Revised & Approved

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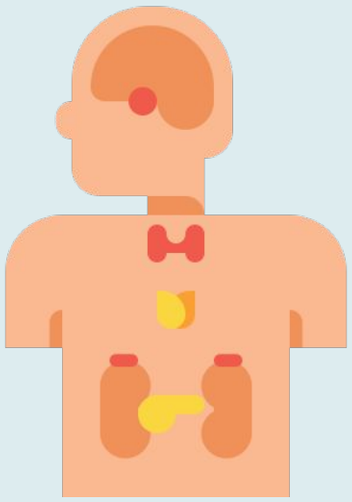
Pharmacology 439

MED439



Endocrine Block

Pharmacology Team 439

Helpful video

**Color index:**

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

# Pharmacology of drugs used in calcium & Vit D disorders

**We highly recommend studying physiology of calcium homeostasis before this lecture**

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.

Editing file | Summary

# Bones

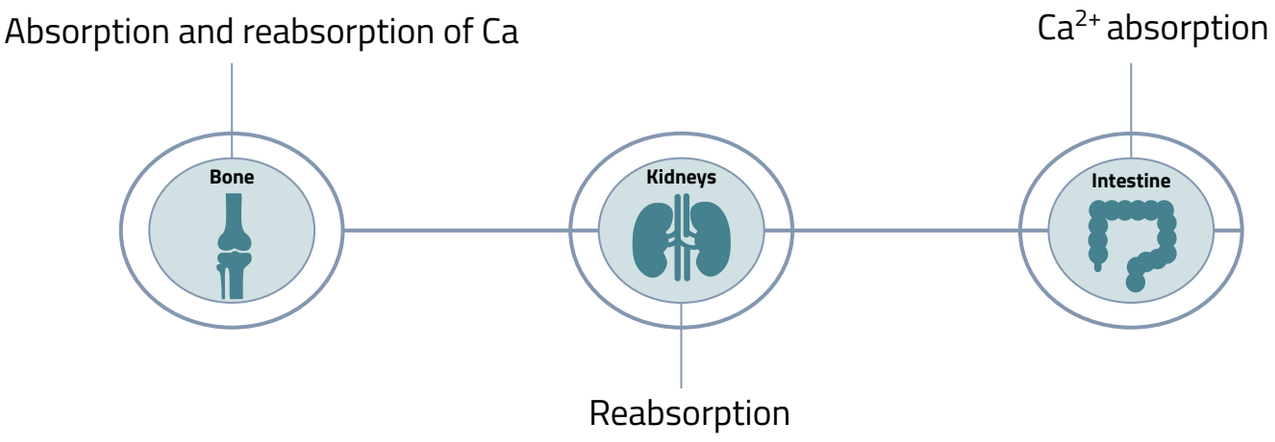
- A dynamic organ that undergoes continuous remodeling process involving resorption of old bone by osteoclast & formation of new bone by osteoblast.
- The dominant site of calcium storage in the body is bone, which contains nearly 99.9% of body calcium.
- Although only a small fraction of total body 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 Vit. D.


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

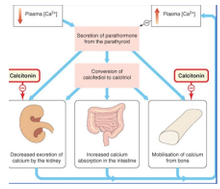
## 3 principal <u>hormones</u> regulate $Ca^{2+}$ homeostasis

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

## 3 target <u>tissues</u> regulate $Ca^{2+}$ homeostasis and Vit. D



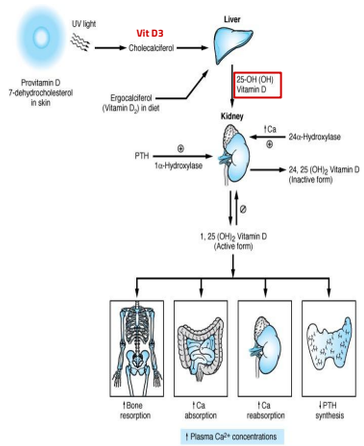
## Parathyroid Hormone

| | |
|---|---|
| **Definition** | ● PTH: A hormone that plays a critical role in controlling calcium, and phosphate balance.<br>● PTH is released from the parathyroid gland in response to low plasma $Ca^{2+}$ level, its secretion is inversely related to [$Ca^{2+}$ ] |
| **Action** | ● **Bone:** Mobilization of $Ca^{2+}$ and $PO_4^{3-}$ from bone.<br>In response to hypocalcemia , PTH stimulates osteoclasts cells to ↑ the outward flux of calcium from bone to restore serum calcium level.<br>● **Kidney:** ↑ calcium active reabsorption and ↑ formation of calcitriol which is the active form of vitamin D (by stimulating 1-α-hydroxylase enzyme in the kidney)<br>● **GIT:** ↑ absorption of calcium in the presence of permissive amount of Vit D<br>**The overall action of PTH is to ↑ plasma $Ca^{2+}$ levels in response to hypocalcemia**<br>  |
| **Effects** | ● **Daily, Intermittent** administration of recombinant human PTH, for 1 to 2 hours/day S.C in the thigh (alternate thigh every day ) leads to a net stimulation of bone formation for treatment of osteoporosis. You must have gaps in administration to avoid fractures<br>- **Mechanism:** ↑ Osteoblast number/function→ ↑ Bone formation→ ↑ Bone mass/strength (Anabolic action)<br>● **Continuous or chronic exposure** elevated PTH leads to bone resorption and risk of fracture (as seen with primary or secondary hyperparathyroidism)<br>- **Mechanism:** ↑ Osteoclast → ↑ Bone resorption → ↑ Serum $Ca^{2+}$ (more than bone formation) |
| **Uses** | ● Treatment of severe osteoporosis<br>● Resistant cases failed to respond to other medications |

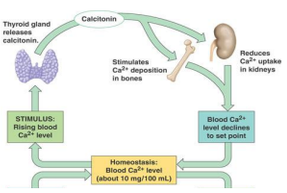
## Teriparatide

| | |
|---|---|
| **Definition** | Synthetic polypeptide form of PTH ( PTH analogue).<br>It belongs to a class of anti- osteoporosis drugs, the so-called "anabolic" agents (=stimulate bone formation). |
| **P.K** | Given once daily as subcutaneous injection |
| **Effects**<br>Female Only | As PTH, the therapeutic effects of teriparatide depend upon the pattern of systemic exposure:<br>- **Once daily administration** → stimulates new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity.<br>- **Continuous administration** → may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation (↑ risk of fracture). |
| **Uses** | ● Should not be used routinely due to carcinogenic effects.<br>● Use in severe osteoporosis or patients not responding to other drugs.<br>● For treatment of osteoporosis in people who have a risk of getting fracture (increase bone mass & strength)<br>● Good for postmenopausal osteoporosis.<br>● **Note:** Patients receiving Teriparatide must have sufficient intake of vitamin D and calcium.<br>(In Hypocalcemia , there will be an exaggerated effect due to PTH release. So it's recommended that the patient complete a supplementation course first) |
| **ADR** | ● **Carcinogenic effect (development of osteosarcoma)** rare but serious<br>● Diarrhea, heartburn, nausea<br>● Elevated serum calcium can occur in some cases leading to kidney stones.<br>● Headache, leg cramps<br>● Orthostatic hypotension |
| **C.I** | Should not be used by people with increased risk for bone tumors (osteosarcoma) including:<br>● People with paget's disease of bone (can transform to malignant bone cancer).<br>● People who had radiation treatment involving bones (malignancy risk)<br>● Not recommended in children |

## Vitamin D

| | |
|---|---|
| **Definition** | • Vitamin D is a steroid hormone that is intimately involved in the regulation of plasma calcium levels. |
| **Forms** | • **Cholecalciferol (Vitamin D3):** found in the skin.<br>- Vitamin D3 is usually for vitamin D-fortified milk & foods.<br>- It's also available in drug combination product.<br>• **Ergocalciferol (Vitamin D2):** found in the plants.<br>- Vitamin D2 is the prescription form of vitamin D<br>- It's also used as food additive (milk + egg yolk, & fish oil)<br>• **Both:** Vit D2 and Vit D3 have equal biological activities.<br>- both travel to the liver and then convert to their active form in the kidneys.<br>• **Calcifediol** is the major circulating form and principle storage form of Vit. D<br>• **Calcitriol** is the active form of Vit D. |
| **Metabolism** | **1. Sunshine** (UV light)**:** Cholecalciferol (D3) is generated in the skin from 7-dehydrocholesterol by the action of ultraviolet radiation (sunshine).<br><br>**2. The Liver:** The initial transformation of (Vit D3) & Vit D2 occurs in liver to (Calcifediol) the main storage form of Vit D in our body.<br><br>**3. In the kidney:** parathyroid hormone stimulates the formation of the active form of vitamin D (calcitriol/1,25 Dihydroxycholecalciferol) by α hydroxylase.)<br>  |
| **Effects** | • **Bone:** Activation of osteoblast cells<br>(↑ resorption ⟶ ↑ Ca in the blood ⟶ stimulate osteoblast activity).<br>• **Kidney:** Increased reabsorption of $Ca^{2+}$ & $PO_4$.<br>• **GIT:** Increased absorption of $Ca^{2+}$ from the intestine.<br>• Decreases the production of PTH by the parathyroid glands<br>(Vit D ⟶ increase Ca ⟶ decrease in PTH).<br>• **The overall effect of vitamin D is to increase plasma $Ca^{2+}$ concentrations.** |

## Calcitonin

| | |
|---|---|
| **Definition** | • **Produced by** the parafollicular cells (C cells) of the thyroid gland.<br>• It is released when there is an elevated level of $Ca^{2+}$ in the blood.<br>• Calcitonin does **not** appear to be critical for the regulation of calcium homeostasis even if thyroid gland is removed. |
| **Effects** | **The major effect of calcitonin administration is a rapid fall in $Ca^{2+}$**<br>• **Bone:** Decrease bone resorption by inhibiting osteoclast activity.<br>• **Kidney:** Decreases reabsorption of $Ca^{2+}$ & $PO_4$, thus increasing their excretion.<br>  |
| **P.k** | **Route of administration:** S.C, Nasal spray. |
| **Uses** | • Osteoporosis (major indication of calcitonin; alternative to other drugs)<br>(by inhibition of osteoclasts ⟶ ↓ bone loss).<br>• Hypercalcemia (short-term treatment of hypercalcemia of malignancy), or in **Paget's disease**. Remember Teriparatide was C.I. for paget's disease |
| **ADRs** | • Nausea<br>• Local inflammation (at site of Injection)<br>• Flushing of face & hands<br>• Nasal irritation (nasal spray) |

# Summary

| Drug | M.O.A | Uses | ADRs |
|---|---|---|---|
| **Parathyroid Hormone** | Released in response to low $Ca^{2+}$ level<br>- ↑ plasma $Ca^{2+}$ levels by:<br>- **Bone**: stimulation of osteoclasts to ↑ outward flux of $Ca^{2+}$ to restore serum calcium level<br>- **Kidney**: ↑ $Ca^{2+}$ active reabsorption and ↑ formation of calcitriol<br>- **GIT**: ↑ reabsorption of $Ca^{2+}$ | - Severe osteoporosis<br>- Resistant cases | - |
| **Teriparatide** | Synthetic polypeptide form of PTH (PTH analogue)<br>same mechanism of action | - Severe osteoporosis<br>- Resistant cases<br>- Osteoporosis in people who have a risk of getting **fracture**<br>- **Postmenopausal** osteoporosis. | - **Carcinogenic** effect (osteosarcoma)<br>- Elevated serum calcium ⟶ kidney **stones**.<br>- Headache, leg cramps<br>- Orthostatic hypotension |
| **Calcitonin** | ● Released in response to ↑ plasma $Ca^{2+}$ levels.<br>● Causes rapid fall in $Ca^{2+}$ through:<br>- **Bone:** ↓ resorption by inhibiting osteoclast activity.<br>- **Kidney:** ↓ reabsorption of $Ca^{2+}$ & $PO_4$ | - Osteoporosis (major indication; **alternative** to other drugs) .<br>- **Hypercalcemia** (short-term treatment of hypercalcemia of malignancy), **Pagets disease.** | - Nausea<br>- Local inflammation (Injection)<br>- Flushing of face & hands<br>- Nasal irritation |
| **Vitamin D**<br>2 Forms:<br>- D3 cholecalciferol [skin]<br>- D2 Ergocalciferol [plant] | - ↑ plasma $Ca^{2+}$ levels:<br>- **Bone**: ↑ bone resorption<br>- **Kidney**: ↑ reabsorption of $Ca^{2+}$<br>- **GIT**: ↑ $Ca^{2+}$ absorption | - | - |

# MCQs

| | | | |
|---|---|---|---|
| Q1: which of the following is C.I of Teriparatide | | | |
| A- CVS disease | B-Elderly | C-renal stones | D-Radiation therapy |
| Q2: Route of administration of Calcitonin | | | |
| A- I.V | B- I.M | C- S.C | D-Capsules |
| Q3: Administration of parathyroid hormone must be : | | | |
| A- continuous | B- intermittent | C- continuous following loading dose | D- |
| Q4: Calcitonin effect on the kidney : | | | |
| A- decrease renal $Ca^{2+}$ absorption and increase PO4 reabsorption | B-Decreases renal $Ca^{2+}$ and PO4 reabsorption | C-increases renal $Ca^{2+}$ absorption and decreases PO4 reabsorption | D-Increases renal $Ca^{2+}$ and PO4 reabsorption |
| Q5: PTH stimulates which of the following Cells to restore normal Ca level | | | |
| A- osteoblasts | B- osteoclasts | C- parafollicular cells | D-chief cells |
| Q6: Which one of the following can be used in case of Paget's disease ? | | | |
| A- PTH analogue | B- Vit D | C- Calcitonin | PTH |
| Q7: Vitamin D's effect on the kidney : | | | |
| A- Decreases renal $Ca^{2+}$ and PO4 reabsorption | B-Increases renal $Ca^{2+}$ and PO4 reabsorption | C-decrease renal $Ca^{2+}$ absorption and increase PO4 reabsorption | D-increases renal $Ca^{2+}$ absorption and decreases PO4 reabsorption |
| Q8: which one of the following is associated with increase the risk of osteosarcoma ? | | | |
| A- Calcitonin | B- Vit D | C- teriparatide | D- PTH |

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| D | C | B | B | B | C | B | C |

# SAQ

**Q1) 50-year old woman visits her family physician and the physician prescribes her medication to prevent postmenopausal osteoporosis**

**a) Name the drug that the physician prescribed**
**b) List the possible responses of the drug based on administration habits**
**c) Mention 3 side effects of the the drug**

**Q2) list 3 forms of Vit D and where can they be found?**

# Answers

A1) Teripeptide ( PTH analogue)

B1) **Once daily administration** → stimulates new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity.

**Continuous administration**→ may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation

C1) Osteosarcoma, diarrhea, nausea, headache, leg cramps,

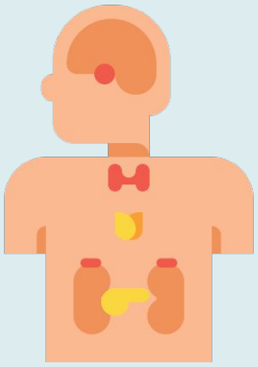
A2)

1-**Cholecalciferol (Vitamin D3):** found in the skin

2-**Ergocalciferol (Vitamin D2):** found in the plants.

3-**Calcifediol :** is the major circulating form and principle storage form of vitamin D

Feedback Form



# Endocrine Block

Pharmacology Team 439

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