Treatment of osteoporosis & Drugs used in calcium and vitamin D disorders

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- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objectives

- Revise the composition, regulation, and remodeling stages of bone turnover.
- Recognize the interlinks of osteoblastic and osteoclastic function.
- Relate changes to the development of osteoporosis.
- Classify drugs according to their replacement, anti-resorptive, or anabolic mechanism of action.
- Detail the pharmacology of such a group of drugs and their clinical utility in combating osteoporosis.
- Recognize the common drugs used in calcium & vitamin D disorders.
- Classify them according to sources & Pharmacological effects.
- Detail the pharmacology of each drug regarding; Mechanism, clinical utility in affecting calcium & vitamin D.

Bone

Is a dynamic organ that undergoes continuous remodeling process involving resorption of old bone by osteoclast & formation of new bone by osteoblast in a process called **remodeling**.

Bone is renewed like skin, hair, and nails.

Bones build from birth until about age 30; steps to building healthy bone include:
Calcium - vitamin D - limit caffeine & alcohol - exercise - don't smoke

The dominant site of **calcium storage** in the body is bone, which contains nearly 99.9% of body calcium.

Although only a small fraction of total body calcium is located in the plasma, it is the plasma concentration of ionized calcium that is tightly regulated, primarily under the control of PTH and Vitamin D.

Principal factors involved in regulation of Ca^{2+} metabolism & bone remodelling are:

- ✧ Parathyroid hormone (PTH)
- ✧ Vitamin D
  - ➥ *PTH and Vitamin D play central roles in the regulation of bone metabolism*
- ✧ Calcitonin

The target tissues regulate Calcium homeostasis

Bones	Kidneys	Intestines
Absorption from blood to bone" & Resorption "from bone to blood" of Ca^{2+}	Reabsorption	Ca^{2+} absorption

Bones

Bones

Types

1) Cortical:
Hard, compact and dense bone
E.g. long bones of arms and legs

2) Trabecular:
Spongy, porous and flexible bone
E.g. end of wrist, hip and spine

Components (two types of tissue)

1) Inorganic: 65% of mass
- Consists of crystalline calcium phosphate salts (hydroxyapatite) *keeps bone **rigidity***

2) Organic: 35% of mass
- Consists: osteoblasts,osteoclasts & osteocytes.
- Bone cells are either: bone forming or bone resorptive

Bone forming cells

Osteogenic cell: mesenchymal in origin →found on all bone surfaces

Osteoblast: forms osteoid framework & helps in mineralization (B for Building)

Bone resorptive cells

Osteoclasts → reside in pits (resorption bays) that form by eaten bone surface.

Secretes lysosomal enzymes (collagenase and metalloproteinase) + hydrochloric acid → dissolve bone matrix (C for Cutting)

Bone Remodeling

➔ Normally, bones are continuously formed and reabsorbed (bone remodeling) under control of:
- Systemic hormones
- Body mineral contents
- Local autocrine-paracrine secretions (cytokines, growth factors and PGs).

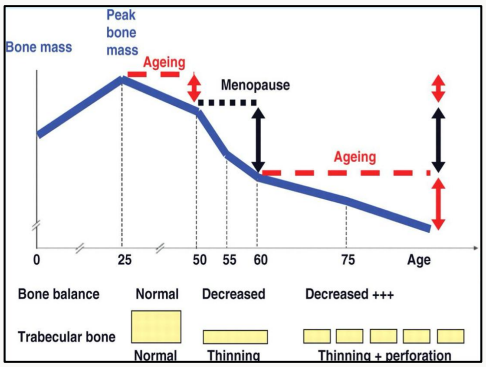
➔ It is meant to maintain calcium homeostasis and to renew bone in repair of microdamage and microcracks

Phase 1: Resorption *removes old bone cells*
Osteoclast seek out old bone or damaged ones and destroy it, leaving a small empty space

Phase 2: Formation *replaces old with new bone cells*
Osteoblasts use minerals like calcium, phosphorus and vit D to fill in this space with new bone cells

Osteoporosis
"The Silent Disease"

- "Osteoporosis" means bones that are full of holes
  Osteo is Latin for **bone** + **Porosis** means porous or full of **holes**
- A complex endocrinological disorder of bone and mineral metabolism causing low bone mass and disruption of bone architecture → reduced bone strength and increased risk for fractures
- **Bone resorption > Bone formation**
- The first 5-15 years after menopause(Low estrogen level) , 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



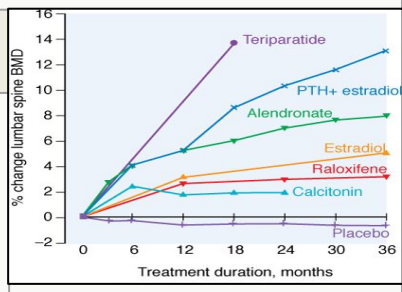
Risk factors

Potentially Modifiable	Non-modifiable
-Current Cigarette smoking - **Diet Low in calcium, Vit D** - Drugs like **Glucocorticoids,** Anticonvulsants - Excessive alcohol intake → Increase resorption - **Sedentary lifestyle** - Body weight - Environmental risks: Aluminum & Cadmium exposure	- Personal history of fractures (1st degree relative) - Race (Caucasian or Asian) - **Elderly age** - Poor health - Dementia:poor memory → Forget to take their drugs/ poor nutrition - Hormonal disorders:hyperparathyroidism - **Neoplastic disorders** - Metabolic abnormalities:diabetes -Ethnic background -Sex

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 there is a ↓ **in the trabecular bone** in the presence of normal cortical bone.
2. **Reset back the balance of remodeling:**

Class	MOA	Drugs
Antiresorptive	Mainly inhibit osteoclasts	**Bisphosphonates** Commonly used **RANKL inhibitors:** Denosumab **Estrogen analogues** **Androgen analogues** **SERMS** Raloxifene **Calcitonin**
Bone Anabolic (building)	Mainly activate osteoblasts	**Parathyroid hormone (PTH)** **Teriparatide** (It is a Low doses of PTH)
Dual action	Both effects	Strontium Additional treatment



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

Treatment of osteoporosis

1A. Antiresorptive: Bisphosphonates forming complex with the bone

	Nitrogenous (Less potent)	Non-Nitrogenous (Stronger)
Drugs	• Alendronate (oral) • Ibandronate (oral) • Risedronate (oral) • Zoledronate (I.V.)	• Etidronate • Clodronate • Tiludronate

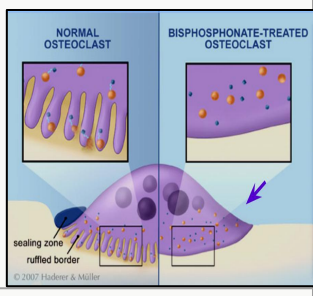
Important

M.O.A

- Bisphosphonates are compounds that have two phosphate groups (PO_3)
- Structurally **similar to pyrophosphate (in our body)** and work by:

1. Preferentially "stick" to calcium → concentrate in bones, bound to hydroxyapatite, decreasing its solubility and making it more resistant to osteoclastic activity.
2. Prevent bone resorption by Inhibiting osteoclast function. How?

   By: It is taken up by osteoclast → block steps in cholesterol synthetic pathway in osteoclast that act as signaling molecules responsible for the osteoclastic hydrolytic & phagocytic activity → osteoclast stops functioning leading to apoptosis (increased death of osteoclast)



P.K.

- **Zoledronate** (3rd generation) : has the **highest potency** for osteoclast inhibition **used for Emergencies -given IV-**
- Poorly absorbed (<10%), **food impair absorption** more → must be given on an empty stomach / infused IV
- T1/2 = 1 hr
- 1/2 of absorbed drug **accumulates** in bones, remainder is excreted unchanged in urine
- **In bones it is retained for months, depending on bone turnover.**

Uses

- **Osteoporosis**; secondary to **menopause or glucocorticoids**..etc
- Paget's Disease: a disorder where there is continuous bone breakdown
- **Malignancy-associated hypercalcemia because it keeps Ca++ inside the bones**

Doses

- Once weekly or on two consecutive days each month
- **Should be taken in upright position with large amount of water to prevent esophagitis**
- Should be given 4 hrs before having any Ca, Mg, Al containing drugs. (chelating agent)

  Note: Calcium and Vit D supplementation, should be given after a gap from ingestion of bisphosphonates because it can inhibit their absorption.

ADRs

- **GIT irritation;** nausea, vomiting, gastritis , **ulceration** → to avoid give large amount of water to avoid risk of the tablet getting stuck in the **esophagus**
- Gastroesophageal reflux ± ulcerations → to avoid give on empty stomach while sitting in upright for 30 min
- Flu like manifestations (fever, chills) upon IV infusion
- **Osteonecrosis** 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 healing** of the jaw is complete **- it prevents healing-**
- **Atrial fibrillation → women with alendronate & zoledronate**

C.I

- Decreased renal function
- **Peptic Ulcer**
- Esophageal reflux
- **Alendronate & Zoledronate in CVD Patients**

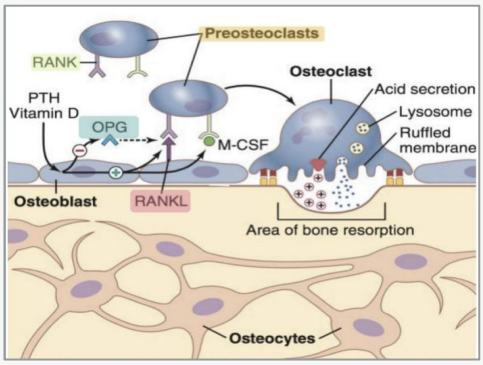
Treatment osteoporosis

1B. Antiresorptive: RANKL inhibitors

Denosumab (new drug)

It is a fully humanized MOA monoclonal antibody that **mimics the activity of osteoprotegerin (OPG)**

Balance of bone remodeling



1. Osteoblasts express a ligand called RANKL1 Receptor Activator of Nuclear factor Kappa-B Ligand (It's a family member of TNF cytokine)
2. RANKL binds to a receptor located on the surface of pre-osteoclasts called RANK.
3. 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.**
4. **RANKL can be inhibited physiologically by an endogenous inhibitor called osteoprotegerin (OPG)2 . OPG binds to RANKL & blocks it's binding to RANK.**
5. On the other hand, GH, PTH, IGF-1 ↑osteoblasts formation → ↑ Bone formation

M.O.A.

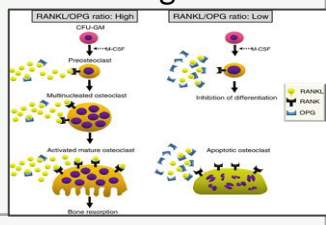
➔ Refer to the picture above for better understanding

- 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:**
  - Binds with high affinity to RANKL, mimicking the effect of OPG → **Blocks RANKL from interacting with RANK receptor** expressed on preosteoclast → ↓ osteoclastogenesis → no mature osteoclasts
  - Binds also to mature osteoclasts → increase their apoptosis

  Net effect → decreasing bone resorption



P.K.

Administered subcutaneously every 6 months

Uses

Extremely expensive and reserved **for patients who cannot tolerate or respond to bisphosphonate**

ADRs

- Infections: urinary & respiratory RANK receptors are present on immune cells
- Eczema & skin rash (biological treatment)
- Pancreatitis (biological treatment)

C.I

Patients with **hypocalcemia**, as denosumab decreases serum calcium concentration. Correct Ca & Vit D levels before starting **denosumab**

Female slide

Treatment osteoporosis

1C. Dual effect: Antiresorptive + Bone Anabolic Agents

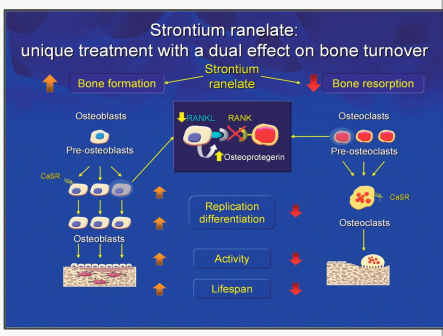
Strontium

Sr^{2+} is a divalent cation resembling Ca^{2+} in atomic and ionic properties

M.O.A.

1st drug to possess "dual effect", i.e has both antiresorptive & anabolic effects,resulting in rebalance of bone turnover in favor of bone formation

- **Effects on osteoblasts:**
  1. Since it is like Ca, it acts as **agonist on Ca Sensing Receptor [CaSR]** ;which is a GP coupled receptor that enhances differentiation of preosteoblast to osteoblast → ↑bone formation
  2. **Stimulate the expression of OPG** → ↑ RANKL binding → -ve of osteoclastogenesis → ↓bone resorption
- **Effects on osteoclasts:**
  Acts as an agonist on **CaSR** → suppress differentiation of preosteoclast to osteoclast → ↑osteoclast apoptosis → ↓ bone resorption



P.K.

- Orally active as **distrontium** with a modest bioavailability of 25%
- **Binds partially to plasma proteins and strongly to bones**
- T1/2 = 60 hrs
- Excreted mainly by the kidney

Uses

- Osteoporosis; secondary to menopause or glucocorticoids..etc

ADRs

- **GIT irritation**; nausea, vomiting, **Headache**, **Eczema** → All resolve in 1st three months

C.I

- Severe renal disease.
- **Phenylketonuria** Phenylalanine metabolism problem - the drug contains phenylalanine-
- Hypersensitivity to the drug
- Increased risk of venous thromboembolism Don't give it to immobile Patients.

Interactions

- Precaution: 2 hrs spacing
  - Food specially containing milk ± its products
  - Antacids
  - Oral Tetracycline and quinolones chelates it (chelates=binds to)

Treatment osteoporosis

2A. Hormonal Therapy: Sex Hormones

Drugs	Estrogen	Androgen
M.O.A	• Estrogen in females and Androgens in males are essential for normal bone remodeling: ○ ↑ osteoclast apoptosis and Inhibit osteoblast apoptosis (protective effect on the bones) ○ ↑ release of growth factors from osteoblasts ○ ↓ number and depth of resorption cavities ○ ↓ release of inflammatory cytokines causing resorption	
Uses	• **Hysterectomy** (Removal of uterus) : use estrogen only • If **uterus is present**: Estrogen + **Progestin** to protect the uterus • Hormonal Replacement therapy **(HRT)**: menopausal symptoms (Sweating, Hot Flushes) • **SERMs** (selective estrogen receptor modulators): Menopause/Elderly	Elderly men
ADRs	HRT (estrogen): • Vaginal bleeding • Risk for breast cancer • Venous thromboembolism -**most common** ADR- • Endometrial proliferation, can lead to cancer of the uterus. (Progestins can protect against this)	-

2B. Hormonal Therapy: Selective Estrogen Receptor Modulators (SERMs)

Raloxifene

Uses

1st SERM for prevention and treatment of osteoporosis *(especially postmenopausal)*

M.O.A

- Anti-Estrogens that exhibits partial agonistic action
- Agonist in bones and Antagonist in some female sex organs
- Works only on women especially post-menopausal women

Selectivity

	Brain	Uterus	Vagina	Breast	Bone	CVS
Estradiol (Estrogen)	++ Excitability	++ Cancer	++ Bleeding	++ Cancer	++ Antiresorptive	++ Thrombosis
Raloxifene	-	-	-	-	+	+

Advantages

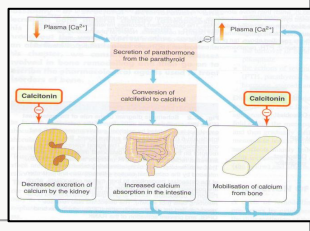
- ↑ bone density by (2%) and ↓ fracture risk by (30%)
- No need for **progestin** in women with a uterus.
- **No stimulation of breasts nor endometrial tissue.**
- **Good for women with a risk of breast and uterine cancer.**
- Lower risk for thromboembolism compared to estrogen.
- ↓ LDL

Disadvantages

- May ↑ hot flushes
- No effect on HDL

Treatment of Osteoporosis

Parathyroid Hormone

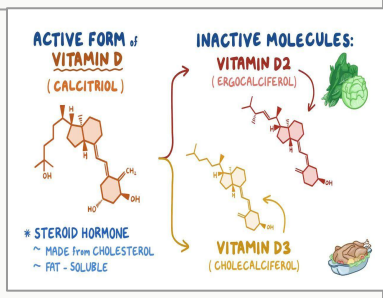
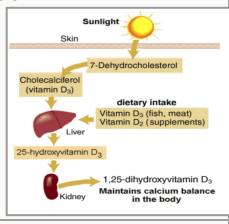
Definition	**PTH is released** from the parathyroid gland **in response to low plasma Ca^{2+}** level.
Action	**The main action is** to restore the normal plasma level of Ca^{2+}, which is done by: • **Bone: Mobilization of Ca^{2+} and PO_4^{3-} from bone**. In response to hypocalcemia, PTH **stimulates osteoclast** cells to increase the outward flux of calcium to restore serum calcium level. • **Kidney: ↑ Ca^{2+} reabsorption** ↓excretion & ↑ **formation of calcitriol** which is the active form of vitamin D • **GIT: ↑ absorption of Ca^{2+}** 
Effects	The effect depends on **the way of administration/Exposure**: • Daily, **Intermittent administration** of PTH, for 1 to 2 hours/day leads to a net **stimulation of bone formation**. the way it's used in the treatment of **Osteoporosis** Mechanism: ↑ **Osteoblast function**/number→ Bone formation→ Bone mass/strength • **Continuous exposure** to elevated PTH leads to **bone resorption and risk of fracture**. Mechanism: ↑ **Osteoclast** → ↑ Bone resorption → ↑ Serum Ca^{2+}
Uses	• Treatment of **severe osteoporosis**. • **Resistant cases** failed to response to other medications. Not first line, but still an option

Teriparatide

Definition	• **Synthetic** polypeptide form of **PTH** (PTH analog). • It belongs to a class of anti- osteoporosis drugs, the so-called **"anabolic" agents**.
P.K.	Given once daily as S.C injection. Not intermittent or with gaps
Effects Exactly like PTH	The therapeutic effects of teriparatide depend upon the pattern of systemic exposure: - **Once daily administration** → stimulates new bone formation by preferential **stimulation of osteoblastic activity** over osteoclastic activity. - By contrast, **Continuous administration** → may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation.
Uses Same as before, but focus on precautions	• Should not be used routinely due to **carcinogenic effects** mainly osteosarcoma • Use in **severe osteoporosis** or patients **not responding** to other drugs. • For treatment of osteoporosis in people who have a risk of getting fracture (increase bone mass & strength) • Good for postmenopausal osteoporosis.
ADRs	• **Carcinogenic effect (osteosarcoma)** Teriparatide→ toxic (serious. cancer) • Diarrhea, heartburn, nausea. • Headache, leg cramps. • Hypotension when standing • Elevated serum calcium can occur in some cases leading to **kidney stones**.
C.I	Should not be used by people with increased risk for bone tumors (osteosarcoma) including: • People with **paget's disease** of bone The disease causes excessive osteoclast function & can lead to osteosarcoma • People who had **radiation treatment** involving bones ↑ risk of bone cancer • Not recommended at all in **children** bone development

Treatment of Osteoporosis

Vitamin D

Definition	Vitamin D is a steroid hormone that is intimately involved in the regulation of plasma calcium levels.
Forms	• **Cholecalciferol (Vitamin D3):** skin. - Vitamin D3 is usually for vitamin D-fortified milk & foods & also available in drug combination products. • **Ergocalciferol (Vitamin D2):** plants. - Vitamin D2 is the prescription form of vitamin D & is also used as food additive (milk, egg yolk & fish oil) • **Vit D2** and **Vit D3** have equal biological activities. - both travel to the liver and then convert to their active form in the kidneys. 
Metabolism	• **Sunshine:** Cholecalciferol (D3) is generated in the skin from 7-dehydrocholesterol by the action of ultraviolet radiation (sunshine). • **In The Liver**: The initial transformation of D3 occurs in liver to (Calcifediol) the main storage form of Vit D in our body. • **In the kidney**: **PTH** stimulates the formation of the active form of vitamin D (Calcitriol) 
Effects	The overall effect of vitamin D is to ↑ **plasma Ca^{2+} concentrations**, which is done by: • **Bone:** Increases bone resorption & activation of osteoblast cells.Although it causes resorption, the net effect is activation of osteoblasts • **Kidney:** Increased reabsorption of Ca^{2+} & PO_4. • **GIT:** Increased absorption of Ca^{2+} from the intestine. • Decreases the production of PTH by the **parathyroid glands** By ↑ plasma levels of Ca^{2+}

Calcitonin

Definition	• Produced by the parafollicular cells (**C cells**) of the **thyroid gland.** • A physiological Antagonist of PTH, it is released when there is an elevated level of Ca^{2+} in the blood. • Calcitonin does not appear to be critical for the regulation of calcium homeostasis even if thyroid gland is removed.
Effects	• **Bone:** Decreases bone resorption by **inhibiting osteoclast activity.** • **Kidney:** Decreases reabsorption of Ca^{2+} & PO_4, thus increasing their excretion. • **No** effect on the GIT.
P.k.	Route of administration: S.C, **Nasal spray.**
Uses	**(it has lower efficacy compared to other drugs)** • **Hypercalcemia** (short-term treatment of hypercalcemia of malignancy). • **Paget's disease.** (Hypercalcemia in **Paget's disease**) • Osteoporosis (major indication; **alternative** to other drugs).
ADRs	• Nausea • Local inflammation (at site of Injection) If given SC • Flushing of face & hands • Nasal irritation If given as nasal spray

MCQ

Q1. Which of these should be taken on an empty stomach with large amounts of water in an upright position to avoid ADRs?

A. Risedronate	B. Denosumab	C. Strontium	D. Raloxifene

Q2. Which of the following works by acting as a Ca Sensing Receptor agonist and Stimulate the expression of OPG?

A. Ibandrinate	B. Denosumab	C. Raloxifene	D. Strontium

Q3. A patient presenting with uncorrected hypocalcemia, which of the following is contraindicated?

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

Q4. What is the mechanism of action of teriparatide?

A. Increase activity of osteoclast	B.Increase activity of osteoblast	C. Inhibit RANKL	D.Stimulate Calcitonin secretion

Q5. Plant form of vitamin D

A. Cholecalciferol	B. calcifediol	C. Ergocalciferol	D. Calcitriol

Q6.What is the mechanism of action of calcitonin?

A. Inhibit osteoclast activity	B.Decrease the production of parathyroid hormone	C. increase the absorption of the renal Ca and phosphate	D.Tones down serum Ca by inhibiting osteoblast activities

1: A ,2: D ,3: B ,4: B ,5: C ,6: A

SAQ

1 50-year old woman visits her family physician and the physician prescribes her medication to prevent postmenopausal osteoporosis. Name the drug that the physician prescribed?

Teriparatide (PTH analogue)

2 Based on Q1 List the possible responses of the drug based on administration habits

-**Continuous administration**→ may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation

- **Once daily administration** → stimulates new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity.

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