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

- Calcium plays an essential role in many cellular processes, including:
  1. muscle contraction,
  2. hormone secretion,
  3. cell proliferation,
  4. gene expression,
  5. bone synthesis,
  6. 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.

Three principal hormones regulate Ca\(^{2+}\) homeostasis:
1. Parathyroid hormone (PTH)
2. Vitamin D
3. Calcitonin

Three target tissues regulate calcium homeostasis and Vitamin D:
1. Bone
2. Kidney
3. Intestine

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

**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:
  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

![Diagram](image)

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\(^{2+}\)

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

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

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

P.K

- 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)

Use

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

- 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)

Contraindication

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

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Teriparatide

Teriparatide

Parathyroid Hormone

Teriparatide (Teriparad) = طيري برا فيو تايد (مد وجزر)
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 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.

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.

**Use**

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

- 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

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\(^1\) 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

**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.

**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 equal biological activities.

**Calcium & Vitamin D**

- increases bone resorption, Activation of osteoblast
- increases Ca\(^{2+}\) absorption from intestine
- increases renal Ca\(^{2+}\) and PO\(_4\) reabsorption
- decreases the production of PTH by the parathyroid glands.

The overall effect of vitamin D is to **increase plasma Ca\(^{2+}\) concentrations.**
### 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)

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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 Ca$^{2+}$ level.

**Response:** “given S.C”
- **Intermittent:** ↑ Osteoblast number/function → Bone formation → ↑ Bone mass/strength
- **Continuous:** ↑ Osteoclast → Bone resorption → ↑ Serum Ca$^{2+}$
  Which will weaken the bones over time

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

**Teriparatide**

**M.O.A.:**
PTH analogue, anti-osteoporosis (anabolic) → stimulate new bone formation if given intermittently
- If given continuously → bone reabsorption
- Should be given **intermittent** 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

**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

**Calcitonin**

**Definition:**
secreted by (C cells) of the thyroid gland. released when there is a rise in plasma Ca$^{2+}$ 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\textsuperscript{++} in plasma except:
A- Teriparatide. B- Vitamin D. C- Calcitonin.

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

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

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.
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?

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.
قادة فريق علم الأدوية:
- جومانا القحطاني
- اللولو الصليهم
- فارس النفيسة

الشكر موصول لأعضاء الفريق المتميزين:
- روان سعد القحطاني
- سعد الرشود
- فيصل العباد
- جواهر ابانمي
- انوار العجمي
- وجدان الزيد

References:
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