Calcium Homeostasis

- Calcium has a lot of cellular and tissue functions involving:

- 1) Nerve functions
- 2) Membrane permeability
- 3) Muscle contraction
- 4) Glandular secretions
- 5) Blood coagulation

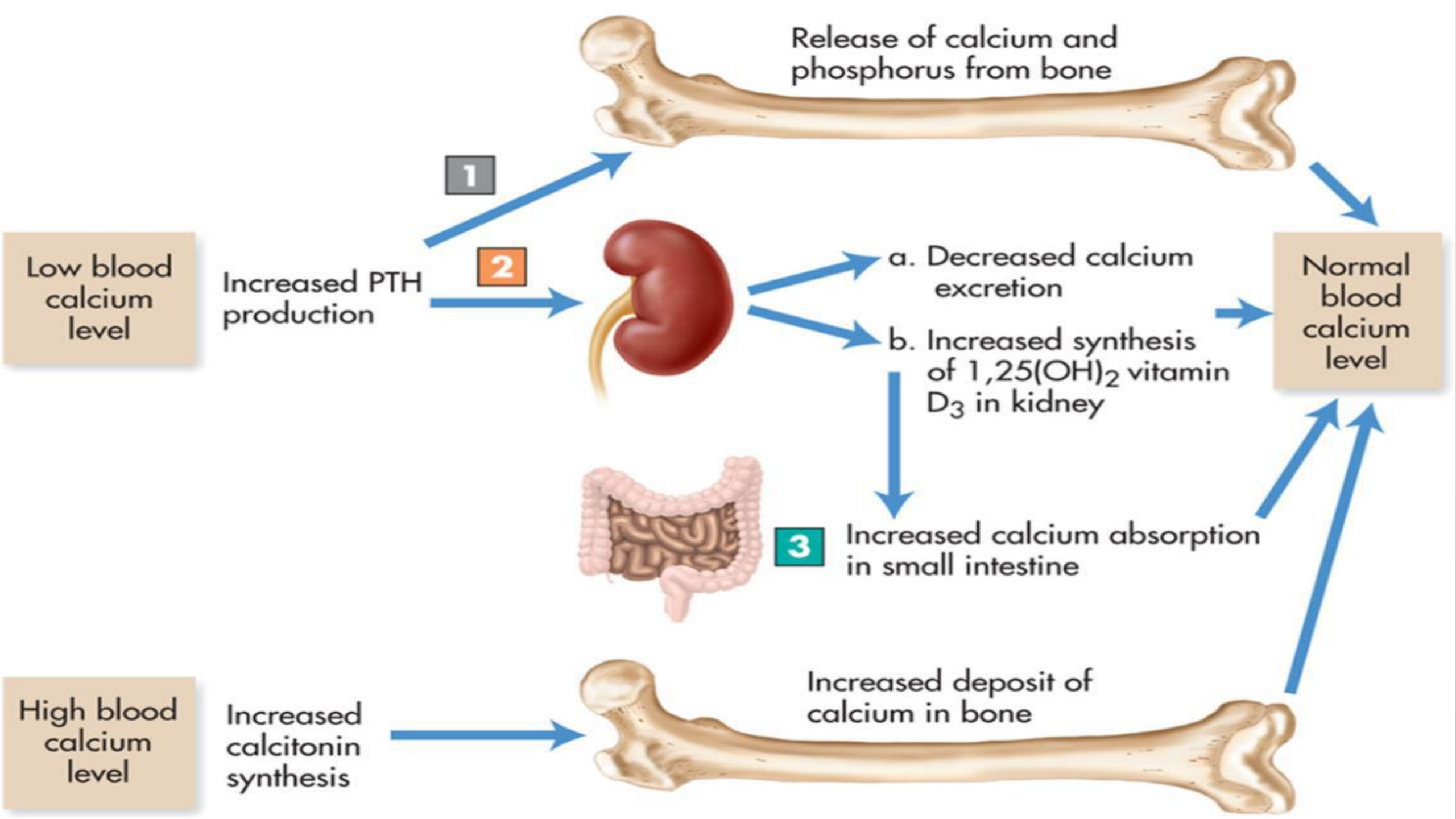
- **99 %** of the body calcium is part of bone and **1%** is present in blood and ECF. Calcium distribution in blood:
- 1) 45% circulates as free calcium ions referred to as **ionized** calcium
- 2) 50% is bound to protein (albumin)
- 3) 5% is bound to anions such as citrate and phosphate
- **- The amount of calcium present in the ECF is very small in comparison to that stored in bone**
- **-** Even in the adult, calcium in bone is not static; some bone is resorbed each day and calcium returned to the ECF.
- **- To maintain calcium balance, an equal amount of bone formation must take place.**

Calcium homeostasis is regulated by

- 1) Parathyroid hormone (PTH)
- 2) Calcitonin
- 3) Calcitriol (Vitamin D)

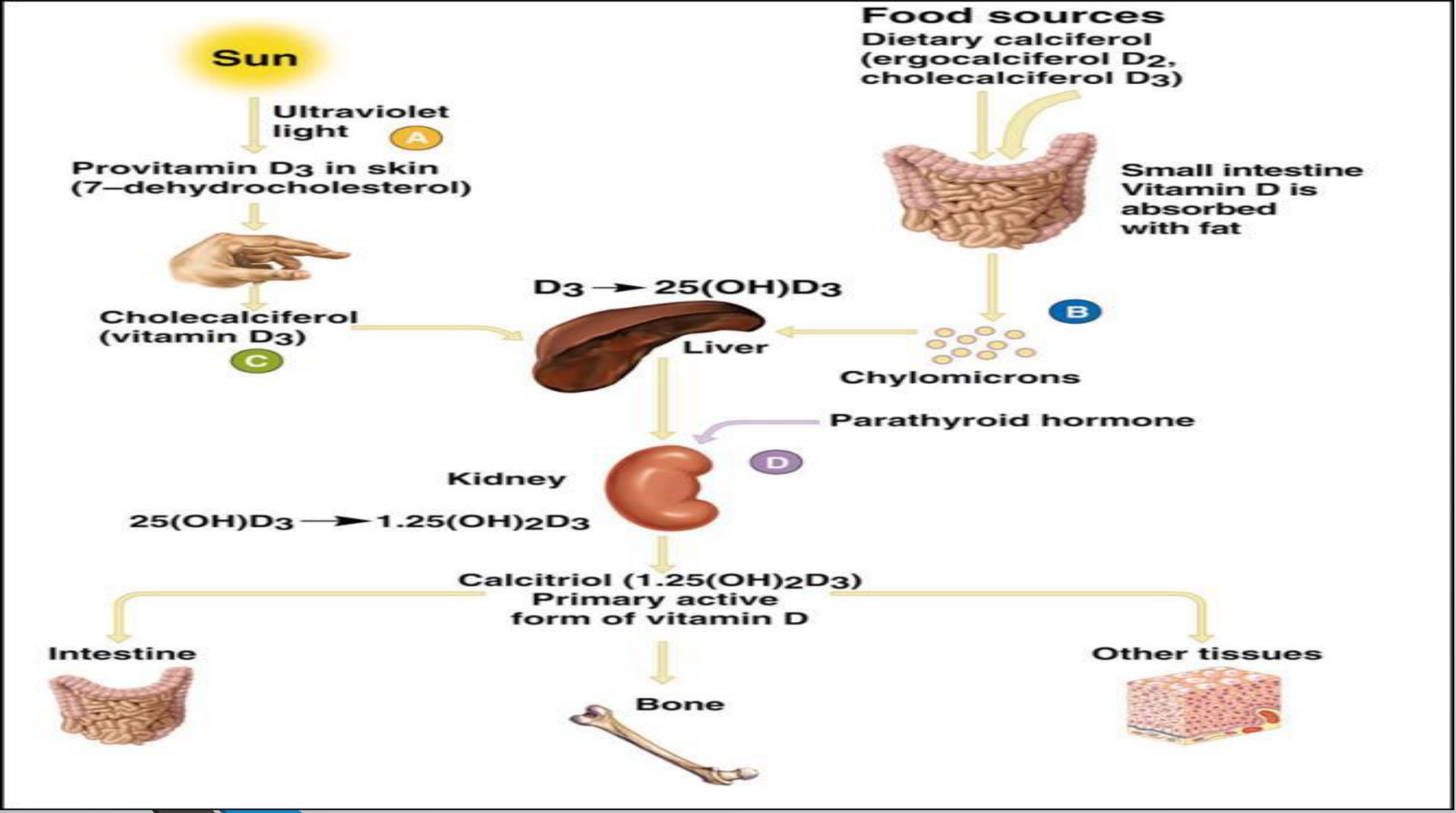
Parathyroid hormone:

- - PTH consists of 84 amino acids, is secreted 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-dihydroxychole-calciferol (1, 25-DHCC or calcitriol) which is the active form of vitamin D. calcitriol increases the intestinal Ca^{2+} absorption.


Release of calcium and phosphorus from bone
1
Low blood calcium level
Increased PTH production
2
a. Decreased calcium excretion
b. Increased synthesis of 1,25(OH)2 vitamin D3 in kidney
Normal blood calcium level
3
Increased calcium absorption in small intestine
High blood calcium level
Increased calcitonin synthesis
Increased deposit of calcium in bone

Vitamin D3

- **-** It increases the serum Ca2+ and decreases serum PO43- by:
- **-** Vitamin D3 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 C25 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 C1 to form 1, 25-dihydroxy cholecalciferol (DHCC) by enzyme *1-□-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 C24 to form 24, 25-dihydroxy cholecalciferol which is **inactive** form of vitamin D, ready for excretion.


Sun
Ultraviolet light
A
Provitamin D3 in skin (7–dehydrocholesterol)
Cholecalciferol (vitamin D3)
C
Food sources
Dietary calciferol (ergocalciferol D2, cholecalciferol D3)
Small intestine
Vitamin D is absorbed with fat
B
Chylomicrons
D3 → 25(OH)D3
Liver
Parathyroid hormone
D
Kidney
25(OH)D3 → 1.25(OH)2D3
Calcitriol (1.25(OH)2D3)
Primary active form of vitamin D
Intestine
Bone
Other tissues

- **- Vitamin D elevates plasma calcium through:**
- **a) On the intestine:** it stimulates intestinal absorption of calcium and phosphate by an increased synthesis of a specific calcium-binding protein.
- **b) On the kidney:** it reduces the renal excretion of calcium.
- **c) On the bones:** it stimulates 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).
- 3) Abnormality of vitamin D activation due to liver and renal diseases or hypoparathyroidism (Deficiency of PTH).

Different forms 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

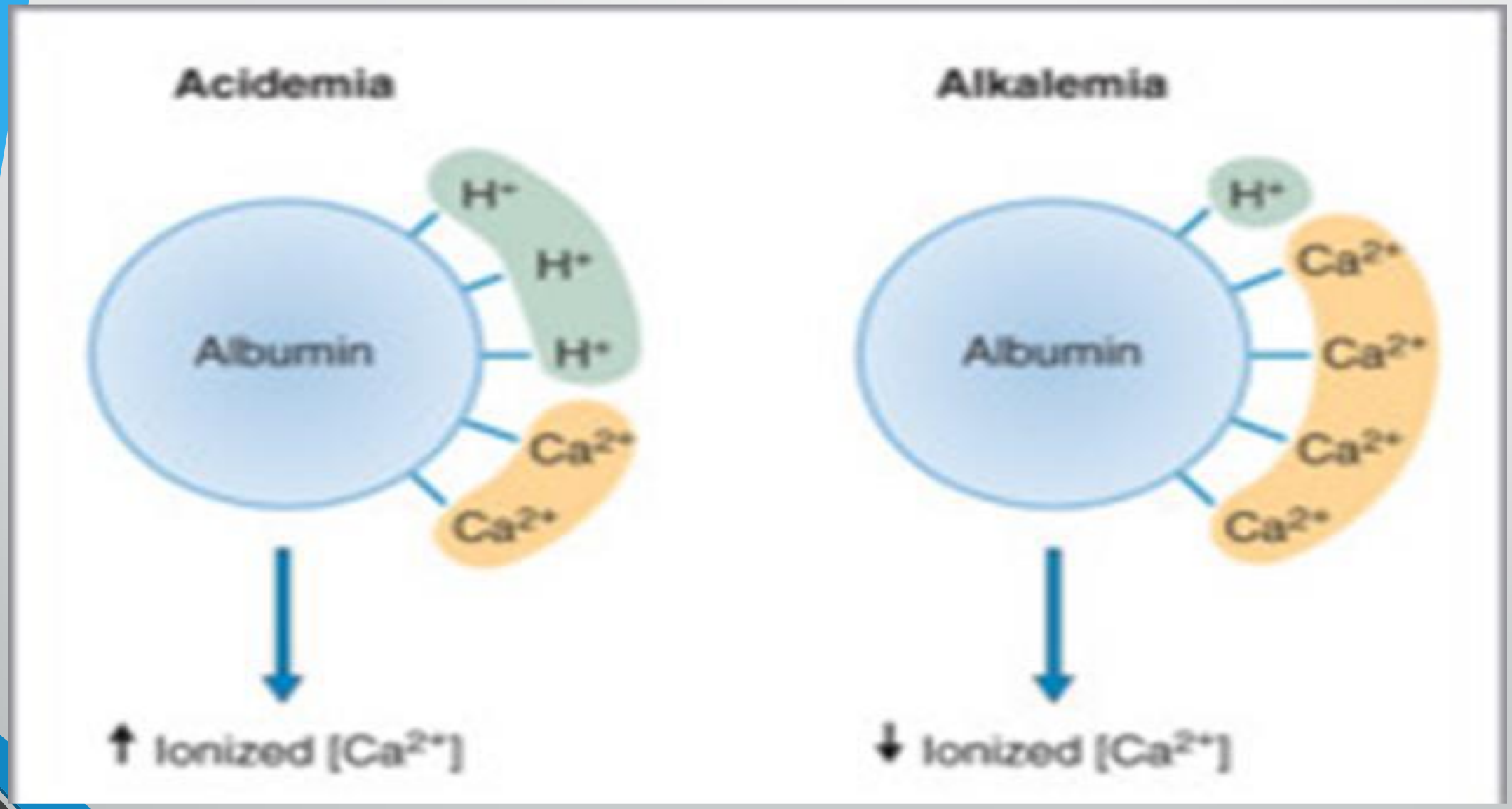
Calcitonin (thyroid hormone):

- **- Calcitonin probably has only a minor role in calcium homoeostasis.**
- **-** It is secreted when plasma calcium concentration rises and also in response to certain gut hormones.
- **-** It decreases both serum calcium and phosphate by:
- 1) Increase the osteoblast activity (bone-forming cells) and decrease the osteoclast activity, so it transports Ca^{2+} from blood to bones.
- 2) 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+} and albumin is pH dependent.
- **- As the acidity increases the +ve charge on albumin → ↓ Ca^{2+} bound**
- 1) Acidosis (↓ pH) → decrease binding between Ca^{2+} and albumin+
- 2) Alkalosis (↑ pH) → increase binding between Ca^{2+} and albumin-

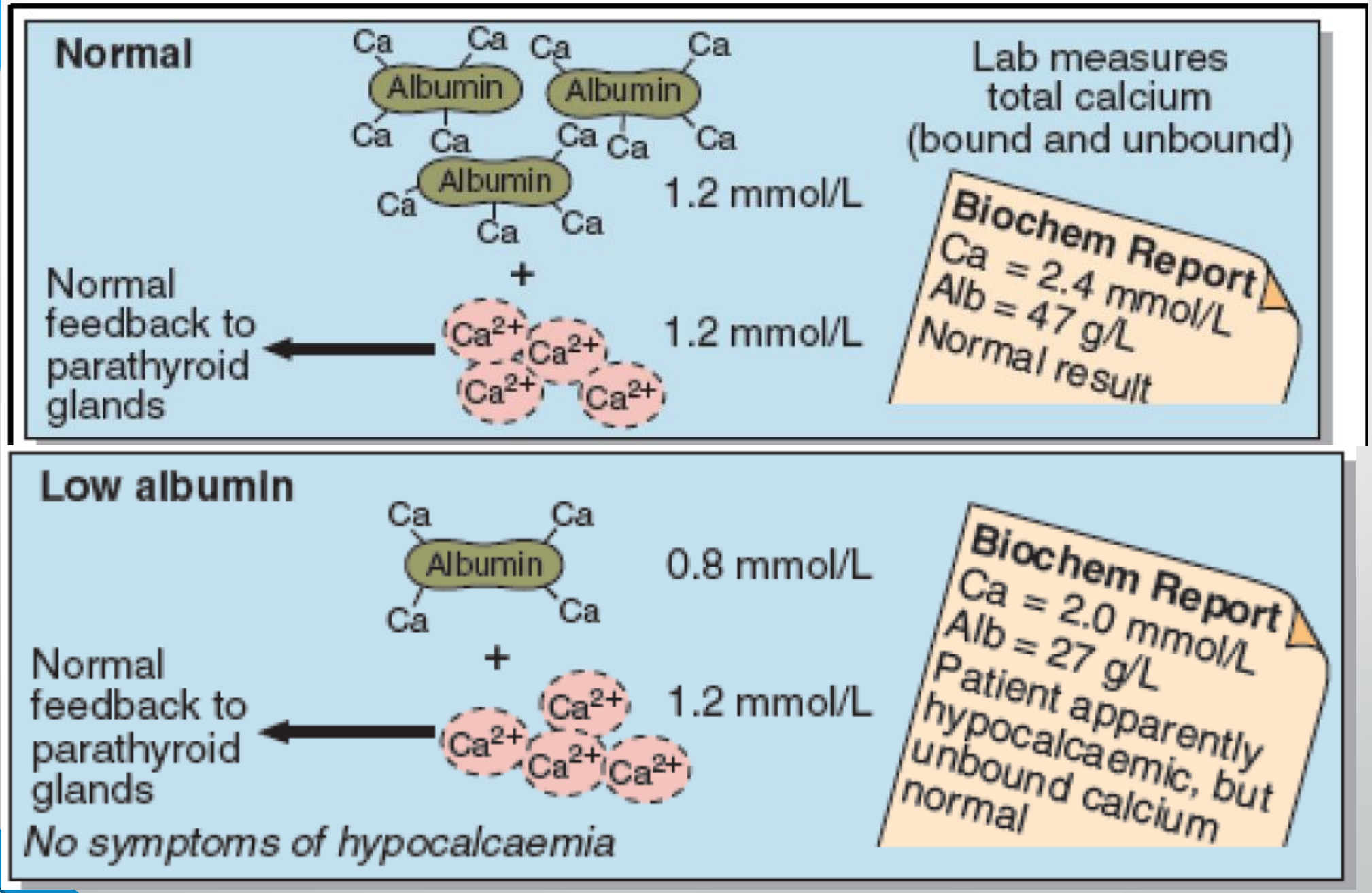
- - Hence, the percentage of free Ca^{2+} increases in acidosis and decreases in alkalosis although the total calcium is unchanged.
- - Free Ca^{2+} (ionized) is the only biologically active form and it is responsible for the feedback regulation of PTH

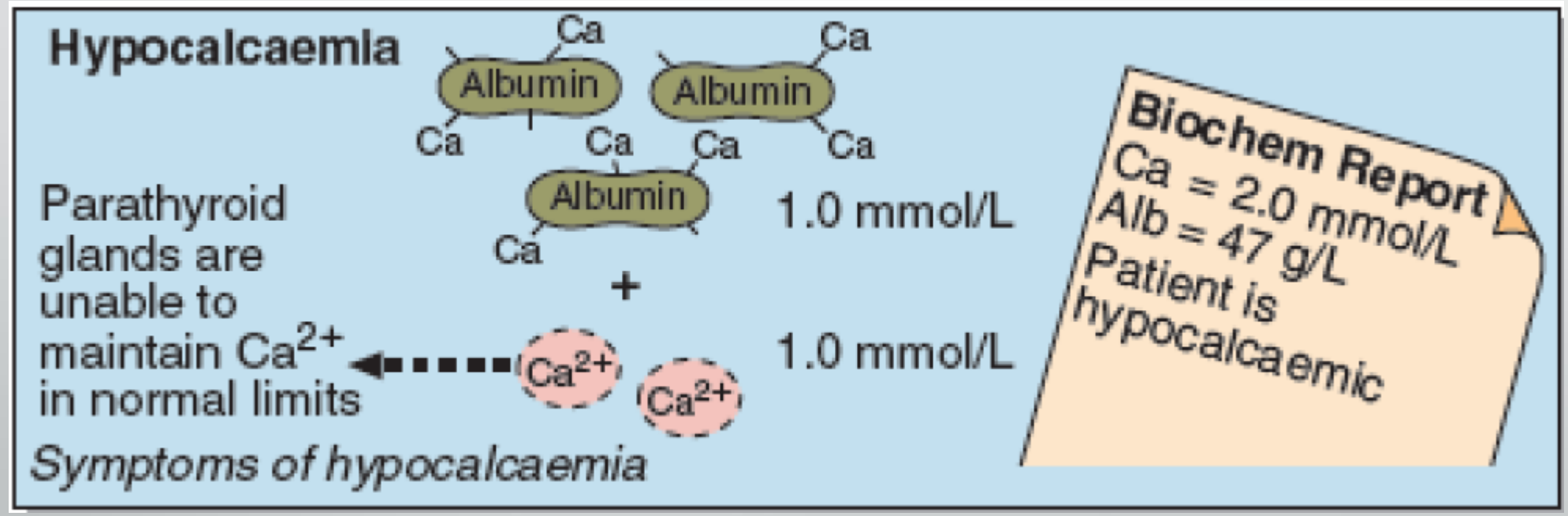

Acidemia
Albumin
H+
H+
H+
Ca2+
Ca2+
Ionized [Ca2+]
Alkalemia
Albumin
H+
Ca2+
Ca2+
Ca2+
Ca2+
Ionized [Ca2+]

- **-** 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 they have **normal free calcium**. These patients should not be diagnosed as hypocalcemic.
- **-** In order to avoid this problem, 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)

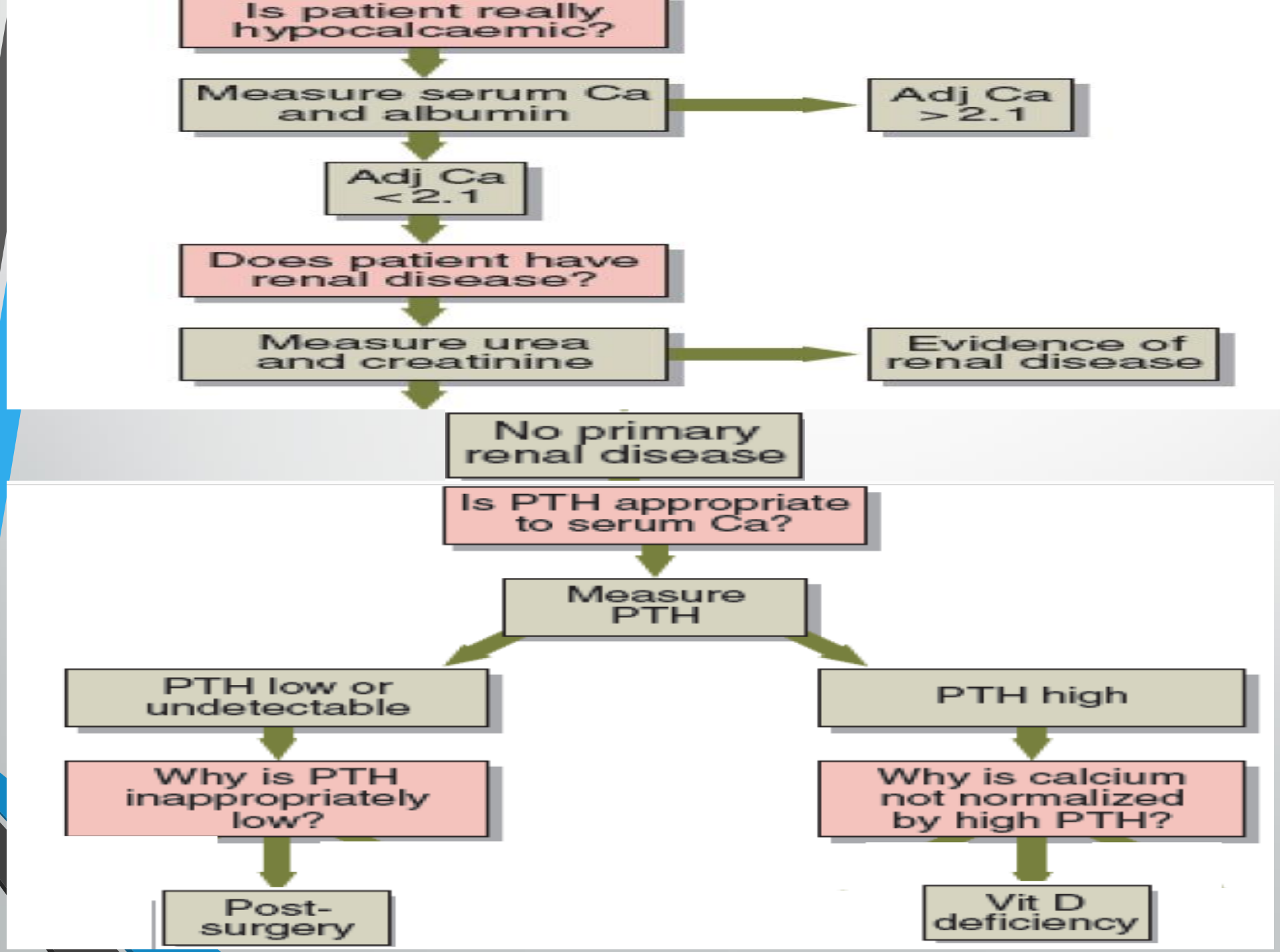
- - Where 47 represents the average albumin level in g/L
- - In other words, each 1 g/L decrease of albumin, will decrease 0.02 mmol/L in measured serum Ca2+ and thus 0.02 must be added to the measured value to take this into account and get a corrected calcium.
- - Example: serum total Ca2+ is **1.8 mmol/L** and Serum Albumin is **39 gm/L**
- Adjusted Ca2+ = 1.8 + 0.02 (47 - 39) = 1.96 mmol/L


Normal
Ca
Albumin
1.2 mmol/L
Lab measures
total calcium
(bound and unbound)
Biochem Report
Ca = 2.4 mmol/L
Alb = 47 g/L
Normal result
Normal
feedback to
parathyroid
glands
Ca2+
1.2 mmol/L
Low albumin
0.8 mmol/L
Biochem Report
Ca = 2.0 mmol/L
Alb = 27 g/L
Patient apparently
hypocalcaemic, but
unbound calcium
normal
No symptoms of hypocalcaemia


Hypocalcaemia
Ca
Albumin
Ca
Ca
Albumin
Ca
Ca
Ca
Albumin
Ca
Parathyroid glands are unable to maintain Ca^{2+} in normal limits
1.0 mmol/L
+
Ca^{2+}
Ca^{2+}
1.0 mmol/L
Biochem Report
Ca = 2.0 mmol/L
Alb = 47 g/L
Patient is hypocalcaemic
Symptoms of hypocalcaemia

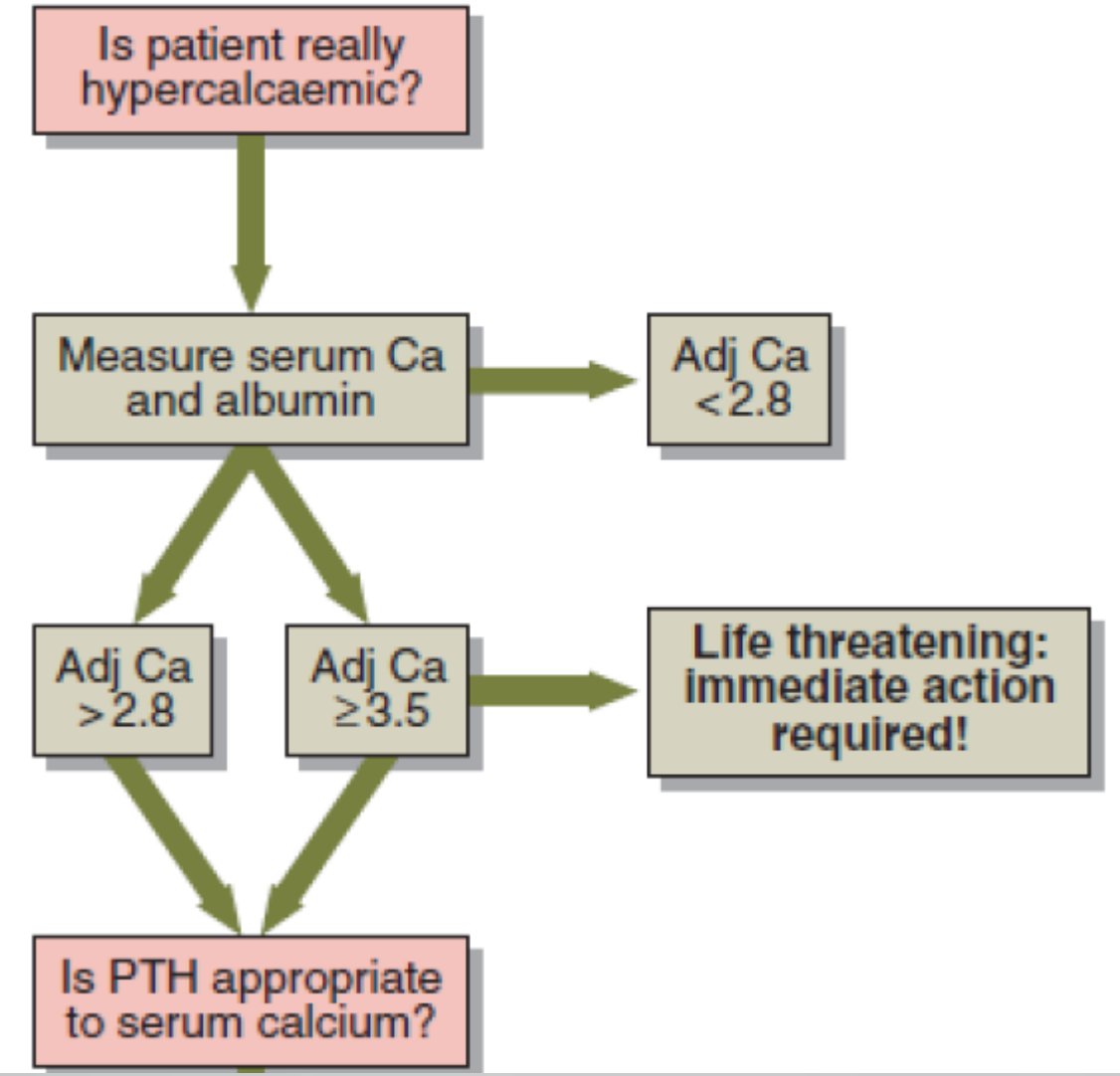
Hypocalcaemia

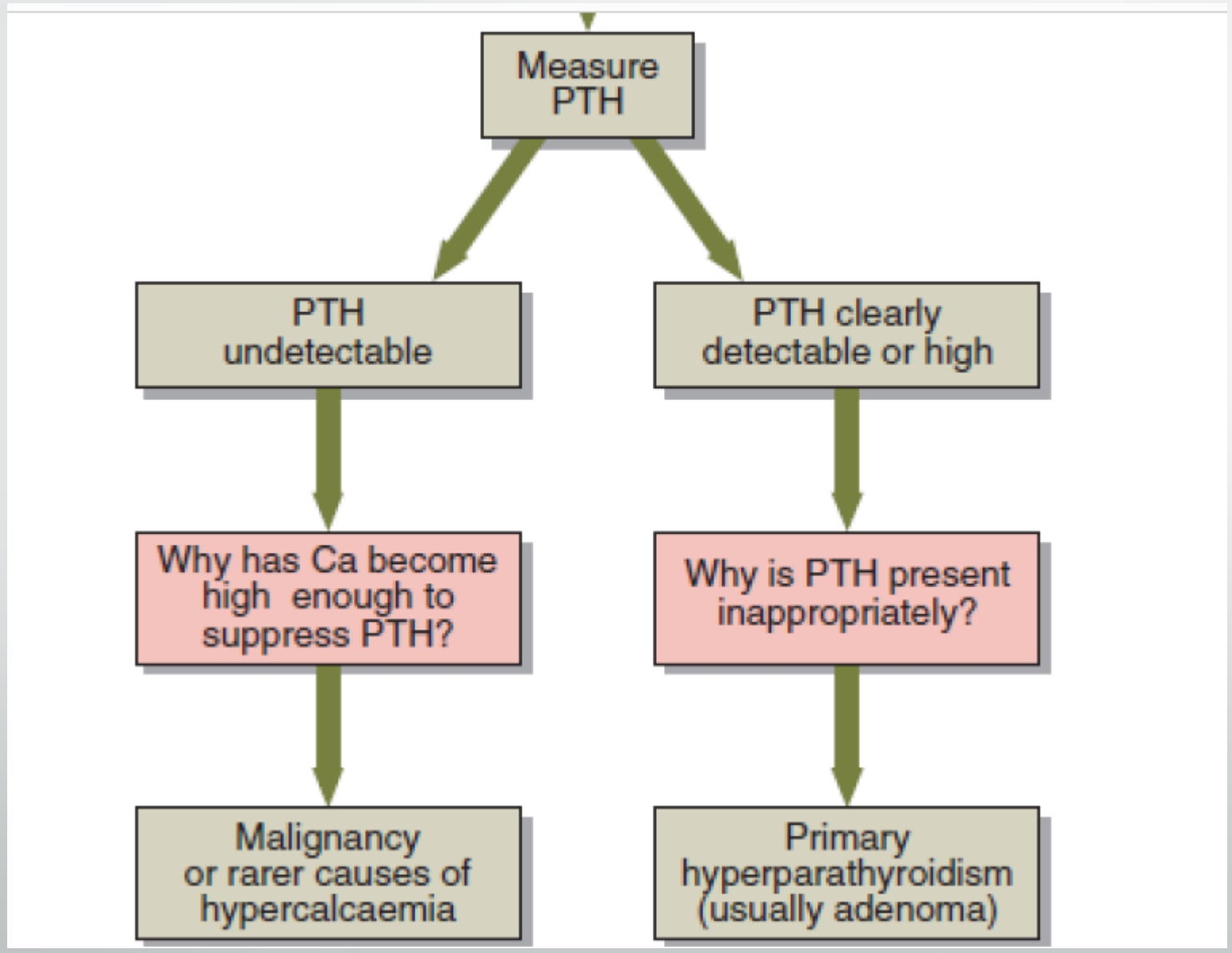
- **- It is decreased** serum total calcium < 2.1 mmol/L. may be caused by:
- **a) Artefactual**: Blood collected in EDTA tubes
- **b) Hypoparathyroidism**
- **c) Vitamin D deficiency** (Osteomalacia and rickets)
- **d) Magnesium deficiency:** Mg affects the secretion of PTH and hypomagnesaemia often 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.


Is patient really hypocalcaemic?
Measure serum Ca and albumin
Adj Ca >2.1
Adj Ca <2.1
Does patient have renal disease?
Measure urea and creatinine
Evidence of renal disease
No primary renal disease
Is PTH appropriate to serum Ca?
Measure PTH
PTH low or undetectable
PTH high
Why is PTH inappropriately low?
Why is calcium not normalized by high PTH?
Post-surgery
Vit D deficiency

Hypercalcaemia

- - It is increased serum total calcium > 2.8 mmol/L. Life threatening if > 3.5 mmol/L. Caused by:
- **a) Common causes:**
- - Primary hyperparathyroidism single parathyroid adenoma.
- - Hypercalcaemia associated with Malignancy some tumors secret a protein called PTHrP (PTH-related protein) which has PTH like properties.
- **b) Rare causes:**
- - Overdose of vitamin D treatment, diuretic therapy, or calcium therapy
- - Milk alkali syndrome (increased Ca^{2+} intake + HCO_3 as in antacids)


Is patient really hypercalcaemic?
Measure serum Ca and albumin
Adj Ca <2.8
Adj Ca >2.8
Adj Ca ≥3.5
Life threatening: immediate action required!
Is PTH appropriate to serum calcium?


Measure PTH
PTH undetectable
PTH clearly detectable or high
Why has Ca become high enough to suppress PTH?
Why is PTH present inappropriately?
Malignancy or rarer causes of hypercalcaemia
Primary hyperparathyroidism (usually adenoma)

- **- Treatment** is urgent if the adjusted calcium is > 3.5 mmol/L
- 1) IV saline to restore GFR and promote diuresis.
- 2) Bisphosphonates are the best calcium-lowering drugs they 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, calcium and phosphate have a **reciprocal** relationship.
- **- Intracellular phosphate:**
- **- Covalently attached to lipids and proteins.**
- **-** Has role in covalent modification of enzyme and ICF buffering.
- **- Extracellular phosphate:**
- **-** At physiological pH phosphate exists in ECF as monohydrogen phosphate and dihydrogen phosphate (inorganic phosphate) which is an ECF buffering.

Disorders of phosphate

Hyperphosphataemia	Hypophosphatemia
Hypoparathyroidism Renal failure Redistribution (cell lysis)	Hyperparathyroidism Insulin administration in DKA Respiratory alkalosis 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