

Endocrine Block

Pharmacology Team 439

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Treatment Of Osteoporosis

Objectives:

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

Healthy Bones

This page is only for your understanding

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

Types of bones

(1) Cortical

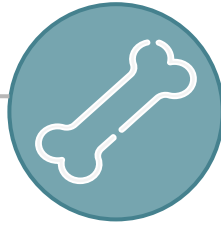
Hard, compact and dense bone.

E.g. Long bones of arms and legs

(2) Trabecular

Spong, porous and flexible bone

E.g. 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

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

Osteogenic Cells

- Mesenchymal in origin
- Found on all bone surface

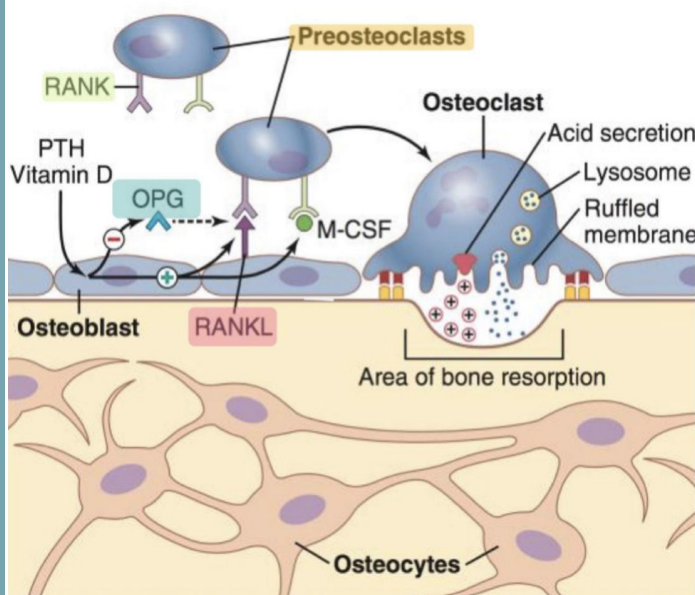
Bone forming cells (Osteoblasts)

- Forms osteoid framework and helps in its mineralization
- Think B for Building

Bone resorptive cells (Osteoclast)

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

Balance of Bone Remodeling



- Osteoblasts express a ligand called **RANKL1** (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 pre-osteoclasts 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

- The higher RANKL number in someone, the higher their chance of developing osteoporosis.
- Osteoprotegerin is the physiological antagonists of RANKL1

Bone Remodeling

This page is only for your understanding

- **Normally**, bones are continuously formed and absorbed (bone remodeling) under the control of systemic hormones, body minerals 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

1

Phase 1: Resorption

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

2

Phase 2: Formation

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

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

Potentially modifiable

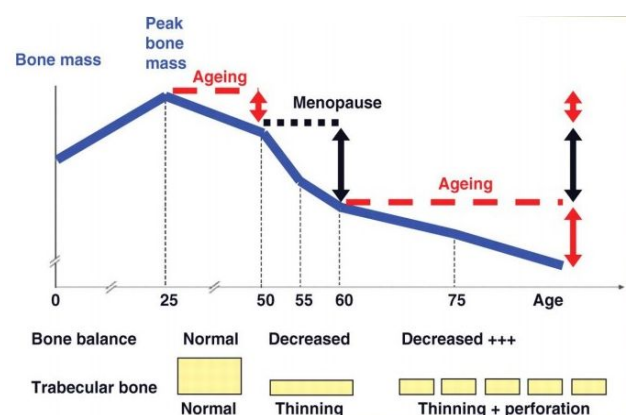
- Current Cigarette smoking
- Diet Low in calcium/Vit D
- Glucocorticoids, Anticonvulsants
- Excessive alcohol intake
- Sedentary lifestyle
- Body weight
- Environmental risks

Non-modifiable

- History of fractures (personal/1st degree relative)
- Race (Caucasian or Asian)
- Elderly age
- Poor health
- Dementia
- Hormonal disorders
- Neoplastic disorders
- Metabolic abnormalities

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



Treatment for Osteoporosis

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

- Used to enhance the strength by the formation of **fluorapatite** which is considered when there is a ↓ **in the trabecular bone density** with normal cortical bone.

2. Reset back the balance of remodeling

Antiresorptive

1. Bisphosphonates (most pop.)
2. RANKL inhibitors (OPG like)
4. Estrogen analogues
4. Androgen analogues
5. SERMS
- Calcitonin

M.O.A

Mainly inhibit osteoclasts

Bone Anabolic

- Parathyroid hormone (PTH)
- **Teriparatide** (PTH analogue)

M.O.A

Mainly activate osteoblasts

Dual effect

3. Strontium

M.O.A

Both effects

1. Antiresorptive: Bisphosphonates

Class	Bisphosphonates Best treatment option	
	Nitrogenous Safer	Non-Nitrogenous Not used anymore (more adrs)
Drug	<ul style="list-style-type: none"> ● Alendronate (oral) ● Risedronate (oral) ● Ibandronate (oral) ● Zoledronate (I.V.) 	<ul style="list-style-type: none"> ● Etidronate ● Tiludronate ● Clodronate
M.O.A	<ul style="list-style-type: none"> ● Bisphosphonates are compounds made of two phosphate groups (PO_3) ● Structurally similar to pyrophosphate and works as: <ol style="list-style-type: none"> 1. Bind to calcium and concentrate in bones, bound to hydroxyapatite decreasing its solubility and make it more resistance to osteoclastic activity. 2. Prevent bone resorption by inhibit osteoclast function. (by inhibiting osteoclast maturation) <p>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.</p>	
P.k	<ul style="list-style-type: none"> ● Zoledronate (3rd generation) has the highest potency for osteoclast inhibition (most unsafe) ● Poorly absorbed (<10%), food impair absorption more so must be given on an empty stomach / infused IV ● $T_{1/2} = 1$ hr ● $\frac{1}{2}$ of absorbed drug accumulates in bones, remainder is excreted in urine ● In bones it is retained for months, depending on bone turnover 	

What's in red is enough

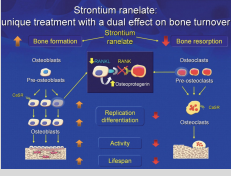
1. Antiresorptive: Bisphosphonates

Class	Bisphosphonates
Uses	<ul style="list-style-type: none"> ● Osteoporosis; secondary to menopause or long term glucocorticoids..etc ● Paget's Disease (excessive bone breakdown & bones are weak/brittle) ● Malignancy-associated hypercalcemia (because the drug keeps the calcium inside bones)
Dose	<ul style="list-style-type: none"> ● Once weekly or on two consecutive days each month ★ Should be taken in upright position and with a large amount of water to prevent esophagitis ● Should be given 4 hrs before having any Ca, Mg, Al containing drugs. <p>Note: Calcium and Vit D supplementation should be given after a gap from ingestion of bisphosphonates because it can inhibit their absorption (bind to calcium which will reduce their efficacy)</p>
★ADR	<ul style="list-style-type: none"> ● GIT irritation: nausea, vomiting, gastritis, Esophagitis*, ulceration → Drinking large amount of water to prevent the risk of tablet from getting stuck in esophagus. *Can lead to carcinogenic changes ● 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 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	<ul style="list-style-type: none"> ● Decreased renal function ● Peptic Ulcer ● Esophageal reflux

2. Antiresorptive: RANKL inhibitors

Drug	Denosumab (Still under investigations)
	A fully humanized monoclonal antibody that mimics the activity of osteoprotegerin (OPG)
M.O.A	<ul style="list-style-type: none"> ● 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 ● RANKL activity will be decreased → apoptosis of osteoclasts
P.k	Administered subcutaneously every 6 months, bone density doesn't change in a few days
Uses	Extremely expensive treatment reserved for patients who can't tolerate nor respond to bisphosphonates
ADRs	<ul style="list-style-type: none"> ● Respiratory and urinary infections ● Eczema and skin rash ● Pancreatitis
C.I	Patients with hypocalcemia , as denosumab decreases serum calcium concentration. Correct Ca and Vit D levels before starting the treatment

3. Antiresorptive + Bone Anabolic Agents (Dual effect)

Drug	Strontium	
	<ul style="list-style-type: none"> • Sr^{2+} is a divalent cation resembling Ca^{2+} in atomic and ionic properties 	
 <p>★ M.O.A</p> <p>Triple mechanism</p> <ul style="list-style-type: none"> • ↑ Osteoblast activity • ↑ OPG in osteoblasts • ↓ Osteoclast activity 	<ul style="list-style-type: none"> • 1st drug to possess a dual effect has both antiresorptive & anabolic effects, resulting in rebalance of bone turnover in favor of bone formation (Increase bone formation & decrease bone resorption) <p>Effects on Osteoblasts:</p> <ol style="list-style-type: none"> 1. Acts as an agonist on Ca Sensing Receptor [CaSR] → <u>enhances</u> differentiation of preosteoblast to osteoblast → ↑ bone formation 2. Stimulate the expression of OPG → increase RANKL binding → ↓ osteoclastogenesis → ↓ bone resorption <p>Effects on Osteoclasts:</p> <p>Acts as an agonist on CaSR → <u>suppress</u> differentiation of preosteoclast to osteoclast → ↑ osteoclast apoptosis → ↓ bone resorption</p>	
P.k	<ul style="list-style-type: none"> • Orally active as distronium with a modest bioavailability of 25% • Binds partially to plasma proteins and strongly to bones • $T_{1/2}$ = 60 hrs • Excreted mainly by the kidney 	
Uses	<ul style="list-style-type: none"> • Osteoporosis; secondary to menopause or glucocorticoids..etc • Malignancy-associated hypercalcemia 	
ADRs	<ul style="list-style-type: none"> • GIT irritation: nausea, vomiting, headache & eczema not serious - All resolve within the first 3 months 	
C.I	<ul style="list-style-type: none"> • Severe renal disease • Hypersensitivity to the drug (not specific) • Risk of venous thromboembolism (can't give it to immobilized person) • Phenylketonuria (inborn error on phenylalanine metabolism, the structure of the drug contains phenylalanine) 	
Interaction Precaution: 2hrs spacing	<ul style="list-style-type: none"> • Food containing milk (calcium) ± its products • Antacids • Oral Tetracycline and quinolones chelates it 	

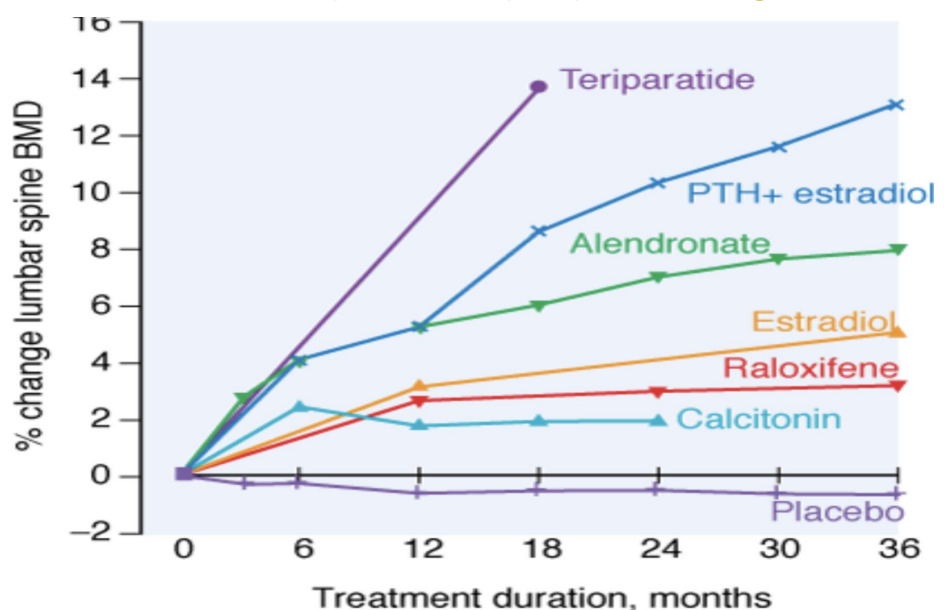
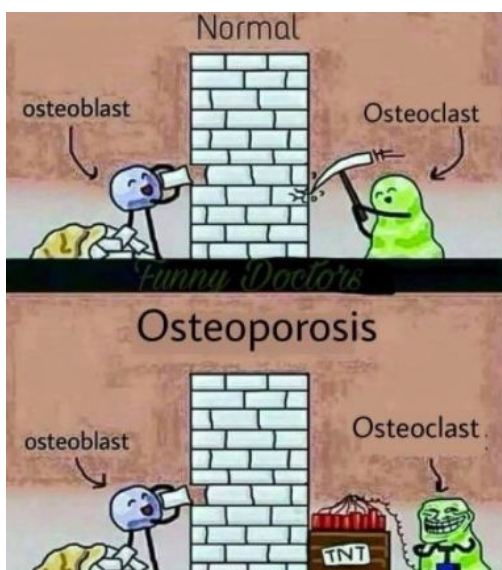
4. Sex Hormones

Class	Estrogen	Androgen
M.O.A	<ul style="list-style-type: none"> • <u>Estrogen in females and Androgens in males</u> are essential for normal bone remodeling: <ul style="list-style-type: none"> ○ ↑ 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 that helps to cause resorption 	
Uses	<ul style="list-style-type: none"> • Hysterectomy: use estrogen only (if the uterus was removed already, it is safe to give estrogen only) • If uterus is present: Estrogen + Progestin to protect the uterus • Hormonal Replacement therapy (HRT): menopausal symptoms • SERMs: Menopause/Elderly 	Elderly men
ADR	<p>These side effects will not be seen if the uterus was removed</p> <ul style="list-style-type: none"> • Vaginal bleeding • Risk for breast cancer • Venous thromboembolism 	

5. Selective Estrogen Receptor Modulators (SERMs)

Drug	Raloxifene						
	<ul style="list-style-type: none"> Raloxifene is the 1st SERM for prevention and treatment of osteoporosis 						
M.O.A	<ul style="list-style-type: none"> Anti-Estrogens that exhibits partial agonistic action Agonist in bones and Antagonist in female sex organs Works only on women especially post-menopausal women 						
Selectivity		Brain	Uterus	Vagina	Breast	Bone	CVS
	Estradiol	++	++ Cancerous	++ Cancerous	++ Cancerous	++	++ Cardio protective
	Raloxifene	-	-	-	-	+	+
Advantages	<ul style="list-style-type: none"> Even though it's efficacy is less than Estradiol, It is much safer because it only contains the good effects of Estradiol ↑ bone density by (2%) and ↓ fracture risk by (30%) (Good after menopause) 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	<ul style="list-style-type: none"> May ↑ hot flashes (sudden feeling of warmth in the upper body, which is usually most intense over the face, neck and chest) No effect on HDL 						

This picture is only for your knowledge



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

Summary

Class	Drug	M.O.A	Uses	ADRs
Bisphosphonates	<p>Nitrogenous: Alendronate, Ibandronate, Risedronate, Zoledronate</p> <p>&</p> <p>Non-Nitrogenous Etidronate, Clodronate, Tiludronate</p>	<p>1. Bind to calcium and concentrate in bones, bound to hydroxyapatite decreasing its solubility and make it more resistance to osteoclastic activity</p> <p>2. Prevent bone resorption by Inhibit osteoclast function</p>	<ul style="list-style-type: none"> - Osteoporosis - Paget's Disease - Malignancy-associated hypercalcemia 	<ul style="list-style-type: none"> - GIT irritation - GERD - Flu-like manifestation (IV) - Osteonecrosis of the of the mandible bone - Atrial fibrillation
RANKL inhibitors	Denosumab	<p>Mimics the activity of (OPG)</p> <p>★ Blocks RANKL from interacting with RANK receptor</p> <p>RANKL activity will be decreased → apoptosis of osteoclasts and decrease maturation</p>	Patients who can't tolerate nor respond to bisphosphonates	<ul style="list-style-type: none"> - Respiratory and urinary infections - Eczema and skin rash - Pancreatitis
Bone Anabolic Agents	Strontium	<p>Triple mechanism</p> <ul style="list-style-type: none"> ● ↑ Osteoblast activity ● ↑ OPG in osteoblasts ● ↓ Osteoclast activity 	<ul style="list-style-type: none"> - Osteoporosis - Malignancy-associated hypercalcemia 	<p>GIT irritation</p> <p>C.I:</p> <ul style="list-style-type: none"> - Venous thromboembolism - Phenylketonuria
Sex Hormones	Estrogen & Androgen	<ul style="list-style-type: none"> ○ ↑ osteoclast apoptosis and Inhibit osteoblast apoptosis ○ ↑ release of growth factors from osteoblasts ○ ↓ number and depth of resorption cavities ○ ↓ release of inflammatory cytokines causing resorption 	<p>Estrogen:</p> <ul style="list-style-type: none"> - Hysterectomy - If uterus is present: Estrogen + Progestin - HRT: menopausal symptoms - SERMs: Menopause/elderly <p>Androgen: Elderly men only</p>	<p>Estrogen:</p> <ul style="list-style-type: none"> ● Risk for breast cancer ● Vaginal bleeding ● Venous thromboembolism
Selective Estrogen Receptor Modulators (SERMs)	Raloxifene	<p>Anti-Estrogens acting as:</p> <ul style="list-style-type: none"> - Agonist in bone - Antagonist in some female sex organs 	post-menopausal women	<ul style="list-style-type: none"> ● May increase hot flashes ● No effect on HDL

MCQs

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

A- Ibandronate	B- Denosumab	C- Strontium	D- Raloxifene
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Q3: A patient presenting with uncorrected hypocalcemia, which of the following is contraindicated?

A- Alendronate	B- Denosumab	C- Strontium	D- Raloxifene
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Q4: A 56-Year-old woman presents complaining of feeling hot in the upper parts of her body, which of the following may be the cause?

A- Zoledronate	B- Denosumab	C- Strontium	D- Raloxifene
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Q5: Which of organ does Estradiol carry a protective effect over?

A- Breast	B- Uterus	C- CVS	D- Vagina
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Q6: Which of the following should be avoided with Strontium intake?

A- Amoxi-clav	B- Milk	C- Caffeine	D- ceftriaxone
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Q7: A 65-year-old female who has been diagnosed with postmenopausal osteoporosis. She has no history of fractures and no other pertinent medical conditions. Which of the following would be most appropriate for management of her osteoporosis?

A- Alendronate	B- Denosumab	C- Strontium	D- Estrogen
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Q8: A 52-year-old postmenopausal patient has evidence of low bone mineral density. 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- Hot flushes	B- Heart failure	C- vaginitis	D- breast cancer
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1	2	3	4	5	6	7	8
A	C	B	D	C	B	A	D

SAQ

Q1) Mentioned Drugs that work by inhibiting osteoclasts, activation osteoblasts.

Q2) Explain the mechanism of action of Strontium

Q3) How does the use of Estrogen for osteoporosis differs in the case of intact uterus? And what risk does it carry?

Q4) 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.

- A) Which is the drug of choice in her case ?
- B) What is the M.O.A of the drug ?
- C) List three uses
- D) List four Side effects

Answers

A1) [Slide. 4](#)

A2)

- Acts as an agonist on Ca Sensing Receptor [CaSR] → ↑ bone formation and ↓ bone resorption
- Stimulate the expression of OPG → ↓ bone resorption

A3) Add Progestin to protect the uterus, it increases risk of vaginal bleeding

4A) Bisphosphonates such as: Alendronate, Risedronate...

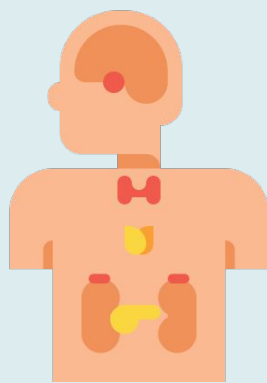
4B) Increase resistance to osteoclasts and inhibit osteoclasts signaling

4C) 1-paget's disease 2-Malignancy associated with hypercalcemia 3-Osteoporosis; secondary to menopause or glucocorticoids

4D) 1-atrial fibrillation 2- fever 3- vomiting 4- nausea



Feedback Form



Endocrine Block

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