activation

Answers: 1-C 2-B 3-A 4-B 5-C 6-C 7-D 8-B

Thank you for checking our team!

Pharmacology 435

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Sources:

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3. Basic & Clinical Pharmacology by Katzung, chapter 42,12th edition.
4. Rang & Dale's pharmacology, chapter 34, 35. 7th edition.
5. Guyton & Hall Textbook of Medical Physiology. 13th edition.