Disorders Of Calcium Metabolism

Outlines

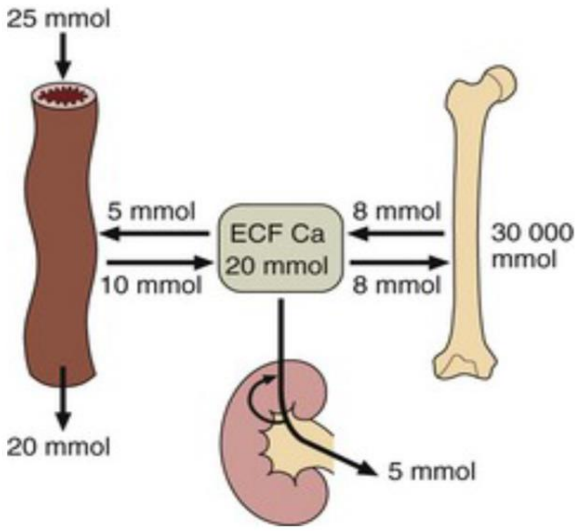
- Functions of serum calcium
- Calcium homeostasis
  1. Parathyroid hormone (PTH)
  2. Vitamin D
  3. Calcitonin
- Serum calcium
- Hypocalcaemia
- Hypercalcaemia
- Serum phosphate
- Bone metabolism markers

Functions of Calcium

- Calcium is the most abundant mineral in the body, there being; about 25 mol (1 kg) in a 70 kg man.
- 99 % of the body calcium is part of bone, mainly as the mineral hydroxyapatite, where it is combined with phosphate. About 85% of the body's phosphate content is in the bone.
- 1% of the body calcium is present in blood and extracellular fluid (ECF)
- Calcium distribution in blood:
  1. 45% circulates as free calcium ions referred to as ionized calcium
  2. 50% is bound to protein (albumin)
  3. 5% is bound to anions such as citrate and phosphate
- The amount of calcium present in the EFC is very small in comparison to that stored in bone.
- Calcium has a lot of cellular and tissue functions involving:
  1. Nerve functions
  2. Membrane permeability
  3. contraction
  4. Glandular secretion
  5. Blood coagulation
- Even in the adult, calcium in bone is not static; some bone is resorbed each day and calcium returned to the ECF.

Normal Calcium Balance

- To maintain calcium balance, an equal amount of bone formation must take place.
- In adults, calcium intake and output are normally in balance. External balance is largely achieved through the body normally matching net absorption over 24 h closely with the corresponding 24-h urinary excretion; this varies with the diet.
- Calcium homeostasis is modulated by:
  1. Parathyroid hormone (PTH)
  2. Calcitriol (Vitamin D)
  3. Calcitonin



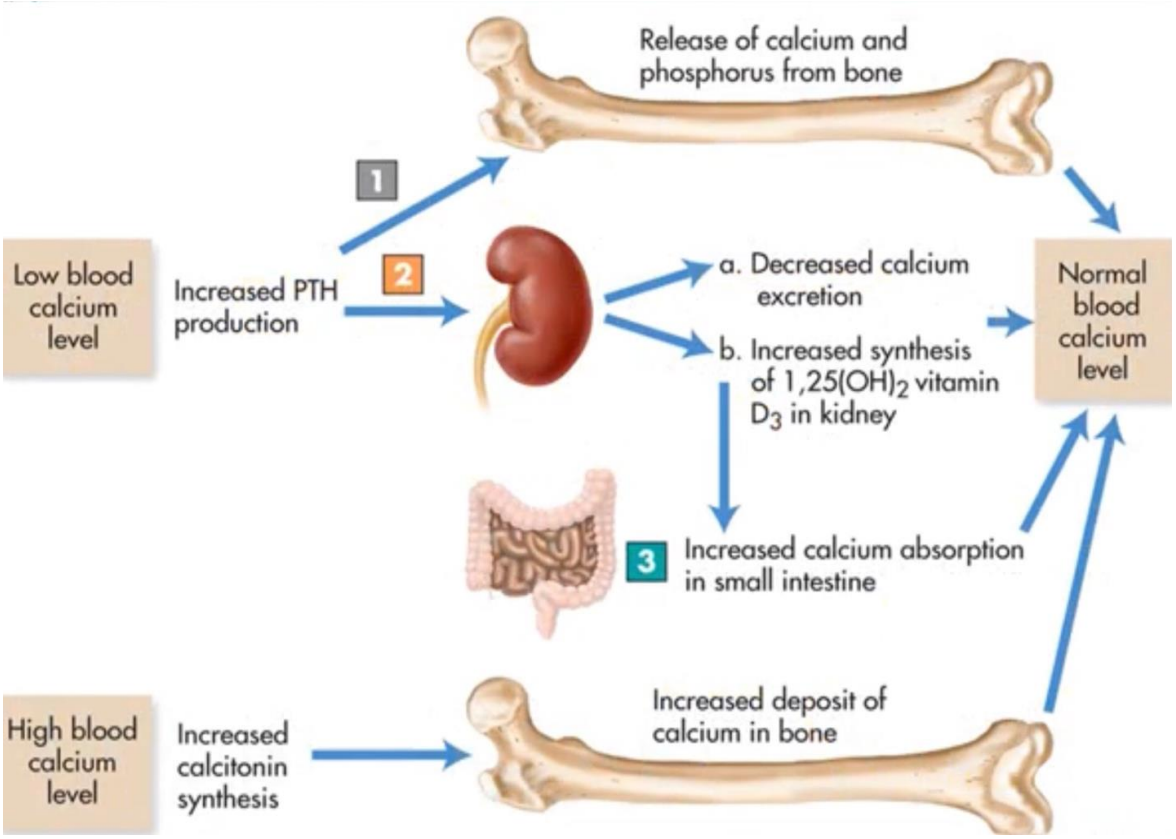
Calcium homeostasis

1. Parathyroid hormone (PTH)

- PTH consists of 84 amino acids, is secrete from parathyroid gland in response to a low ionized calcium

- ***It increases the serum Ca^{2+} and decreases serum PO_4^{3-} by :***

1) **Increase bone resorption (transport of Ca^{2+} from bone to blood) by increase the activity of osteoclasts (bone eating cells).**
2) **Increase renal reabsorption of Ca^{2+} and decrease renal reabsorption of PO_4^{3-}**
3) **Converts 25-hydroxycholecalciferol (calcidiol) into 1, 25-dihydroxy- chole-calciferol (1, 25-DHCC or calcitriol) which is the active form of vitamin D. calcitriol increases the intestinal Ca^{2+} absorption from GIT.**



2. ***Vitamin D3:*** **it increases the serum Ca^{2+} and decreases serum PO_4^{3-}**

- **Vitamin D_3 is a prohormone and must be converted into the active form which is 1, 25 dihydroxy cholecalciferol or calcitriol. The activation occurs in:**

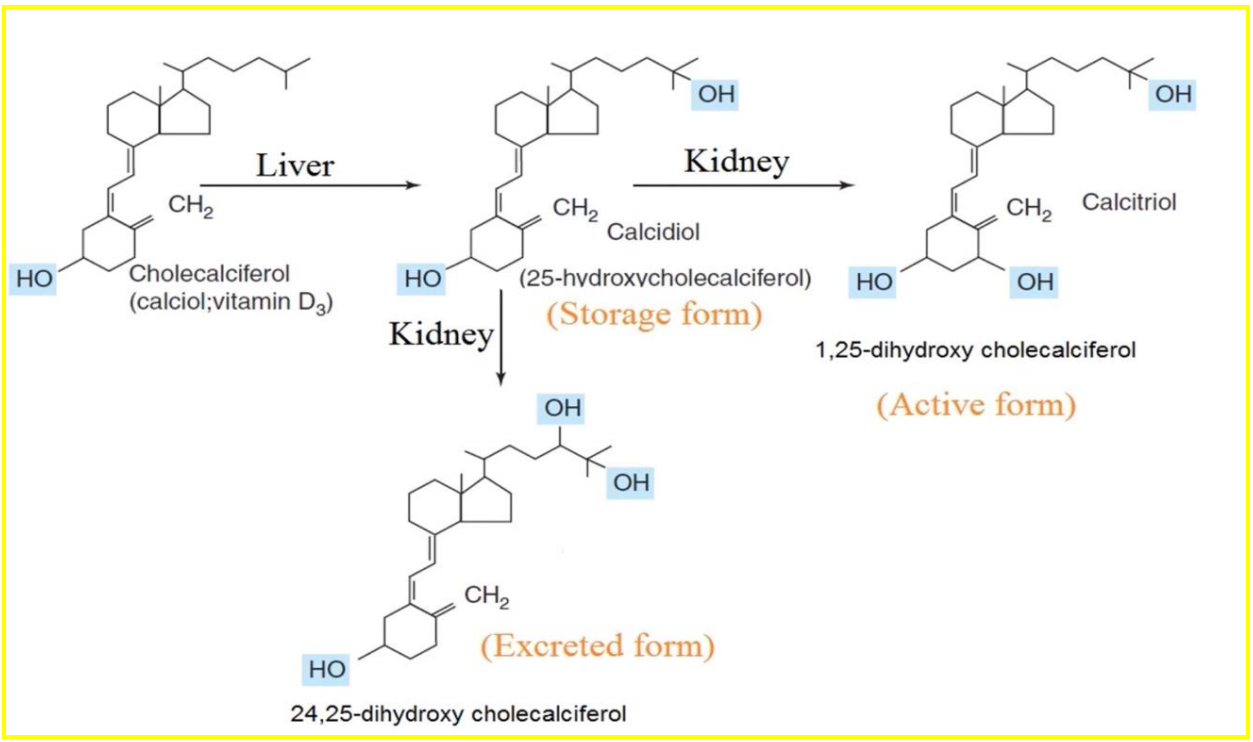
a) **In liver, hydroxylation at C_{25} position occurs, to form 25-hydroxy chole- calciferol (25-HCC) or calcidiol. 25-HCC is the major storage form.**

b) **In plasma, 25-HCC is bound to vitamin D binding protein (VDBP).**

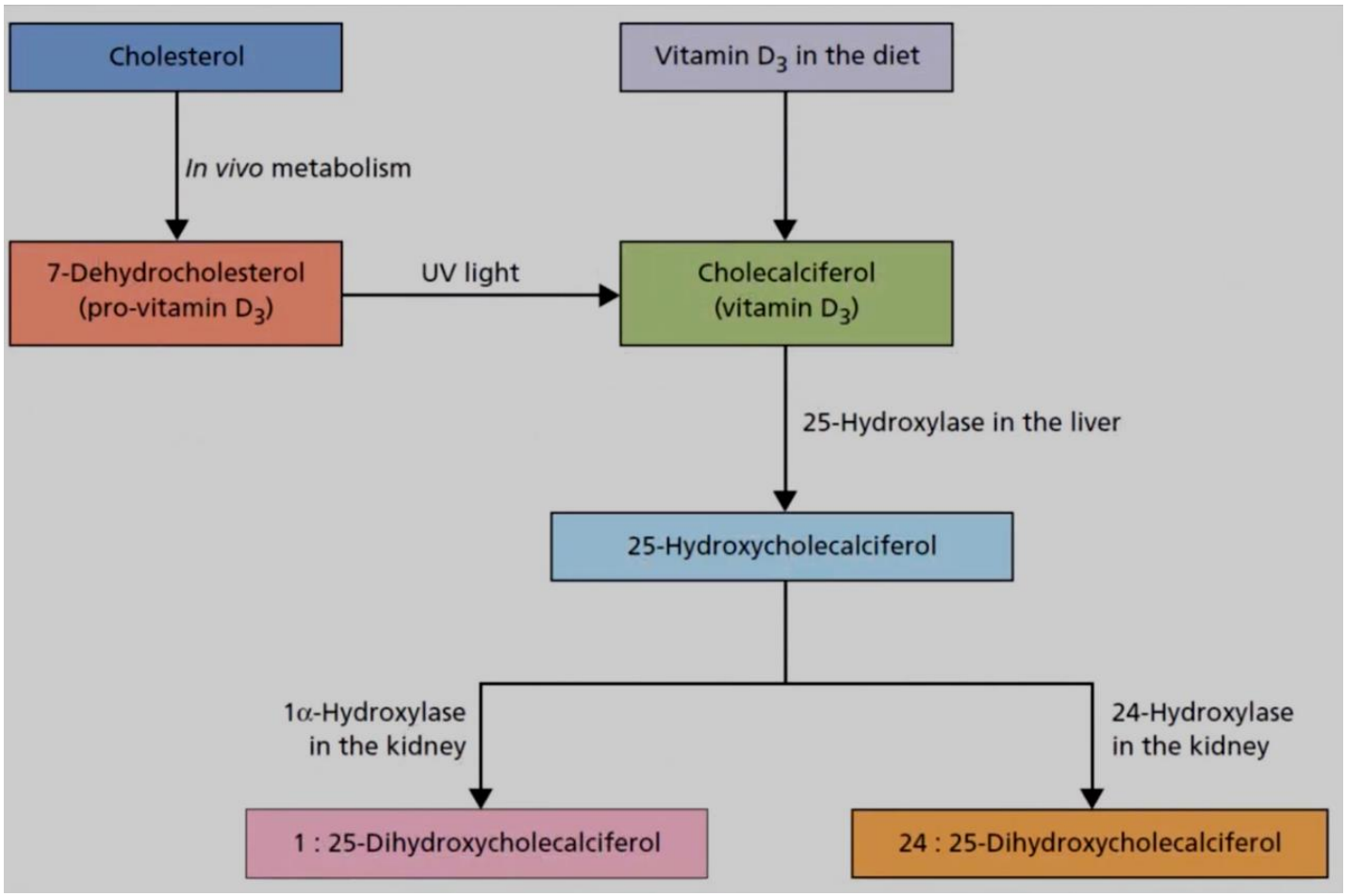
c) **In the kidney, it is further hydroxylated at C_1 to form 1, 25-dihydroxy cholecalciferol (DHCC) by enzyme 1-α-hydroxylase (stimulated by PTH). Since it contains three hydroxyl groups at 1, 3 and 25 positions, it is also called Calcitriol.**

d) **In the kidney OH-group may added to C_{24} to form 24, 25-dihydroxy cholecalciferol which is inactive form of vitamin D, ready for excretion.**

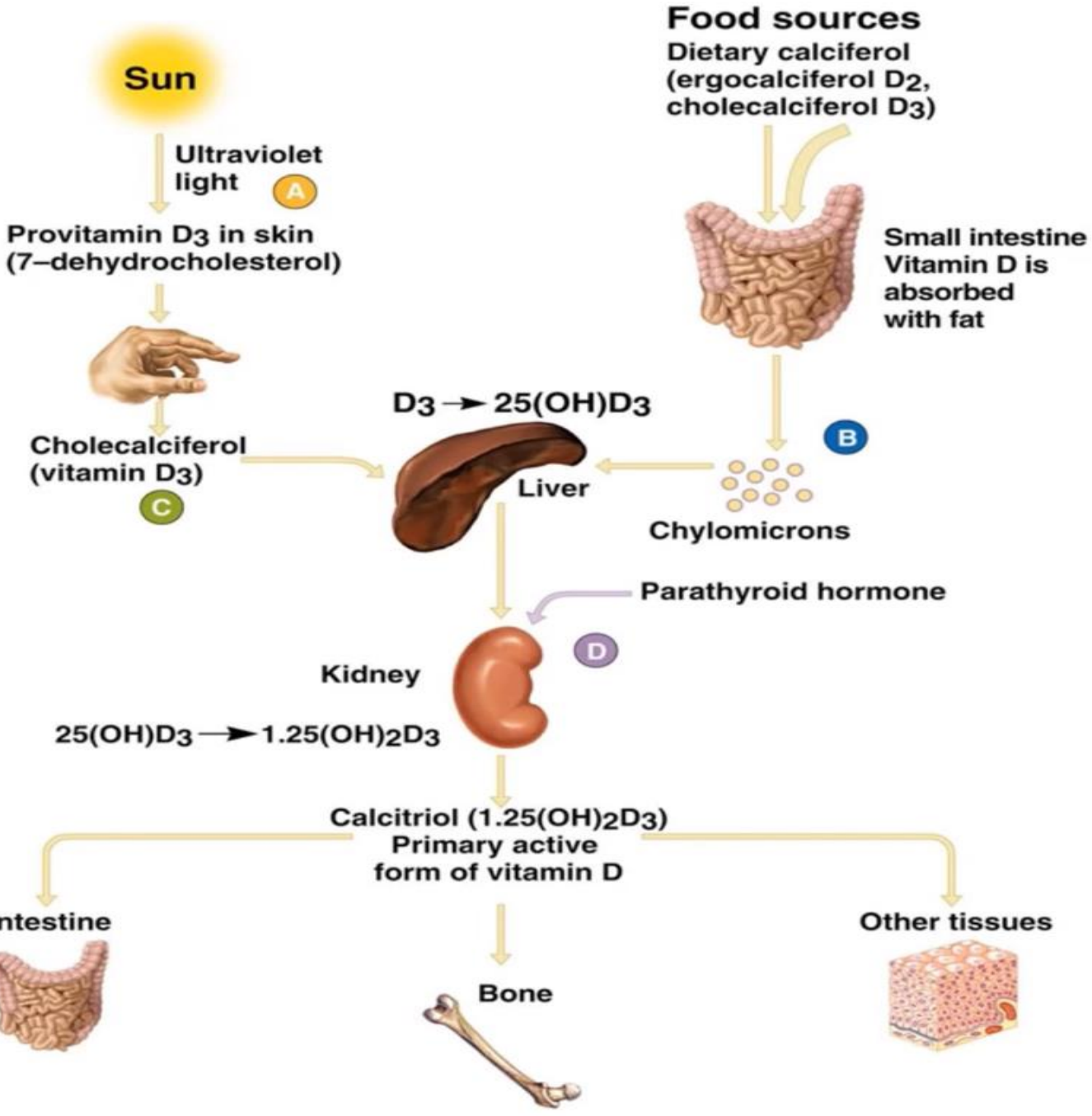
Metabolism of Vit.D:



Metabolism of vitamin D



Name	Generic name	Function
Vitamin D_2	Ergocalciferol	Plant form
Vitamin D_3	Cholecalciferol	Animal form
25-hydroxy Vitamin D_3	Calciferol	Storage form
1,25-dihydroxy Vitamin D_3	Calcitriol	Active form
24,25-dihydroxy Vitamin D_3	Secalciferol	Excretory form



Biochemical role of Vitamin D

- **The main function of Vitamin D is to regulate plasma levels of calcium through .Vitamin D elevates plasma calcium through**

1) **On the intestine: it stimulates intestinal absorption of calcium and phosphate by an increased synthesis of a specific calcium-binding protein.**
2) **On the kidney: it reduces the renal excretion of calcium**
3) **On the bones: it stimulate the mobilization of calcium and phosphate from bones to the blood (Bone resorption) when necessary**

- **Causes for Vitamin D Deficiency:**
  1. **People who are not exposed to sunlight properly**
  2. **Malabsorption of vitamin D (obstructive jaundice and steatorrhea).**
  3. **Abnormality of vitamin D activation due to Liver and renal diseases or Hypoparathyroidism (Deficiency of parathyroid hormone)**

3. Calcitonin (thyroid hormone):

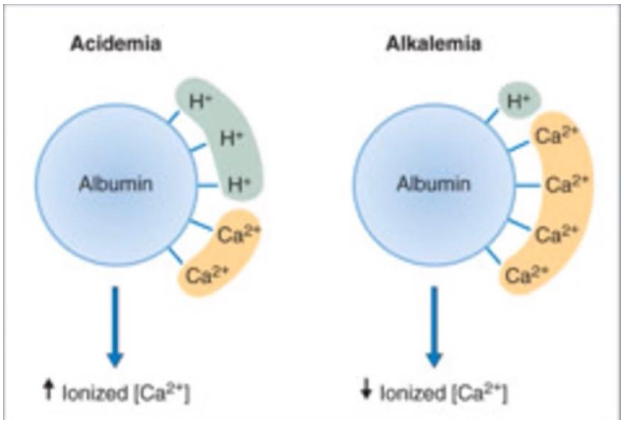
- **Calcitonin probably has only a minor role in calcium homoeostasis.**
- **It is secrete when plasma calcium concentration increases and also in response to certain gut hormones**
- **It decreases both serum calcium and phosphate by:**

a) Increase the osteoblast activity (bone-forming cells) and decrease the osteoclast activity, so it transports Ca^{2+} from blood to bones.

b) Decrease the renal reabsorption of Ca^{2+} and PO_4^{3-}

Serum Calcium

- **A healthy person has a total serum calcium of around 9 -11 mg% (2.4 mmol/L)**
- **About 50% of serum Ca^{2+} is bound to albumin. Binding between Ca^{2+} is pH dependent**
- **As the acidity increases the +ve charge on albumin ⟶ ↓Ca^{2+} bound**
- **Acidosis (↓pH) ⟶ decrease binding between Ca^{2+} and albumin$^+$**
- **Alkalosis (↑ pH) ⟶ increase binding between Ca^{2+} and albumin$^-$**
- **Hence, the percentage of free Ca^{2+} increases in acidosis and decreases in alkalosis although the total calcium is unchanged.**
- **pH affects free but not total Ca^{2+}**
- **Free Ca^{2+} (ionized) is the only biologically active form and it is responsible for the feedback regulation of PTH. (4.5–5.6 mg %)**



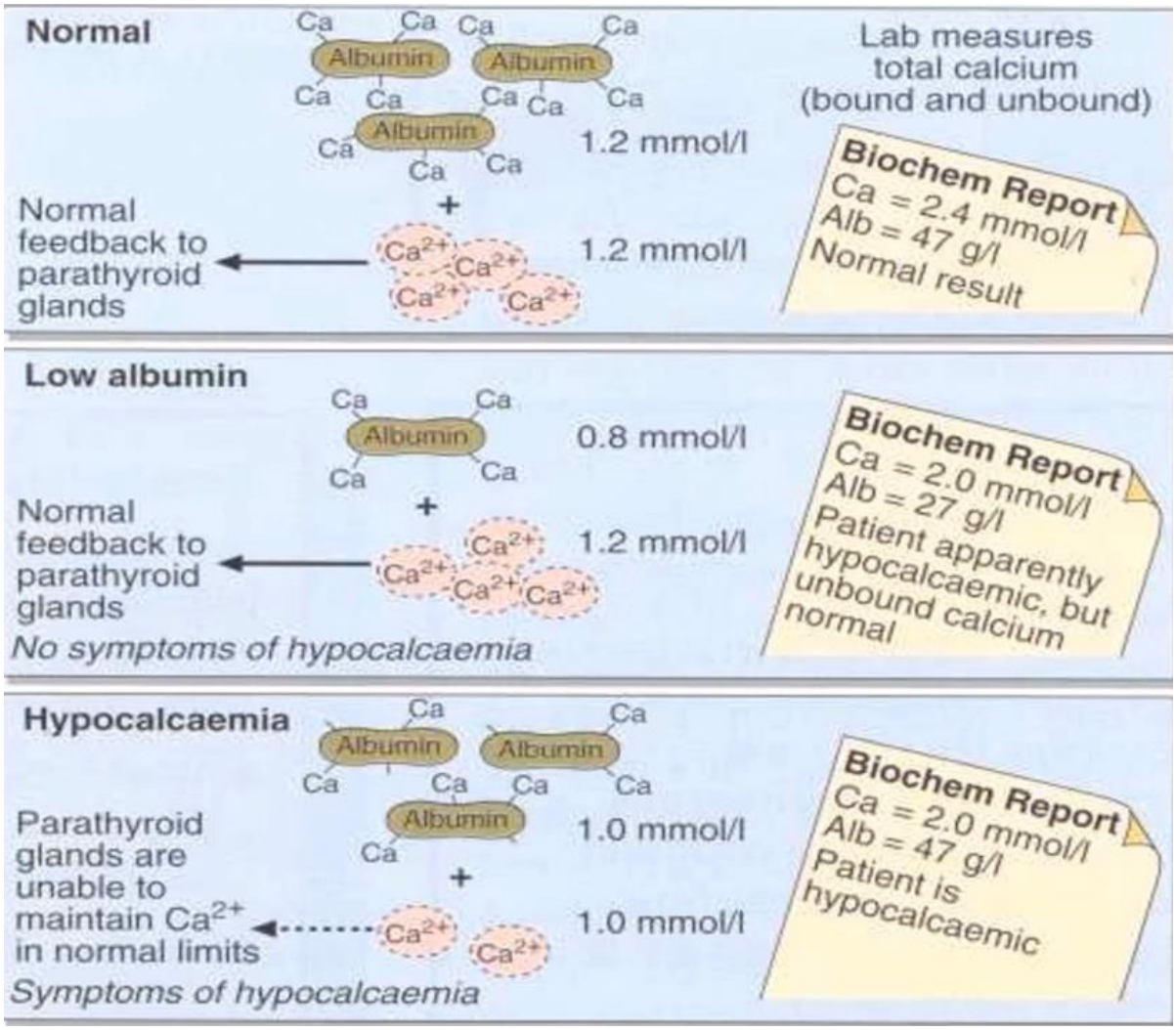
- **Free Ca^{2+} is difficult to be measured, while the total Ca^{2+} is easier (changes in serum albumin cause changes in total Ca^{2+}).**

- **Patients with low serum albumin have total serum calcium lower than normal, while have normal free calcium. These patients should not be diagnosed as hypocalcemic.**
- **In order to avoid this problem and to ensure that patients with low albumin are not mistakenly labelled as a hypocalcemic, clinical biochemists use the convention of the Adjusted Calcium**
- **Most laboratories measure both total calcium and albumin, and when the albumin is abnormal, calculate what the total calcium would have been if the albumin had been normal**
- **Adjusted Ca^{2+} (mmol/L) = total Ca^{2+}(mmol/L) + 0.02 * (47-albumin g/L) Where 47 represents the average albumin level in g/L in other words, each 1 g/L decrease of albumin, will decrease 0.02 mmol/L in measured serum Ca^{2+} and thus 0.02 must be added to the measured value to take this into account and a corrected Ca^{2+} .**
- **Example: serum total Ca^{2+} is 1.8 mmol/L and Serum Albumin is 39 gm/L**

$$\text{Adjusted } Ca^{2+} = 1.8 + 0.02\,(47\ 39)$$

$$= 1.96 \text{ mmol/L}$$

Changes in plasma albumin will affect total Ca^{2+} independently of ionized Ca^{2+}



Hypocalcaemia

- **Serum total calcium < 2.1 mmoL. may be caused by:**

a) Artefactual: Blood collected in EDTA tubes

b) Hypoparathyroidism

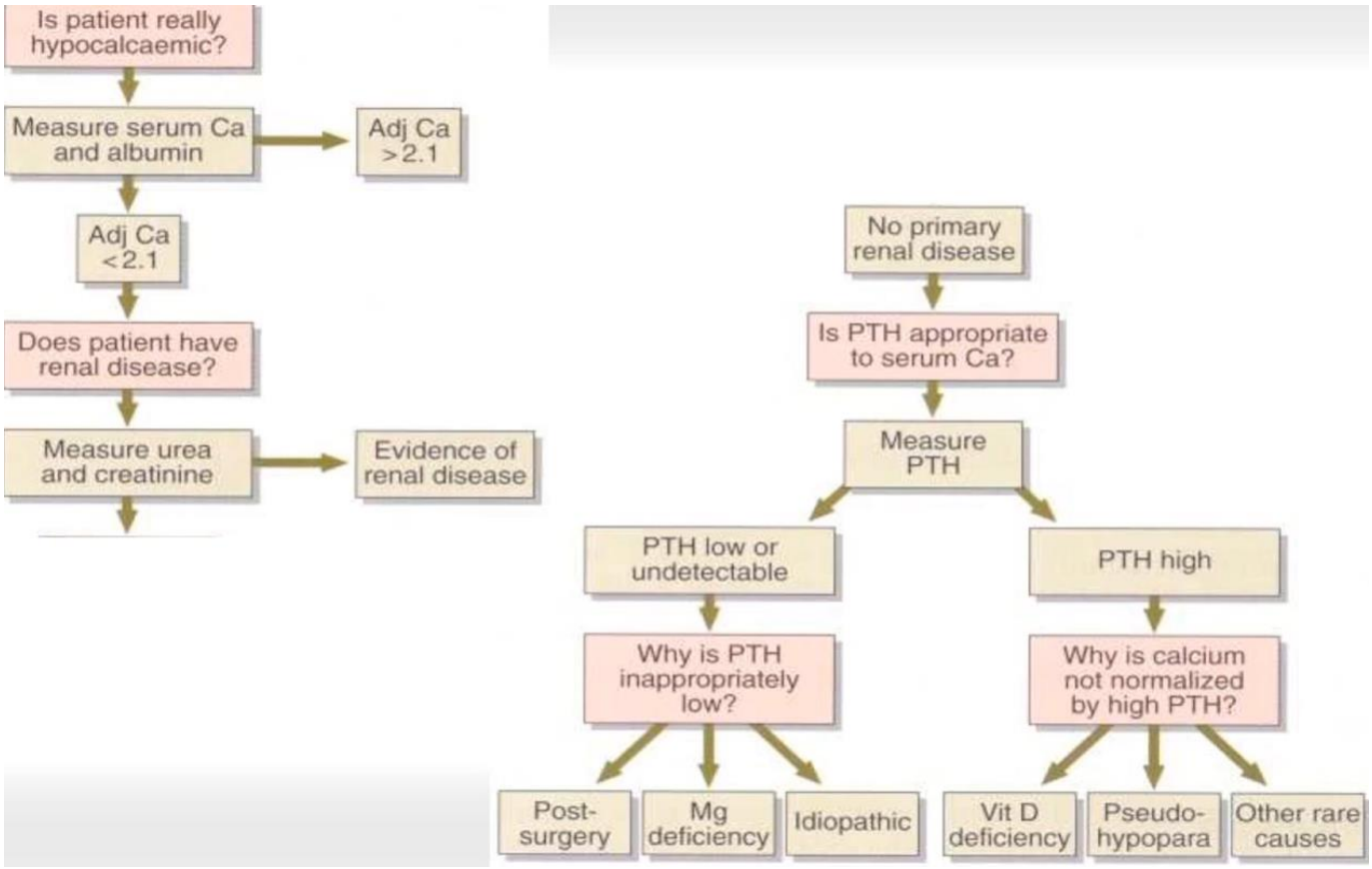
c) Vitamin D deficiency (Osteomalacia and rickets): this may be due to

1. **People who are not exposed to sunlight properly**
2. **Malabsorption of vitamin D (obstructive jaundice and steatorrhea).**
3. **Abnormality of vitamin D activation due to Liver and renal diseases**

d) Magnesium deficiency: Mg affects the secretion of PTH and hypomagnesaemia often leads to hypocalcemia, by inhibition of PTH.

- **Treatment: identification and treatment of the primary cause, oral Ca^{2+} supplements and active form of vitamin D**

Diagnosis of Hypocalcaemia



Hypercalcaemia

- **Serum total calcium > 2.8 mmol/L. life threatening if > 3.5 mmol/L**
- **Cause by ;**

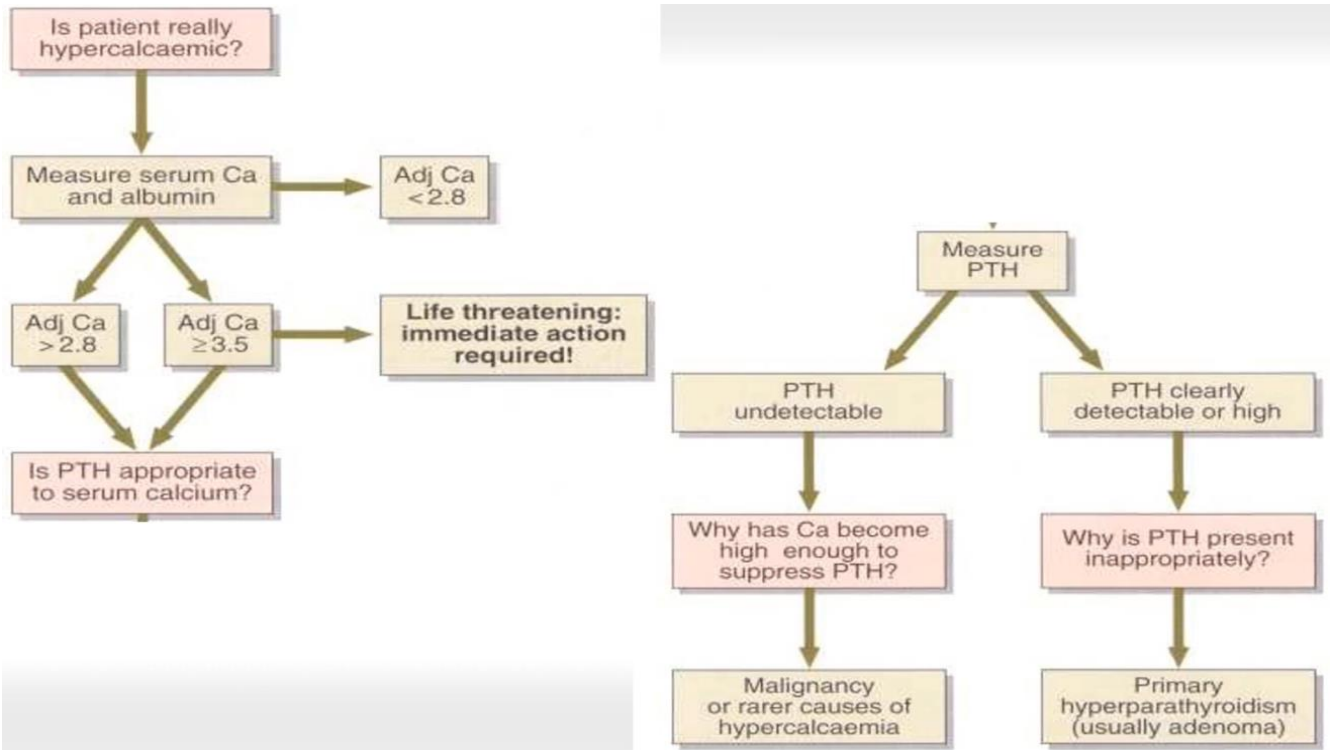
a) Common causes:

1. **Primary Hyperparathyroidism single parathyroid adenoma**

2. **Hypercalcaemia associated with Malignancy some tumour secret a protein called PTHrP (PTH-related protein) which has PTH like properties**

b) Rare causes:

3. **Overdose of vitamin D treatment**
4. **Diuretic therapy**
5. **Calcium therapy**
6. **Milk alkali syndrome (increased Ca^{2+} intake + HCO_3 as antacids)**



Treatment of Hypercalcaemia

- **Treatment is urgent if the adjusted calcium is > 3.5 mmol/L**

1. **IV saline to restore GFR and promote diuresis**
2. **Bisphosphonates (pamidronate) are the best calcium lowering drugs act by inhibiting bone resorption**
3. **The cause of hypercalcaemia should be treated if possible. Surgical removal of parathyroid adenoma**

Phosphate

- **Phosphate is abundant in the body and is an important intracellular and extracellular anion. In plasma, Ca^{2+} and PO_4 have a reciprocal relationship**

Intracellular phosphate	Extracellular phosphate
Covalently attached to lipids and proteins Has role in Covalent modification of enzyme (phosphorylation and deP) ICF buffering	At physiological pH phosphate exists in ECF as monohydrogen phosphate and dihydrogen phosphate (inorganic P) ECF buffering

Hyperphosphataemia	Hypophosphatemia
1. Hypoparathyroidism 2. Renal failure 3. Redistribution (cell lysis)	1. Hyperparathyroidism 2. Insulin administration in DKA 3. Respiratory alkalosis 4. Non-absorbable antacid (aluminium hydroxide) that prevents the absorption

Bone metabolism

- **Bone is constantly being broken down and reformed in process of bone remodeling .(osteoblast vs osteoclast activities)**
- **Biochemical markers of bone resorption and bone formation can be useful in assessing the extent of disease as well as monitoring treatment.**
- **Bone markers:**

1. **Urinary hydroxyproline: indicates bone resorption. However; is markedly affected by dietary gelatin.**
2. **Deoxypyridinoline: indicates bone resorption. Is better than hydroxyproline as it is not affected by diet**
3. **ALP: indicates increased osteoblast activity**
4. **Osteocalcin: best indicator for increased osteoblast activity**
5. **Serum calcium, albumin, phosphate, magnesium, PTH and vitamin D**