King Saud University

College of Medicine

2nd Year, Endocrine Block

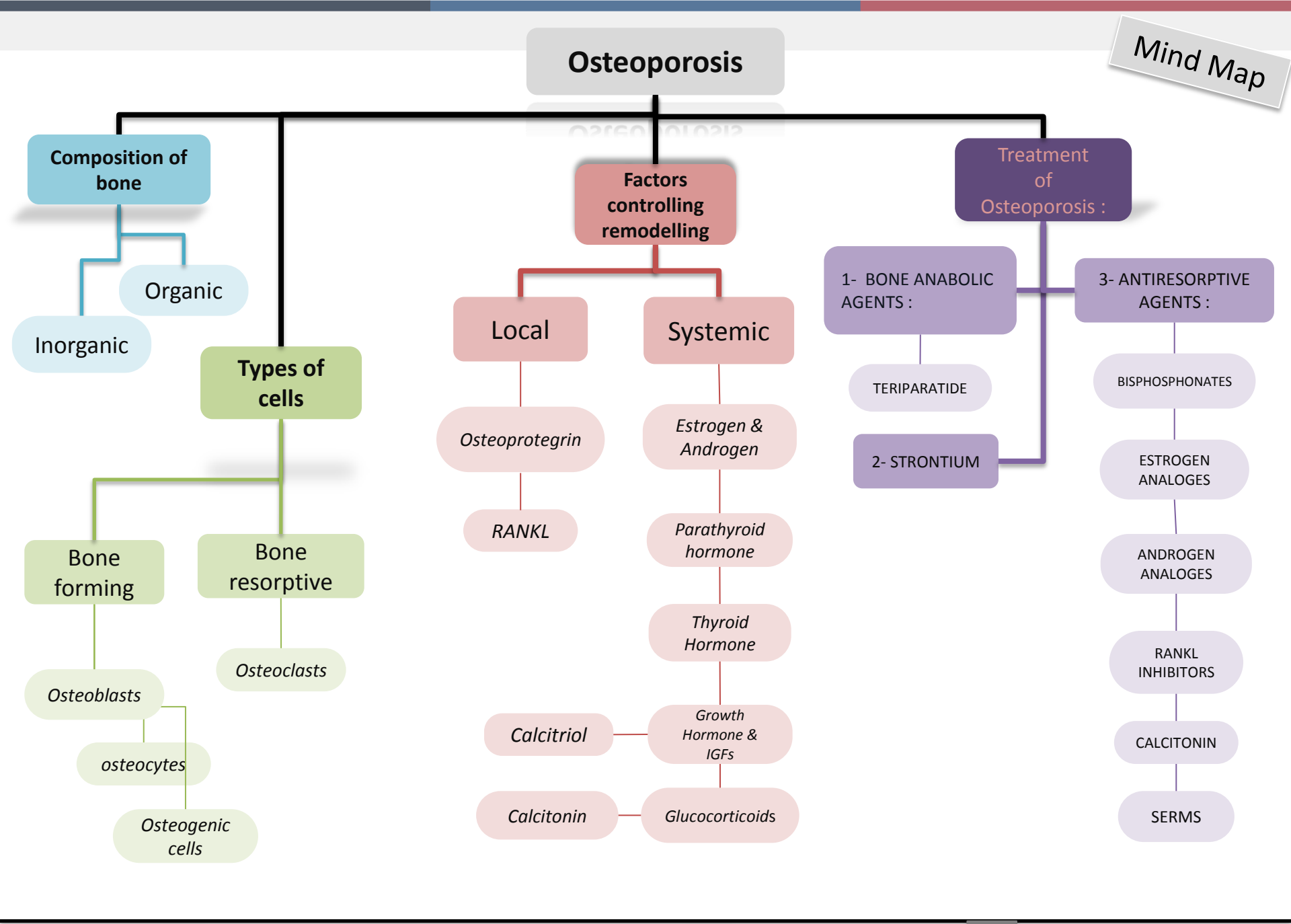
PHARMACOLOGY 433

MED 433 Teams

L3-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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INTRODUCTION

Bone is basically composed of 2 types of tissues:

1. **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.**
2. **Organic: 35% of mass. Consists of:**
   - **Organic matrix [OSTEOID] → produced by osteoblasts → Bone Framework.**
   - **Bone cells are either; Bone Forming or Bone Resorptive**

A. 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: sense mechanical stress → signals to both blasts & clasts**

B. Bone Resorptive Cell:

- **Osteoclastes: myloid in origin → made by fusion of multiple progenitors of monocytes.**
- **Reside in pits (resorption bays) that form by eaten bone surface. Secretes lysosomal enzymes (collagenase & metalloproteinase) + hydrochloric a. → dissolve bone matrix.**

INTRODUCTION

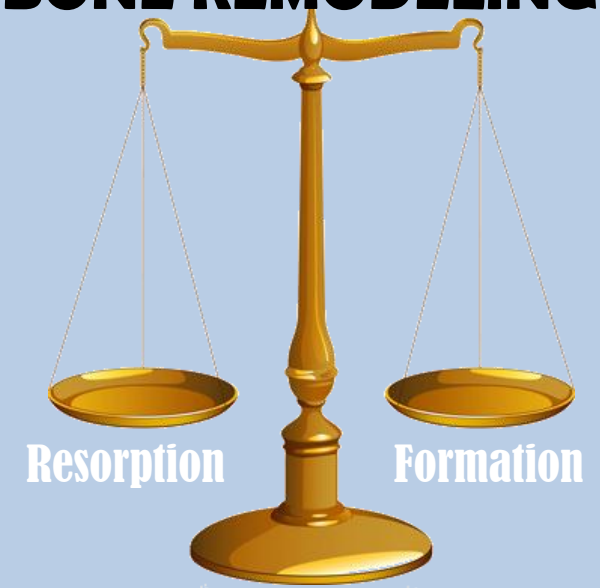
NORMALLY bones continuously form & resorb → BONE REMODELING

- **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.**

Systemic Hormones Controlling Remodeling:

1. **PARATHORMONE: Maintains calcium homeostasis via**
   ↑ bone formation (intermittent) / ↑ bone resorption (continuous)
   ↑ renal tubular calcium reabsorption
   ↑ renal calcitriol production
2. **CALCITROL:**
   ↑ intestinal Ca & phosphorus absorption → ↑ bone mineralization
   ↑ bone resorption when they are deficient
3. **ESTROGEN & ANDROGEN: ↓ Resorption 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. **CLUCOCORTICOIDS: ↑ apoptosis of osteoblasts & osteocytes → ↑ resorption**
6. **THYROID HORMONE: ↑ Bone turn-over i.e. resorption & formation**
7. **Growth Hormone & IGFs: ↑ skeletal growth & endochondral bone formation.**

BONE REMODELING

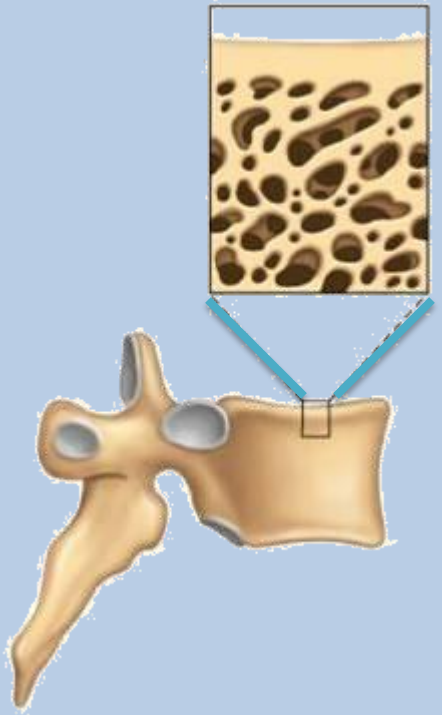


OSTEOPOROSIS

A complex endocrinologic disorder of bone & mineral metabolism (bone resorption > formation)

Low bone mass
Disruption of bone architecture

Reduced bone strength
Risk of fractures



INTRODUCTION

Osteoporosis Risk Factors

Modifiable

- Current cigarette smoking
- Diet low in calcium/vitamin D
- Glucocorticoids, anticonvulsants
- Excessive alcohol intake
- Sedentary lifestyle
- Body weight less than 127 lb
- Lack of estrogen
- Environmental risks
- Poor eyesight
- History of organ transplants

Non-modifiable

- Personal history of fracture
- 1st-degree relative has fracture
- Race (Caucasian or Asian)
- Elderly age
- Poor health
- Dementia
- Hormonal disorders
- Neoplastic disorders
- Metabolic abnormalities
- Connective tissue disorders

TREATMENT OF OSTEOPOROSIS

In treatment of osteoporosis we need to do two things :

1\ replace what is missed (we start with it but it is never enough, we mostly use them as a prophylactic).

2\ Reset the balance of remodeling (increase the formation and decrease the reabsorption).

The drugs we use for reset the balance are either Antiresorptive agents or Anabolic agents (increase bone formation). " we have only one drug" **STRONTIUM**" has dull effect which do the two actions together".

We have drugs which have permissive effect on treatment such as ***Thiazide diuretics, statins***. *(but we don't use them for treatment !)*.

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

Fluorapatite;

To ↑ trabecular bone when it ↓ in presence of normal cortical bones

2. Reset back the balance of remodeling

Anti-resorptive Agents

- 1-Bisphosphonates
- 2-Rankl Inhibitors
- 3-Strontium
- 4-Androgen Analoges
- 5-Estrogen Analoge
- 6-Serms
- 6-Calcitonin

Bone Anabolic Agents

- Teriparatide
- Strontium

1- BISPHOSPHONATES

Are compounds that have two phosphonate (PO3) groups.

- **Non-Nitrogenous:**
  Etidronate, Clodronate (10), Tildronate (10)
- **Nitrogenous: (available in markets)**
  Alendronate (500), Ibandronate (1000), Risedronate (2000), Zoledronate (10000)

The nitrogenous are the ones existent in the markets now so the non-nitrogenous are not that important

Mechanism of Action:*Prevent the action of Pyrophosphate*

- **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"**
- **BLOCK STEPS IN CHOLESTROL SYNTHETIC PATHWAY IN OSTEOCLAST that act as signaling molecules responsible for the osteoclastic hydrolytic & phagocytic activity → (Stop function → apoptosis).**
- **How do they inhibit osteoclasts? It is taken up during osteoclast resorptive activity → blocks steps in cholestrol synthetic pathway within osteoclast → end up by osteoclast apoptosis**

You Have to know that they are different in potency !! And the strongest the ones gevin I.V or I.M and the oral are the weaker. (Dr.Omnia said you may be asked about this).

slide | doctor's note | important | explanation

1-BISPHOSPHONATES

Kinetics	- **Poorly absorbed (< 10%), food impair absorption more → must be given on an empty stomach. / infused IV. *Food decreases it's absorption that's why the new preparations are given I.V*** - **t1/2 1 hr.** - **Half of absorbed drug accumulates in bones, remainder → excreted unchanged in urine.** - **In bone it is retained for months "or even years" , depending on bone turnover**
Indications	- Osteoporosis, 2ndry to menopause, glucocorticoids. - Paget's Disease - Malignancy- associated hypercalcaemia
Dosing	- **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 - 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.
ADRs	1. GIT irritation; nausea, vomiting, gastritis , ulceration to avoid **give large amount of water** 2. **Gastro-esophageal reflux + ulcerations** to avoid give on empty stomach while sitting in upright 3. Flue like manifestations upon IV infusion 4. Osteo-necrosis of the jaw [mandible > jaw] more upon long use with IV infusion preparation usually after dental surgical procedures. It is due to activation of matrix metalloproteinase that cause lysis. 5. Atrial fibrillation > women with alendronate & zolidronate***Rare ADRs and to prevent this we start first with I.V drugs than we switch to the Oral preparations.*** *
Contra-indications	**Decreased renal function** **Peptic ulcer / esophageal reflux**

The indications are almost the same in all the drugs in this lecture but the variations are in the the patient himself (ex. Patient's age)

الاختلاف كون في استجابة المريض وقابليته للعلاج حسب عمره وظروفه الصحية الأخرى «غير هشاشة العظام»

2-RANKL INHIBITORS (DENOSUMAB)

It is a fully human MOA that mimics the activity of osteoprotegrin.	
Mechanism of Action	- It binds to RANKL, expressed by osteoblasts → -ve RANKL from interacting with RANK expressed on preosteoclasts → osteoclastogenesis (no mature osteoclasts). - It binds also to mature osteoclast → its apoptosis Net effect: prevent bone resorption .
Administration	Subcutaneous every 6 month
Contraindications	In patients with hypocalcemia. (Correct Ca & Vit D levels before starting denosumab) *And it will activate TB if the patient had it before so we try to avoid giving it to TB patients.*
ADRs	- Infections: urinary & respiratory - Eczema & skin rash - Constipation - Cataract - Joint pains

3-STRONTIUM

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

Mechanism of Action:

1st drug to possess (dual action) i.e has both anabolic & antiresor-ptive effects resulting in a rebalance in favor of bone formation.

On Osteoblast

- Like Ca, it is an agonist on Ca Sensing Receptor [CaSR]; that ↑ differentiation of pre-oteoblast to osteoblast → ↑ bone formation.
- It stimulate expression of OPG → ↑ RANKL binding and inhibit RANKL activity → -ve of osteo-clustogenesis → ↓ bone resorption.

On Osteoclast

- Agonist on Ca Sensing Receptor [CaSP] →↓differentiation of pre-oteoclast to osteoclast →↑ osteoclast apoptosis →↓ bone resorption

سبحان الله

The Ca Sensing Receptor are exist in the Osteoblast and Osteoclast and the drug works on them both but it will give different results in both of them .. It will stimulates the osteoblast and inhibits the osteoclast . (same recepter and same drug but different results on different cells) .

3-STRONTIUM

Pharmacokinetics	- Orally with a modest bioavailability → 25% - Binds partially to plasma proteins and strongly to bones - t ½ → 60 hrs - Excreted mainly by the kidney
Indications	- SEVER osteoporosis in Elderly , 2ndry to menopause, glucocorticoids - Malignancy- associated hypercalcaemia
Contraindications	• In severe renal disease. • In hypersensitivity to it • In increased risk of thromboembolism & MI • In phenylketonuria
Interactions	- Food specially containing milk+ its products - Antacids - Oral tetracycline & quinolones chelate it Therefore, 2 hrs spacing for precautions
ADRs	MI *myocardial infarction* GIT irritation, headache, eczema resolve in 1st 3 months

slide doctor's note important explanation

4&5 ANDROGEN &ESTROGEN ANALOGE

In females:

1-Estrogen:

- **In fertile period if hystrectomy.** (young female without uterus and her body doesn't produce Estrogen we give Estrogen alone).
- **With progestins if uterus is present.** (young female with uterus and her body doesn't produce Estrogen we give Estrogen + progestins).

2-Hormone Replacement Therapy (HRT):

- **At Menopause, if menopausal Symptoms present** (for example, hot flashes)

3-SERMs "Selective Estrogen Receptor Modulators" :

- **Menopause /Elderly** *We use it mainly with Elderly men*

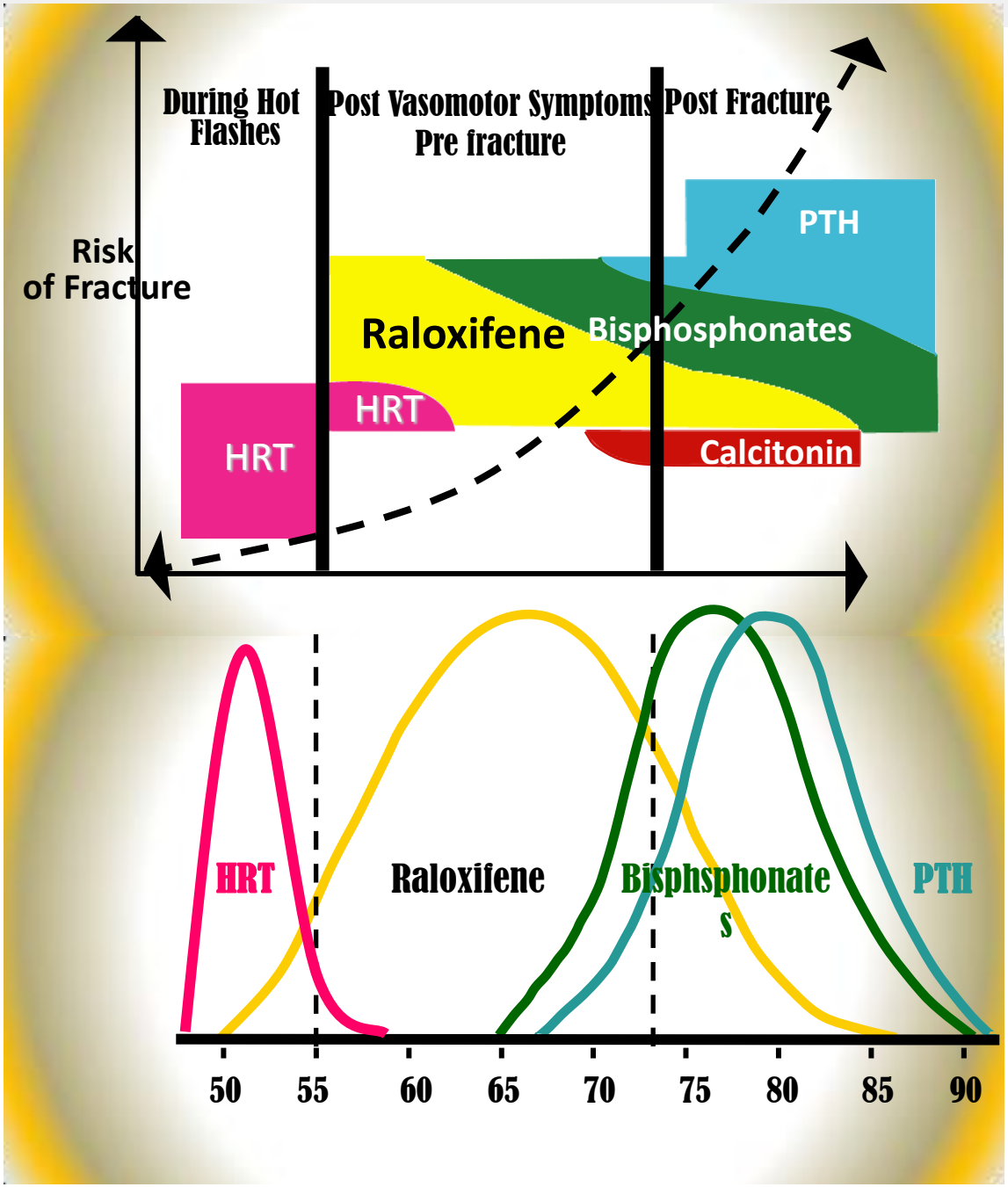
In elderly males:

1-Androgen

Estrogen in females & **Androgen** in males is essential for **normal bone remodeling.** By:

- ↑ osteoclast apoptosis
- ↓ No. & depth of resorption cavities
- ↑ release of growth factors from osteoblasts
- ↓ release of inflammatory cytokines causing resorption

slide | doctor's note | important | explanation


During Hot Flashes
Post Vasomotor Symptoms Pre fracture
Post Fracture
Risk of Fracture
PTH
Raloxifene
Bisphosphonates
HRT
HRT
Calcitonin
HRT
Raloxifene
Bisphsphonates
PTH
50
55
60
65
70
75
80
85
90

6-SERMS (RALOXIFENE)

-1st selective estrogen R modulator for prevention of osteoporosis.

-Mechanism of Action: *It only works on Bone and treat osteoporosis. It doesn't treat other Post Menopausal symptoms.*

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

	Brain	Uterus	Vagina	Breast	Bone	CVS
Estradiol	++	++	++	++	++	++
Raloxifene better than estradiol	—	—	—	—	+	+

Advantages	- ↑ bone density (2%) & ↓ fracture risk (30%) - No stimulation of breast or endometrial tissue - No need for progestin in women with uterus - ↓ LDL
Disadvantages	- ↑ risk of thromboembolic events - Doesn't treat well Post-menopausal Symptoms - May ↑ hot flushes - No effect on HDL

SUMMARY

SYSTEMIC HORMONES Controlling Remodeling	
HORMONE	FUNCTION
1- parathormone	Maintain Ca homeostasis , ↑ renal ca reabsorption , ↑ bone formation , ↑ calcitriol .
2- calcitrol	↑ intestinal Ca & phosphorus absorption
3-estrogen & androgen	↑ osteoclast apoptosis & growth factors from osteoblasts ↓ No. & depth of resorption cavities & release of cytokines
4-calcitonin	Dec. osteoclasts & bone resorption
5- glucocorticoids	↑ apoptosis of osteoblasts & osteocytes → ↑ resorption ↑ differentiation of osteoblasts → ↑ formation
6- thyroid hormone	↑ resorption & formation

SUMMARY

Drug	therapeutic use	Adverse effect	Comment
1-Bisphosponate	1-Osteoporosis, 2ndry to menopause, glucocorticoids, …. 2- Paget's Disease Malignancy- associated 3-hypercalcaemia	1-Gastro-esophageal reflux 2-Flue like manifestations upon IV infusion 3-Osteo-necrosis of the jaw 4-Atrial fibrillation	Contraindicated in : 1-Decreased renal function 2- Peptic ulcer / esophageal reflux
2-RANKL inhibitors "denosumab"	-	1-urinary & respiratory 2- Eczema & skin rash 3- Constipation 4- Cataract 5- Joint pains	Contraindicated In: patients with hypocalcemia.
3- storntium	1-Osteoporosis, 2ndry to menopause, glucocorticoids, …. 2-Malignancy- associated hypercalcaemia	GIT irritation; nausea, vomiting, headache, eczema	Contraindicated in : 1-In severe renal disease. 2-In hypersensitivity to it 3-In increased risk of venous thromboembolism 4-In phenylketonuria

SUMMARY

Drug	Therapeutic use	Adverse effect	Comment
4 & 5- Estrogen & androgen	-	HRT (estrogen): vaginal bleeding, risk of breat cancer, and venous thrmboembolism	-
6- SERM		1- ↑ hot flush 2- no effect on HDL	Advantage : 1-↑bone density, ↓ fracture 2- ↓ LDL 3- no need for progesteron 4- Good for women with risk of uterine and breast cancer

Quiz yourself

Q1- A 65 year-old women came to clinic with pain in her knee , lap investigations confirm an osteoporosis condition, which one best choice
A- strontium
B- bisphosphonates
C- denosumab
D- androgens

Q2- A patient who had a long standing treatment of glucocorticoids, he developed an osteoporosis secondary to glucocorticoids , which one of the following is recommended in his status :
A- bisphosphonates
b- denosumab
C- estrogens

Q3- A renal failure patient came with osteoporosis condition , what we should avoid ?
A- bisphosphonates
b- denosumab
C- strontium

Q4- Patient came with vitamin d deficiency, that resulting of hypocalcemia , whish develop osteoporosis , whish one is avoiding to start immediately ?
A- androgens
b- denosumab
C- strontium

Q5- In prevous question , what the doctor should do to manage his status ?
A- correct vit D and ca level then start DENOSUMAB
B- start with very low dose .
C- start with a another adjunctive therapy .

Q6- An elderly female came to ER with **sever** osteoporosis , which one best choice ?
A- androgens
b- denosumab
C- strontium

Q7- An 65 male present with a past history of MI , which one must avoid?
A- androgens
b- denosumab
C- strontium

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

PHARMACOLOGY
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