



The Endocrine System



PHARMACOLOGY

☒ Sheet

☐ Slide

☐ Handout

Number:

7

Subject:

Agents that Affect Bone & Mineral
Homeostasis #2

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❖ Topics will be discussed in this sheet :

1. Interaction of PTH, FGF23, & Vitamin D.
2. Secondary Hormonal Regulators of Bone Mineral Homeostasis.
3. Introduction to DM treatment .

❖ Interaction of PTH , FGF23 & Vitamin D.

➤ The net effect :

1. The net effect of PTH is to raise serum calcium and reduce serum phosphate.
2. The net effect of vitamin D is to raise both calcium and phosphate.
3. The net effect of FGF23 is to decrease serum phosphate.

➤ Note that these net effects are result from many things some are going together , others against each others .

❖ PTH regulation :

1. It's mainly regulated by calcium through a GPCR (G-protein coupled receptor) and that receptor links the changes in extracellular calcium concentrations to changes in intracellular calcium ; as the serum calcium levels rise and activate this receptor, intracellular calcium levels increase and inhibit PTH secretion. ((Feedback mechanism)).

✓ **NOTE :**

we said that calcium **will inhibit the PTH secretion** and we know that **calcium increase the secretion** of most of hormones (Insulin ,ACH ,, etc) , Be careful !!

2. Phosphate regulates PTH secretion directly and indirectly by forming complexes with calcium in the serum that will decrease the ionized calcium in the blood that reflect the reduction of intracellular calcium that will stimulate the PTH secretion .

❖ Vitamin D regulation :

1. Just to remember , we said that vitamin D controls Calcium & phosphate homeostasis by affecting **the kidney**(decrease the excretion of both calcium and phosphate) , **GIS** (increase calcium and phosphate absorption) and **bone** (it increase the bone resorption and formation , let's take the resorption now) so **it will increase the calcium and phosphate concentrations** , then they will **negatively feedback** on vitamin D and prevent its formation in the kidney >>> **Both calcium and phosphate at high levels reduce the amount of 1,25(OH)2D produced by the kidneys.**
2. High serum phosphate works directly and indirectly by increasing FGF23 levels. And FGF23 will facilitate the excretion of the phosphate by the kidney , so at high doses will lead to hypophosphatemia, which in turn inhibits FGF23 production will stimulate the vitamin D secretion .
3. 1,25(OH)2D directly inhibits PTH secretion (independent of its effect on serum calcium) by an effect on **PTH gene transcription**. This provides a **negative feedback loop**.
 - ✓ Patients with chronic renal failure will not have enough 1,25(OH)2D that will lead to loss of 1,25(OH)2D-mediated feedback loop coupled with impaired phosphate excretion and intestinal calcium absorption lead to secondary hyperparathyroidism. When there is hyperparathyroidism the calcium level will increase then precipitates everywhere, so in kidney diseases we should look at the bone we will find areas of bone formation and deposition , in addition to other clinical symptoms .
 - ✓ Patients will suffer from three problems :
 1. Deficiency of Vitamin D.
 2. impaired phosphate excretion.
 3. Impaired intestinal calcium absorption.

Note : 2& 3 as a result of Vitamin D deficiency because as we know, Vitamin.D is the main stimulus for intestinal absorption and decrease the renal excretion of both calcium and phosphate .

- ✓ In this case the kidney cannot perform its function in the hydroxylation and activation of the Vitamin D , then we should give analogs that can be converted into active form in the liver rather than the kidney .

❖ **FGF23 regulation :**

- ✓ 1,25(OH)2D also stimulates the production of FGF23.

The doctor said that we should now the interaction between those hormones and the direct/indirect actions of each one .

❖ **Secondary Hormonal Regulators of Bone Mineral Homeostasis :**

- Hormones are found normally in the body their physiological effects are minor but when you give them in large doses (pharmacological doses) they can be effective therapeutically but not as the primary regulators (PTH ,VD , FGF23).

- **Secondary regulators :**

1. Calcitonin
2. Glucocorticoids.
3. Estrogens
4. Denosumab
5. Strontium Ranelate.

6. Nonhormonal Agents Affecting Bone Mineral Homeostasis

- i) Bisphosphonates (**the most important one**)
- ii) Calcimimetics
- iii) Plicamycin (Mithramycin) .
- iv) Thiazides

1. Calcitonin:

- Secreted by parafollicular cells in thyroid gland .
- Can be used in pharmacological doses for osteoporosis .
- It lowers serum calcium phosphate and inhibits osteoclastic bone resorption (that why we use it in the osteoporosis) .
- At pharmacological amounts , it decreases the gastrin secretion then decrease the gastric acid secretion . Pentagastrin is a potent stimulator of calcitonin secretion , when the gastrin increase for any reason the pentagastrin will stimulate the secretion of calcitonin to decrease the acid secretion.

2. Glucocorticoids:

- They are not beneficial to the bone, they produce osteoporosis and early closure of the epiphysis (in children , they will be short).
- We can consider them as vitamin D antagonists , so they are used to treat the hypercalcemia (secondary to cancer , metastasis ,,etc) to reduce the calcium concentration .
- Their bad effect on the bone due to their action as Vitamin D antagonist .

Remember vitamin D has two effects on bone :
lower dose >>> bone formation.
higher dose >>> bone resorption.

3. Estrogen :

- Bones of women in fertile ages are intact and there are no cardiovascular diseases (very Rare) because the NORMAL estrogen will protect them against these diseases .
- NOTE : we said NORMAL estrogen not EXOGENOUS !
- But in menopausal women , there is an accelerated bone loss , it's very fast and very high increase of ischemic heart diseases , what can we do ?!
giving Estrogen will be useful , but clinical trials were stopped early because the risk of Cardiac diseases, breast ,uterine and other female-related cancers increase . it does improve the bone but it is associated with other severe diseases !
- Males also have estrogen receptors in their bone , so men with aromatase deficiency will develop accelerating bone loss.
- So What ?!
there is drug called Selective Estrogen Receptor Modulator (SERM) , **Raloxifene**, it maintains the benefit to bone without increased risk of breast and uterine cancer, and cardiovascular risk but it is not as effective as estrogen in increasing bone density so we cannot use it alone.
- When we say Modulator , it's neither agonist nor antagonist ; they have estrogen like effect in some tissues and anti estrogen like effect in other tissues !

4. Nonhormonal Agents Affecting Bone Mineral Homeostasis :

- **Bisphosphonate :**
 - ✓ The most important group, we will talk about them in more details because they protect the bone (in the osteoporosis and metastasis ; when there is metastazing bone cancer they are effective) .

- ✓ Are analogs of pyrophosphate in which the P-O-P bond is replaced by a nonhydrolyzable P-C-P bond. So in the P-C-P now isn't hydrolyzed so it deposits in the bone and stays there; that means it replace the pyrophosphate in the hydroxyapatite then deposited in the bone and stay for long period of time depending on the bone turn over in the adults , so that how its protection effect occurs .
- ✓ Drugs available for clinical use include:
Etidronate, Pamidronate, Alendronate, Risedronate, Tiludronate, Ibandronate, Zoledronate.
- ✓ You can notice that they end by “” Dronate “”.
- ✓ **Why there are a lot of these drugs ?!**
because it's a successful trade and some can be given daily , weekly ,monthly ,,,etc . remember the compliance !
- ✓ They retard formation and dissolution of hydroxyapatite crystals within and outside the skeletal system. But how do they deposit in the bone and retard the formation and dissolution !! **retard means reduce the rate not stops .**
- ✓ They localize to regions of bone resorption and so exert their greatest effects on osteoclasts. In the osteoporosis usually there is no homogenous dissolution of bone. **Bisphosphonate** deposits in the areas where the activity of the osteoclast is the greatest and inhibit osteoclast activity . So where there is osteoclast, **Bisphosphonate** will deposit then reduce bone dissolution and their presence as depositors give some strength to the bone .
- ✓ the problem is not the absorption although it's weak but you can increase the dose and usually the recommended doses will give us the effect we want but they are irritant to the esophagus !!they can lead to perforation!
- ✓ They cause perforation and may lead to mediastinitis (it's a very important complication of this drug)
to avoid that there are some recommendations :

1) **large** class of water ((not only for passage of water)) why ?!
if you take small amount it may stick in the esophagus rather
than the dissolution issues related to the drugs
it's not good to swallow drugs without water , it's really
BAD !

2) **Upright position** and stays upright for **30 mins.**

✓ Other actions :

- They inhibit 1,25[OH]₂D production.
- They inhibit intestinal calcium transport and absorption .
- They Inhibit bone cell glycolysis.
- They Inhibit bone cell growth.
- They produce changes in acid and alkaline phosphatase activity.
It's important because when there is elevation in the alkaline phosphatase (related to liver) and acid phosphatase (related to the bone) specially the acid phosphatase , that warning that drugs increase the alkaline and acid phosphatase so don't panic!
when there is an increase in the acid phosphatase level in female we think of breast cancer unless proven otherwise. So we should be careful in our interpretation !

- They are effective in men as well as women and for various forms of osteoporosis

✓ There is a kind of the **Bisphosphonate called amino Bisphosphonate** .
The amino bisphosphonates, alendronate, inhibit farnesyl pyrophosphate synthase, an enzyme in the mevalonate pathway that is responsible for cholesterol synthesis and appears to be critical for osteoclast survival.

✓ statins which are used to treat the hypercholesterolemia Also blocks mevalonate synthase and stimulate bone formation in animals but that is not applied to human .

✓ Thus, the mevalonate pathway appears to be important in bone cell function and provides new targets for drug development.

✓ Maybe , after one or two years we will find a drug to treat the osteoporosis by block the mevalonate synthase .

✓ The amino bisphosphonate only can do that .

Adverse Effects:

1. Gastric and esophageal irritation. Advise the patient to take the drug with a full glass of water and remain upright for 30 minutes.


2. High doses produce mineralization defect.

- The rule that any increase in the dose will increase the effectiveness of the drug isn't always true !
we all know the dose/response curve the increase of dose will increase the effectiveness until reach the maximum then increase the dose now may increase sides effects and may lead to drop in the effect (defective) .
- This rule might kill a lot of patients so we should tell them to Commit to the recommended dose .

3. High doses cause renal deterioration and osteonecrosis of the jaw. **We don't know why ?!**

4. Over-suppression of bone turnover may cause subtrochanteric femur fractures in patients on long-term treatment.

They are not very safe but they are effective !

 There are two types of contraindications : absolute and relative . When We say contraindication we mostly mean the absolute contraindication
Contraindications:

1. Decreased renal function.
2. Esophageal motility disorders.
3. Peptic ulcer disease.

Therapeutic uses:

1. Hypercalcemia associated with malignancy and metastasis .

2. Paget's disease.

remember :

is a chronic disorder that can result in enlarged and misshapen bones. Paget's is caused by the excessive breakdown and formation of bone, followed by disorganized bone remodeling.

This causes affected bone to weaken, resulting in pain, misshapen bones, fractures and arthritis in the joints near the affected bones

3.Osteoporosis.

5. Denosumab

- is a human monoclonal antibody that binds to and prevents the action of RANKL.
- RANKL is produced by osteoblasts and other cells, including T lymphocytes. It stimulates osteoclastogenesis via RANK, the receptor for RANKL that is present on osteoclasts and osteoclast precursors. By interfering with RANKL function, denosumab inhibits osteoclast formation and activity.
- It is at least as effective as the potent bisphosphonates in inhibiting bone resorption.
- Can be used in the treatment of:

1. Postmenopausal osteoporosis.

2. Some cancers (prostate and breast) to limit the development of bone metastases or bone loss resulting from the use of drugs that suppress gonadal function.

➤ Side effects :

1. Increased risk of infection (chronic and dormant infections . also, the fungal infections ,this is common feature of all monoclonal antibodies, they increase the risk of chronic and dormant infection) because some immune cells express RANKL, so you inhibit them and this leads decrease the immunity . there are exceptions but denosumab do it .
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.

Let's say that the menopause is reached , within one year , you will see osteoporosis and if you let it without treatment , the bone will fragile , easily broken

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But if you want to treat it there are two groups of drugs leads to :

1. improvement but is not very good . Estrogen , Denosumab , Calcitonin and bisphosphonate .
2. good improvement by Vitamin D , PTH and Strontium

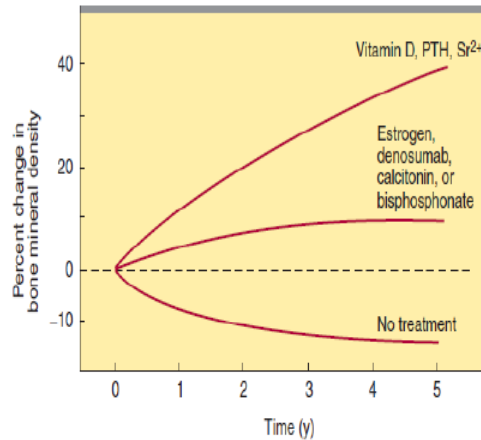


FIGURE 42-5 Typical changes in bone mineral density with time after the onset of menopause, with and without treatment. In the untreated condition, bone is lost during aging in both men and women. Strontium (Sr^{2+}), parathyroid hormone (PTH), and vitamin D promote bone formation and can increase bone mineral density in subjects who respond to them throughout the period of treatment, although PTH and vitamin D in high doses also activate bone resorption. In contrast, estrogen, calcitonin, denosumab, and bisphosphonates block bone resorption. This leads to a transient increase in bone mineral density because bone formation is not initially decreased. However, with time, both bone formation and bone resorption decrease with these pure antiresorptive agents, and bone mineral density reaches a new plateau.

➤ It's a very important graph, it's in menopausal women ,

6. Calcimimetics (Cinacalcet)

- Activates the calcium sensing receptor (CaSR) in the parathyroid gland, which blocks PTH secretion. ((physiological negative feedback)).
- Indicated for treatment of secondary hyperparathyroidism in chronic kidney disease and for treatment of parathyroid carcinoma. It's NOT used for osteoporosis.

7. Plicamycin (Mithramycin)

- Is a cytotoxic antibiotic. used in cancer treatment .
- Binds to DNA and interrupts DNA directed RNA synthesis and thus protein synthesis.
- Indicated for treatment of Paget's disease and hypercalcemia (1/10 cytotoxic dose).

8. Thiazide Diuretics

- calcium oxalate renal stone formation which is a result of excess excretion of the calcium in the urine (hypercalciuria) . To treat this we use Thiazide Diuretics which will decrease urine oxalate excretion and increase urine magnesium and zinc levels, both of which inhibit calcium oxalate stone formation.
- They reduce renal calcium excretion through these mechanisms
 - I. Enhance the effectiveness of PTH in stimulating reabsorption of calcium by the renal tubules.
 - II. In the distal tubule, thiazides block sodium reabsorption at the luminal surface. (when the sodium reabsorption is blocked then more sodium excretion and water go with sodium) increasing the calcium-sodium exchange at the basolateral membrane and thus enhancing calcium reabsorption.it's exchange and cotransport, so there is a decrease of sodium reabsorption then an increase calcium reabsorption
 - III. Enhance calcium reabsorption secondary to increased sodium reabsorption in the proximal tubule as a compensation.
- It's may be difficult to understand that because we don't take UGS but just know , it inhibits calciuria or calcium loss or enhance the calcium reabsorption. It's used to treat the calcium oxalate stone .

9. Strontium Ranelate

- It's metal in the Periodic Table. Strontium ranelate is composed of two atoms of strontium bound to an organic ion, ranelic acid.
- It is used in Europe for the treatment of osteoporosis. it's an effective drug . it's not universal
- It blocks differentiation of osteoclasts while promoting their apoptosis, thus inhibiting bone resorption. It also promotes bone formation.

❖ Introduction to diabetes mellitus treatment :

- DM type 1 >>> treated by giving Insulin because there is severe insulin deficiency .
- DM Type 2 >>> oral hypoglycemic drugs , control the diet, 20% finally are going to required Insulin .
- DM type 1 are about 10% of the total diabetic patients , so as total 30% of the diabetic patients need Insulin treatment .
- There are some stimulants to insulin secretions we have to memorize them as our names !
- Insulin : peptide , dosed in units not in grams ,,, it was extracted from animal tissue pigs or cows (either cow insulin or porcine insulin) but now we don't have these types because of DNA technology now we use recombinant human Insulin .
- the doctor started talking about the diabetes treatment but said that we have to study the first slides until the end of the insulin . next lecture, he will start from oral hypoglycemic drugs !

*The doctor said that what he didn't discuss in the lecture are self-study and are important ; we should study them .
So please refer to slides there are a lot of things aren't mentioned in the sheet! Don't misunderstand him !!!*

sorry for any mistake .
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