Endocrine System

PHARMACOLOGY 432 TEAM

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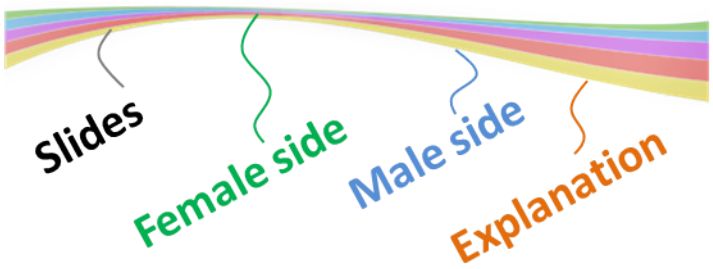
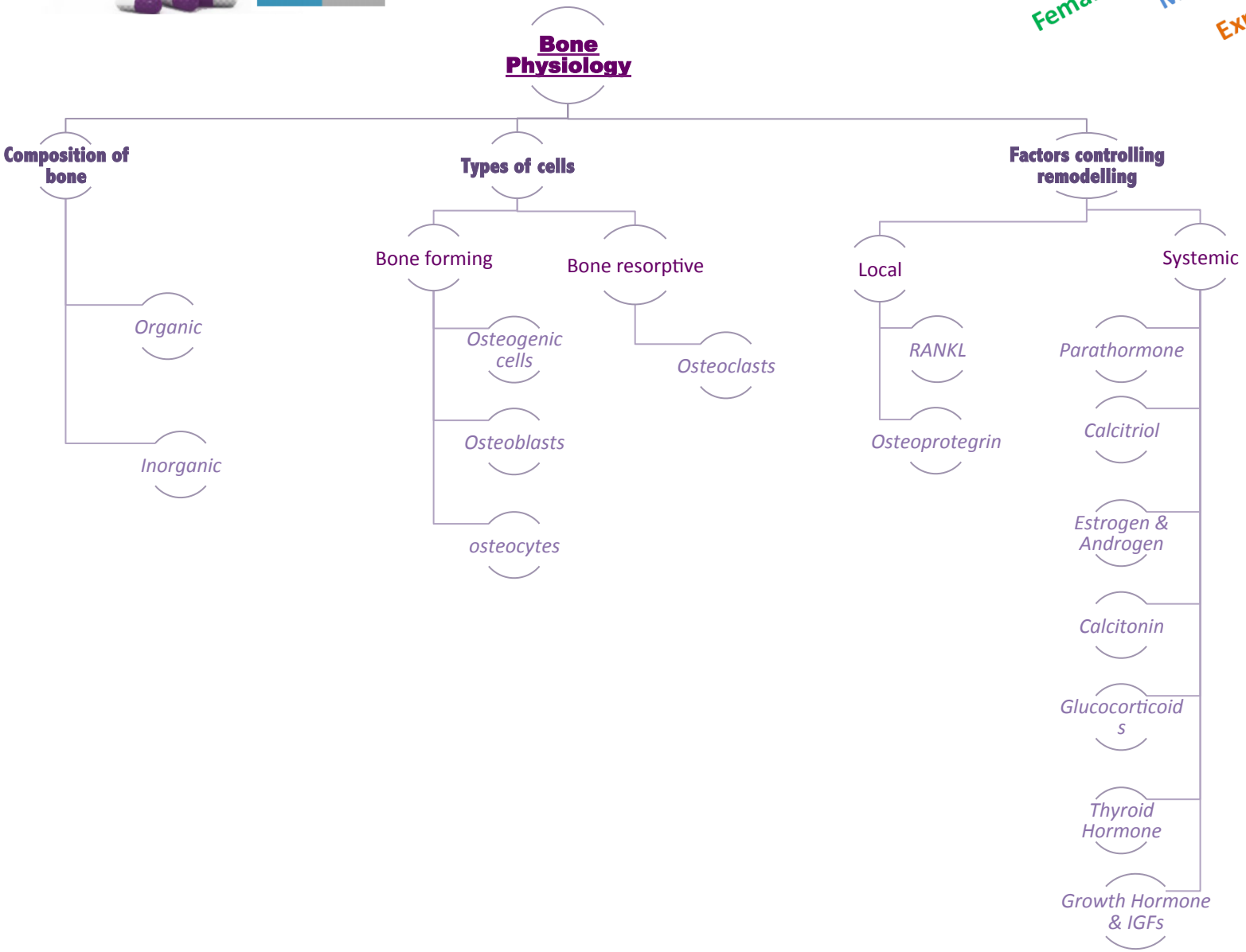
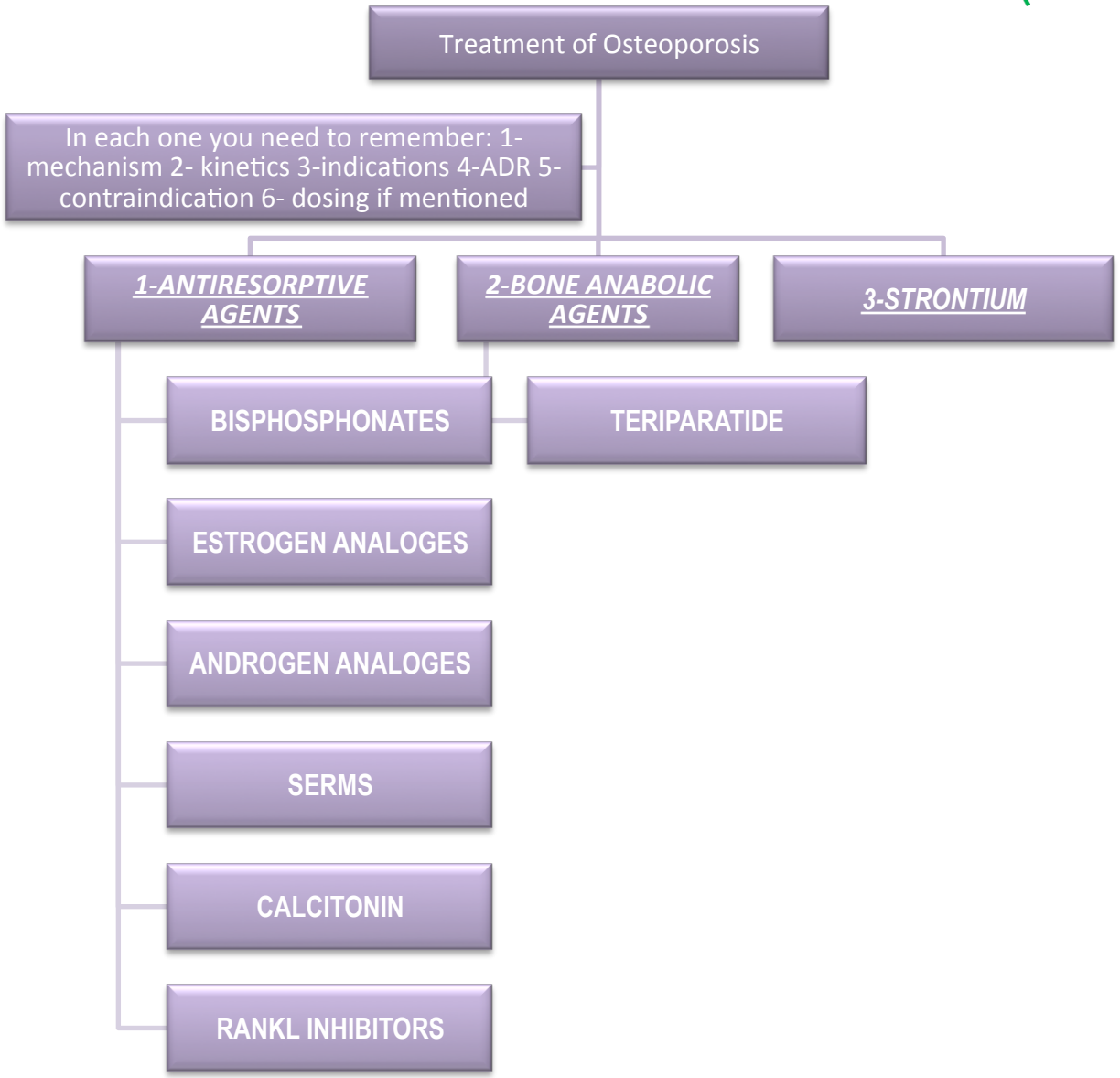


TREATMENT OF OSTEOPOROSIS

Learning Objectives:

1. Revise the composition, regulation & the remodeling stages of bone turnover
2. Recognize the interlinks of osteoblastic & osteoclastic function
3. Relate changes to the development of osteoporosis
4. Classify drugs according to their replacement, antiresorptive or anabolic mechanism of action
5. Detail the pharmacology of such group of drugs& their clinical utility in combating osteoporosis


Bone Physiology
Composition of bone
Organic
Inorganic
Types of cells
Bone forming
Osteogenic cells
Osteoblasts
osteocytes
Bone resorptive
Osteoclasts
Factors controlling remodelling
Local
RANKL
Osteoprotegrin
Systemic
Parathormone
Calcitriol
Estrogen & Androgen
Calcitonin
Glucocorticoids
Thyroid Hormone
Growth Hormone & IGFs


Treatment of Osteoporosis
In each one you need to remember: 1- mechanism 2- kinetics 3-indications 4-ADR 5- contraindication 6- dosing if mentioned
1-ANTIRESORPTIVE AGENTS
2-BONE ANABOLIC AGENTS
3-STRONTIUM
BISPHOSPHONATES
TERIPARATIDE
ESTROGEN ANALOGES
ANDROGEN ANALOGES
SERMS
CALCITONIN
RANKL INHIBITORS

Physiology
(not important)

Slides | Female side | Male side | Explanation

BONE IS COMPOSED OF 2 TYPES OF TISSUE:

Inorganic

- **65%** of mass
- **Consists of:** •Hydroxyapatite •Calcium •Phosphorus salts
- Formed during **osteogenesis** by **mineralization** of the organic matrix (osteoid Frame work) & is mediated by alkaline phosphatase

Organic

- **35%** of mass
- **Consists of**
  - Organic matrix [OSTEOID]➜ produced by **osteoblasts** ➜it is the Bone Framework (it is formed first then the inorganic tissue is added to it)
  - Bone cells are either: •Bone Forming or •Bone Resorptive

BONE CELLS (IN ORGANIC TISSUE) ARE 2 TYPES:

Bone Forming Cells

- **Osteogenic cells** ➜ mesenchymal in origin ➜ are progenitor of blasts & cytes ➜ are found on all bone surfaces
- **Osteoblasts** ➜ forms osteoid framework & help in its mineralization
- **Osteocytes** (formed from osteoblasts)➜ sense mechanical stress ➜ signals to both blasts & clasts (during the day we get microfractures in our bones. Osteocytes sense them and promote remodeling to fix them)

Bone Resorptive Cells

- **Osteoclasts** ➜ myeloid in origin ➜ made by *fusion of multiple progenitors of monocytes.*
- Reside in pits (resorption bays) that form by eaten bone surface. Secretes lysosomal enzymes from its ruffled edges (collagenase & metalloproteinase) + hydrochloric acid ➜ dissolve bone matrix

BONE REMODELING

Normally bone is continuously formed and resorbed
Must be balanced (Formation = Resorption)

Remodeling is 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 in repair of microdamage & microcracks

It occurs at periosteal and endosteal surfaces

The process takes around 6 months (insidious) (so any drug will take a long time to show improvement)

(1) LOCAL FACTORS DRIVING REMODELING

- **RANKL RANK Ligand (Ligand that attaches to RANK receptor)**
- **Osteoprotegrin (OPG)**

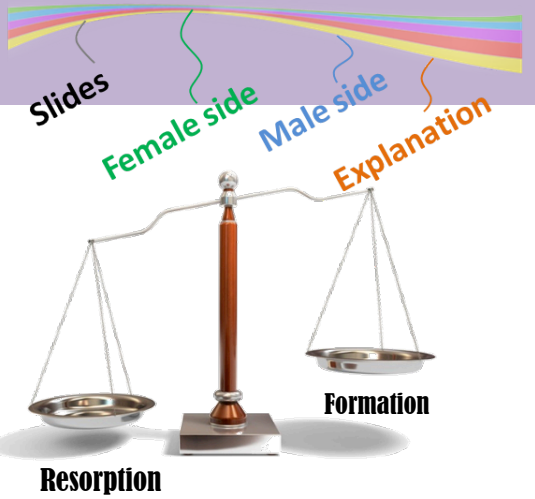
Mechanism: When the osteoblasts are activated and start forming bone they secrete local factors like RANKL as well as OPG. Normally these two are secreted at an equal rate and bind to each other so that RANKL doesn't reach its receptor. If at a later stage when the osteoblast has formed enough bone it decreases OPG formation so RANKL reaches its receptor on osteoclasts causing their maturation and stimulates bone resorption.

Physiology (not important)
Not concerned with this lecture

(2) SYSTEMIC HORMONES CONTROLLING REMODELING

1) PARATHROMONE	➔Maintains calcium homeostasis via ↑ bone formation (intermittent) /↑ bone resorption (continuous) ↑renal tubular calcium reabsorption ↑ renal calcitriol production
2) CALCIRIOL	↑ intestinal Ca & phosphorus absorption➔ ↑bone mineralization ≤ bone resorption when they are deficient
3) ESTROGEN & ANDROGEN	↓rate of bone loss by acting on many local factors ↑ osteoclast apoptosis & growth factors from osteoblasts ↓No. & depth of resorption cavities & release of cytokines
4) CALCITONIN	Not much physiological role in man Pharmacologically➔ ↑osteoclasts & bone resorption
5) GLUCOCORTICOIDS	↑apoptosis of osteoblasts & osteocytes➔ ↑resorption
6) THYROID HORMONE	↑Bone turn-over i.e. resorption & formation
7) GROWTH HORMONE & IGFS	↑ skeletal growth & endochondral bone formation.

Pathology
(not important)



OSTEOPOROSIS

- A complex endocrinologic disorder of bone & mineral metabolism
- Resorption > formation ➔ low bone mass➔ Disruption of bone architecture➔ Reduced bone strength➔ Risk of fractures
- Female > Males
- Bone mass decreases greatly after menopause
- Causes pathological fractures

CAUSES OF OSTEOPOROSIS

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

TREATMENT OF OSTEOPOROSIS (aim of treatment)

- **Replace what is missing: (because you can't start therapy before this step)**

Ca,
Vit D
Na fluoride : ***Used to enhance the strength by the formation of fluorapatite.***
Is considered only when trabecular bone is ↓ in presence of normal cortical bones
(In dental hygiene it plays an important role in the prevention if cracking and fissuring of the teeth)

- **Reset back the balance of remodeling (to its normal physiological state) via :**

1-ANTIRESORPTIVE AGENTS

BISPHOSPHONATES

ESTROGEN ANALOGES : converted to estrogen in the body and has cardio protective function along with bone formation

ANDROGEN ANALOGES

SERMS : (selective estrogen receptor modulation) , is a modified estrogen where it will selectively work on the bone and the CNS without producing its feminizing features and so can be used on both male and female patients

CALCITONIN : a hormone that decrease s bone resorbtion

RANKL INHIBITORS : works as OPG and prevents the RANKL from binding to its receptors in the osteoclast

3-STRONTIUM
(Has dual effect of both 1,2)

2-BONE ANABOLIC AGENTS
TERIPARATIDE (para-thormone derivative)

- ***Others: not as main therapy***

Thiazide diuretics : its ADR is to produce hyper-calcemia , which is in a way good for the bone
Statins : decreases bone resorbtion

and so its expected that people who are taking these drugs wont develop osteoporosis on the long run , but its not definite

BISPHOSPHONATES

BISPHOSPHONATES : Are compounds that have two phosphonate (PO_3) groups
(since phosphates are highly concentrated in the bone this drug will have a direct effect on the bone)

Categories

A-Non-Nitrogenous (old therapy)	B-Nitrogenous
Etidronate	Alendronate (500) (potent)
Clodronate (10)	Ibandronate (1000)
Tildronate (10)	Risedronate (2000) (higher potency)
	Zoledronate(10000) (highest potency)
	N.B (Dr. said what's in red is most important)

Kinatics :

Poorly abs (< 10%), food impair absorption more ➔ must be given on an empty stomach./infused IV.t1/2 1 hr.
Half of absorbed drug accumulates in bones (a good thing)remainder➔excreted unchanged in urine (the part that didn't bind to bone)
In bone it is retained for months(another good effect since the healing process of the bone takes months), depending on bone turnover

Indications :

- Osteoporosis, 2ndry to menopause, glucocorticoids, ….
- Paget's Disease(a disease of abnormal bone remodeling where there is excess deposition of the bone , in a way giving bone feature s resembling acromegaly)
- Malignancy- associated hypercalcaemia (a state by which bony lyses is increased and therapy will decrease this effect an so it will decrease the pathological fractures)

Dosing :

In oral **Alendronate** :Once weekly, or on two consecutive days each month ,Taken 1st thing in Moring with ½ glass of water, on empty stomach then nothing taken after for ½ hr.
Should be taken in upright position.(to avoid the GERD (an ADR caused by the drug)
Separate 4 hrs before giving Ca, Mg, Al containing drugs (also laban)
Laban combine with Ca+PO4 in the stomach
In case of IV **Risedronate , Zoledronate :** 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. (should be given slowly otherwise severe irritation would happen (zoledronate has more ADR effect)

BISPHOSPHONATES

Mechanism:

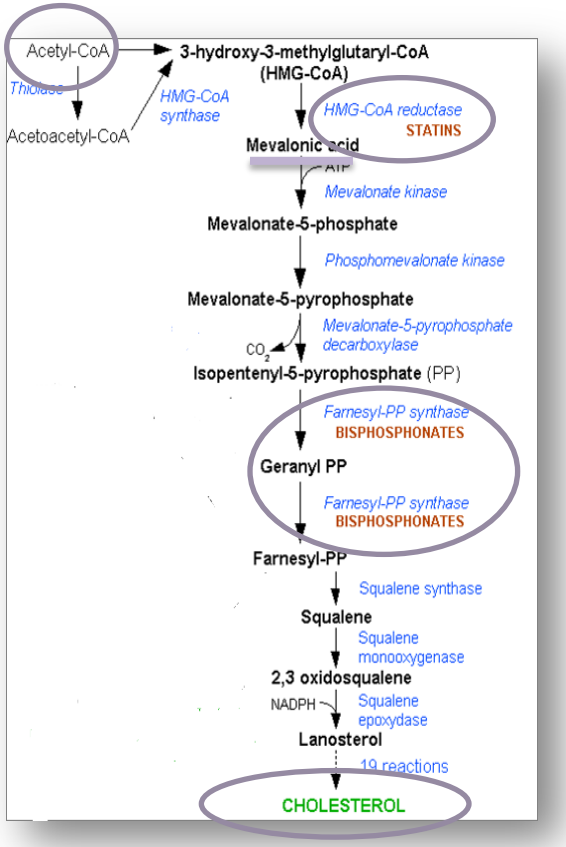
-Are structurally similar to pyrophosphate, thereby inhibiting activation of enzymes that utilize it.

They preferentially "stick" to calcium ➔ concentrate in bones, bound to hydroxapatite.

They prevent bone resorption by inhibiting osteoclast function.

Their relative potencies for osteoclast inhibition is the most with 3rd generation "Zoledronate"

How do they inhibit osteoclasts??? ➔ It is taken up during osteoclast resorptive activity ➔ blocks steps in cholestrol synthetic pathway that act as signaling molecules responsible for the osteoclastic hydrolytic & phagocytic activity →Stop function → within osteoclast ➔ end up by osteoclast apoptosis (this is basically what she wants from the picture)



N.B : picture explanation

- Within the osteoclast Acetyl-CoA is required to produce cholesterol . As the process goes on you'll notice that there are a lot of phosphates ,the drug can inhibit the pyrophosphate that is needed to form prenylated smallGP (a signaling molecule found in our body and is important for mobilization) and thus inhibit osteoclast signaling , so the osteoclast will no longer be able to form pseudopodia , it will feel hopeless and kill itself)
- Mevalonic acid is the rate limiting step
- Statins can block this pathway at an earlier step , however they are non selective in their action

BISPHOSPHONATES

ADR

- GIT irritation; nausea, vomiting, gastritis , ulceration ➜ to avoid give large amount of water
- Gastro-esophageal reflux + ulcerations ➜ to avoid give on empty stomach while sitting in upright
- Flue like manifestations upon IV infusion
- Osteo-necrosis of the jaw [mandible > jaw] more upon long use (8,9 years)with IV infusion preparation usually after dental surgical procedures. It is due to activation of matrix metalloproteinase that cause lysis (to avoid this we should put the patient on IV then Oral therapy) especially by liso /zoli/rirodronate)
- Atrial fibrillation > (not common) women with alendronate & zolidronate (thus give the drug parentally, slow IV,to avoid irritations)

Contraindications

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

RANKL inhibitors (DENOSUMAB):

It is a fully human MOA (monoclonal antibodies)so expensive therapy that mimics the activity of osteoprotegrin

Mechanism of Action:	Administration:	contraindication
•It binds to RANKL, expressed by osteoblasts → -ve RANKL from interacting with RANK expressed on preosteoclasts → **decrease osteoclastogenesis (no mature osteoclasts).** •It binds also to mature osteoclast → Increase its apoptosis So net effect → decrease bone resorption. Inhibit osteoclastogenesis	Subcutaneous every 6 month	•In patients with hypocalcaemia. •Correct Ca & Vit D levels before starting denosumab

ADRs:	•Infections; urinary & respiratory. increase infections thresold since it's a monoclonal antibody •Eczema & skin rash •Constipation •Cataract •Joint pains due to immune reactions

STRONTIUM:

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

Mechanism of action:	Pharmacokinetics :	Indications:
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](work like+replace Ca) ; which is a GP coupled receptor that enhances differentiation of preoteoblast to osteoblast→increase bone formation. It stimulate the expression of OPG→increase RANKL binding→ -ve of osteo-clustogenesis →reduce bone resorption **On osteoclast:** Acts as agonist on Ca Sensing Receptor [CaSP]→suppress differentiation of preoteoclast to osteoclast → increase osteoclast apoptosis → reducing bone resorption	•Orally with a modest bioavailability→25% •Binds partially to plasma proteins and strongly to bones • t ½ → 60 hrs • Excreted mainly by the kidney	•Osteoporosis , 2ndry to menopause, glucocorticoids, …. •Malignancy-associated hypercalcaemia

STRONTIUM

Contraindication:	Interactions:	ARDs:
•In severe renal disease. •In hypersensitivity to it •In increased risk of venous thromboembolism •In phenylketonuria	•Food specially containing milk+ its products •Antacids •Oral tetracycline & quinolones chelate it(cuz it antagonizes the drug effect) Precaution; 2hrs spacing to make sure they're fully absorbed	•GIT irritation; nausea, vomiting, headache, eczema •All resolve in 1st 3 months

Other drugs;

• **Estrogens**; in case of If hystrectomy (no uterus) or given with progestins if uterus present (estrogen increases the risk for breast cancer+endometruim cancer in menopausal women so pregestins must be coadministred, also causes depression + hot flushes

•**HRT** (hormone replacing therapy); menopausal symptoms e.g. flushing (estrogen +progestrone)

• **SERMs**; menopause or elderly

• **Androgens;** for elderly men

• Estrogen in females & Androgen in males is essential for normal bone remodeling;

-increase osteoclast apoptosis

-decrease No. & depth of resorption cavities

-increase release of growth factors from osteoblasts

-decrease release of inflammatory cytokines causing resorption

SERMs (RALOXIFENE)

- 1st selective estrogen Receptor modulator for prevention of osteoporosis
- Antiestrogens that exhibits partial agonistic action; acting as an **agonist in bone** & an **antagonist** in some **female sex organs.** It decreases bone resorption in males & females and has no effect on sex organs.
- Safe in all patients except those who have tendency to thromboembolic events,
- Ralofexine has effect on Bone and CVS only in contrast to estradiol which has effect on brain,uterus,vagina,breat,bone and CVS

Advantages:

- Increase bone density (2%) & reduce fracture risk (30%)
- No stimulation of breast or endometrial tissue
- No need for progestin in women with uterus
- Decrease LDL

Disadvantages:

- High risk of thromboembolic events like storntium
- Doesn't treat well Post-menopausal Symptoms
- May casue hot flushes
- No effect on HDL

Drug	Bisphosphonates	RANKL inhibitors	sirtonium	SERMs
Mechanism of action	similar to pyrophosphate	Inhibits osteoclastogenesis.	It has dual action. Increase bone formation and decrease resoprtion	Antiestrogens it acts as agonist on bones, antagonist on sex organs
Contraindication	•Decreased renal function •Peptic ulcer / esophageal reflux	In patients with hypocalcaemia	In severe renal disease. In hypersensitivity to it In increased risk of venous thromboembolism, In phenylketonuria	
Precaution/ interaction	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. Separate 4 hrs before giving Ca, Mg, Al containing drugs		Interacts with food containing milk products, antacids, tetracyclines & quinulols	
ADRs	GI irritation, GERD, flu-like manifestation, osteonecrosis, AF	Infection,rashes, joint pain, cataract, constipation	GIT irritation headache, eczema	thrombolotic events, hot flushes

Questions

Q1-A 29-year-old female was diagnosed with ovarian cancer 2 years ago and did a hysterectomy. Which one of the following drugs would you put her on;

A. Estrogen
B. Hormone replacing therapy
C. Zolidronate

Q2-In the previous case , If uterus is present which drug should be co-administred to prevent endometrial cancer?

A. Androgens
B. Progestins
C. Strontuim

Q3-A 63-year-old male was diagnosed with chronic renal failure 1 year ago. Which one of the following drug is contraindicated in such a case:

A. RALOXIFENE
B. Sintorium

Answers:1- A 2-B 3-B

Q4-if a female was known to have osteoporosis , yet she has a history of peptic ulcer, which one of the following therapies should be avoided ?

A. A- zolidronate
B. B- STRONTIUM
C. C-SERMS
D. D-CALCITONIN

Q5-55 years old male was diagnosed with cancer associated hypercalcemia, the doctor put him on Strontuim ,but the patient still complains from bone aches, which drug interaction causes that?

A. Ralofexine
B. Calcitonin
C. Tetracycline

Q6-An osteoporotic patient has undergone tooth extraction, he developed jaw necrosis after the IV therapy of his drug ,Which drug causes that?

A. Denosumab
B. SERMS
C. Risedronate

Answers: 4-A 5-C 6-C

Q7- Denosumab is used in the treatment of osteoporosis because:

A- it inhibits the maturation of osteoclasts
B- it promotes the maturation of osteoblasts
C- it promotes the apoptosis of osteoclasts
D- A&C

Q8- Denosumab should not be used in patients with ..... except after the correction of the levels :

A) High Ca
B) Low Ca
C) High Vit D

Answers: 7-D 8-B

Endocrine System

PHARMACOLOGY 432 TEAM

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