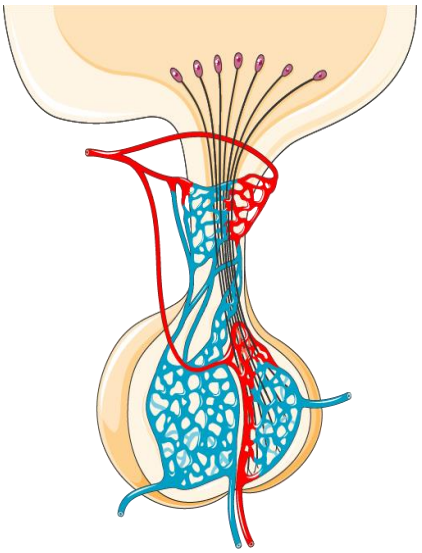
MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology



3: Pharmacology of drugs used in calcium & vitamin D disorders

Objectives

1. Recognize the common drugs used in calcium & vitamin D disorders
2. Classify them according to sources & pharmacological effects
3. Detail the pharmacology of each drug regarding; mechanism, clinical utility in affecting calcium & vitamin D

Color index

- Extra information and further explanation
- **Important**
- **Doctors' notes**
- **Drugs names**
- **Mnemonics**

Kindly check the editing file before studying this document

Calcium Metabolism

المحاضرة فيها تكرار كثير من الفيزيولوجي والبايو، بليز ذاكروهم قبل ما تدرسون هذي المحاضرة عشان تفهمون

- Calcium plays an essential role in many cellular processes, including: (1) muscle contraction, (2) hormone secretion, (3) cell proliferation, and (4) gene expression, (5) bone synthesis , (7) blood clotting mechanisms.
- Calcium balance is a dynamic process that reflects a balance between:
  - ✓ calcium absorption by the **intestinal tract,**
  - ✓ calcium excretion by the **kidney**,
  - ✓ release and uptake of calcium by **bone** during bone formation and resorption. (deposition of calcium in the bone)

Three principal **hormones** regulate Ca^{2+} homeostasis

1. Parathyroid hormone (PTH) 2. Vitamin D 3. Calcitonin

Three target **tissues** regulate calcium homeostasis and Vit D:

1. Bone  2. Kidney  3. Intestine 

Absorption and reabsorption of Ca

Ca absorption

Bone:

- The dominant site of calcium storage in the body is bone, which contains nearly 99.9% of body calcium. There is a small amount of calcium in the serum (ECF) and (ICF)
- **Most body calcium is stored in bone** (~1000 g) which is a very dynamic site as bone is remodelled continuously by resorption of old bone by osteoclasts & formation of new bone by osteoblasts
- Although only a small fraction of total body calcium is located in the plasma, it **is the plasma concentration of ionized calcium that is tightly regulated**, primarily under the control of **PTH** and **vitamin D** and calcitonin .

Hormones in Ca metabolism:

- The following are principal factors involved in calcium metabolism & bone remodelling (the drug and the hormones replacement we gonna talk about in this lecture):
  1. Parathyroid hormone (PTH)
  2. Teriparatide
  3. Vitamin D
  4. Calcitonin (doesn't effect the regulation that much)

- **PTH and vitamin D play central roles in the regulation of bone metabolism.**

Parathyroid Hormone

المحاضرة شرحتها لنا بروف. يلدز، اللي ركزت عليه حطيناه لكم **بالعنابي**

Parathyroid Hormone

Definition

- PTH: A hormone that plays a critical role in controlling **calcium** , and **phosphate balance.**
- PTH is released from the parathyroid gland in response to **low plasma Ca^{2+} level .**
- The stimulus for parathyroid hormone (PTH) is hypocalcaemia .
- Secretion of PTH is inversely related to [Ca^{2+}].

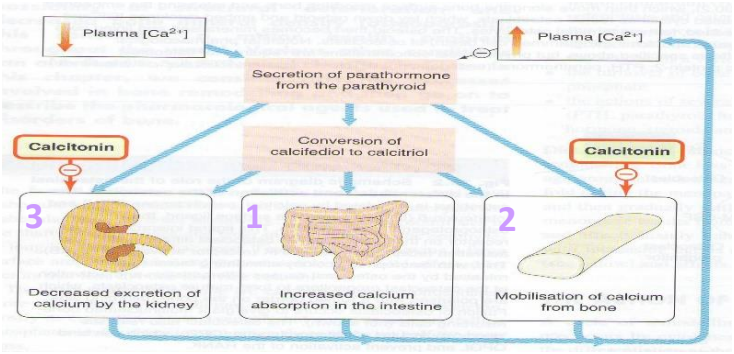
Action

The overall **action** of PTH is to **increase plasma Ca^{2+}** levels in response to hypocalcaemia:

(Parathyroid H) يطلع الكالسيوم برا العظام

1. First, PTH enhances **intestinal** calcium **absorption** of calcium in the presence of permissive amounts of vitamin D.
2. Second, PTH stimulates **bone resorption** by stimulating osteoclasts to increase the outward flux of calcium to restore serum calcium level.
3. Third, PTH stimulates the active **reabsorption** of calcium from the **kidney**

increase formation of calcitriol which is the active form of vitamin D



Calcitonin is a physiological antagonist to PTH with regard to Ca^{2+} homeostasis ,decreases the calcium levels in the blood.

Response

- Daily, **intermittent** (have an **anabolic** effect) administration of recombinant human PTH, SC in the thigh (alternate thigh every day) leads to a **net stimulation of bone formation** for treatment of osteoporosis.
- **Continuous** or chronic exposure to high serum PTH concentrations (as seen with primary or secondary hyperparathyroidism) results in bone resorption and risk of fractures, so we can use PTH for treatment but not contiously

✓ **Intermittent:** ↑ Osteoblast number/function, ↑ Bone formation, ↑ Bone mass/strength

✓ **Continuous:** ↑ Osteoclast, ↑ Bone resorption, ↑ Serum Ca^{2+}

Continuous = Osteoclast

Use

- Treatment of severe **osteoporosis**
- **Resistant** cases failed to respond to other medications

Parathyroid Hormone

Teriparatide

طيري برا فيه تايد (مد وجزر) = Teri-para-tide

M.O.A

Have the same affect as PTH but it is:

- Synthetic polypeptide form of PTH (**PTH analogue**).
- It belongs to a class of anti-osteoporosis drugs, the so-called "anabolic)" agents. (increases bone formation ,osteoblastic activity and bone density)
- Given, once / daily by subcutaneous injection

P.K

Therapeutic effects of teriparatide depend upon the pattern of systemic exposure.

- Once-daily administration of teriparatide stimulates **new bone formation** by preferential stimulation of osteoblastic activity over osteoclastic activity.
- By contrast, continuous administration of teriparatide , may be detrimental to the skeleton because **bone resorption** may be stimulated more than bone formation.
- Should be given intermitted not continuous

Use

- Good for **postmenopausal** osteoporosis.
- For treatment of **osteoporosis** in people who have a risk of getting fracture (increased bone mass & strength)
- Used in severe osteoporosis or patients not responding to other drugs.
- Should not be used routinely due to **carcinogenic effects**. thus Should be given for a limited time (for 2-3 months)

تخيل إن سرطان العظم يضعف العظام ويخليها هشة وسهل تتفتت مثل بودرة تايد

Contraindication

Teriparatide should not be used by people with increased risk for bone tumours (osteosarcoma) including:

بقيت لي شيء ؟ لا، طيري برا

- People with **Paget's** disease of bone. abnormal bone formation because this disease increase osteoclast activity ⟶ resorption of bone + high Ca in blood
- People who had **radiation treatment** involving bones
- Not recommended in **children** (because they still have growing bones)

Tide powder should keep it away from children

ADRs

- Carcinogenic effect (osteosarcoma) documented on rats and it is the most serious effect

Let's suppose that Tide powder is carcinogenic substance

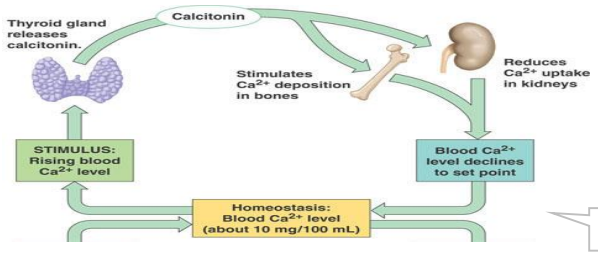
- Elevated serum calcium which may occur in some cases can lead to kidney stones (calcium stones)
- Hypotension when standing (orthostatic hypotension)
- Diarrhea, heart burn, nausea
- Headache
- leg cramps

Calcitonin

Calcitonin

Definition

- Calcitonin is synthesized and secreted by the **parafollicular cells** (C cells) of the thyroid gland.
- It is **released** when there is a rise in plasma Ca^{2+} levels. In opposition to PTH and Vit.D
- While PTH and vitamin D act to increase plasma Ca^{2+}, **only calcitonin causes a decrease in plasma Ca^{2+}**
  Calcitonin, Cancel the calcium from plasma.
- Calcitonin protects against development of hypercalcemia caused by a variety of conditions (released upon stimulus): including increased calcium absorption (milk-alkali syndrome[1]) and decreased calcium excretion (thiazide use) very important diuretic.
  I order a milk, cancel it please
  (calcitonin) ذا يزيد الكالوري ؟



Calcitonin does not appear to be critical for the regulation of calcium homeostasis even if thyroid gland is removed.

The stimulus of calcitonin is Hypercalcemia.

Effect

The major effect of calcitonin administration is a rapid fall in Ca^{2+} (serum calcium) caused by:

- Inhibiting bone resorption by **inhibiting osteoclast** activity.
  The osteoclast bone cells appear to be a particular target of calcitonin
- **Decreasing reabsorption** of Ca^{2+} & PO_4 by the kidney, thus increasing their excretion.

P.K

Routes of administration:
S.C., Nasal spray or solution (Calcitonin Salmon) has more affinity towards human calcitonin receptors in the lumen.

Use

Used clinically in treatment of **hypercalcemia** (biggest indication) and in certain bone diseases in which sustained reduction of osteoclastic resorption is therapeutically advantageous.

cancel ym bucket list. (calcitonin), (Paget's)

- Osteoporosis (major indication; alternative to other drugs).
- Hypercalcemia (short-term treatment of hypercalcemia of malignancy), Paget's disease.
- It has **lower efficacy** compared to other drugs. (it is not very effective clinically)

ADRs

- Nausea
- Local inflammation at site of injection
- Flushing of face & hands
- Nasal irritation

[1] Milk-alkali syndrome: back in the time they were treating patient with peptic ulcers by giving a lot of milk and absorbable alkaline, calcium and alkaline accumulated which caused metabolic alkalosis

Vitamin D

Vitamin D

Important for SAQ

Definition

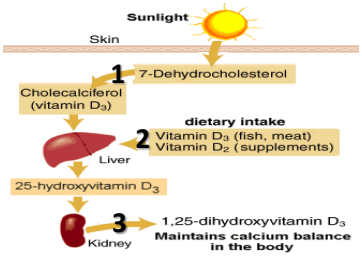
- Vitamin D is a **steroid** hormone that is intimately involved in the regulation of plasma calcium levels. (phosphate as well)
- Its role in calcium metabolism first was recognized in the childhood disease **rickets** and **osteomalacia** in adult, which is characterized by hypocalcaemia and various skeletal abnormalities.

Metabolism

1. dietary intake or Exposure to the ultraviolet rays in the sunlight convert 7-dehydrocholesterol to cholecalciferol (vitamin D3)

2. The initial transformation ,Vitamin D3 is metabolically inactive until it is hydroxylated in the liver then the in the kidney : parathyroid hormone stimulates the formation of active form of vitamin D **(calcitriol)** (by α hydroxylase) the **active form** 1,25 Dihydroxycholecalciferol. Vitamin D stored in liver, when needed it will go to the kidney and get activated

١- بكل بساطة راح تتعرض للشمس وتكسب فايتمن د٣
٢- بعدين بيروح للكبد ويصير هايدروكسليشن
٣- واخيراً بيروح للكلية ويصير هايدروكسليشن مره ثانيه ويصير اكتف



Forms

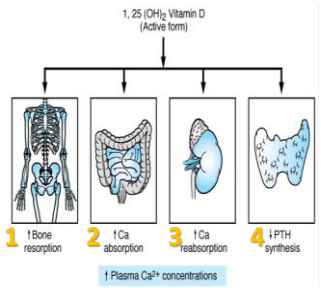
- Cholecalciferol (Vitamin **D3**) in skin:
  Vitamin D3 is usually for vitamin D- fortified (a way to add the micronutrients 'Vit.D' to the food) milk & foods & also available in drug combination products.
- Ergocalciferol (Vitamin **D2**) in plants:
  Vitamin D2 is the prescription form of vitamin D & is also used as food additive (milk).

Vit D2 and Vit D3 have <u>equal</u> biological activities.

Calcium & Vitamin D

Vitamin D:

1. increases bone resorption, Activation of osteoblast
2. increases Ca^{2+} absorption from intestine
3. increases renal Ca^{2+} and PO4 reabsorption
4. decreases the production of PTH by the parathyroid glands.



The overall effect of vitamin D is to <u>increase</u> plasma Ca^{2+} concentrations.

Vitamin D

Vitamin D	
Deficiency	• Rickets (الكساح) in small children • Osteomalacia • Osteoporosis
Use	• Rickets & Osteomalacia • Osteoporosis • Psoriasis (autoimmune disease that affects the skin and administration of vit.D help improve it) • Cancer prevention (prostate & colorectal)

SAQ

Remember that:

1,25-dihydroxyvitamin D (calcitriol) is the most **active** form of vitamin D.

25-hydroxyvitamin D (calcidiol, 25-hydroxycholecalciferol): an **inactive** form of vitamin D. (but, more than calcitriol)

1alpha-hydroxylase: The **enzyme** that converts the inactive form of vitamin D.

Summary

Parathyroid Hormone

Definition:
released from the parathyroid gland in response to low plasma Ca2+ level .

Response: "given S.C"

- **Intermittent:** ↑ Osteoblast number/function → Bone formation→ ↑Bone mass/strength

- **Continuous:** ↑ Osteoclast → Bone resorption →↑ Serum Ca^{2+}
  Which will weakens the bones over time

Use:
1-Treatment of severe **osteoporosis**
2-Resistant cases failed to respond to other medications

Vitamin D

Definition:
a steroid hormone involved in the regulation of plasma calcium levels & increase its level.

Forms:

- Cholecalciferol (Vitamin D3) in skin
- Ergocalciferol (Vitamin D2) in plants
- Calcitriol 1,25-dihydroxyvitaminD is the active form

Deficiency lead to:
Rickets , Osteomalacia, Osteoporosis

Use:
Rickets & Osteomalacia, Osteoporosis, Cancer prevention

Teriparatide

M.O.A:
PTH analogue, anti-osteoporosis (anabolic) → stimulate new bone formation if given intermittently

- If given continuously → bone reabsorbtion
- Should be given intermitted not continuous

Use:
postmenopausal osteoporosis
Should not be used routinely due to carcinogenic effects

Contraindication:
(osteosarcoma) →Paget's disease, radiation treatment, children

ADRs:
Carcinogenic effect, lead to kidney stones ,orthostatic hypotension

Calcitonin

Definition:
secreted by (C cells) of the thyroid gland.
released when there is a rise in plasma Ca2+ levels to ↑ its absorption

- Inhibit osteoclast activity→ inhibiting bone reabsorption.
- It has lower efficacy compared to the other drugs.

Roots of administration:
S.C , Nasal spray or solution → has more affinity towards human calcitonin receptors

Use:
Osteoporosis, Hypercalcemia of malignancy → Paget's disease

ADRs:
1-Local inflammation at site of injection
2-Flushing of face & hands
3-Nasal irritation

MCQ

Q1: All of the following increase the level of Ca^{++} in plasma except :

A- Teriparatide. B- Vitamin D. C- Calcitonin.

Q2: What is the stimulus for parathyroid hormones to be secreted from parathyroid gland ?

A- Hypercalcemia. B- Hypocalcaemia. C- Low phosphate concentration in plasma.

Q3: What is the stimulus for calcitonin hormones to be secreted from thyroid gland ?

A- Hypercalcemia. B- Hypocalcaemia. C- High phosphate concentration in plasma.

Q4: Which one of the following methods is preferred to be used in case of PTH & Teriparatide to treat osteoporosis ?

A- Continuous. B- intermittent. C- Both of them.

Q5: Which one of the following increase the rate of bone resorption ?

A- Continues administration of Teriparatide.
B- Intermitted administration of PTH.
C- Both of them.

Q6: Which one of the following treatment is recommended in case of primary osteoporosis ?**

A- PTH. B- Teriparatide. C- Calcitonin.

Q7: Which one of the following is shown carcinogenic effect in animal experimentation?

A- Chronic exposure to PTH.
B- continuous administration Teriparatide.
C- Vitamin D toxicity.

Q8: Which one of the following is recommended in people with Paget's disease ?

A- Vitamin D. B- Teriparatide. C- Calcitonin.

** Teriparatide is Good for postmenopausal osteoporosis which is primary osteoporosis.

1. C
2. B
3. A
4. B
5. A
6. B
7. B
8. C

MCQ

Q9: Which one of the following should be avoided in people with Paget's disease ?

A- Vitamin D. B- Teriparatide. C- Calcitonin.

Q10: Which one of the following may lead to develop renal stone ?

A- Vitamin D. B- Teriparatide. C- Calcitonin.

Q11: which one of the following is associated with increase the risk of osteosarcoma ?

A- PTH. B- Teriparatide. C- Calcitonin.

Q12: Hypertensive patient who is on hydrochlorothiazide as diuretic, which one of the following is recommended in his case to maintain normal plasma level of calcium ?

A- PTH. B- Teriparatide. C- Calcitonin.

Q13: Orthostatic hypotension is one of adverse effect of which one of the following treatment?

A- PTH. B- Teriparatide. C- Calcitonin.

Q14: Patient with peptic ulcers was treated by giving a lot of milk and absorbable alkaline which caused metabolic alkalosis and electrolytes disturbance, which one of the following can be used to correct his plasma level of calcium ?

A- PTH. B- Teriparatide. C- Calcitonin.

Q15:Which one has more affinity towards human calcitonin receptors ?

A- Recombinant human calcitonin. B- Calcitonin Salmon. C- Synthesized calcitonin.

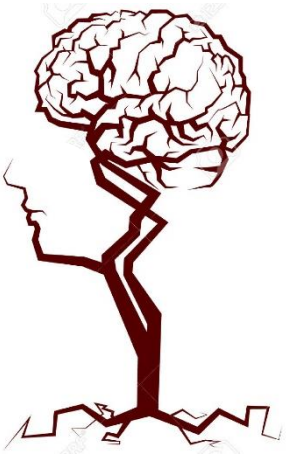
Q16: 5 years old child who has Rickets, which one of the following can be helpful to be given to him ?

A- Teriparatide. B- Vitamin D. C- Calcitonin.

Q17: Which one of the following has shown protective effect against colorectal cancer ?

A- Teriparatide. B- Vitamin D. C- Calcitonin.

9. B
10. B
11. B
12. C
13. B
14. C
15. B
16. B
17. B



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قادة فريق علم الأدوية :

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References :
1- 436 Prof. Yieldez's slides and notes
2- 436 Dr. Ishfaq's slides and notes