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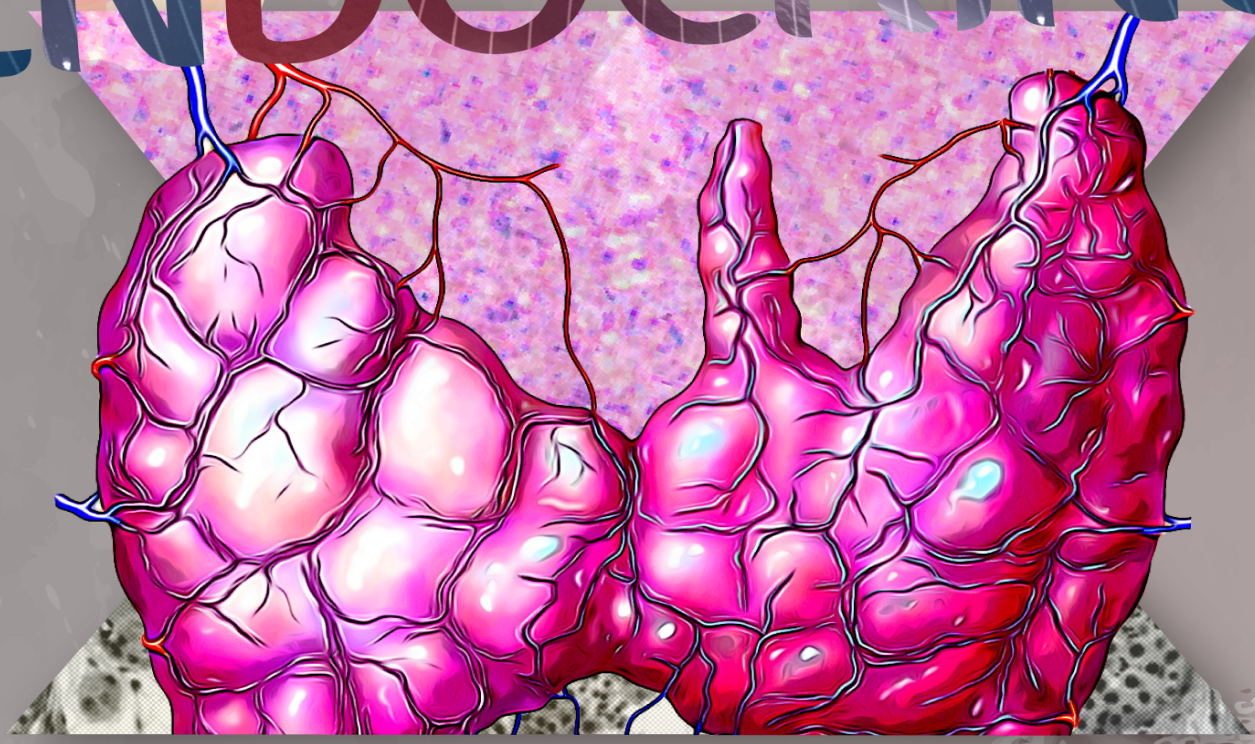


SUBJECT: Pharmacology

DONE BY: Assem Al Refaei

CORRECTED BY: Assem Jr

DOCTOR: Malik

In this lecture we wil discuss osteoporosis, hyperparathyroidism and hypoparathyrodism.

Last lecture, we talked about antagonism of GH and prolactin drugs, while for today here's the checklist:

1- Intro to PTH.

2- Teriparatide.

3- nonhormonal agents that affect bone.

4- Bisphosphonates.

5- Calcimemetics.

6- Strontium Ranelate.

Introduction to PTH (Revision Of Physiology)

- What's the primary function of PTH?

Increasing calcium levels and decreasing phosphate level.

- Which stimulator is the main one for PTH secretion?

Hypocalcemia

- What are the mechanisms by which PTH works?

1- On Bone:-
— It increases osteoclastation (formation of osteoclasts from monocytes) by acting over osteoblasts increasing RANKL that binds to RANK receptor on the surface of these preosteoclasts increasing differentiation and functionality.
— It increases osteoblastation by inhibiting sclerostin which is a protein secteted by osteocytes to decrease osteoblastation (formation of osteoblasts), the inhibition of the inhibitor leads for activation of osteoblastation.(Note: this is an indirect effect.)
2- On Kidney:-
— It'll increase calcium reabsorption and phosphate excretion.
— It increases the rate of conversion of Vit D into its active form.
3- On Gut:-
— Calcium and phosphate absorption through Vit D

- What is the effect of PTH over bone since it activates both osteoclastic and osteblastic functions?

  Excess endogenous parathyroid hormone leads for net bone resorption while the administration of exogenous PTH in low and intermittent doses increases bone formation without first stimulating bone resorption.

- We've said that calcium is the main stimulator and regulator for PTH, as we know hypocalcemia increases it and hypercalcemia decreases it, but what's the mechanism of hypercalcemia inhibition of PTH?

1- Calcium-sensitive protease cleaves the intact PTH into fragments.
2- Calcium-sensing receptor (CaSR) at the membrane of parathyorid gland cells is stimulated by calcium, to reduce PTH production and secretion.

- How does the active form of Vit D (1,25-dihydoroxycalciferol inhibits PTH)?

1- The parathyroid gland vitamin D receptor (VDR) activation, and the enzyme CYP27B1, that produces 1,25(OH)2D, suppress PTH production.
2- 1,25(OH)2D also induces the CaSR, making the parathyroid gland more sensitive to suppression by calcium.

Teriparatide (A Recombinant PTH)

Where is it used?	• Osteoporosis that isn't caused by hyperparathyrodism******* • In sports, as it decreases incidence of fractures and increase bone deposition.
Method of administration and timing	Subcutaneously, daily.
Effects	It stimulates normal bone formation and reduces incidence of fractures.
Treatment regimen	Requires adequate intake of calcium and Vit D.

****** because high amount of PTH leads for net bome resorption.

Note: The Dr escaped Vit D saying we know everything about it (you can see it in the sides, there're additional stuff that we don't know ☹), he also escaped the fibroblast growth factor slides without saying anything. I sent him an email to clear it out.

Nonhormonal agents that affect bone

We've already talked about the hormonal agent that does (**Teriparatide**), now we will discuss non hermonal agents.

1- Bisphosphonates

Used for osteoporosis.

2- Calcimemetics

Used for hyperparathyrodism.

3- Plicamycin (Mithramycin)

Pliamycin Is an anticancer drug that was used to reduce osteoclasts and their activity In Osteoporosis but it's cytotoxic and no longer used due the availability of others options for treatment. (They were given 1/10 of the cancer dose).

4- Thiazides

Thiazides are anti-hypertensive diuretic that Increases water and sodium excretion at the proximal tubules and also Increases calcium reabsorption and that' why It can be used for osteoporosis.

I'll add a table summarizing the uses of all the drugs mention at the end of the sheet.

Bisphosphonates

Structure	analogs of pyrophosphate in which the P- O-P bond is replaced by a nonhydrolyzable P- C-P bond.
Pharmacodynamics	It's high affinity for bone as it attaches to the hydroxyapatite crystals (mainly Ca) in bone and then get into the osteoclasts as they try to resorb bone, this leads for induction of osteoclastic apoptosis and other effects like inhibition of cholesterol synthesis in these cells.
Pharmacokinetics	• Bisphosphonates have low oral absorption (10%), food also reduces their absorption and that's why they're given 2 hours before eating. • Half of the absorbed amount accumulates in bone and the other half is excreted with urine. • The portion retained in bone stay there for months, depending on the turnover of bone itself
Effects	They increase bone mineral density and reduce the risk of fractures in the hip, spine and other locations
Administration method	Orally, take the drug with a full glass of water and remain upright for 30 minutes.
Adverse effects	1. Gastric and esophageal irritation that we the patient had to take the drug with a full glass of water and remain upright for 30 minutes. 2. High doses produce mineralization defect.**** 3. High doses cause renal deterioration and osteonecrosis of the jaw. 4. Over-suppression of bone turnover may cause subtrochanteric femur fractures in patients on long-term treatment.****
Contraindications	1. Decreased renal function.(M: third adverse effect) 2. Esophageal motility disorders.(M: first adverse effect) 3. Peptic ulcer disease. (M: first adverse effect)
Therapeutic uses	1. Hypercalcemia associated with malignancy.**** 2. Paget's disease.**** 3. Osteoporosis.

- What's the difference between different Bisphosphonates in the market?

  They differ In their administration time as some are taken daily, some monthly and some yearly. **DON'T MEMORIZE THEM.**

- Why is it used for hypercalcemia associatied with malignancies and paget disease?

  As you remember, the last stage of paget disease Is the lytic where bone resorption Is high and Bisphosphonates would decrease that.

  While In hypercalcemia associated with malignancies, it reduces calcium by inhibiting bone resorption.

- Why does Bisphosphonates lead for bone mineralization defects when give in high doses?

  Because It becomes a permanent part of bone minerals and composition.

  A study regarding the last adverse effect (Over-suppression of bone turnover may cause subtrochanteric femur fractures in patients on long-term treatment) included 2700 patients with osteoporosis and found that only 34 suffered from it (1-2%) unlike its effect in reducing spine and hip fractures by 50% so the benefit outweighs the risk.

Denosumab

Structure	Monoclonal antibody that binds to RANKL
Half life	Long like all monoclonal antibodies
Administration time	Twice yearly subcutaneously
Drawbacks	• immunosuppressive -rare.*** • expensive unlike Bisphosphonates
How it works?	By binding with RANKL inhibiting it from binding to its receptor and eventually inhibting osteoclast formation and differentiation.

- Why it has an immunosuppressive effect?

  Because of the fact that RANKL Is secreted by osteoblasts and T Lymphocytes so it also plays a role In Immunity.

- What are the therapeutic uses?

• Postmenopausal osteoporosis. (**M: It inhibit osteoclasts differentiation and function).**

• Some cancers (prostate and breast)

Some cancer like these are hormonal dependent as they need these hormones as vital survival signals, take Into example breast cancer as some are classified as ER+ breast cancer (they have abundance of estrogen receptor expression). Those patients are given ER blockers, GnRH antagonists or Aromatase Inhibitors (the enzyme that converts testosterone to estrogen). In the two cases of GnRH and Aromatase Inhibition, the levels of sex hormones will fall leading for estrogen deficiency osteoporosis so as an add on drug to this regimen to avoid bone resorption as much as possible, we add Denosumab.

• To limit the development of bone metastases or bone loss as metastasis prefer a spongy bone microenvironment that Is a result of bone resorption so Inhibiting It, Inhibits the formation of the optimal microenvironment for metastasis.

Note: this Is used In lung cancer as Its untreatable and highly metastatic.

- What are the adverse effects of Denosumab?
  drug appears to be well tolerated but main concerns are:
  1. Increased risk of infection because some immune cells express RANKL.
  2. It can lead to transient hypocalcemia, especially in patients with marked bone loss or compromised calcium regulatory mechanisms, including chronic kidney disease and vitamin D deficiency as they will have limited sources for calcium.

Calcimemetics (Cinacalcet)

•MOA: Activates the calcium sensing receptor (CaSR) in the parathyroid gland, which blocks PTH secretion.

• USAGE: secondary hyperparathyroidism in chronic kidney disease and for treatment of parathyroid carcinoma.

Explanation: it'll reduce PTH in these cases where it's elevated.

Note: CaSR (calcium sensing receptors) antagonists may be used in treatment of hypoparathyrodism leading to osteoporosis (rare cases) as it'll induce a little bit more PTH that will increase bone formation. (Remember that the high PTH leads for resorption)

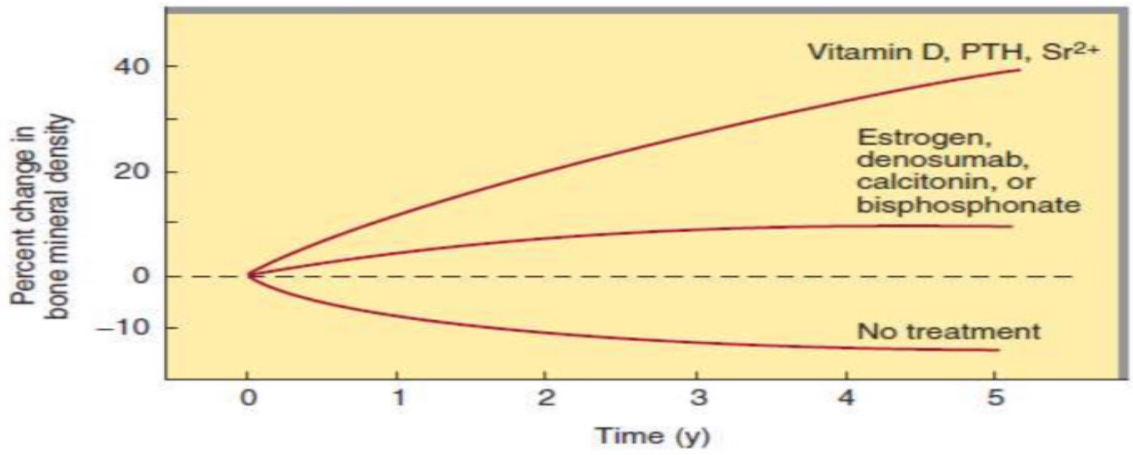
Note: The doctor passed diuretics and plicamycin and read them fast, the stuff in the beginning of the sheet are sufficient for what he emphasized as he said that know that thiazides reduce calcium excretion and plicamycin is no longer used in addition to the stuff I wrote in page 4.

Strontium Ranelate

- This drug is approved in Europe but not US
- It's highly effective in increasing bone density (highest nonhormonal in effectiveness)
- Unlike bisphosphonates, denosumab, or teriparatide, this drug increases bone formation markers while inhibiting bone resorption markers.
- Large clinical trials have demonstrated its efficacy in increasing bone mineral density and decreasing fractures in the spine and hip.

The doctor ends here and he said the we will continue talking about strontium ranelate in the next lecture.

Efficacy (memorize itttt)



Drug	Usage
Teriparatide	• Osteoporosis that isn't caused by hyperparathyrodism. • In sports, as it decreases incidence of fractures and increase bone deposition.
Bisphosphonates	1. Hypercalcemia associated with malignancy. 2. Paget's disease. 3. Osteoporosis.
Denosumab	Hormonal dependent cancers (do you remember why?) To prevent metastasis (do your remember how?) Postmenopausal osteoporosis
Calcimemetics	Secondary hyperparathyrodism in chronic kidney diseases and parathyroid carcinoma.
CaSR Antagonist	Hypothyodism induced osteoporosis

If you're studying this sheet befoe the exam, stay postive. Don't think of what you should've done better, think of what you should do now and what to do better in the future. Give up your phone and any source of attraction or time wasting. Focus on your mission, make a reasonable studying course for whatever left for the exam and get into it. It won't determine your future, but it's a step in it and every step and word counts.

GOOD LUCK, FUTURE DOCTOR