CALCIUM AND PHOSPHATE DISORDER

Supervisor by : Dr. Ahmed ALshayab

By : Marah Hussein
Lujain Abdallah
Lujain Al-Wlaidat
Dana Hazaimeh
Maram Ayyad
Bilsan Alhroot

- The normal serum calcium (ca^{2+})range is 2.2–2.6 mmol/L (8.5 to 10.6 mg/dl)

- The normal phosphate levels 0.8–1.4 mmol/L (3.0 to 4.5 mg/dl)

THE DISTRIBUTION OF CALCIUM AND PHOSPHATE IN THE BODY

* Calcium :

About 0.1% of total body ca^{2+} is in the extracellular fluid.

1% in the cells.

The rest is stored inside the bones.

* Phosphate :

About 85% of the body's phosphate is stored in bones.

14 to 15 % presents in the cells.

Less than one percent in the extracellular fluid.

CALCIUM IN PLASMA

Three forms :

1- about 41% of ca^{2+} is combined with plasma proteins (non-diffusible)

2- about 9% of ca^{2+} is combined with anionic substances (citrate and phosphate for instance)

3- 50% of the ca^{2+} in plasma is ionized

Both 2 & 3 are diffusible

Calcium and Phosphate Function

Calcium	Phosphate
Contraction of skeletal	Energy production
Cardiac and smooth ms	Part of nucleic acid
Blood clotting	Part of cell membrane
Transmission of nerve impulses	

Calcium balance is regulated by hormonal control, but the levels are also affected by albumin and pH.

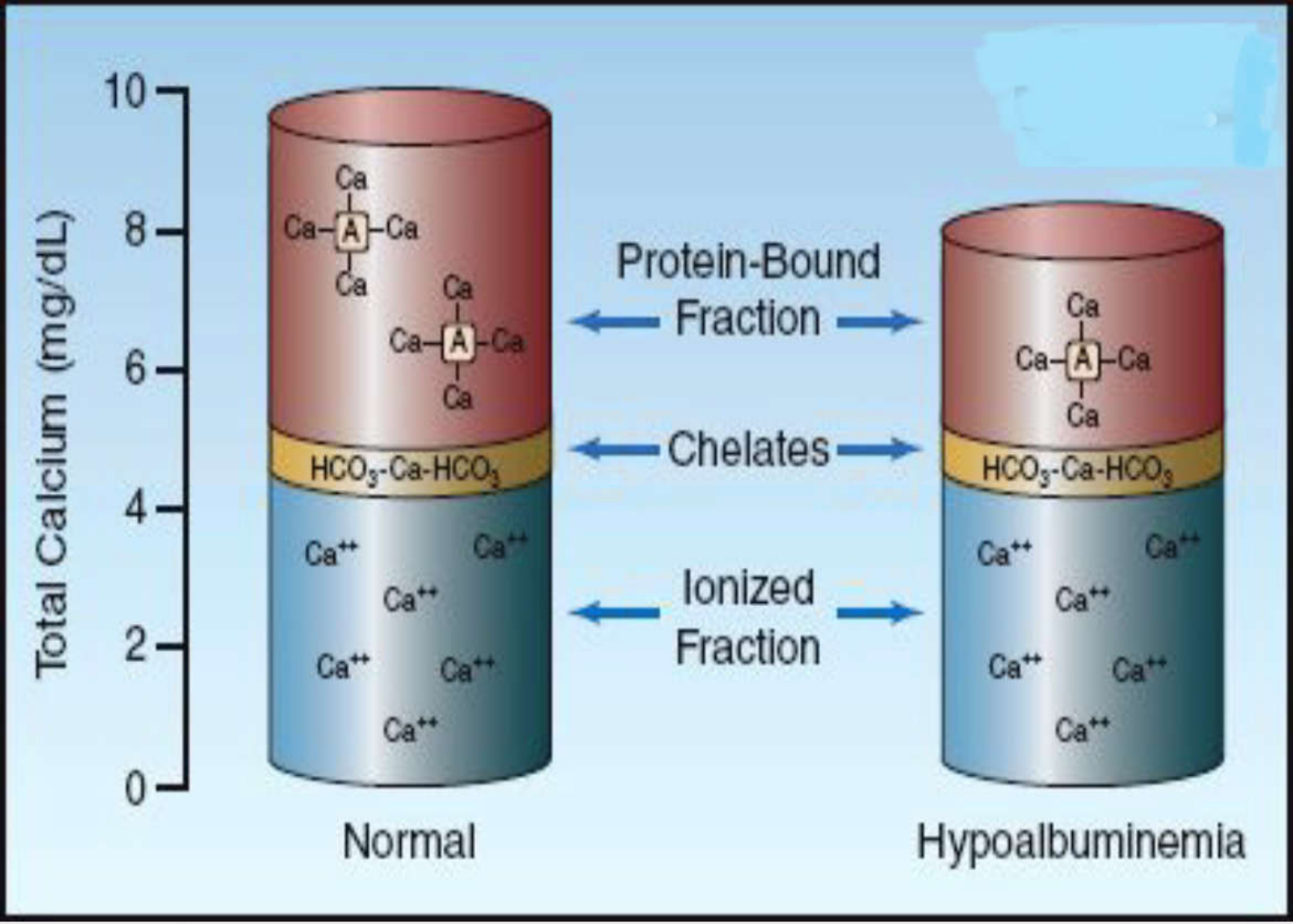
1- Albumin :

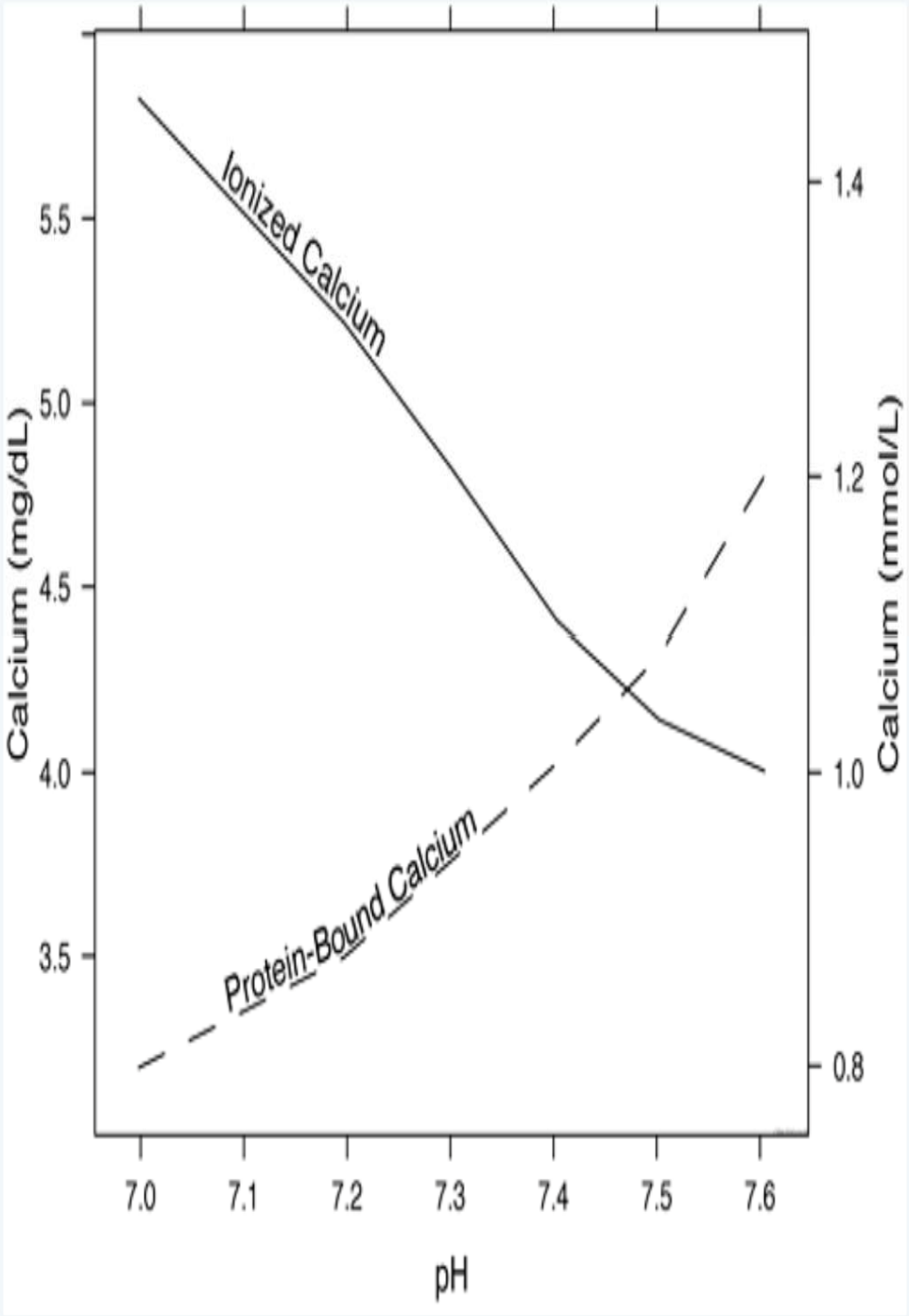
protein - bound form : most calcium ions are bound to albumin, so the total calcium concentration fluctuates with the protein (albumin) concentration.

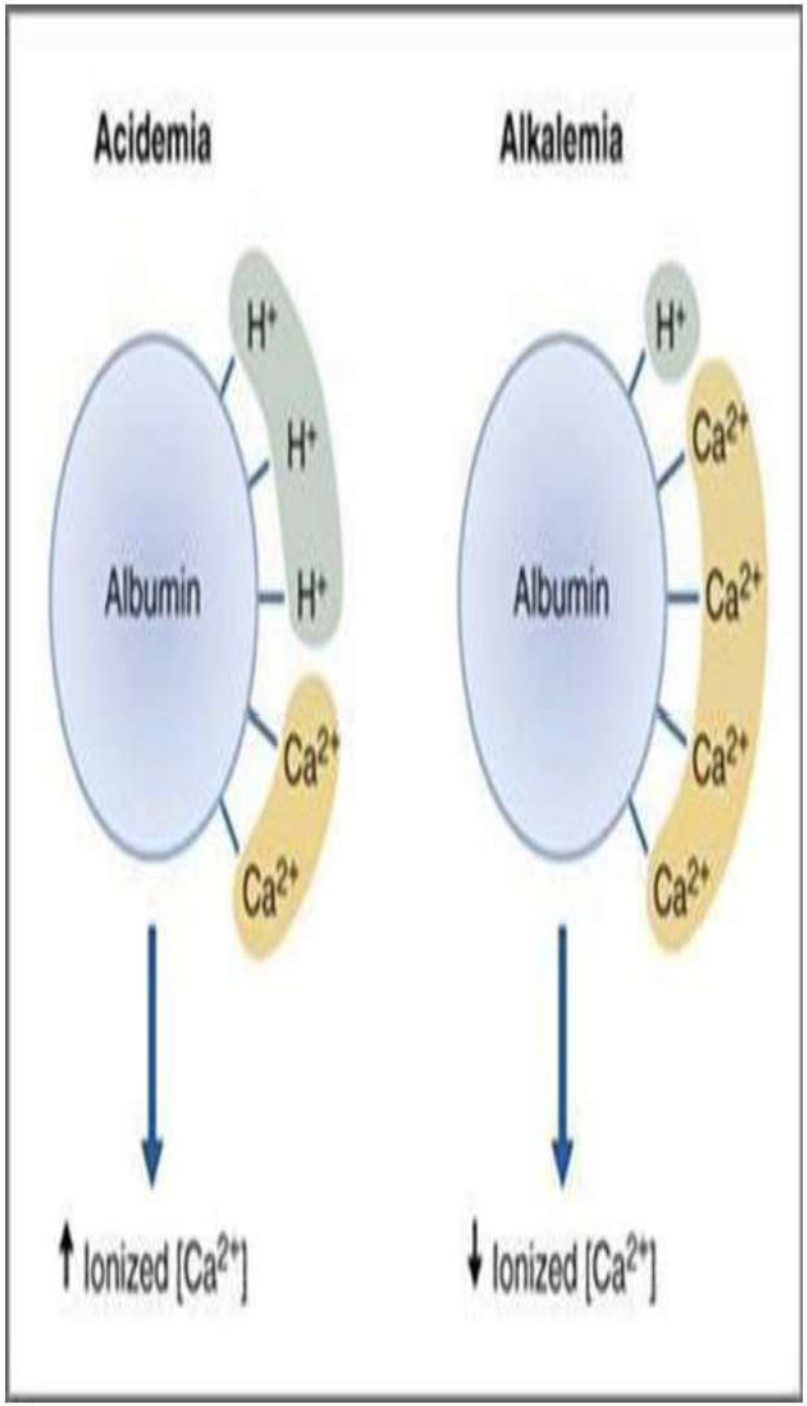
Free ionized form: physiologically active fraction; under tight hormonal control (PTH), independent of albumin levels.

In hypoalbuminemia the total calcium is low, but ionized calcium is normal.

2-Changes in pH alter the ratio of calcium binding.


Total Calcium (mg/dL)
10
8
6
4
2
0
Ca
Ca–A–Ca
Ca
Ca
Ca–A–Ca
Ca
HCO_3-Ca-HCO_3
Ca^{++}
Protein-Bound Fraction
Chelates
Ionized Fraction
Normal
Hypoalbuminemia


Ionized Calcium
Protein-Bound Calcium
Calcium (mg/dL)
Calcium (mmol/L)
5.5
5.0
4.5
4.0
3.5
1.4
1.2
1.0
0.8
7.0
7.1
7.2
7.3
7.4
7.5
7.6
pH


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

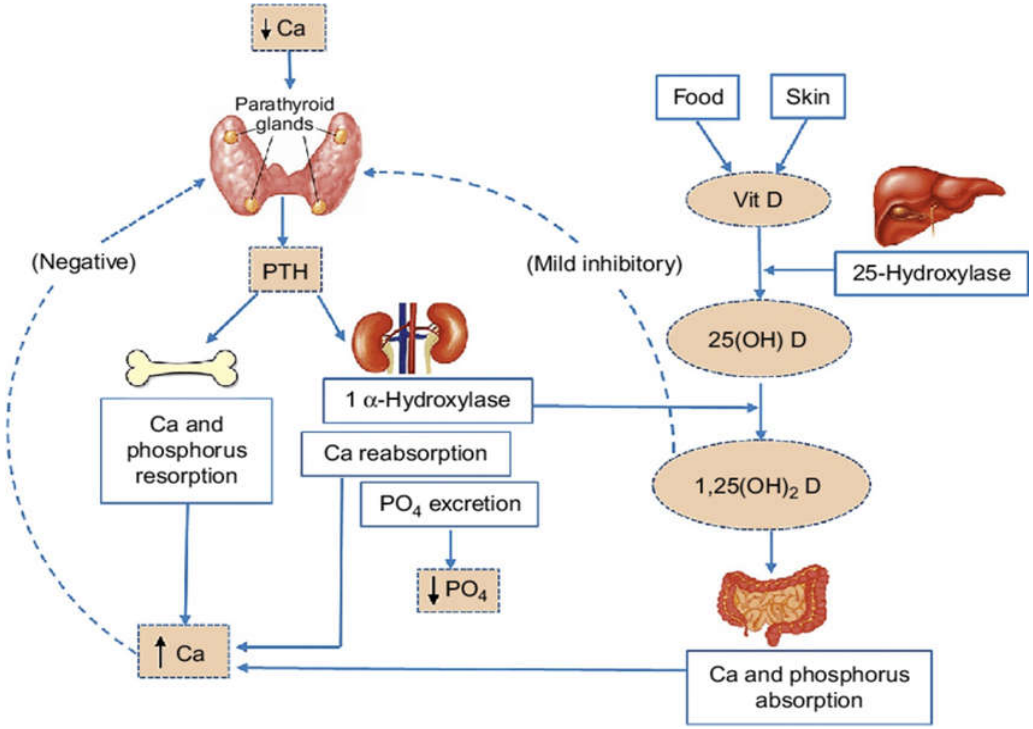
CALCIUM AND PHOSPHATE HOMEOSTASIS

Hormonal control :

1-PTH

2-VIT D

3-calcitonin



PARATHYROID HORMONE

PTH is the major hormone for the regulation of serum [Ca2+]. Is synthesized and secreted by the chief cells of the parathyroid glands.

Actions of PTH:

Increase serum ca^{2+} and decrease serum phosphate

- PTH is controlled by the serum [Ca^{2+}] binding to Ca^{2+}–sensing receptors in the parathyroid cell membrane.
- Decreased serum [Ca^{2+}] increases PTH secretion, whereas increased serum Ca^{2+} decreases PTH secretion.
- Mild decreases in serum [Mg^{2+}] stimulate PTH secretion.
- Severe decreases in serum [Mg^{2+}] inhibit PTH secretion and produce symptoms of hypoparathyroidism (e.g., hypocalcemia).

ACTIONS OF PTH

1. PTH increases bone resorption.
2. PTH inhibits renal phosphate reabsorption in the proximal tubule.
3. PTH increases renal Ca^{2+} reabsorption in the distal tubule, which also increases the serum $[Ca^{2+}]$.
4. PTH increases intestinal Ca2+ absorption indirectly by stimulating the production of 1,25-dihydroxycholecalciferol in the kidney.

PTH AND BONE

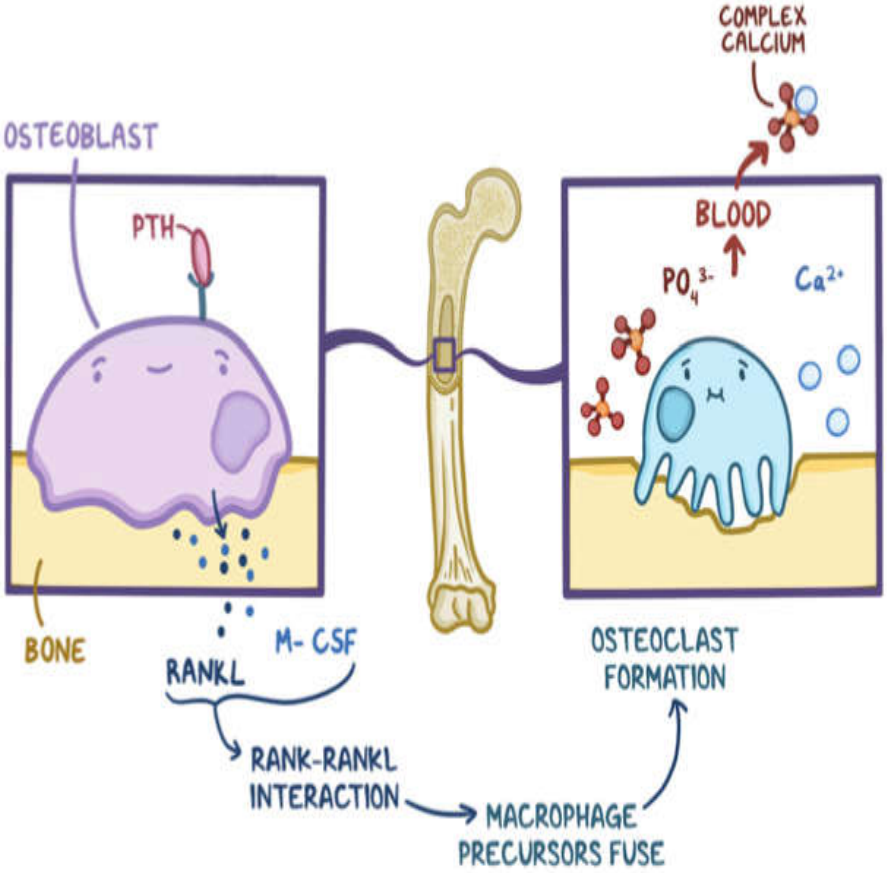


Figure 35.5 One way PTH increases extracellular calcium levels is by stimulating osteoclast formation in bone.

PTH AND KIDNEY

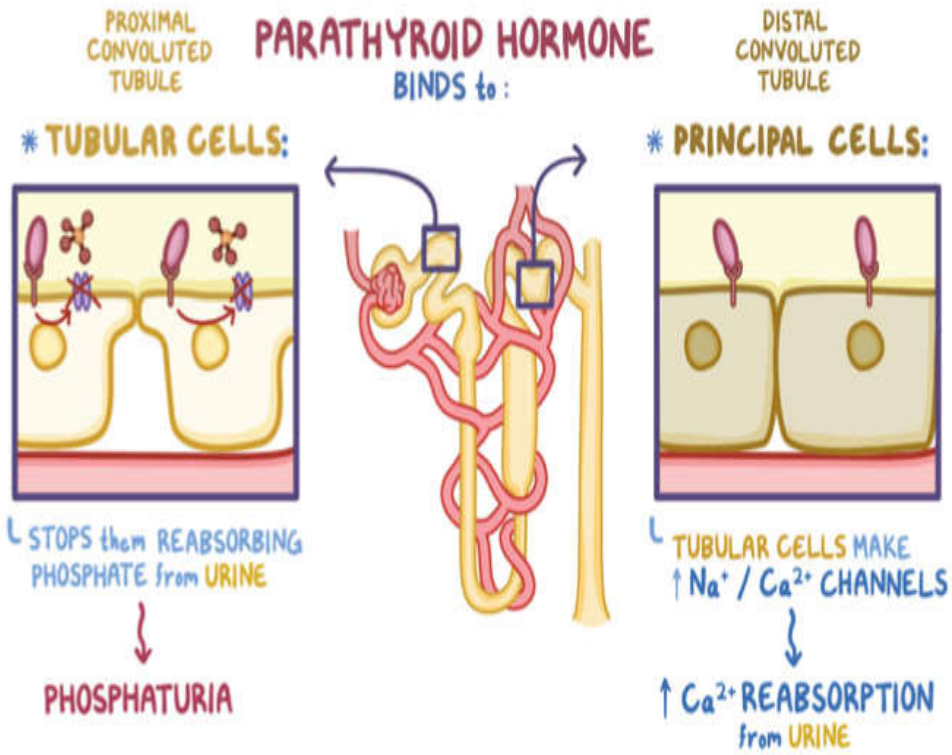


Figure 35.6 The second way PTH increases extracellular calcium levels is by ↑ urinary phosphate excretion and ↑ calcium reabsorption from urine.

PTH AND INTESTINE

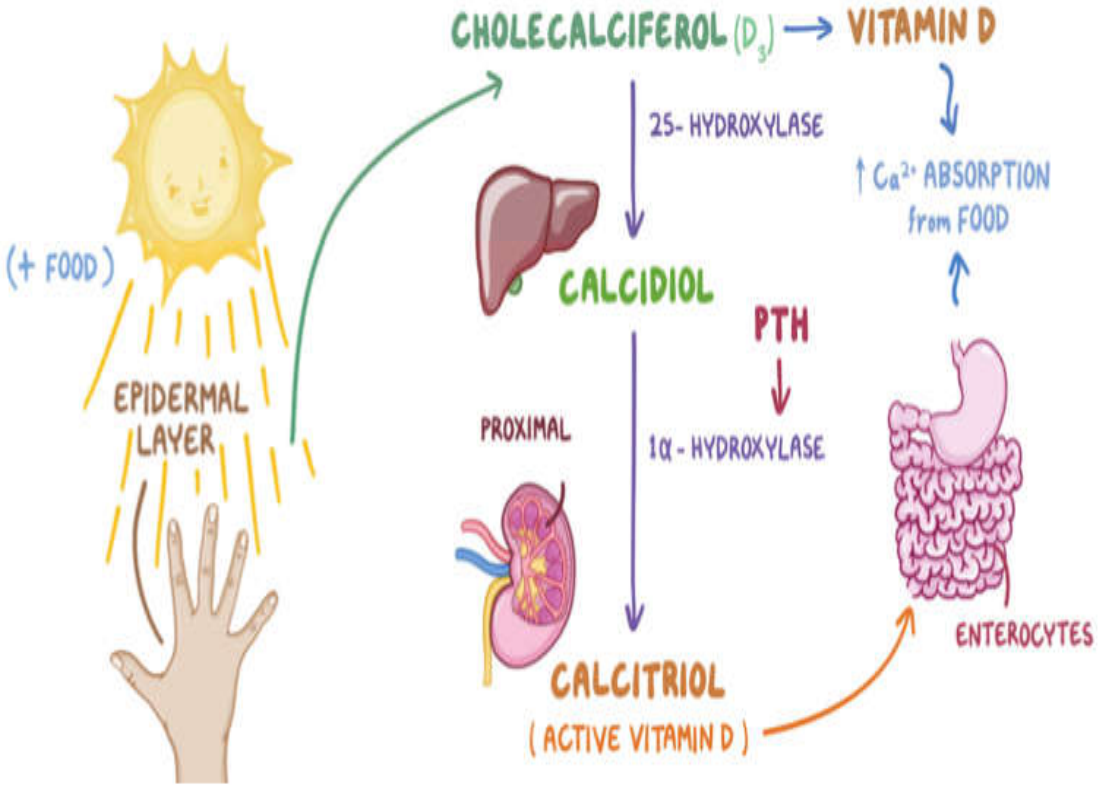
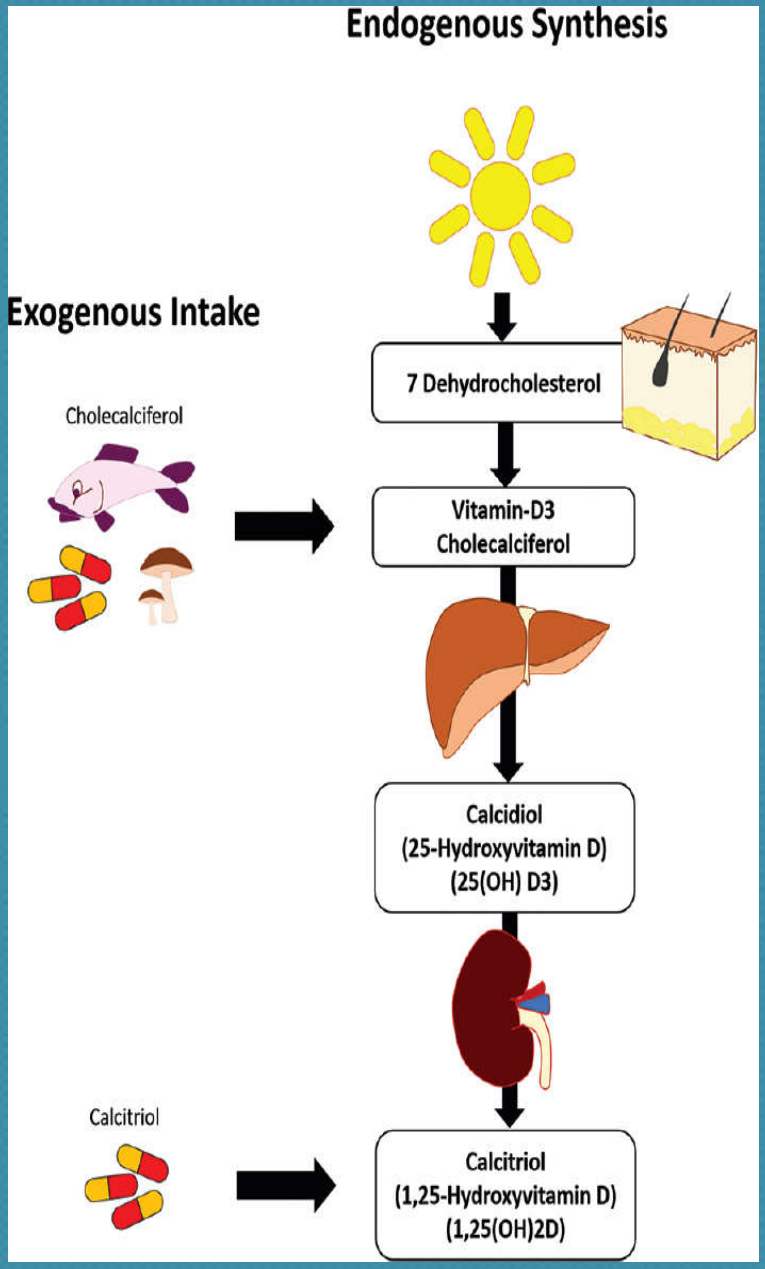


Figure 35.7 The third way PTH increases extracellular calcium levels is by helping convert cholecalciferol into vitamin D. It does so by upregulating enzyme 1α-hydroxylase.

VITAMIN D

- Vitamin D-3 (cholecalciferol) is formed in the skin when a cholesterol precursor, 7-dehydroxycholesterol, is exposed to ult raviolet light
-Vit D conversion to 25-hydroxycholecalciferol occurs in the liver
-1,25–dihydroxycholecalciferol is formed in the proximal tubules of the kidney
The production of 1,25-dihydroxycholecalciferol in the kidney is catalyzed by the enzyme 1α-hydroxylase
-1a-hydroxylase activity is increased by the following:
a. ↓ serum [Ca2+]
b. ↑ PTH levels
c. ↓ serum [phosphate]



ACTIONS OF VIT D

Vitamin D increases plasma ca^{2+} and plasma PO_4^{3-} by acting on :

1. Bone : Inc bone resorption.
2. kidney : Inc calcium and phosphate reabsorption.
3. GUT : Inc calcium absorption and phosphate reabsorption.

VIT D AND BONE

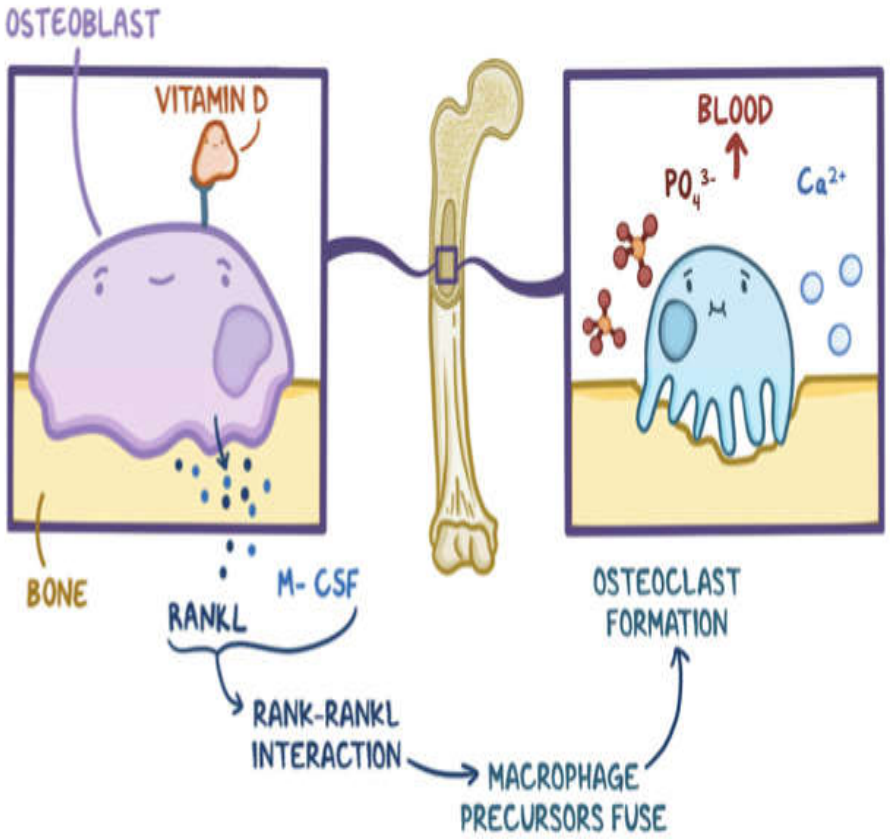


Figure 35.9 Vitamin D stimulates osteoclast formation, increasing blood calcium and phosphate concentrations.

Vit D and kidney

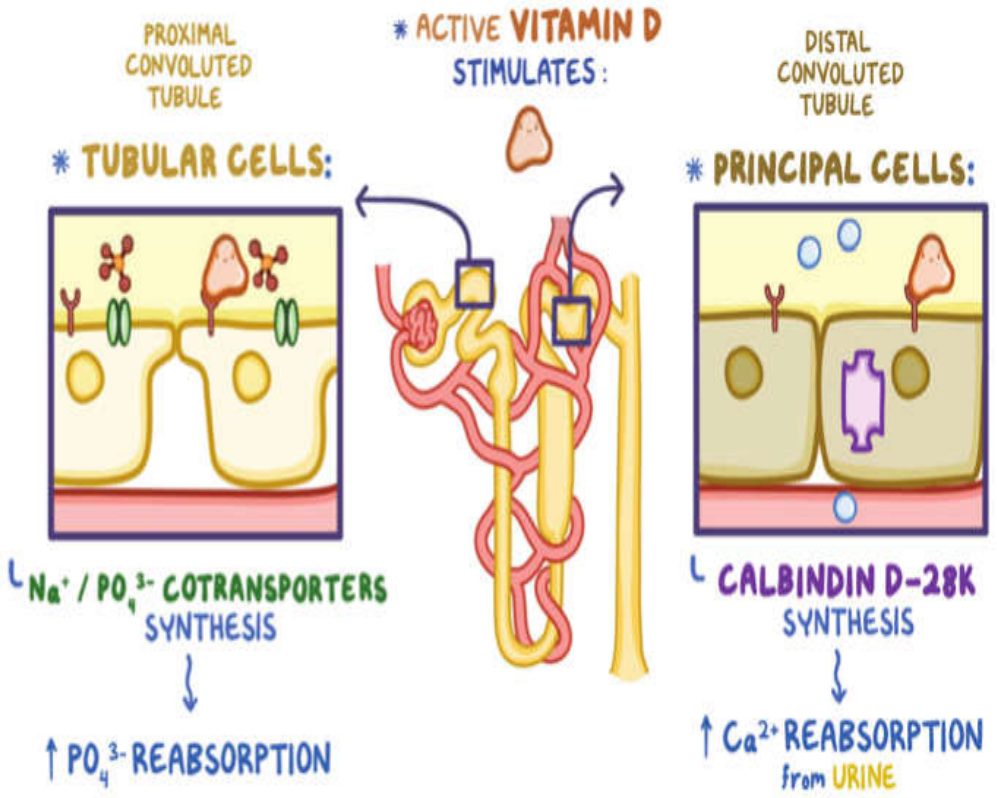


Figure 35.10 Vitamin D stimulates calcium and phosphate reabsorption in kidneys.

VITAMIN D AND INTESTINE

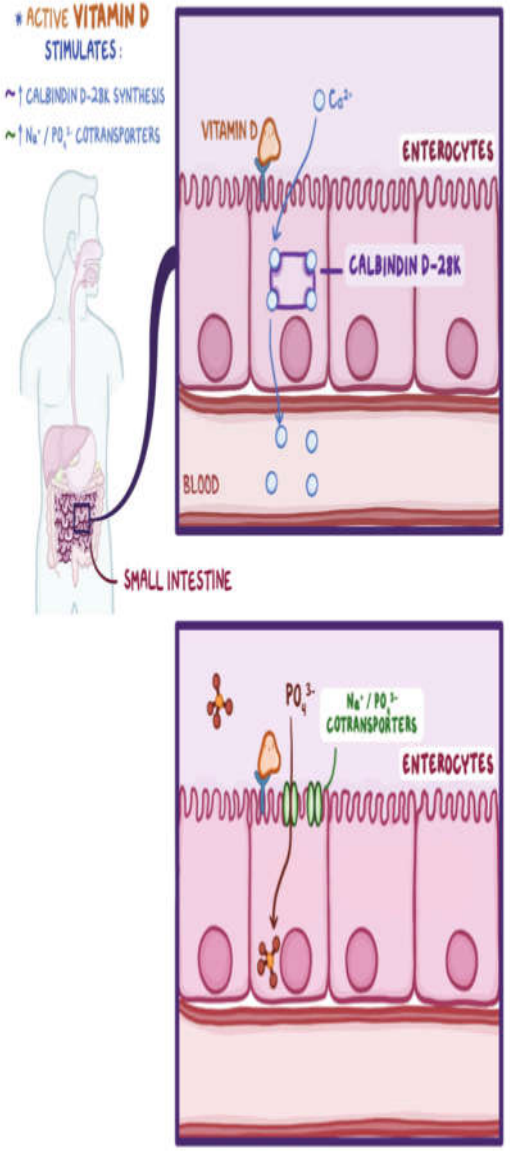


Figure 35.11 Vitamin D stimulates calcium and phosphate absorption in the small intestine by increasing synthesis of calbindin D-28K and sodium/phosphate cotransporters.

CALCITONIN

- It is a 32 amino acid peptide hormone secreted by the thyroid gland from C cells or parafollicular cells.
- The main physiologic function of calcitonin is to decrease plasma Ca^{2+} and phosphate concentrations, mainly by decreasing bone resorption. This effect is opposite to that of PTH (Stimulates osteoblasts, inhibits osteoclasts). However, in the adult human PTH effect overrides that of calcitonin.
- The release of calcitonin is regulated by plasma calcium levels through a Ca^{2+} receptor on the parafollicular cells. Elevations in plasma Ca^{2+} higher than 9 mg/dl stimulate the release of calcitonin. In contrast, PTH secretion is stimulated by decreased calcium concentration.
- The ability of calcitonin to inhibit osteoclast-mediated bone resorption has made it a useful agent for the treatment of osteoporosis.

HYPOCALCEMIA

HYPOCALCEMIA

- It is a condition in which calcium level is below normal.

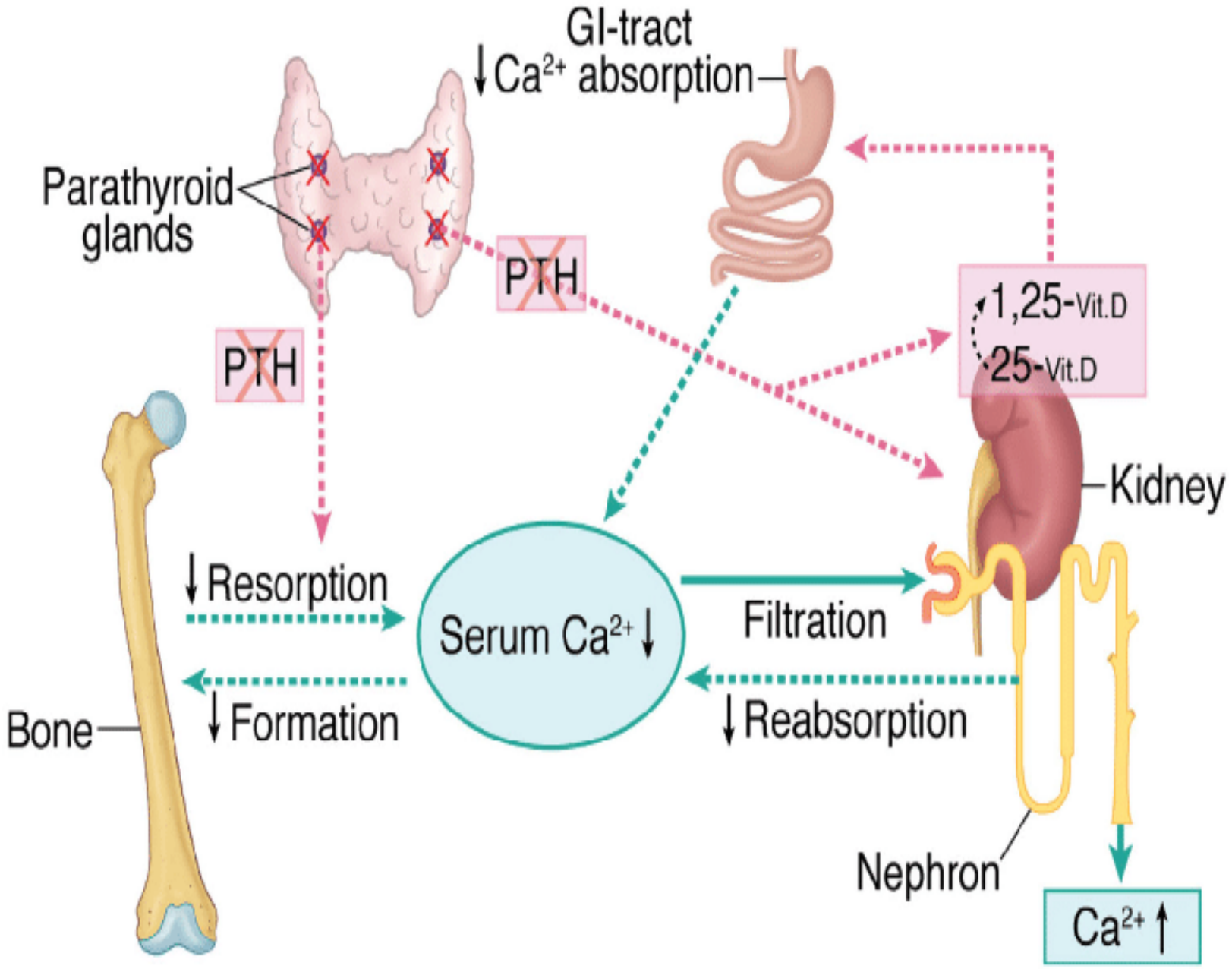
- Symptoms start showing when calcium level is under 8.5mg/dL of serum calcium.

CAUSES OF HYPOCALCEMIA :

- Hypoparathyroidism (most common cause): due to surgery in the thyroid gland with damage to nearby parathyroid gland
- Renal insufficiency: due to decreased production of 1,25dihydroxy vitamin D.
- Hyperphosphatemia
- Hypomagnesemia: results in decreased PTH
- Vitamin D deficiency
- Blood transfusion

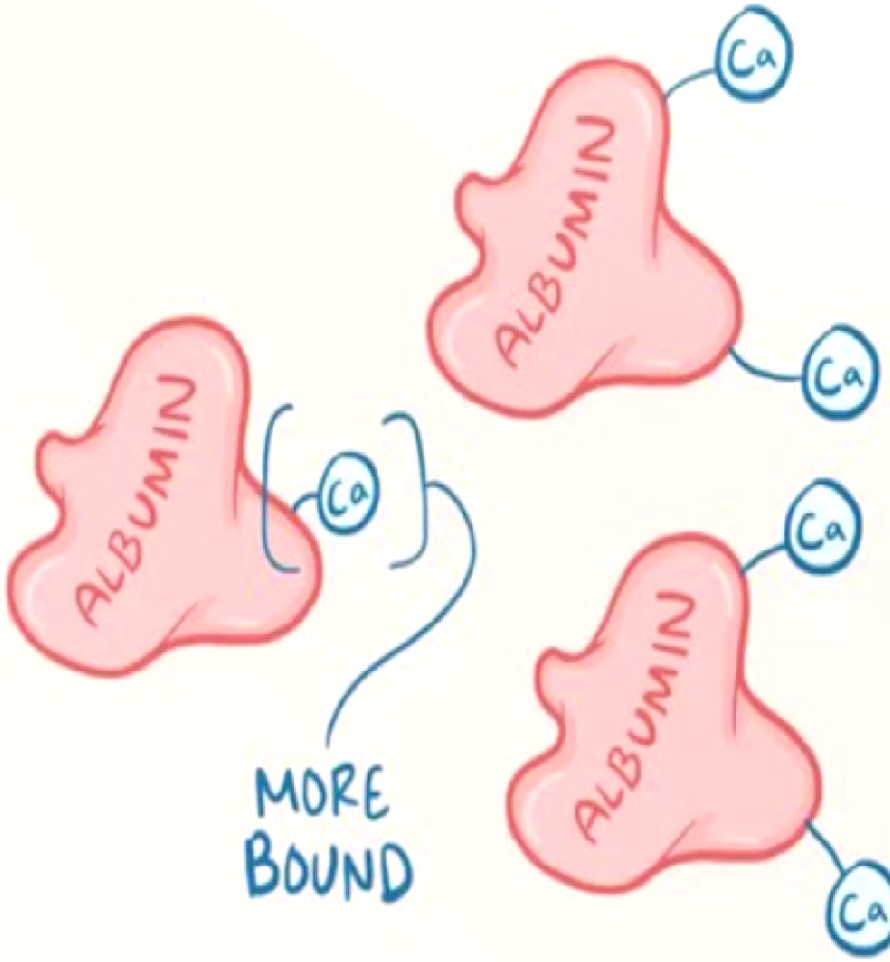
CAUSES OF HYPOCALCEMIA :

- Pseudohypoparathyroidism : autosomal recessive causing congenital endorgan resistance to PTH
- Alkalemia : Increase in pH causes increased calcium binding
- Hypoalbuminemia
- Malabsorption: celeac disease leads to low vitamin D or magnesium
- Osteoblastic metastases
- Acute pancreatitis
- DiGeorge syndrome


GI-tract
↓Ca2+ absorption
Parathyroid glands
PTH
PTH
1,25-Vit.D
25-Vit.D
Kidney
↓Resorption
Serum Ca2+ ↓
Filtration
Bone
↓Formation
↓Reabsorption
Nephron
Ca2+ ↑

(THE BLOOD)

ALKALOSIS: HIGH pH ~ FEW PROTONS $\{ {}^{+}H \}$



TOTAL: SAME

$[{}^{2+}Ca]$

LESS FREE-IONIZED

* SYMPTOMS of HYPOCALCEMIA

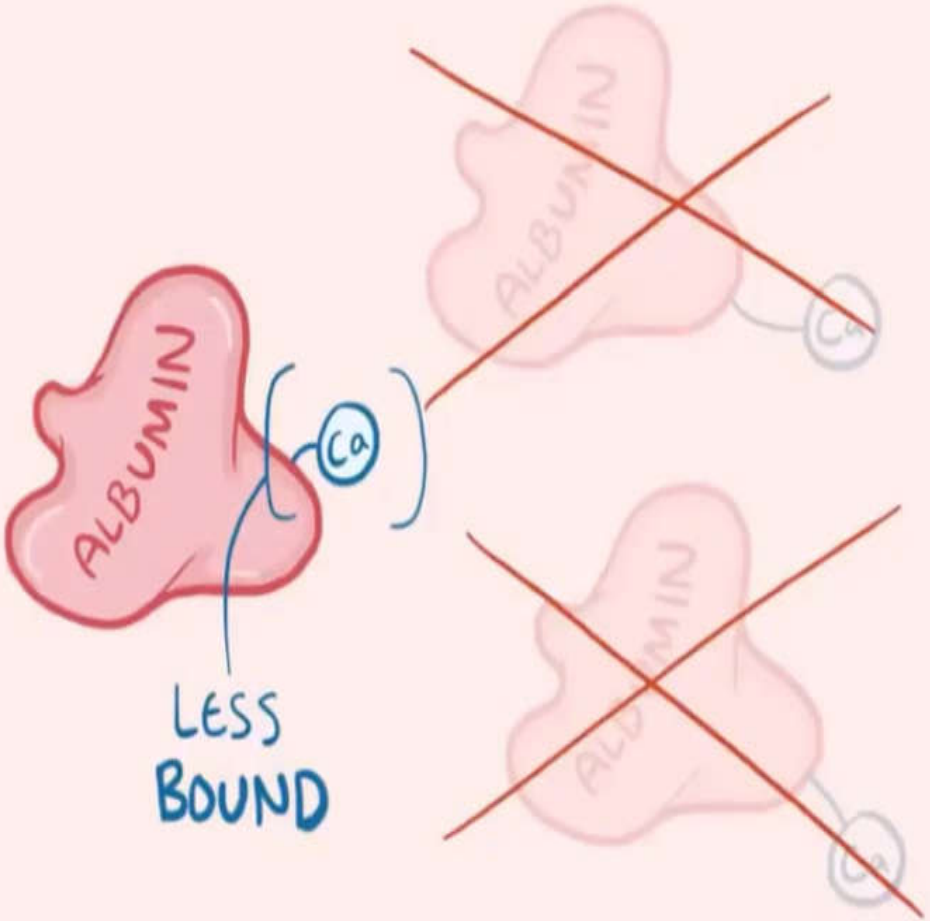
(THE BLOOD)

LOW in the BLOOD

HYPOALBUMINEMIA → FALSE HYPOCALCEMIA

(PSEUDOHYPOCALCEMIA)

TOTAL: LESS



LESS BOUND

SAME FREE-IONIZED

*hormonally regulated

CORRECTION OF CALCIUM

-:Formula:-

- Thus ,calcium level should be corrected in patients with low serum albumin levels ,using the formula :
- Corrected calcium(mg/dL)= measured total Ca(mg/dL)+0.8(4.0-serum albumin <g/dL>).
- Where 4 respresents the average albumin level.

CLINICAL FEATURES

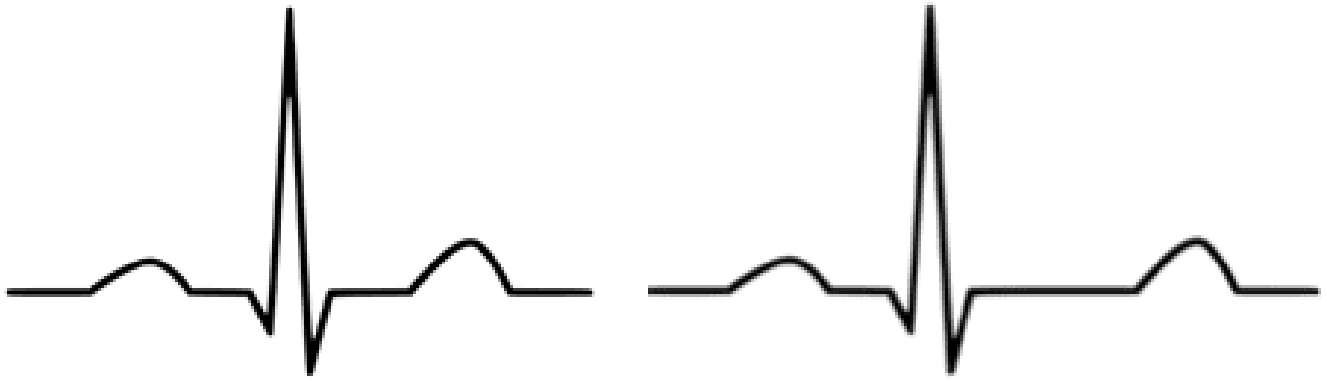
1. Asymptomatic
2. Rickets and osteomalacia
3. Increased neuromuscular irritability :

- Numbness/tingling : Circumoral in fingers and in toes
- Seizures
- Tetany :

a) Hyperactive deep tendon reflexes
b) Chvostek sign: Tapping of facial nerve leads to contraction of facial muscles
c) Trousseau sign: Inflate BP cuff to a pressure higher than patient's systolic BP for 3 minutes.

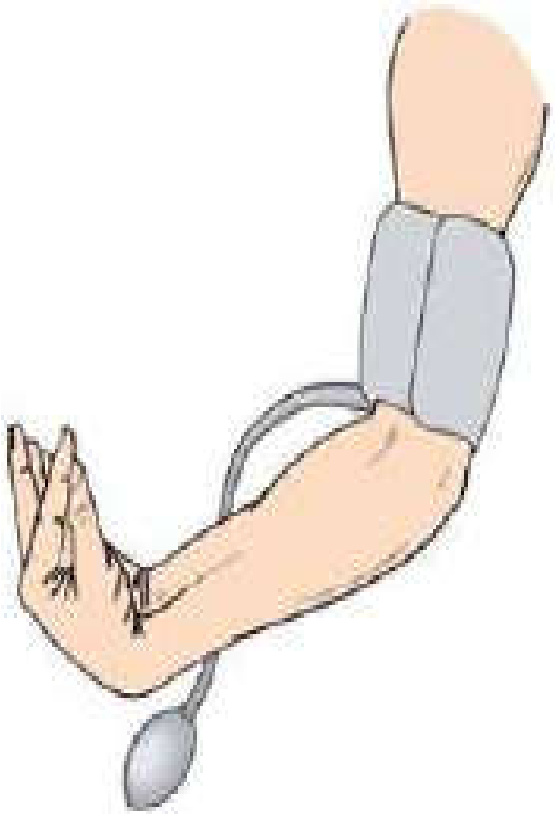
Clinical features

4. Basal ganglia calcifications
5. Cardiac manifestations :
   a) Arrhythmias
   b) Prolonged QT interval on ECG

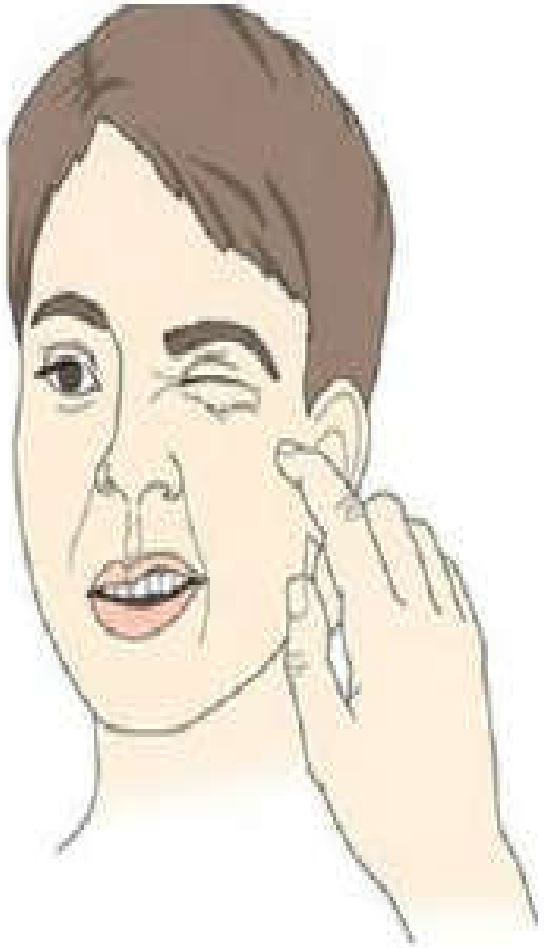


Normal HYPOcalcaemia

Trousseau's sign



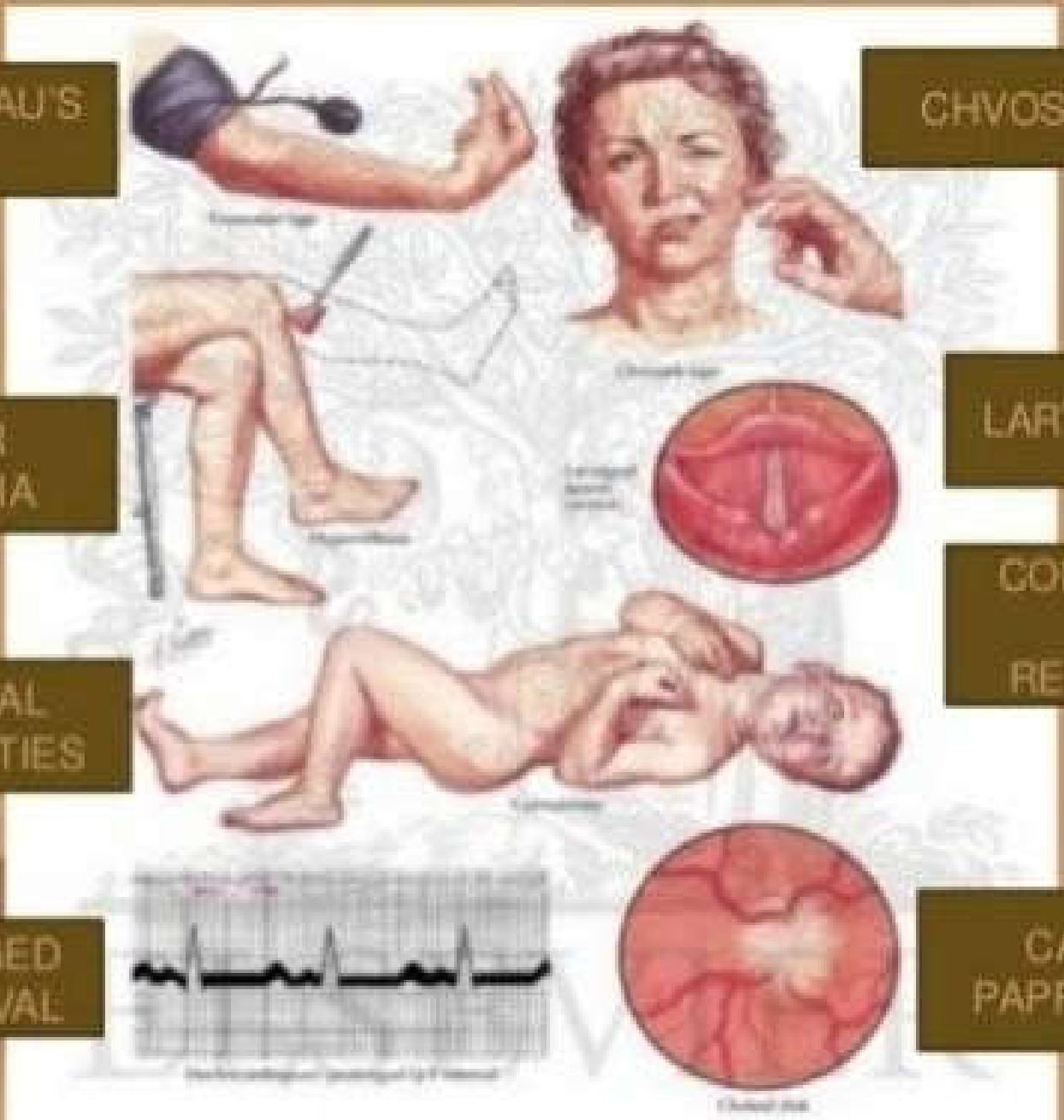
Chvostek's sign



HYPOCALCEMIA

TROUSSEAU'S SIGN

CHVOSTEK SIGN



HYPER REFLEXIA

LARYNGOSPASM

CONVULSIONS, MENTAL RETARDATION

SKELETAL DEFORMITIES

PROLONGED QT INTERVAL

CATARACT PAPPILOEDEMA

DIAGNOSIS

1. BUN, Cr, magnesium, albumin, and ionized calcium. Amylase, lipase, and liver function tests may also be warranted.
2. Serum PO_4^{3-}: high in renal insufficiency and in hypoparathyroidism, low in primary vitamin D deficiency
3. PTH:
    a. Low in hypoparathyroidism
    b. Elevated in vitamin D deficiency

TREATMENT

1-For sever hypocalcemia use IV calcium gluconate.

2-For long-term management, use oral calcium supplements (calcium carbonate) and vitamin D

3-For PTH deficiency:

a. Replacement therapy with vitamin D (calcitriol) plus a high oral calcium intake.

b. Thiazide diuretics

4-It is also important to correct hypomagnesemia. It is very difficult to correct the calcium level if the magnesium is not replaced first.

HYPERCALCEMIA

HYPERCALCEMIA

Mild hypercalcemia: 10.3-11.9 mg/dL

Moderate hypercalcemia : 12-13.9 mg/dL

Severe hypercalcemia : >14 mg/dl

CAUSES

- 1.Endocrinopathies

  a. Hyperparathyroidism

  b. Renal failure

  c. Paget disease of the bone

  d. acromegaly, Addison disease

- 2. Malignancies

  Metastatic cancer

  Multiple myeloma

  Tumors that release PTH–like hormone (e.g., squamous cell cancer)

  Tumors that release PTH (lung, ovarian cancer)

  Tumors that release vitamin D (lymphoma)

- 3. Pharmacologic

  a. Vitamin D intoxication

  b. Milk–alkali syndrome

  c. Drugs—thiazide diuretics , lithium

- 4. Other

  a. Sarcoidosis

  b. Familial hypocalciuric hypercalcemia

CLINICAL FEATURES

"Stones"

a. Nephrolithiasis

b. Nephrocalcinosis

"Bones"

a. Bone aches and pains

b. Osteitis fibrosa cystica ("brown tumors") predisposes to pathologic fractures

"Grunts and groans"

Muscle pain and weakness

Pancreatitis

Peptic ulcer disease

Gout

Constipation

"Psychiatric overtones"

:

depression, fatigue, anorexia, sleep disturbances, anxiety, lethargy

Other findings

A. Polydipsia, polyuria

B. Nephrogenic DI

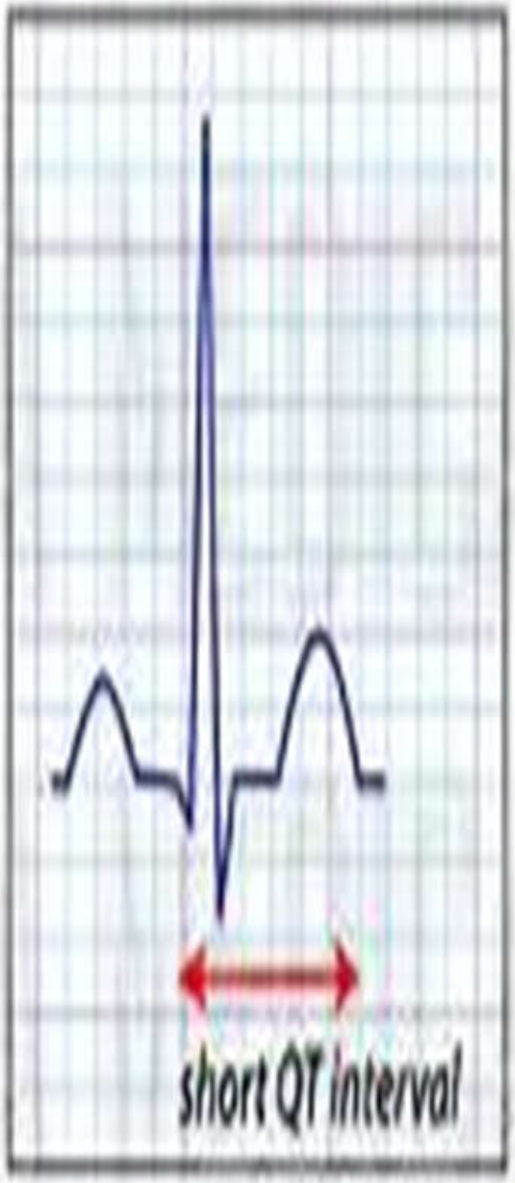
C. Hypertension

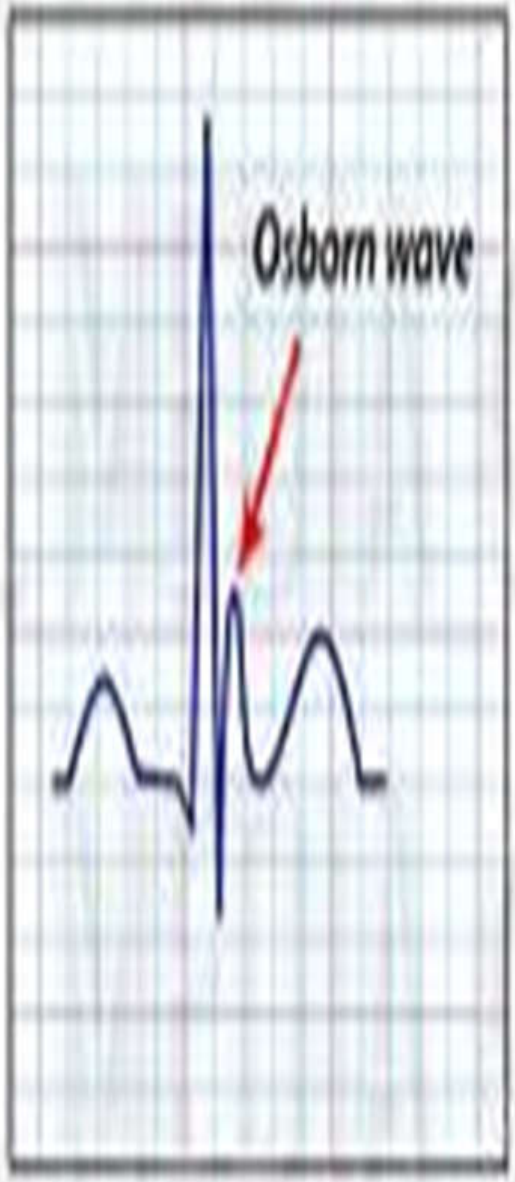
D. Weight loss

E. Patients may be asymptomatic

ECG ABNORMALITIES

- The main ECG abnormality seen with hypercalcemia is shortening of the QT interval
- In severe hypercalcemia, Osborn wave (j wave) may be seen





Hypercalcemia

DIAGNOSIS

- Same laboratory tests as in hypocalcemia
- Radioimmunoassay of PTH
- Radioimmunoassay of PTH-related protein
- Bone scan or bone survey to identify lytic lesions
- Urinary cAMP

TREATMENT

- Usually patients don't require management beyond correction of the underlying etiology unless hypercalcemia is severe or significant symptoms are present
- Increase urinary excretion

a. IV fluids (NS)—first step in management

b. Diuretics (furosemide)—further inhibit calcium reabsorption

- Inhibit bone resorption in patients with osteoclastic disease (e.g., malignancy)

a. Bisphosphonates (pamidronate)

b. Calcitonin

- Give glucocorticoids if vitamin D–related mechanisms (intoxication, granulomatous disorders) and multiple myeloma are the cause of the hypercalcemia.

However, glucocorticoids are ineffective in most other forms of hypercalcemia

- Use hemodialysis for renal failure patients
- Phosphate is effective but incurs the risk of metastatic calcification

PARATHYROID HORMONE (PTH)

Actions of PTH are on bone, kidneys and small intestines

The main action of it is to increase plasma CA++

1- Bone : ↑ bone resorption

2- kidney : ↑ Ca++ reabsorption

3- Gut : ↑ Ca++ absorption

HYPERPARATHYRODISM

Definition :

All forms of Hyperparathyrodism are characterised by elevated PTH levels.

*Primary Hyperparathyrodism: hypercalcemia results from abnormally active parathyroid glands.

*Secondary Hyperparathyrodism: hypocalcemia results in reactive overproduction of PTH.

*Tertiary Hyperparathyrodism: Hypercalcemia results from untreated sHPT ,With continuously elevated PTH levels

PRIMARY HYPERPARATHYROIDISM

One or more glands produce inappropriately high amounts of PTH relative to the serum calcium level. Causes:

1: ADENOMA : 80% of cases majority involve one gland

2:HYPERPLASIA : 15% to 20% of cases all four glands usually affected

3:CARCINOMA : <1% of cases

PRIMARY HYPERPARATHYRODISM

Clinical Features :

1.Stones : Nephrolethiasis , nephrocalcinosis
2.Bones: Bone aches and pains , Osteites fibrosis cystic
3:Groans :
a. Muscle pain and weakness
b. Pancreatitis
C. PUD
D. Gout
E. Constipation
4."Psychateic overtones" : depression ,fatigue, anorexia, sleep disturbances, anxiety, lethargy

SECONDARY HYPERPARATHYROIDISM

* Chronic kidney disease (most frequent cause)

* Vit.D deficiency (eg. Reduced exposure to sun light,nutritional deficiency ,liver cirrhosis)

* Cholestasis

TERTIARY HYPERPARATHYROIDISM

In long standing sHPT,the parathyroid glands May become severly enlarged and continue to be overactive ,even if the original stimulus (hypocalcemia) is no longer present.

	Primary Hyperparathyroidism	Secondary Hyperparathyroidism	Tertiary Hyperparathyroidism
Calcium	↑	↓/N	↑
PTH	↑	↑	↑↑
Phosphate	↓	↑/N	↑

PTH - LIKE PEPTIDE

- PTH-like peptide is usually produced by SCC of the lung
- Characterized by hypercalcemia with suppressed PTH levels

HYPOPARATHYRODISM

Causes :

Removal of glands during head and neck surgery account for the majority of cases __thyroidectomy, parathyroidectomy,radical surgery for head and neck malignancies

(Nonsurgical hypoparathyroidism is rare).

HYPOPHOSPHATEMIA

DEFINITION

Serum phosphate level of less than 2.5 mg/dL (0.8 mmol/L) in adults.

CAUSES

Etiologies by Mechanism

Decreased GI Absorption	Increased Urinary Excretion	Internal Redistribution
↓ Intake of dietary phosphate (only seen in malnourished alcoholics)	Vitamin D deficiency	Refeeding syndrome
Malabsorption	Hyperparathyroidism	Hungry bones syndrome
Phosphate binders (e.g. calcium acetate, Al^{3+} and Mg^{2+} containing antacids)	Variety of rare genetic diseases	During treatment of DKA or HHS
	Fanconi syndrome (general proximal tubule dysfunction) Wilson's disease (in children) Cystinosis (in children) Multiple myeloma (in adults)	Acute respiratory alkalosis
	Tumor-induced osteomalacia	

DECREASE IN ABSORPTION

- Not enough absorbed in gastrointestinal tract
- Alcohol and medication bind with phoasphate so it cant be absorbed by GI T
- Midication like antiacid contain Al+3,Ca+2,Mg+2

HYPERPARATHYROIDISM

Increase PTH level that will increase the activation of the osteoclasts and they will increas the breakdown of the bone to Ca+2 and PO4

There level will increase in the blood then they will go to the nephron in the kidney

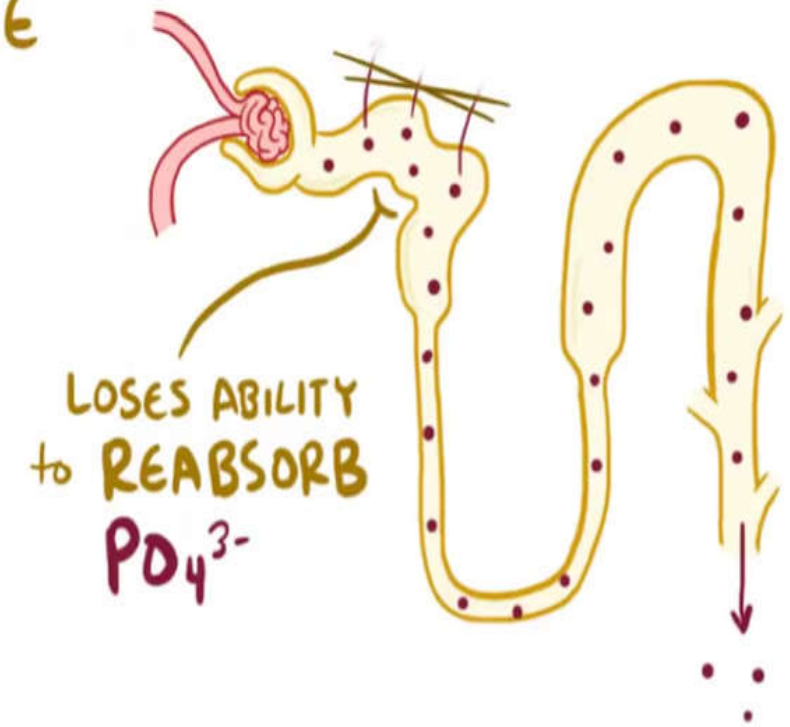
The PTH hormon will inhibit(sodium phosphate cotransporter this will absorbed the PO4 from proximal tubule) and increas ca+2

Level in the blood

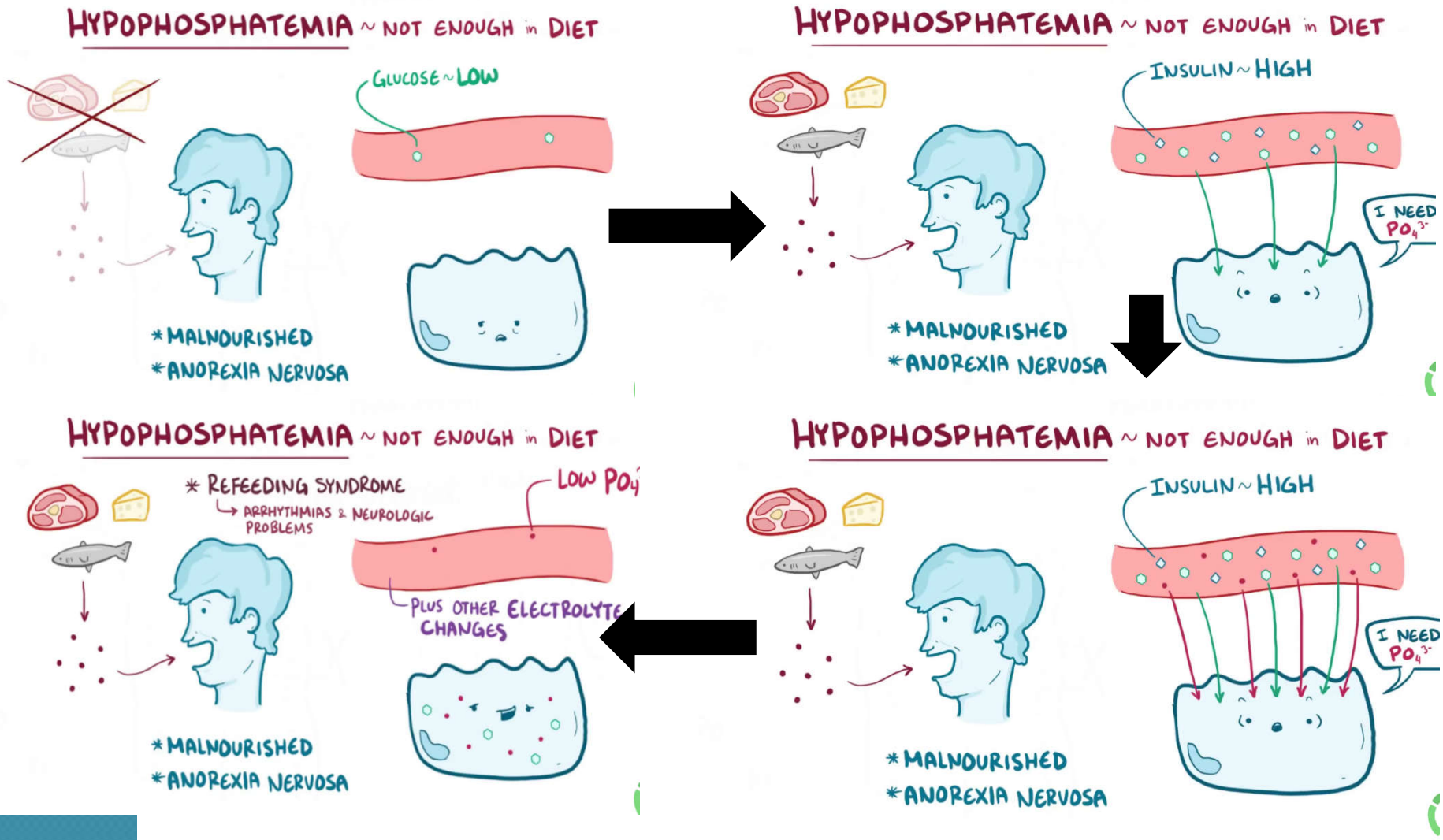
HYPOPHOSPHATEMIA ~ EXCESS LOSS of PO_4^{3-}

* PRIMARY HYPERPARATHYROIDISM
  - HYPER = TOO MUCH
  - → EXCESS PO_4^{3-} LOST in URINE

* FANCONI SYNDROME
  - → EXCESS PO_4^{3-} LOST in URINE



Refeeding syndrome



HYPOPHOSPHATEMIA

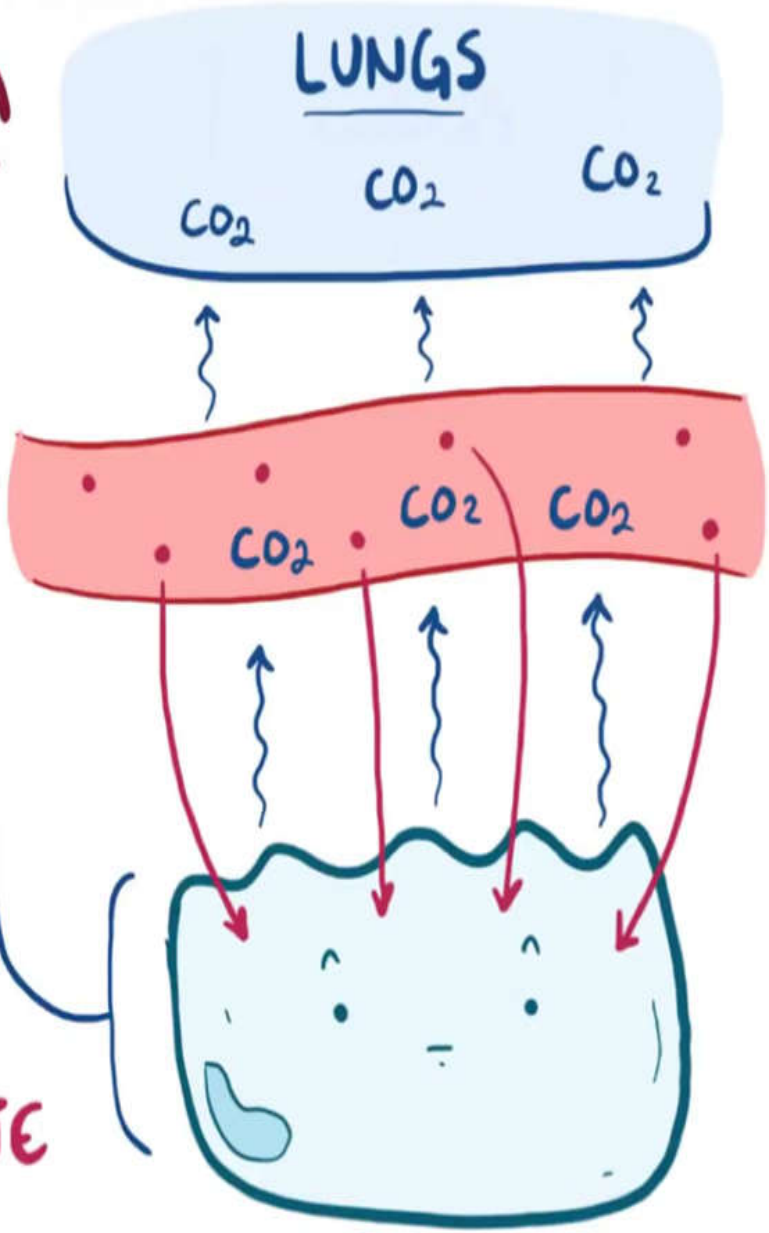
* RESPIRATORY ALKALOSIS

INCREASED pH
inside cell

↓

GLYCOLYSIS

* REQUIRES PHOSPHATE



CLINICAL FEATURES

The manifestations depend on the severity of the hypophosphatemia and for how long , with the plasma phosphate concentration usually being below 1 mg/dL (0.32 mmol/L) in symptomatic patients

1. None, if the hypophosphatemia is mild.

2. Any of the following, if the hypophosphatemia is severe:

a. Neurologic: encephalopathy, confusion, seizures, numbness, paresthesias

b. Musculoskeletal: muscular weakness, myalgias, bone pain, rickets/osteomalacia

c. Hematologic: hemolysis, RBC dysfunction, WBC dysfunction, platelet dysfunction

d. Cardiac: cardiomyopathy and myocardial depression secondary to low ATP levels, may lead to cardiac arrest

e. Rhabdomyolysis

f. Anorexia

g. Difficulty in ventilator weaning ,Polyuria ,gallbladder and kidney stones ,constipation .

EFFECTS OF HYPOPHOSPHATEMIA

- Distal tubular reabsorption of calcium and magnesium are inhibited, and striking hypercalciuria ensues.
- The initial response of bone to hypophosphatemia is increased resorption; Increased bone resorption is likely mediated by the phosphate depletion–induced rise in the synthesis of calcitriol
- More prolonged hypophosphatemia leads to rickets and osteomalacia due to decreased bone mineralization.
- Intracellular adenosine triphosphate (ATP) levels fall with severe hypophosphatemia, and cell functions dependent upon energy-rich phosphate compounds begin to fail.

DIAGNOSIS

- The first step is measurement of 24 hour urine phosphate excretion
- **measuring the concentration of phosphate in the blood**. Concentrations of phosphate less than 0.81 mmol/L (2.5 mg/dL) are considered diagnostic of hypophosphatemia

TREATMENTS

- 1. If mild (>1 mg/dL): oral supplementation
- 2. If severe/symptomatic or if patient is NPO: parenteral supplementation
- We stop phosphate supplementns when the serum phosphate is greater than or equal to 2.0 mg/dL unless there is an indication for chronic therapy such as persistent urinary phosphate wasting.

HYPERPHOSPHATEMIA

Phosphate ions storage in body as :

- 85% in bone – Combined with calcium (hydroxyapatite) .
- ~14% intercellular
- ~1% extracellular – what get measured

* Hyperphosphatemia when PO4 level is above 4.5mg/dl

Causes of **hyperphosphatemia** are :

1- Decrease excretion of phosphate (most common cause),

Advanced renal insufficiency (glomerular filtration rate [GFR] < 30 mL/minute) reduces excretion sufficiently to increase serum phosphate.

Defects in renal excretion of phosphate in the absence of chronic kidney diseasee also occur in pseudohypoparathyroidism , hypoparathyroidism, and parathyroid suppression .

2- from a transcellular shift of phosphate into the extracellular space.

This transcellular shift occurs most frequently in :

- Diabetic ketoacidosis
- Crush injuries
- Nontraumatic rhabdomyolysis
- Overwhelming systemic infections
- Tumor lysis syndrome

3- Increased intake :

- Vitamin D intoxication
- Excessive parenteral administration of PO4 (enemas)
- Excessive oral phosphate administration (oral laxative

PATHOPHYSIOLOGY

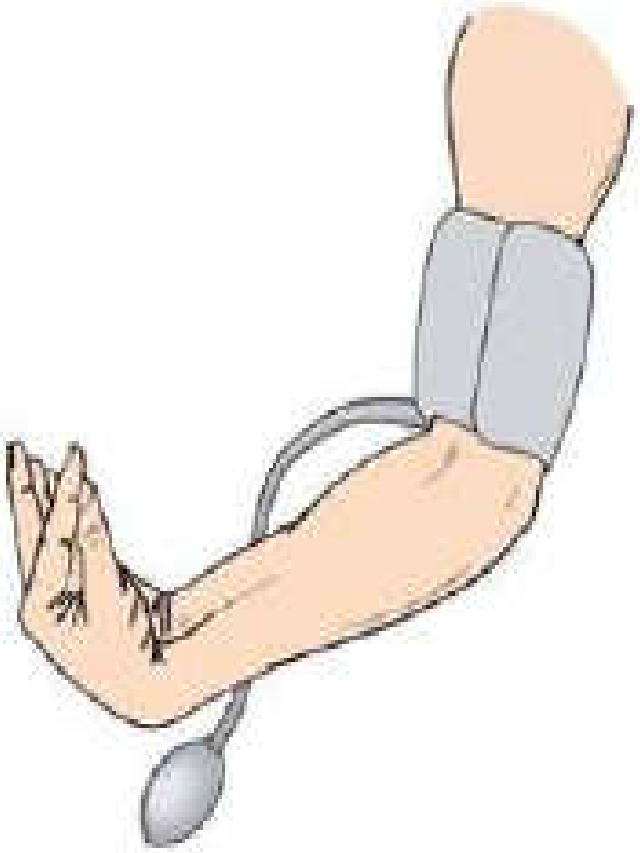
Hyperphosphatemia plays a critical role in the development of secondary hyperparathyroidism and renal osteodystrophy in patients with advanced chronic kidney disease as well as in patients on dialysis .

SYMPTOMS AND SINGS

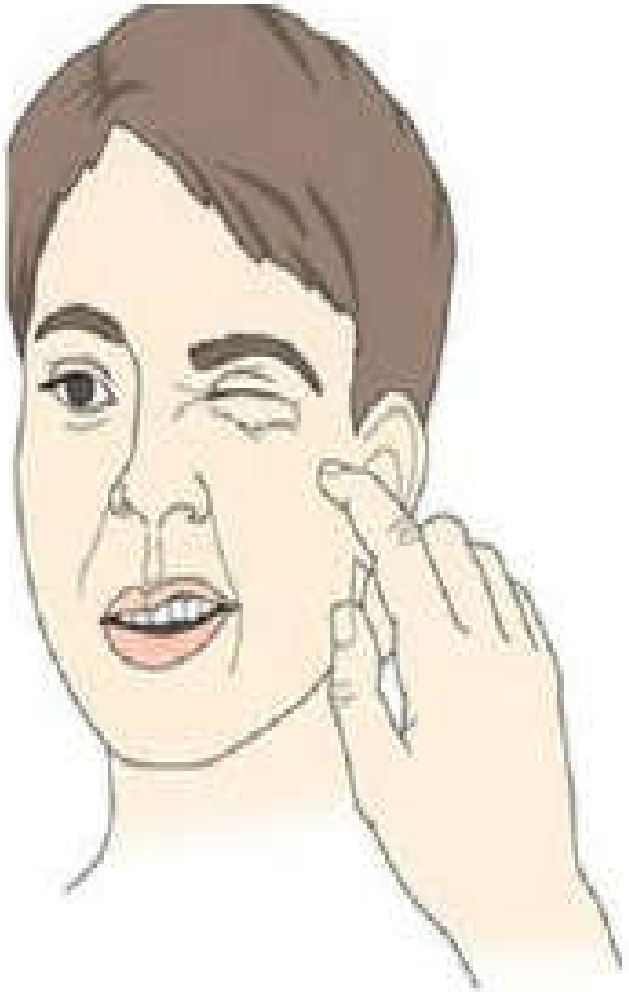
-Most patients with hyperphosphatemia are asymptomatic (mild)

- sever cases lead to symptoms of hypocalcaemia , which present as neurological changes (tetany, neuromuscular irritability) .
- Metastatic calcification Soft-tissue calcifications .
- Sings : Chvostek's sing / Trousseau's sing

Trousseau's sign



Chvostek's sign



DIAGNOSIS :

Phosphate concentration > 4.5 mg/dL (> 1.46 mmol/L) .

- Full chemistry profile
- Low serum Ca levels with High serum PO4 (Observed in RF and Hypoparathyroidism)
- BUN and Creatinine values, Help to determine if renal failure is the cause.

TREATMENT

- Phosphate restriction
- Phosphate binders

(Calcium-based Phosphate binders, lanthanum)

- Sometimes saline diuresis or hemodialysis

THANK YOU