Calcium, phosphate and vit D

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Slides from Dr Nibras and Dr Walaa

Vitamin D

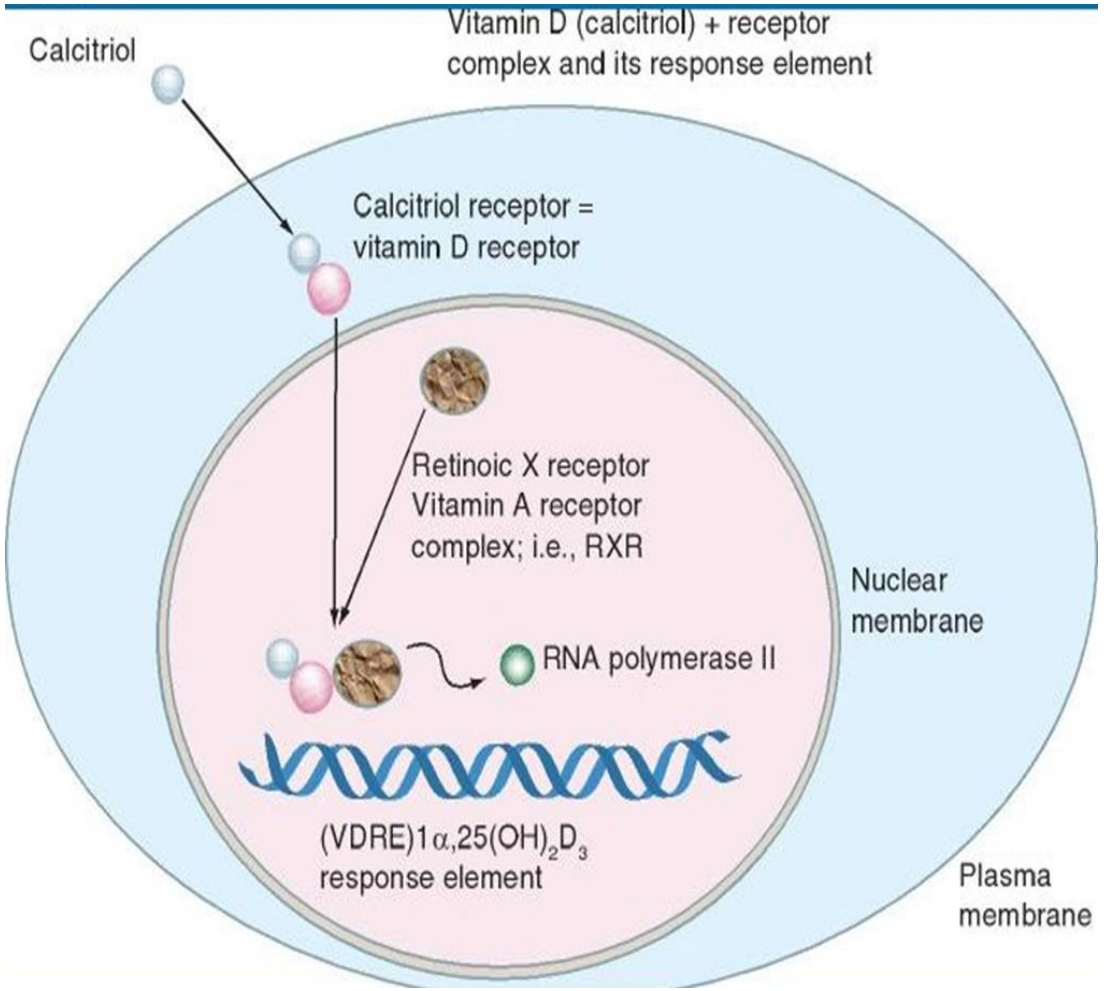
I. Calcitriol has a ***receptor protein*** in target cells which specifically binds calcitriol

II. → binds to a ***vitamin D response element*** in the nuclear DNA.

III. → regulation of transcription of specific genes in target cells → controlling the synthesis of proteins

The target genes can be either upregulated or downregulated.

An example of ***upregulation*** is ***calcium-binding proteins (CaBPs), which facilitate intestinal calcium absorption***.



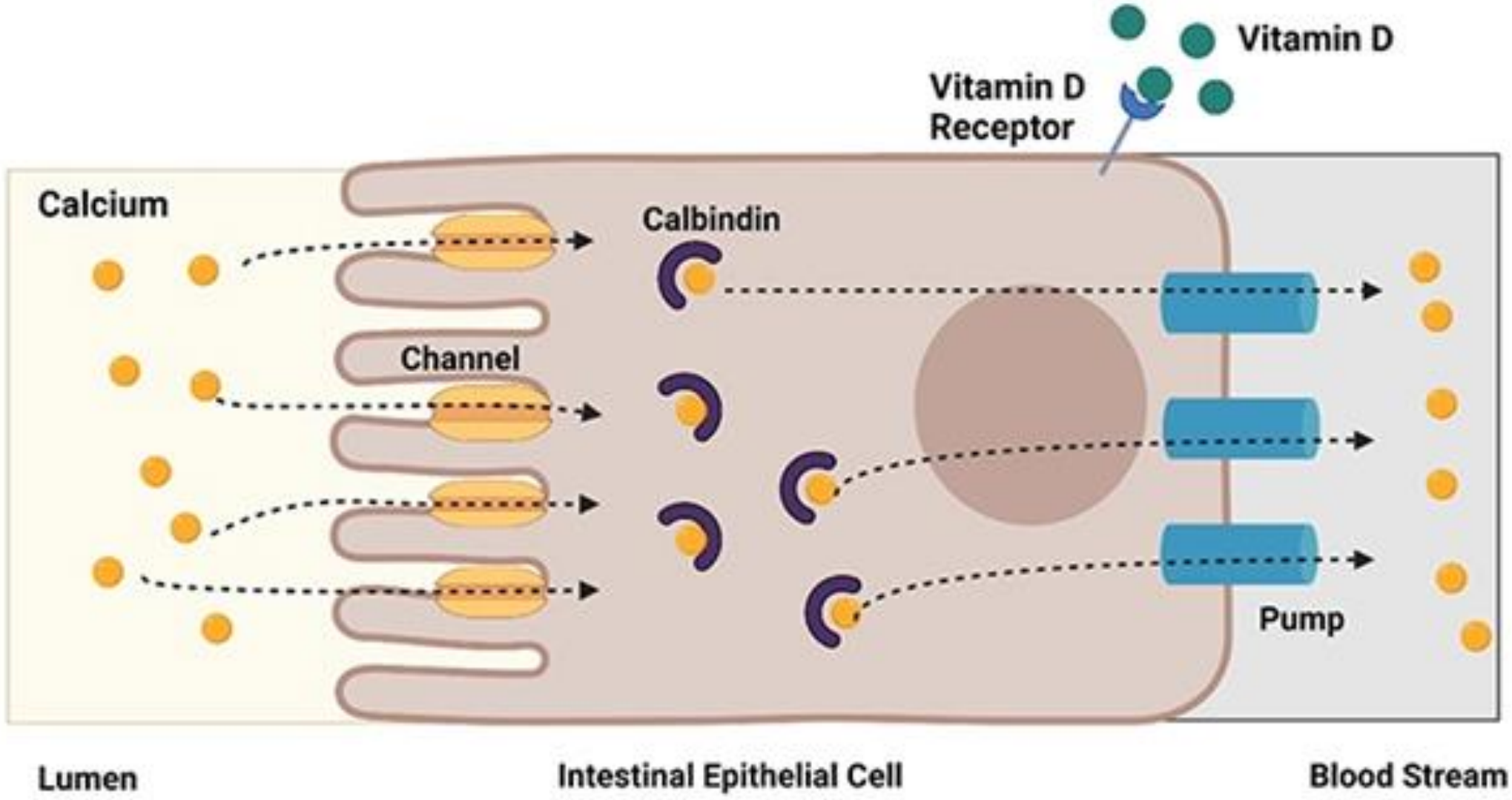
Function of Calcitriol

The main function of calcitriol is the **maintenance of serum calcium level** through its effect on *intestine, kidney, bones*.

1. ↑ calcium absorption by ***intestinal mucosal cells***.
   - This is mainly through increasing the synthesis of mRNA responsible for synthesis of a ***calcium binding protein*** (calbindin)
   - Also increases the transport of calcium ions through the brush and lateral borders of mucosal cells.

2. ↑ reabsorption of calcium and phosphorus by ***renal tubules***.

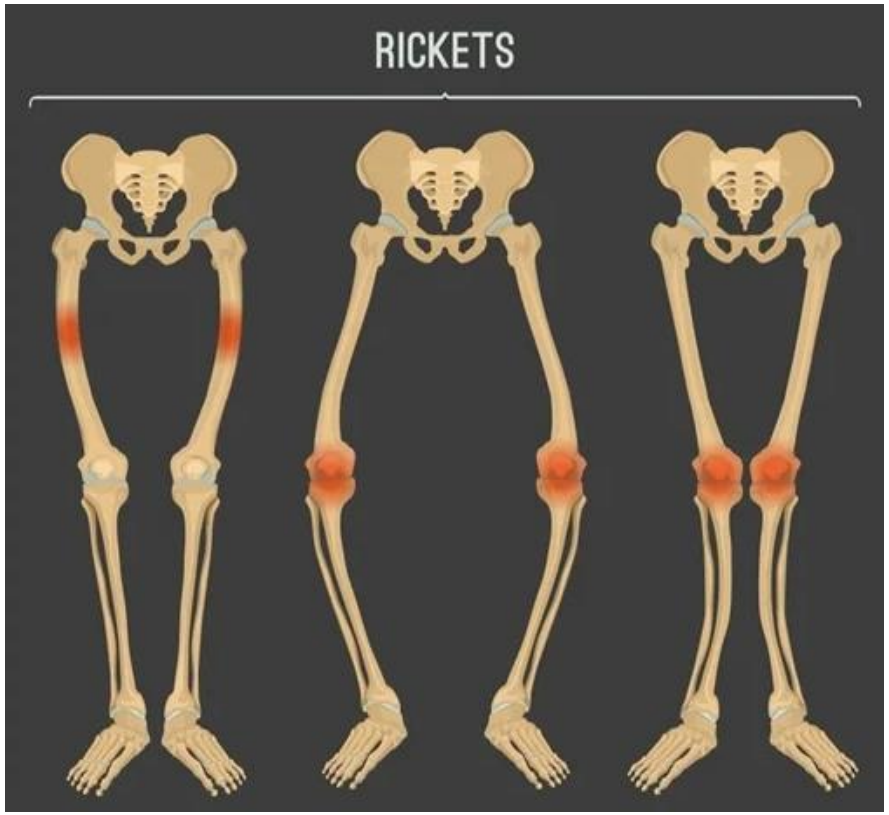
3. It promotes ***bone*** calcification by providing calcium and phosphate.
   - At low levels; calcitriol increases bone mineralization,
   - At higher levels; calcitriol increases bone resorption (likely minor)


Vitamin D
Vitamin D
Receptor
Calcium
Calbindin
Channel
Pump
Lumen
Intestinal Epithelial Cell
Blood Stream

Vitamin D Deficiency Manifestations

In adults: *Osteomalacia*
In infants: *Rickets*

Both diseases are treated by injections of vitamin D and calcium.



❖ **Rickets:**

Causes of rickets include the following:

- ❑ Malnutrition
- ❑ No exposure to sunlight
- ❑ Hereditary; due to
  Deficiency of ***1- hydroxylase***
  Defects that lead to non-functional calcitriol receptors.

Rickets

The main changes that occur in rickets are mainly as follows:

I. Changes in plasma level of calcium and phosphate:

- Level of calcium ***only slightly decreased*** or even ***not changed***.
- Level of phosphate is ***greatly decreased***.

  - Due to **increased activity of parathyroid hormone** which ***prevents the calcium level from falling*** by promoting mobilization of calcium from bones.

The increased activity of parathyroid hormone also increases excretion of phosphates in urine which produces ***decrease in plasma phosphate level.***

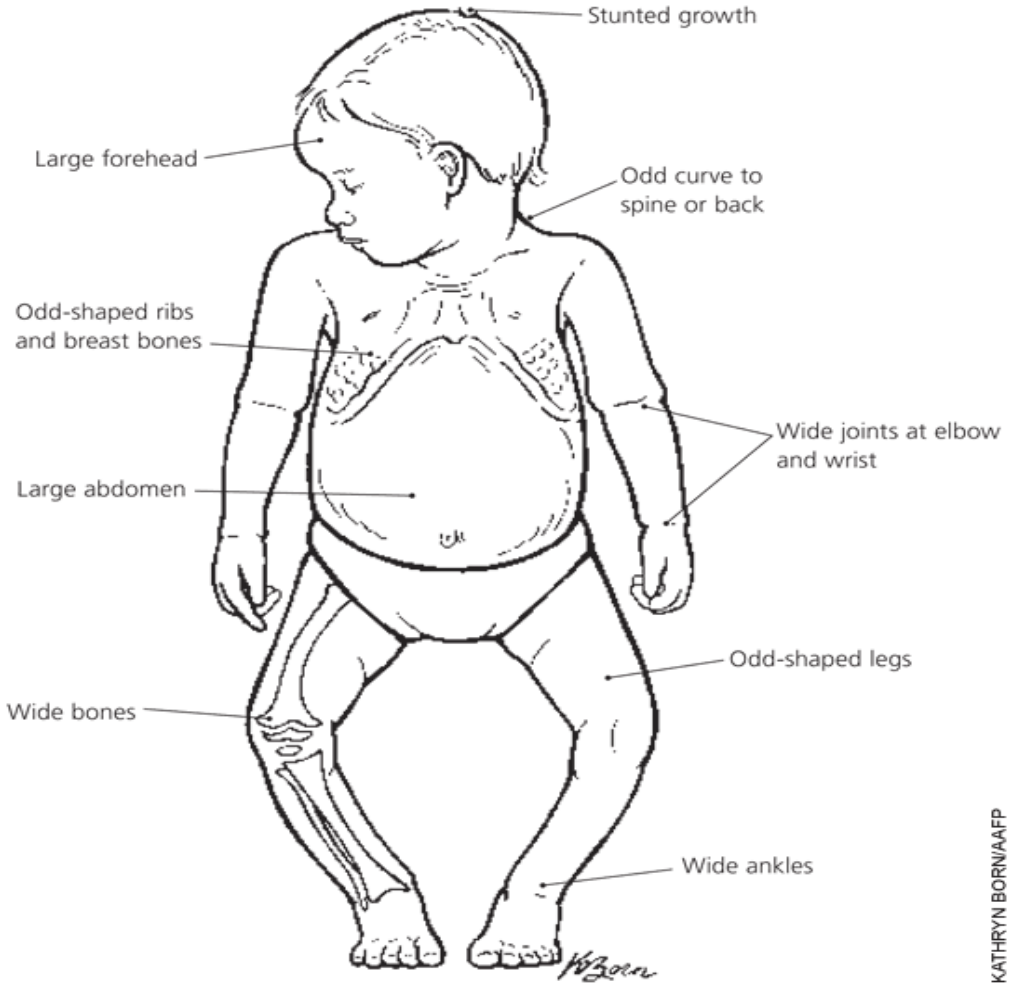
❖ Decreased level of plasma calcium occurs very late in rickets when calcium of bones becomes exhausted and if the drop is severe (below 7 mg/dl) produces **tetany.**

Rickets

II. Changes in teeth and bones:

- Delayed eruption of teeth and delayed closure of fontanelles are early symptoms of rickets.

- Decalcification of bones produce very weak and soft bones which produce bone deformities.



Renal Rickets

- It is a type of rickets or osteomalacia produced due to ***prolonged renal damage***.
- The cause is mainly due to ***failure of the damaged kidneys to form 1,25 $(OH)_2D3$***.
- It is treated by injection of 1,25 $(OH)_2D3$

Vitamin D resistant rickets

Also known as **Congenital hypophosphatemia** or **X-linked hypophosphatemia** (**XLH**).

Form of rickets (or osteomalacia) that differs from most cases of rickets in that ***calcium and vitamin D supplementation do not cure it.***

- XLH is associated with a mutation in the **PHEX gene sequence**, located on the human X chromosome.
- The PHEX protein regulates another protein called fibroblast growth factor 23 (produced from the FGF-23 gene).
- FGF-23 normally ***inhibits*** the kidneys' ability to reabsorb phosphate into the bloodstream.

Vitamin D resistant rickets

- Gene mutations in PHEX prevent the kidney from correctly regulating FGF-23.
- The resulting overactivity of FGF-23 ***reduces*** vitamin D ***1α-hydroxylation*** and ***phosphate reabsorption*** by the kidneys, leading to hypophosphatemia.
- This type of rickets is *treated with phosphate compounds and calcitriol.*

Calcium in the body

- Total amount in the body is appx 1kg (99% as hydroxyapatite in bone)
    - 0.2% in soft tissues + EC fluid
    - 400mg of Ca exchanged daily btwn EC fluid and bone

- Blood Ca (normal is 8.5-10.4 mg/dl): most is present in plasma
    - Non-diffusible form (40%) → bound to plasma proteins and is inactive
    - Diffusible form (60%)
        - Complexed with citrate/ phosphate/ biocarb (10%) → unionized (inactive)
        - Ionized (50%) → CaCl: physiologically active and regulated

- Factors affecting plasma Ca level:
    - PTH and active Vit D (↑ Ca via ↑ absorption from intestines & reabsorption from renal tubules, mobilization from bones)
    - Calcitonin: ↓ Ca by inhibiting mobilization of Ca from bones
    - Plasma proteins: ↓ albumin → ↓ non-diffusible form of Ca → ↓ total plasma Ca (but ionized Ca not affected)
        - Corrected Ca (mg/dl) = Total Ca (mg/dl) + 0.8 (4-albumin (g/dl))
    - Plasma phosphate: if plasma phosphate ↑(e.g. in renal failure) → ↓ plasma ionized Ca

Factors ↑ Ca absorption in intestines

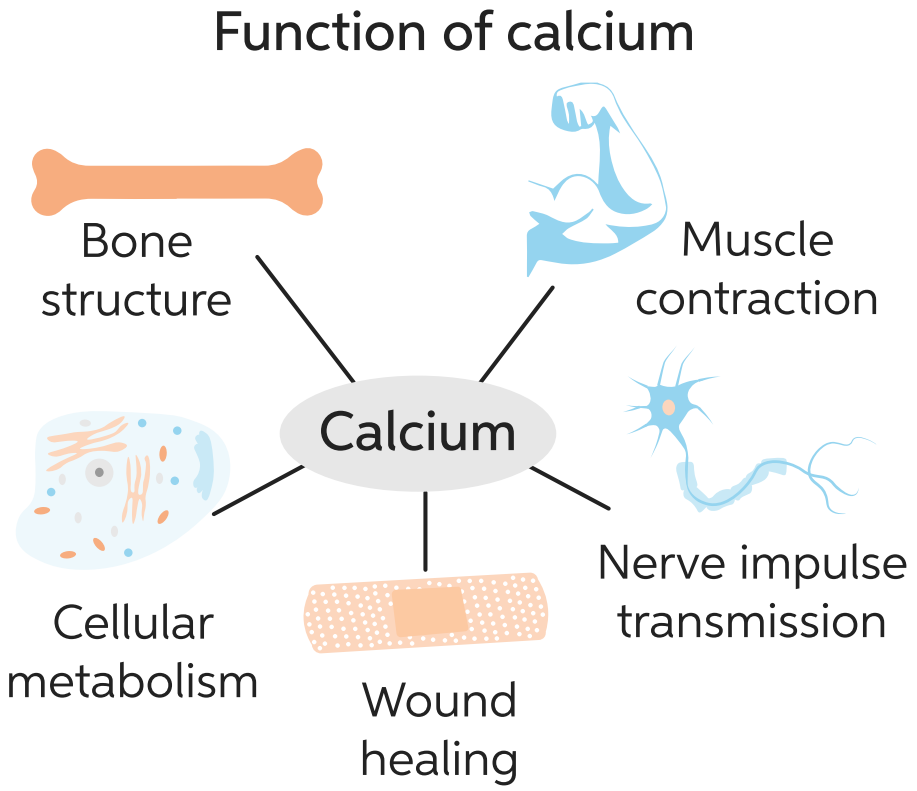
1. **Vitamin D: Calcitriol** induces the synthesis of the carrier protein (**Calbindin)** in the intestinal epithelial cells
2. **Parathyroid hormone:** It increases calcium transport from the intestinal cells.
3. **Acidity:** It favors calcium absorption.

Dietary sources: The best is milk and its products. Egg, fish and vegetables are medium sources for calcium.

Daily Requirement:

Adult men and women: 800 mg/day

Children ,pregnant and lactating women : 800-1200 mg/day



Functions of Calcium

1. Bone/ tooth formation
2. Important in normal contractility of muscle/ nerve transmission
3. It decreases neuromuscular excitability → hypocalcemia leads to tetany
4. Activation of enzymes
5. Secretion of hormones
6. Blood coagulation (factor IV)

Parathyroid hormone (PTH)

PTH is the ***main regulator*** of calcium homeostasis

1. A decrease in plasma calcium concentration is sensed by a **calcium-sensing, G protein–coupled receptor** (CaSR) present in the chief cells of the parathyroid gland and in the kidney tubule.
2. This activates **adenyl cyclase** with consequent increase in intracellular calcium concentration.
3. A kinase is activated, and enzyme systems are activated

- The PTH has three major independent sites of action; bone, kidney and intestines. All the three actions of PTH increase serum calcium level.

Parathyroid hormone (PTH)

↑ calcium and ↓ phosphorus levels in blood through its action on:

1. Bone

In the bone, PTH causes demineralization or decalcification.

It induces **osteoclasts.** The number of osteoclasts are also increased.

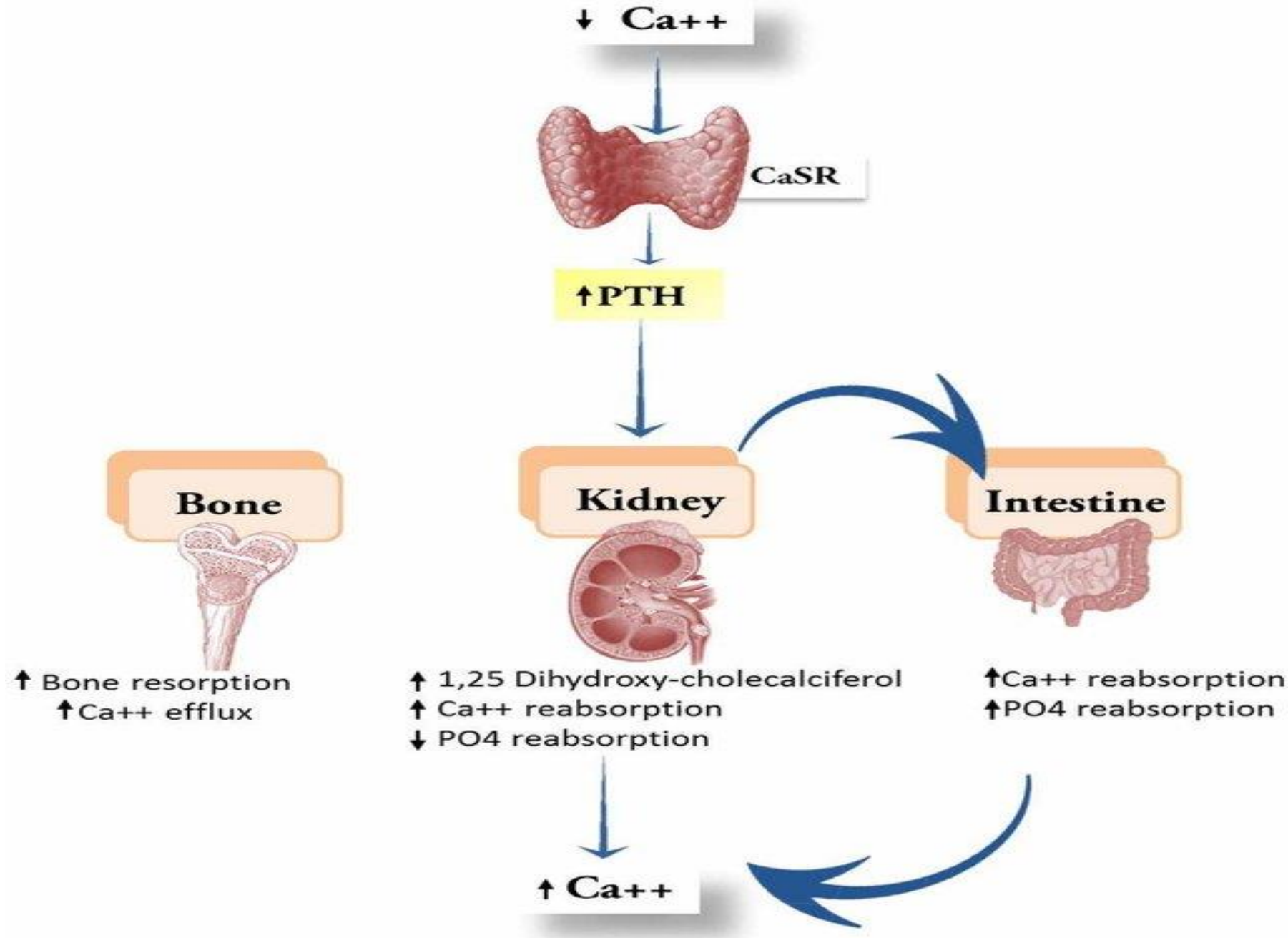
2. Kidney

In kidney, PTH causes ***decreased renal excretion of calcium*** and ***increased excretion of phosphates***. The action is mainly through increase in **reabsorption of calcium** from kidney tubules.

3. Intestines

Stimulates 1α-hydroxylation of 25-hydroxycalciferol in kidney to produce calcitriol.

This **indirectly** increases calcium absorption from intestine.


↓ Ca++
CaSR
↑PTH
Bone
Kidney
Intestine
↑ Bone resorption
↑Ca++ efflux
↑ 1,25 Dihydroxy-cholecalciferol
↑ Ca++ reabsorption
↓ PO4 reabsorption
↑Ca++ reabsorption
↑PO4 reabsorption
↑ Ca++

Calcitonin

Calcitonin inhibits bone resorption

- Calcitonin is secreted by the **thyroid parafollicular cells** when the concentration of Ca2+ in blood ***increases***.

- Calcitonin ***lowers the level of Ca2+*** by inhibiting the actions of both ***PTH and vitamin D.***

❖Its secretion is regulated by plasma calcium through the CaSR: an increase in serum calcium results in a proportional increase in calcitonin, and a decrease elicits a corresponding calcitonin reduction.

Calcitonin level is highly increased in cases of medullary carcinoma of the thyroid gland, so it acts as a tumor marker.

Calcitonin

<u>↓ calcium and ↓ phosphorus levels</u> in blood through its action on

1. Bone

↑ the deposition of calcium and phosphorus in bone by ↓ in the activity of osteoclasts & ↑ the activity of osteoblasts.

2. Kidney:

↓ reabsorption of calcium and phosphorus and ↑ their excretion.

3. Intestine:

↓ calcium absorption by ↓ activity of vitamin D.

DISORDERS OF CALCIUM METABOLISM

I. Hypocalcemia

Serum calcium level of less than 7.5 mg/dL

Clinical features:

1. Neuromuscular irritability, causing muscle twitching (Chvostek sign), spasms (Trousseau sign) and tetany.
2. Seizures
3. Cardiovascular signs; abnormal ECG (QT prolongation).

Chronic hypocalcemia may lead to

- ***Osteomalacia***

Softening of bones caused by defective bone mineralization secondary to inadequate amounts of available Ca and P, or overactive resorption of bone. Osteomalacia in children is known as rickets.

- ***Osteoporosis***

Disease of bones that leads to an increased risk of fractures. Bone mineral density is reduced, bone microarchitecture deteriorates and the amount and variety of proteins in bone is altered.

DISORDERS OF CALCIUM METABOLISM

Causes of Hypocalcemia

1. Hypoparathyroidism
2. Vitamin D deficiency
3. Renal disease
4. Inadequate calcium intake or defect in intestinal absorption of calcium
5. Pseudo – hypoparathyroidism
6. Hypomagnesemia or hypermagnesemia

DISORDERS OF CALCIUM METABOLISM

II. Hypercalcemia

Serum calcium level of more than 11 mg/dL

***Clinical features**:*

1. Psychiatric overtones; anxiety and altered mental status
2. Stones (renal)
3. Bones (pain)
4. Groans (abdominal pain)
5. Thrones (↑ urinary frequency)

DISORDERS OF CALCIUM METABOLISM

Causes of Hypercalcemia

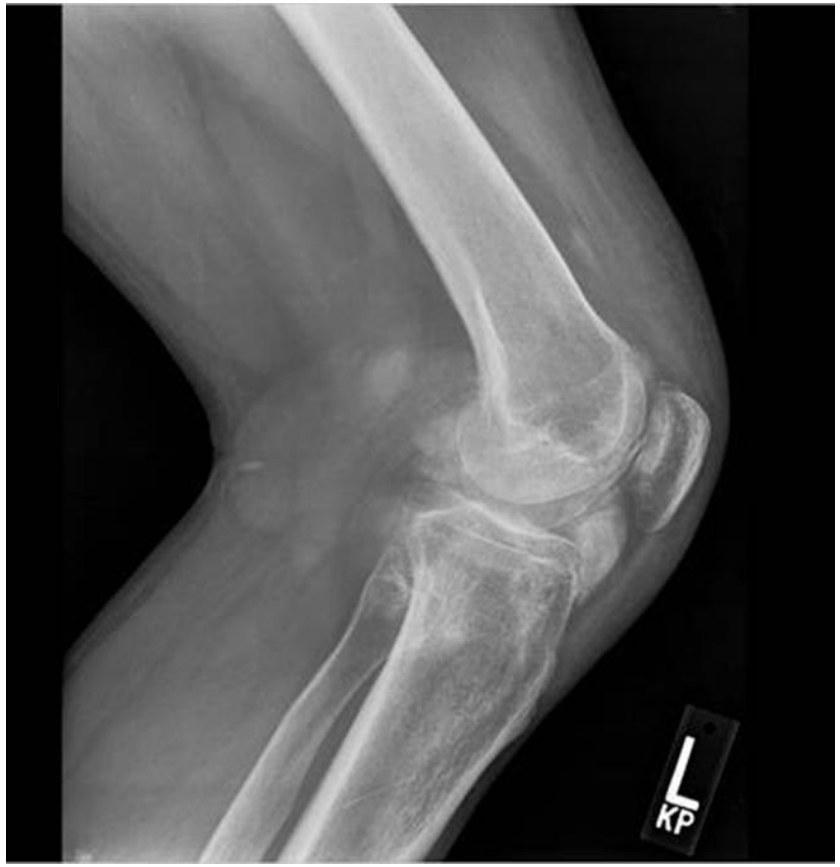
most commonly caused by primary hyperparathyroidism or by malignancy.

Causes:

1. Calcium therapy.
2. Multiple myeloma or secondary bone tumors.
3. Benign familial hypocalciuria
4. Hyperparathyroidism; parathyroid adenoma and PTH secreting tumors
5. Rare; vitamin D toxicity, tuberculosis.

Calcium pyrophosphate deposition disease

- Previously called pseudogout.
- Deposition of calcium pyrophosphate crystals within the joint space.
- Occurs in patients > 50 years old; both sexes affected equally.
- Usually idiopathic, sometimes associated with hemochromatosis, hyperparathyroidism, joint trauma.
- Pain and swelling with acute inflammation (pseudogout) and/or chronic degeneration (pseudo-osteoarthritis).
- Most commonly affected joint is the knee.



Phosphorus, P

Total body phosphate is about 1 kg; 80% of which is seen in bone and teeth and 10% in muscles.

- Phosphate is mainly an intracellular ion and is seen in all cells.
  Serum levels: 2.5 – 4.5 mg/dL in adults and 4 – 6 mg/dL in children.
  40% of phosphorus is found as complexes with Ca, Mg, Na and K, while the rest is protein bound.

Sources: Milk, meat, cereals.

Absorption occurs in small intestine; vitamin D dependent, active transport and through simple diffusion.

Phosphorus, P

Functions of Phosphorus

1. Bone and teeth formation
2. Participates in important compounds; ATP, GTP, creatine phosphate – High energy compounds.
3. Coenzymes: NAD, NADP – Nucleotide
4. Phospholipid synthesis.
5. Acts as phosphate buffer in blood.
6. Covalent modification of enzymes.

Disorders of Phosphate metabolism

Hyperphosphatemia

Causes:

1. Hypoparathyroidism
2. Hypervitaminosis D
3. Renal failure.

Clinical features

1. Renal stones
2. Metastatic calcifications
3. Hypocalcemia

Hypophosphatemia

Causes:

1.Hyperparathyroidism
2. Vitamin D deficiency
3. Malnutrition, Malabsorption
4. Hereditary hypophosphatemia
5. Hypercalcemia

Clinical features:

1. Bone loss
2. Osteomalacia (adults)
3. Rickets (children)