بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Endocrine Pharmacology | FINAL 3

Drugs affecting Bones

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Drugs That Effect Bone Mineral Homeostasis

Introduction

❑ Parathyroid Hormones and Calcitonin

- Both are working on the bone mineral homeostasis and functioning against each others :
  - PTH → Increases Calcium level in the blood.
  - Calcitonin → Decreases Calcium levels in the blood.
- There is an unnecessary relation between the bone diseases like osteoporosis and calcium level in the blood. (which means the patient with osteoporosis does not have to be hypocalcemia)
- We will talk about hormones released from different glands and there effects on the bone mineral homeostasis, such as, **PTH, Calcitonin, Estragon, Glucosteroid.**

Introduction

- **Calcium and phosphorus** are the main two elements of bone.
- **Parathyroid hormone (PTH) and vitamin D** are primary regulators, whereas **calcitonin, glucocorticoids and estrogen** play secondary roles.

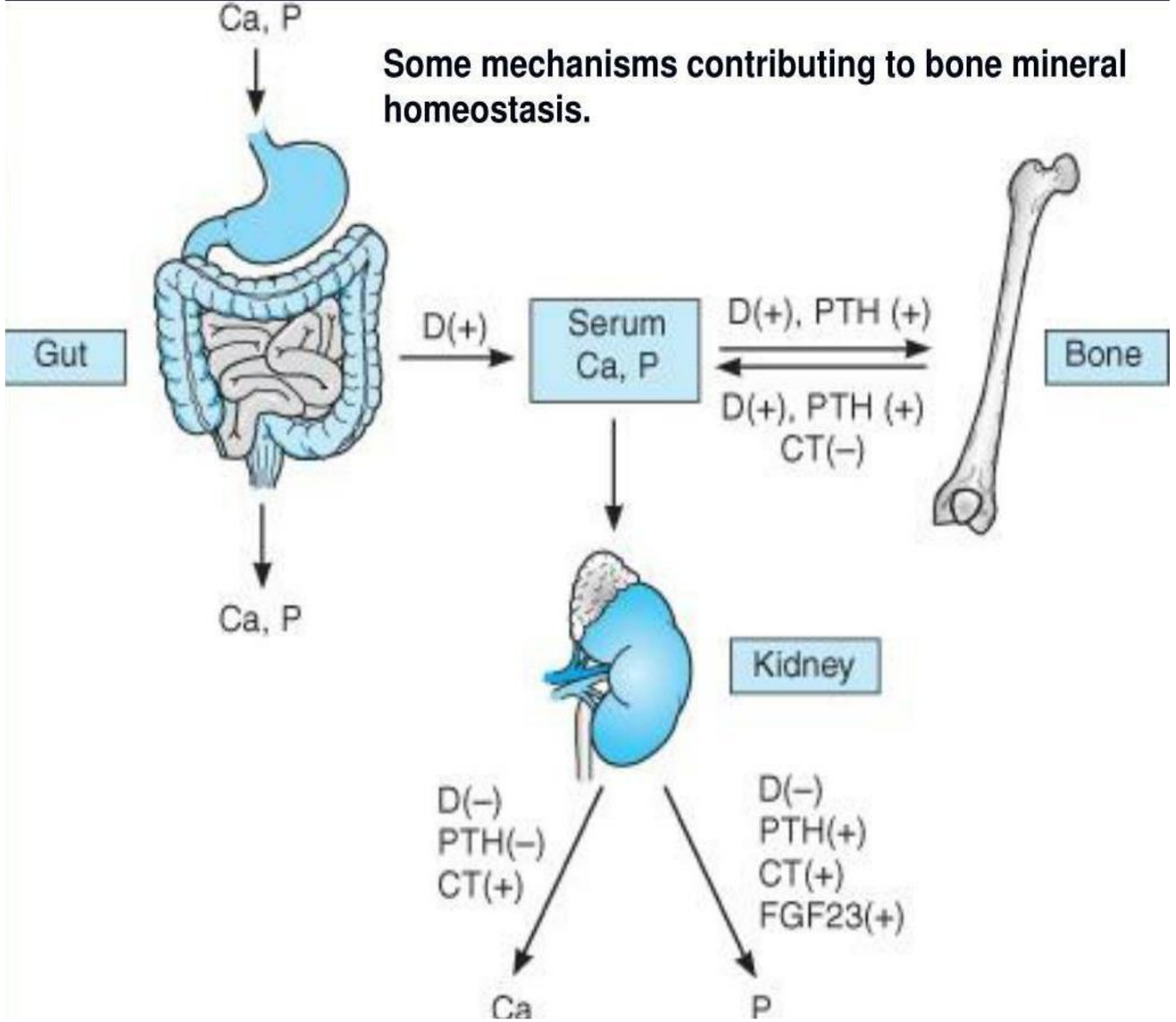
Introduction

- The Graph shows that calcium has different paths inside our bodies, it can be :

  - Deposited into the bone.
  - Resorbed from the bone to the blood plasma.

  - Execrated to the urine through kidney.
  - Reabsorbed from the urine through kidney.

  - Increase its absorption through gastrointestinal tract.
  - Decrease its absorption through gastrointestinal tract.



Parathyroid Gland

- Parathyroid gland releases parathyroid hormones (PTH).

- Parathyroid hormones (PTH) are released in response to low [calcium] in the plasma, it is going to increase calcium concentration through :

  ❖ Kidney :
  - **Increases excretion of Phosphorus.**
  - **Decreases excretion of Calcium.**

  - **Increases activity of vitamin D :** unique for its characteristic :
    - **Lipid soluble**, as a result it has intracellular receptor, Function through changing the activity of the transcription of a specific genes.
    - **large distribution inside our bodies.**
    - **Increases the absorption of calcium from the gastrointestinal tract.**

  - Results in : high [Ca] in blood and low[Ca] in urine

- Calcitonin released in response to high [calcium] in the blood through increasing the activity of the osteoblast (bone building cells).

Parathyroid Gland

❑ **Important Note Regarding Vitamin D ::**

- When vitamin D3 is administered to patients with vitamin D deficiency, it primarily works by increasing the absorption of calcium and, to a lesser extent, phosphorus from the gastrointestinal tract.

- When **vitamin D levels** become **high**, they **inhibit the release of parathyroid hormone (PTH)** from the parathyroid glands. This occurs through a **negative feedback mechanism**, in which vitamin D acts on receptors in the parathyroid glands themselves. This mechanism is particularly important in certain medical conditions associated with hyperparathyroidism.

❑ **Bone ::**

- Bone is mainly composed **of calcium and phosphorus**, and bone homeostasis is maintained by two types of cells that **have opposing functions:**

    - **Osteoblasts:** Cells responsible for bone **deposition** and formation.
    - **Osteoclasts**: Cells responsible for bone **resorption** and breakdown.

❑ The Parathyroid hormones (PTH) activity is dependent on two factors:

1) The **amount** of the parathyroid gland hormones.
2) The **activity** of the parathyroid gland hormones.

Parathyroid Gland

❑ **Important Note::**

- Any drug that activates osteoblasts can be used for the treatment of osteoporosis.
- Any drug that inhabits the osteoclasts can be used for the treatment of osteoporosis.

- **Remember from Physiology ::**

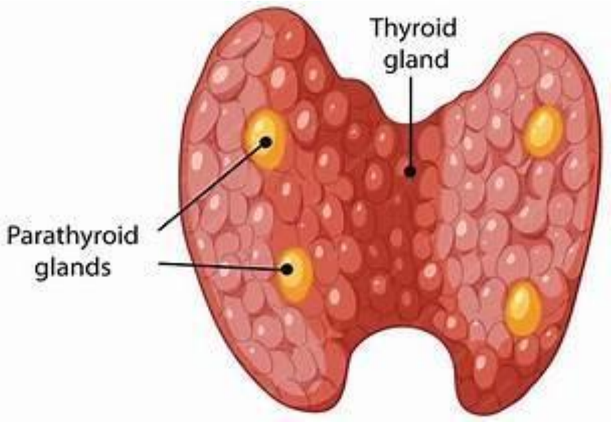
- PTH **activates both osteoblasts and osteoclasts**. It **primarily stimulates osteoblasts** initially, but with prolonged exposure, **it leads to increased activation of osteoclasts.**
- The net result is increased bone resorption and increased calcium levels in the blood.

Hormonal Regulators of Bone Mineral Homeostasis

- PTH
- Vitamin D
- Calcitonin
- Estrogen
- Glucocorticoids

Parathyroid Hormone

- 84- amino acid peptide
- In **kidney:** -inhibit Ca excretion , promote phosphate excretion and stimulate the production of vitamin D.
- In **Intestine:** Indirectly increase calcium and phosphorus absorption due to the production of Vitamin D.



Parathyroid Hormone

- In **Bone:** Increase calcium and phosphate resorption by increasing the activity of both osteoclast and osteoblast. So, increase bone turnover.
- The net result is: ↑Serum calcium
  ↓Serum Phosphate
  ↑Bone resorption

Parathyroid Hormone

- At moderate doses: ↑Bone formation. As a result: **Teriparatide** is a drug modified from PTH used in treatment of osteporosis.

What is Teriparatide?

- **Teriparatide is a recombinant PTH analogue.**
- It is a **peptide hormone**, so it cannot be given orally because it would be degraded/denatured in the gastrointestinal tract.
- Therefore, it is administered **parenterally by injection.**

Teriparatide

❑ **Clinical use**

- Mainly used for the **treatment of osteoporosis**, particularly in patients at high risk of fractures.

❑ **But if PTH causes bone resorption, <u>how can Teriparatide treat osteoporosis?</u>**

- This depends on **the dose and duration of PTH exposure**.
- **Continuous/high PTH exposure → bone resorption → osteoporosis.**
- **Intermittent PTH exposure → Activation of osteoclast in a manner that don't exceed osteoblast activity → net increased bone formation.**

Therefore, the pattern of exposure is extremely important.

❑ **Teriparatide's mechanism ::**

<u>Moderate</u> administration of Teriparatide:

→ Stimulates **osteoblast activity**

→ Increases **bone formation**

→ Increases **bone mass**

→ Helps treat **osteoporosis**

It is therefore considered an **anabolic (bone-forming) drug**.

❑ **PTH** increases blood calcium and can cause **hypercalcemia**.

❑ **Teriparatide**, when given intermittently at therapeutic doses, has a **<u>less effect</u> on serum calcium** than continuous PTH exposure.

Vitamin D

- Can be synthesized in the skin from 7-dehydrocholesterol under influence of ultraviolet light.
- Absorb from the diet (Cholecalciferol) or from the plant (Ergocalciferol).
- Active metabolites form in liver (25 hydrovitamin D or calcidiol) and Kidney (1,25 dihydrovitamin D or calcitriol).

Vitamin D

- Lipid soluble Vitamin

- Activated through sunlight (UV light), then distributed inside our body. Should be activated since it is synthesised in the inactive form and has multiple activation steps, one in the liver, other in the kidney.

- Activation is through enzymes called **Cytochrome P-450**, generally they add oxygen (oxidation).
- After Vitamin D is metabolized in the liver and kidney, it becomes in the **active form**.

- What does **1,25** in the vitamin D active formula (1,25-dihydroxychalciferol) means? – It means the location of carbons where activation (Hydroxylation) happens.
- In the liver → Hydroxylation on 25th carbon.
- In the kidney → Hydroxylation on 1st carbon.

- **Remember → Deficiency is treated by Replacement therapy ::**

- We can get Vitamin D replacement from animal source → **cholecalciferol** → 5000 units per day.

- Most pharmaceutical forms of Vitamin D are taken once per week → **<u>50000</u>** international units per weak.

- Also there are other forms taken daily **(<u>2000-5000</u>) International units/day**.

- Recent research prefers the daily low dose over the weekly huge dose.

Biodal is very common in **Jordan**

Vitamin D

- It has a great effect in increasing the absorption of calcium and phosphate from the gastrointestinal tract.
- 1$^{\alpha}$ - hydroxyvitamin D (**Doxecalciferol**) is a prodrug that is concerted in the liver to 1,25-dihydroxyvitamin D. Therefore, it is useful in patients with chronic kidney disease (CKD), where renal activation of vitamin D is impaired.
- Clinical use Mainly used for:
- Secondary hyperparathyroidism
- in CKD patients.

Vitamin D

- **Vitamin D deficiency** → ↓ absorption of calcium from GI tract.

- Our body has to continuously deposit calcium from the plasma into the bone to maintain homeostasis between deposition and resorption, if the calcium levels in the blood are low, the process of bone densing will be impaired, which leads to osteoporosis since **osteoclast > osteoblast**.

- **Vitamin D deficiency** → leads to decreased Calcium gastrointestinal absorption ↓ → ↓ Plasma [Calcium] → ↓ Bone density.

- **Chronic kidney disease (CKD),** where renal activation of Vitamin D is impaired.
  - If the patient is having Vitamin D deficiency caused by renal failure, giving Vitamin D supplement in the form of **cholecalciferol will not be sufficient** since it is in the **inactive** form and it has to be **metabolized to Doxecalciferol in the kidney, which is impaired.**
  - So you should give **1α-hydroxyvitamin D (Doxecalciferol)**, which is in the semi-active form of VitaminD.

- When we measure the concentration of Vitamin D, we measure the concentration of the active form of Vitamin D **(1,25-Dihydroxy Vitamin D).**

Vitamin D

- **1-hydroxyvitamin D (Doxecalciferol)** is semi-active Vitamin D; it is already activated on carbon number 1 (the function of the kidney has been done outside in laboratory since kidney is having a specific issue).
  It only need to be activated in the **liver**.

- When you want to prescribe Vitamin D, ask the patient first to assess their kidney function by measuring the **creatinine concentration**.
- Don't prescribe cholecalciferol for patient with Vitamin D deficiency with kidney impairment.
  Prescribe **Doxecalciferol**.

❑ **Clinical use of Vitamin D deficiency – patients (Doxecalciferol) ::**

➢ **Secondary hyperparathyroidism with Chronic kidney disease (CKD) :**

- [PTH] ↑ in the plasma = Hyperparathyroidism

- Kidney impairment → ↓ excretion of phosphate → ↑ [Phosphate] → Activation of PTH release → [PTH] ↑
- **Problem is not from the gland itself; it is from the kidney problem → That's why it is called Secondary.**

- Kidney impairment → ↓ excretion of phosphate.

- **So why we give Vitamin D (Doxecalciferol) not (Cholecalciferol) !?**

  - **Doxecalciferol → Calcitriol (in the liver) → bind to parathyroid gland receptors → inhibit the PTH release which prevent them from overactiving osteoclasts which prevent osteoporosis.**
  - **If we give cholecalcifirol it needs to be activated in the kidney which is not functioning due to disease.**

Vitamin D

- **Paricalcitol** and **Calcipotriene** are analogs of calcitriol.
- These drugs causes less hypercalcemia than calcitriol.
- Paricalcitol suppress PTH hormone secretion. Unlike calcitriol, it has much less effect on intestinal calcium and phosphate absorption. Therefore, it lowers PTH without markedly increasing serum calcium or phosphate. Clinical use: Secondary hyperparathyroidism in patients with chronic kidney disease.

Vitamin D

- **Paricalcitol** Difference from Doxecalciferol that it's the final active form, a **calci** analog *(1,25 Dihydroxycalcitriol)*. No need for activation from the liver neither the kidney. Given in cases of **secondary hyperparathyroidism with chronic kidney disease**.

You give either:

- ✓ **Doxecalciferol**
- ✓ **Paricalcitol**
  - ❖ not cholecalciferol.

- **<u>What the difference between them?!</u>**

- If the patient has **liver disease → give Paricalcitol** since it is in the final active form (no need for liver of kidney activation). Both of them can be prescribed for **Secondary HyperParathyroidism with CKD**, but Paricalcitol is given in cases with liver disease (since it don't needs liver activation, opposites to doxecalcifireol).

- We can give Vitamin D supplements as a treatment for **osteoporosis**.

- **Without vitamin D supplements :: Hyperparathyroidism → PTH ↑ → Bone resorption ↑ → Osteoporosis.**

- **With Vitamin D supplements :: Vitamin D ↑ → inhibits the parathyroid gland → As a final result inhibits bone resorption and treats osteoporosis.**

Vitamin D

- **Paricalcitol and Calcipotriene** Drugs that increases the calcium in the blood, they don't necessarily cause bone resorption or bone calcium deposition.

- These drugs **cause less hypercalcemia than calcitriol, why?**
- **Also, Why giving calcitriol analog (paricalcitol) rather than calcitriol itself?**

- → The difference between them is **their activity on intestines.**
- **Paricalcitol** → effects on calcium absorption is **less than calcitriol.**
- → If there is a patient with Vitamin D deficiency and CKD and you are afraid of the hypercalcemia effect of calcitriol, give **paricalcitol**, since it **has lower effect on absorption of calcium from intestine.**
- Patient that have hypercalciemia may develop **severe hypercalcemia when administerating calcitriol which** may leads to the development of **Arrhythmia**.

- **Hypercalcemia → may cause hypercalciuria, but how? Since Vitamin D doesn't have any relation to the kidney excretion function.**

  - Kidney calcium excretion and bone resorption or deposition is maintained directly through **PTH and Calcitonin, not through Vitamin D.**
  - Calcium will be excreted in urine because of much high concentration in the blood.

Vitamin D

- **<u>Over dose</u> of vitamin D:**
  - Hypercalcemia
  - Hyperphosphatemia
  - Hypercalciuria

- **General role:** ↑ blood Ca in urine / ↑ minimum ↓ in blood.
- **This a case is an exception : Hypercalcemia causes hypercalciuria,** both are high since its very high in concentration that it overcomes the kidneys reabsorption ability, which results in high calcium in the blood and high in urine.

Patients may develop

- Kidney stones
- Constipation ↑ Calcium → affects smooth muscles (causes shock) → decrease gastric mobility → constipation.
- Confusion Hypercalciemia can affects neutrons → causes confusion.

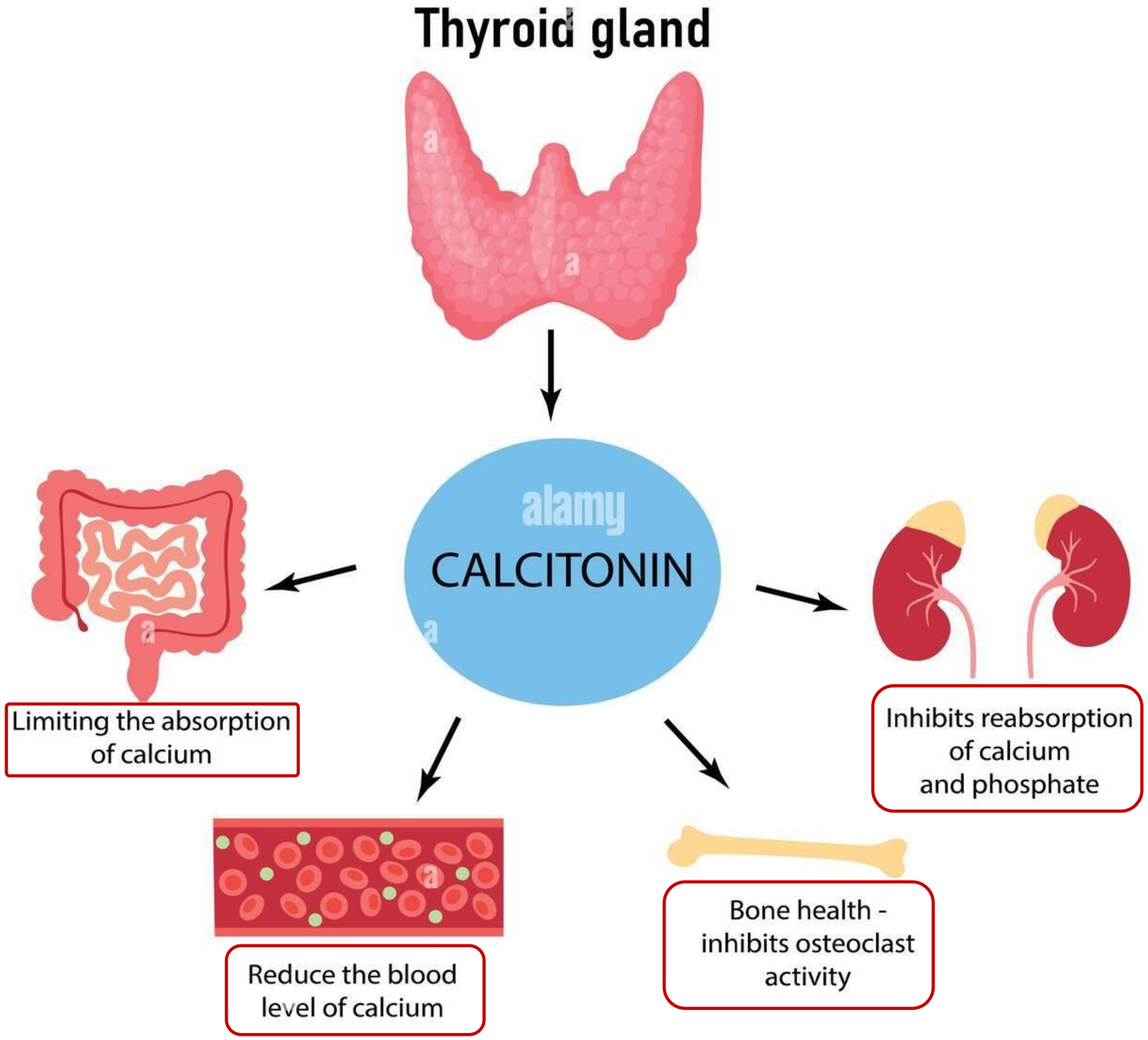
- Arrhythmias WHY??? The pacemaker of the heart depends mainly on calcium concentration for their function. When there is calcium imbalance, it will cause **Arrhythmia**

Calcitonin

- Peptide hormone secreted by thyroid gland.
- ↓Calcium and Phosphate in serum by inhibition of bone resorption.
- Used in a acute conditions where high serum calcium should decreased.
- Used in treatment of osteoporosis.

- Opposite to the **PTH** in function.
- **Most important** : inhibits osteoclast in the bone.

- Decreases the [Calcium]
- Decreases the [Phosphate] – Similar to PTH function only on this.


Thyroid gland
CALCITONIN
Limiting the absorption of calcium
Inhibits reabsorption of calcium and phosphate
Reduce the blood level of calcium
Bone health - inhibits osteoclast activity

Calcitonin

- **Salmon calcitonin** is used by injection and nasal spray because of it is high half life and potency.

- Calcitonin **has Short duration of action**. So, it is replaced by **Salmon calcitonin**.
- **Has longer half-life and more potent.**
- **Higher Potency:** gives the same **effect as human calcitonin with lower concentration.**
- Clinical Uses → for the **treatment of osteoporosis (because it inhibits osteoclasts).**

Estrogens

- Estrogens and selective estrogen receptor modulators (**Raloxifene**)prevent and delay bone loss in postmenopausal women.
- Their action involve the inhibition of PTH-stimulated bone resorption.
- Estrogens may cause breast and endometrial cancers where

raloxifene <u>does not</u> cause it.

Estrogens

- Estrogen in females is responsible for many characteristics of females, such as skin glowing, soft voice and other female characteristics

- Women who reached menopause → **Sharp Decline in estrogen** causes decrease in skin glow and **causes osteoporosis**.

- So if there is a woman that has reached menopause, **how can we prevent post menopausal osteoporosis !?**

- **Giving estrogen?!** The problem with giving estrogen is that **it is cancerous and responsible for many cancers, such as breast cancer and uterine cancer.**

❑ **Raloxifene**

- Works on estrogen receptor (**estrogen agonist**).

- Estrogen receptors present in many areas such as breast, uterus and bone.
- When Raloxifene binds to estrogen receptor in the bone, **it causes inhibition of bone resorption, preventing osteoporosis.**

  - In case of estrogen being used, it does the same **with additional to that it binds to estrogen receptors in the breast and uterus which can result in the development of cancer due to overactivation.**

- Raloxifene works in bone as **agonist**, while at breast and uterus as **antagonist**.

Glucocorticoids

- Inhibit bone mineral maintenance.
- Chronic use of glucocorticoids (Cortisone andprednisolone) is a common cause of osteoporosis.
- Might be useful in ↓hypercalcimia.
- Decrease osteoblast activity, increase osteoclast survival, decrease intestinal calcium absorption, and increase renal calcium excretion.

Glucocorticoids

- **Stress hormones**
- **<u>What's the relation of glucocorticoids and bone homeostasis?!</u>**
  - Glucocorticoids has a lot of advantages and disadvantages, **if glucocorticoids given to patient for long duration → cause activation of osteoclast → ↑ bone resorption → osteoporosis → also decreases calcium in blood** (Even that some resources suggest using it for hypercalcemia cases (**however you should not be prescribing it for hypercalcemia.**
  - **<u>How does Glucocorticoids decreases blood calcium!?</u>**
    - **It increases calcium excretion from the kidney to the urine, and decreases calcium absorption.**
    - So glucocorticoids **should not be used in patients with osteoporosis** (with some exceptions).

    Clinical note: Be cautious when prescribing glucocorticoids to patients with osteoporosis, as long-term glucocorticoid therapy can worsen bone loss and increase the risk of fractures.

Nonhormonal agents

Treat osteoporosis

- Bisphosphonates most common (alendronate).

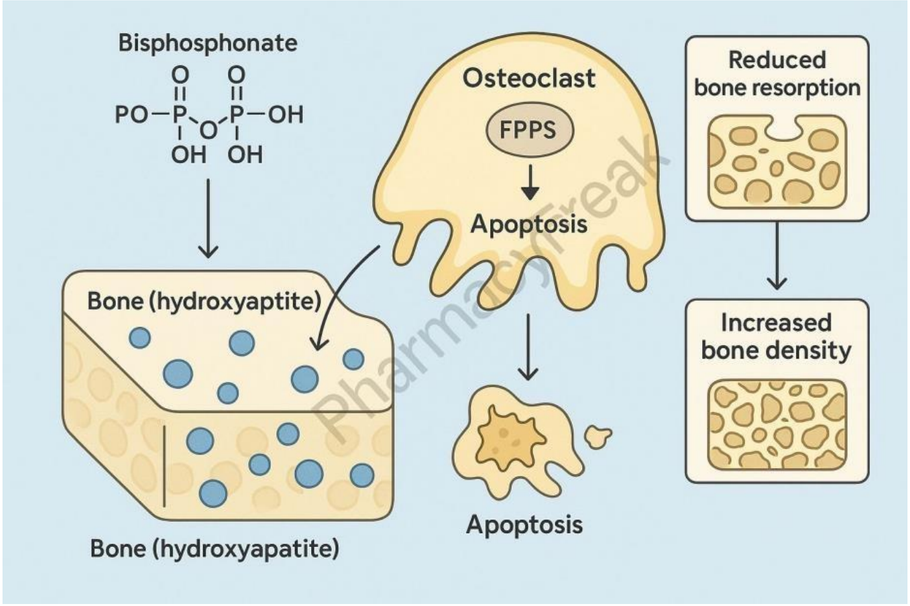
  - Alendronate goes to osteoclast and inhibits its activity.

  ❑ **Alendronate**
  - Inhibit bone resorption.
  - Alendronate →inhibit **farnesyl phosphase enzyme** → survival of osteoclast →decrease bone resorption.
  - This drug is taken orally and **it is very irritant especially for the esophagus. Causes esophageal ulcer if not taken with enough amount of water or taken before sleep or laying down. Since this lead to sticking at the esophagus mucosa and ulcer development,**
  - Swallowing the alendronate alone is a **huge mistake**, it should be taken with **250 mL of water (or more)** and keep standing or sitting still while administering it until it reaches stomach.

- Calcimimetics

Bisphosphonates

- Reduce both bone formation and resorption of the bone.
- Has a direct effect on the osteoclast cell by inhibition of farnesyl pyrophosphate which play a role in the survival of the osteoclast.



Bisphosphonates

- Is used for managment of hypercalcemia.
- Chronic administration of bisphosphonate is used in treatment of all kinds of osteoporosis.
- **The primary toxicity of bisphosphonate is gastric and esophageal irritation.** To reduce the irritation, patient is advised to take a large quantity of water and avoid situations which permit esophageal reflex.

Bisphosphonates

- Examples of bisphophonate: **Alendronate** and pamidronate.

Calcimimetics

- Lower the parathyroid hormone by activation of calcium-sensing receptor in the parathyroid gland. The gland thinks calcium is high >>>> ↓Less PTH secretion>>>>>
- ↓Lower calcium. Uses: Secondary hyper parathyroidism, and parathyroid carcinoma.
- Reduce serum calcium.
- Toxicity: hypocalcemia.
- Example: Cinacalcet

Calcimimetics

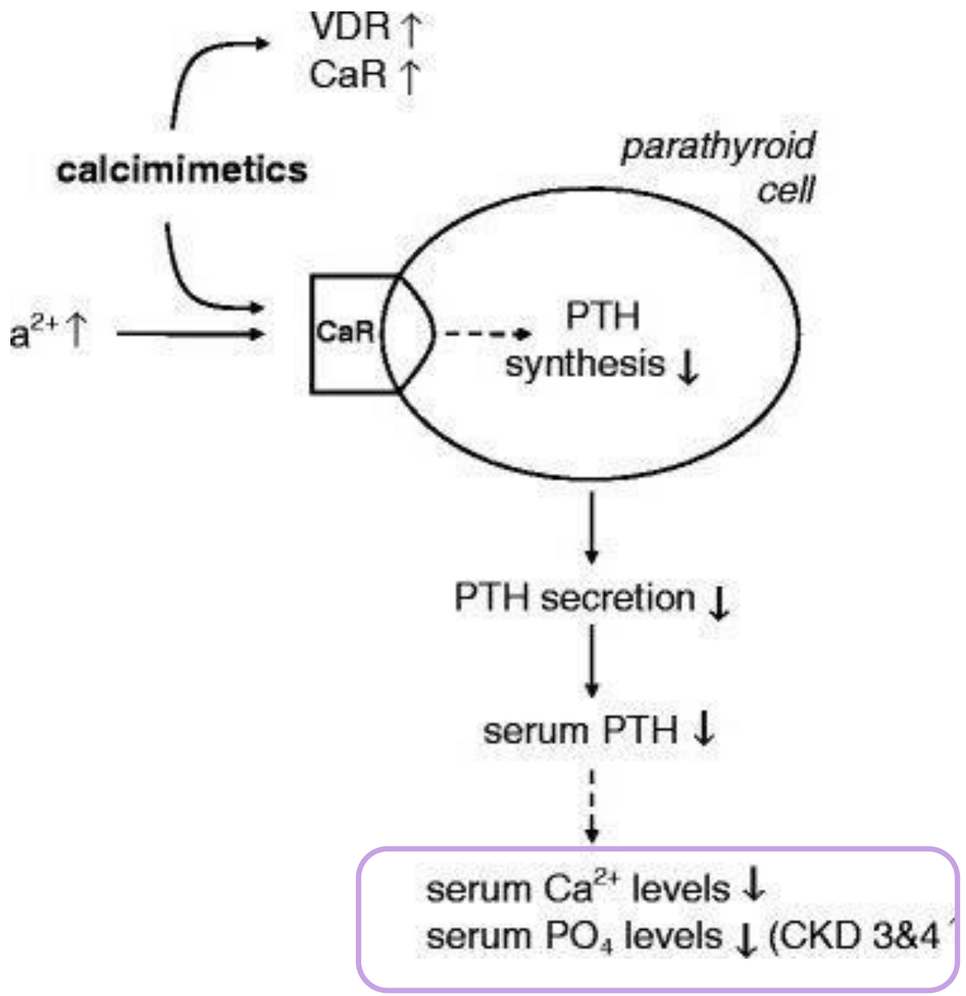
- **Cinacalcet** — **Calcium analogue**
  (mimics calcium)

- Most important, most common drug we use in Jordan is **Cinacalcet**.

- ↑ [Calcium] → bind to **calcium-sensing receptor** on parathyroid gland → inhibit PTH release → inhibits bone resorption.

- **Cinacalcet** → activates calcium sensory receptors on parathyroid gland
  → ↓ parathyroid hormone secretion
  → inhibits PTH release
  → inhibits bone resorption.

- Useful in cases of **hyperparathyroidism**, **parathyroid carcinoma** (usually we treat it by surgery).
- It reduces calcium but indirectly by inhibiting the PTH release.



رسالة من الفريق العلمي:

“If you hold a gun and I hold a gun, we can talk about the law.

If you hold a knife and I hold a knife, we can talk about rules.

If you come empty handed and I come empty handed, we can talk about reason.

But if you have a gun and I only have a knife, then the truth lies in your hands.

If you have a gun and I have nothing, what you hold isn't just a weapon, it's my life.

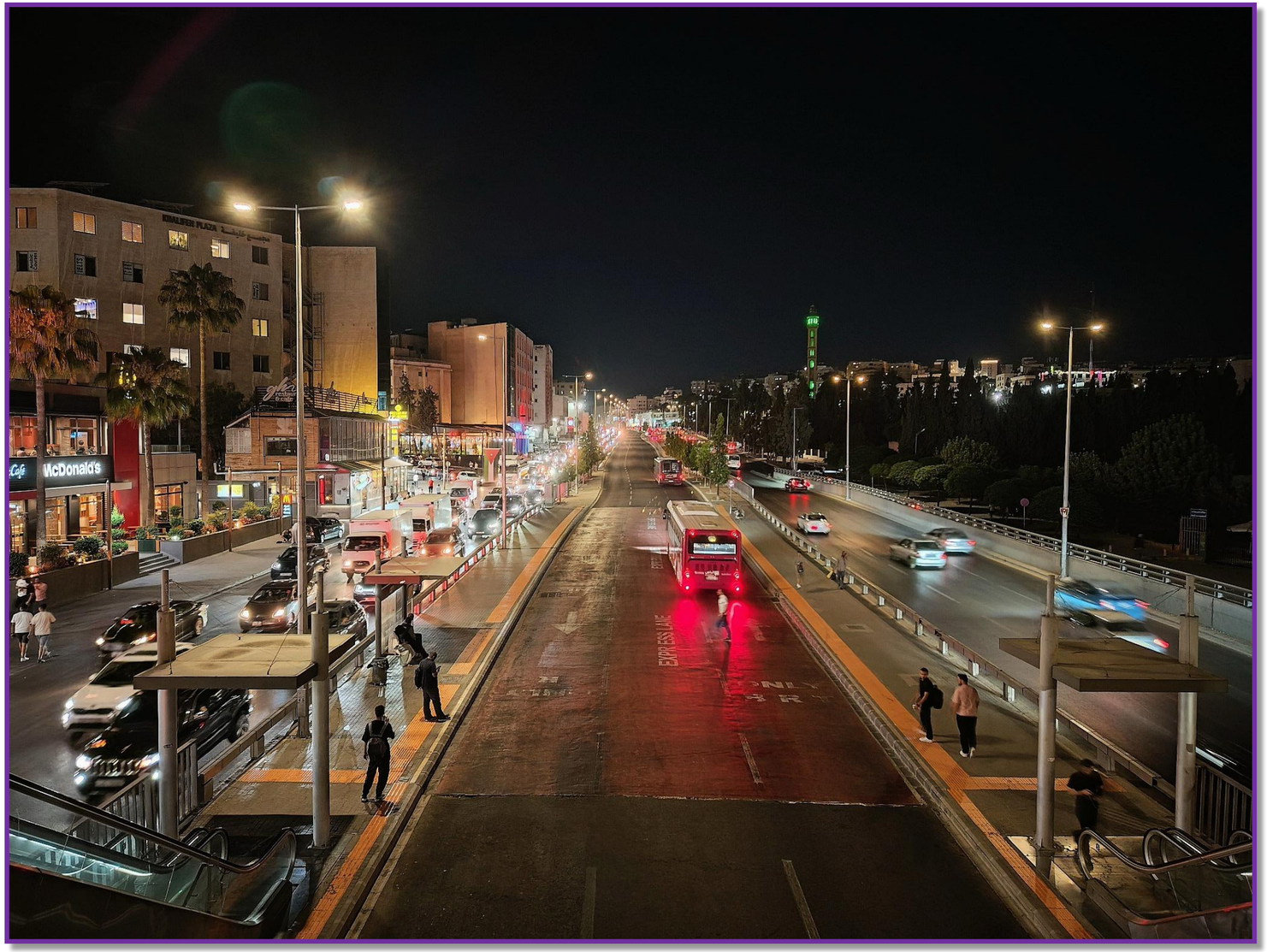
The concepts of laws, rules and morality only hold meaning when they are based on equality.

The harsh truth of this world is that when money speaks, truth goes silent. And when power speaks, even money takes three steps back.

Those who create the rules are often the first to break them. Rules are chains for the weak, tools for the strong.

In this world, anything good must be fought for.

The masters of the game are fiercely competing for resources while only the weak sit idly, waiting to be given a share.”



For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	6	Glucocorticoids is released in response to **low phosphate concentrations**	Note was deleted (it is actually released in response to high phosphate concentrations
	29	Glucocorticoids **decreases** calcium excretion from the kidney to the urine	Glucocorticoids **increases** calcium excretion from the kidney to the urine
	29		Note is added
V1 → V2			