Vitamin D deficiency

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Outlines:

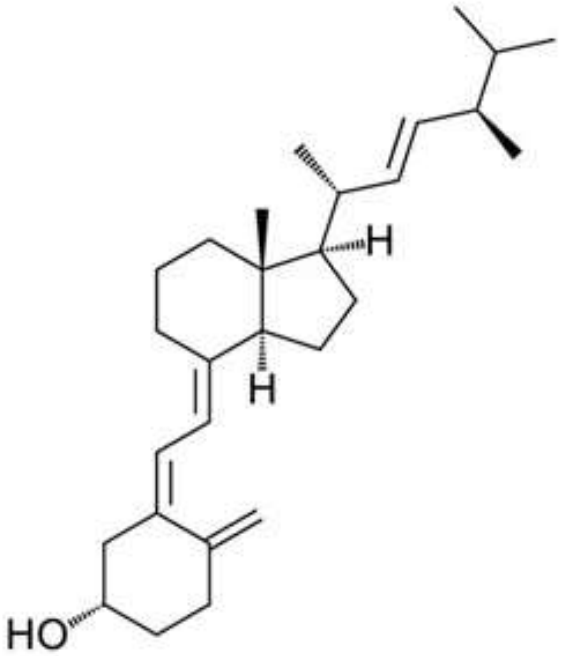
- Definition of vitamin D & structure
- Sources & metabolism
- Mechanism of action
- Calcium homeostasis
- Functions of vitamin D
- Regulation
- Causes of deficiency and risk factors
- Clinical features & Complications
- Diagnosis
- Treatment
- References

Definition of vitamin D, structure, sources, & metabolism

by: Momen Hajali

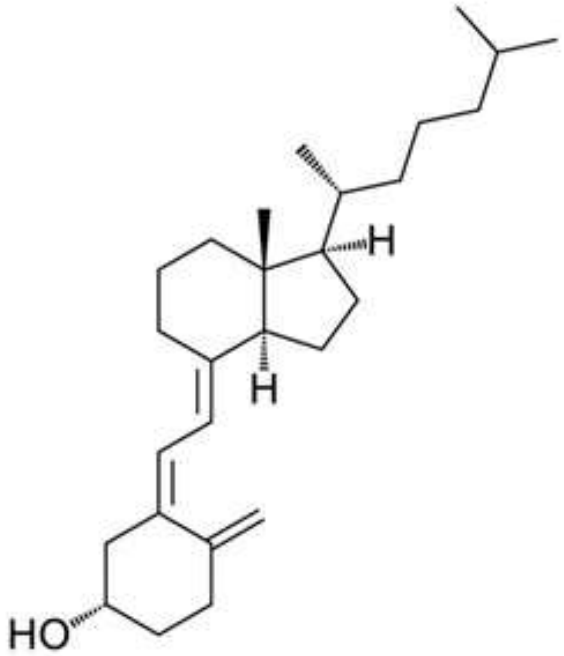
What is vitamin D

- Vitamin D is the collective name for cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2)
- Steroid fat-soluble vitamins
- Precursors of a hormone (active vit D) with an important role in regulation of the metabolism of calcium and phosphates.
- Exogenous (dietary) and endogenous sources



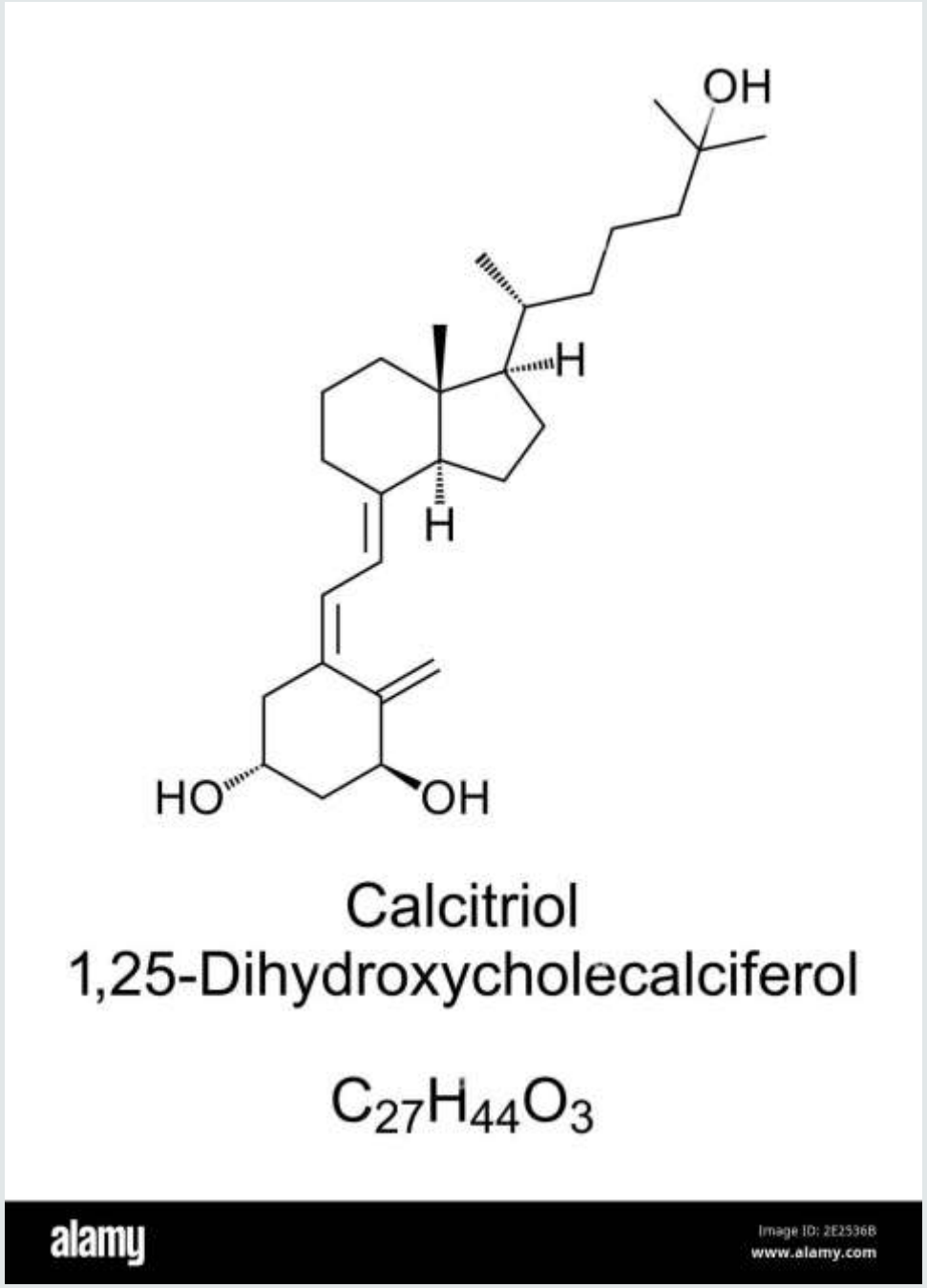
Vitamin D_2
Ergocalciferol

$C_{28}H_{44}O$



Vitamin D_3
Cholecalciferol

$C_{27}H_{44}O$


OH
H
H
HO
OH
Calcitriol
1,25-Dihydroxycholecalciferol
$C_{27}H_{44}O_3$
alamy
Image ID: 2E2536B
www.alamy.com

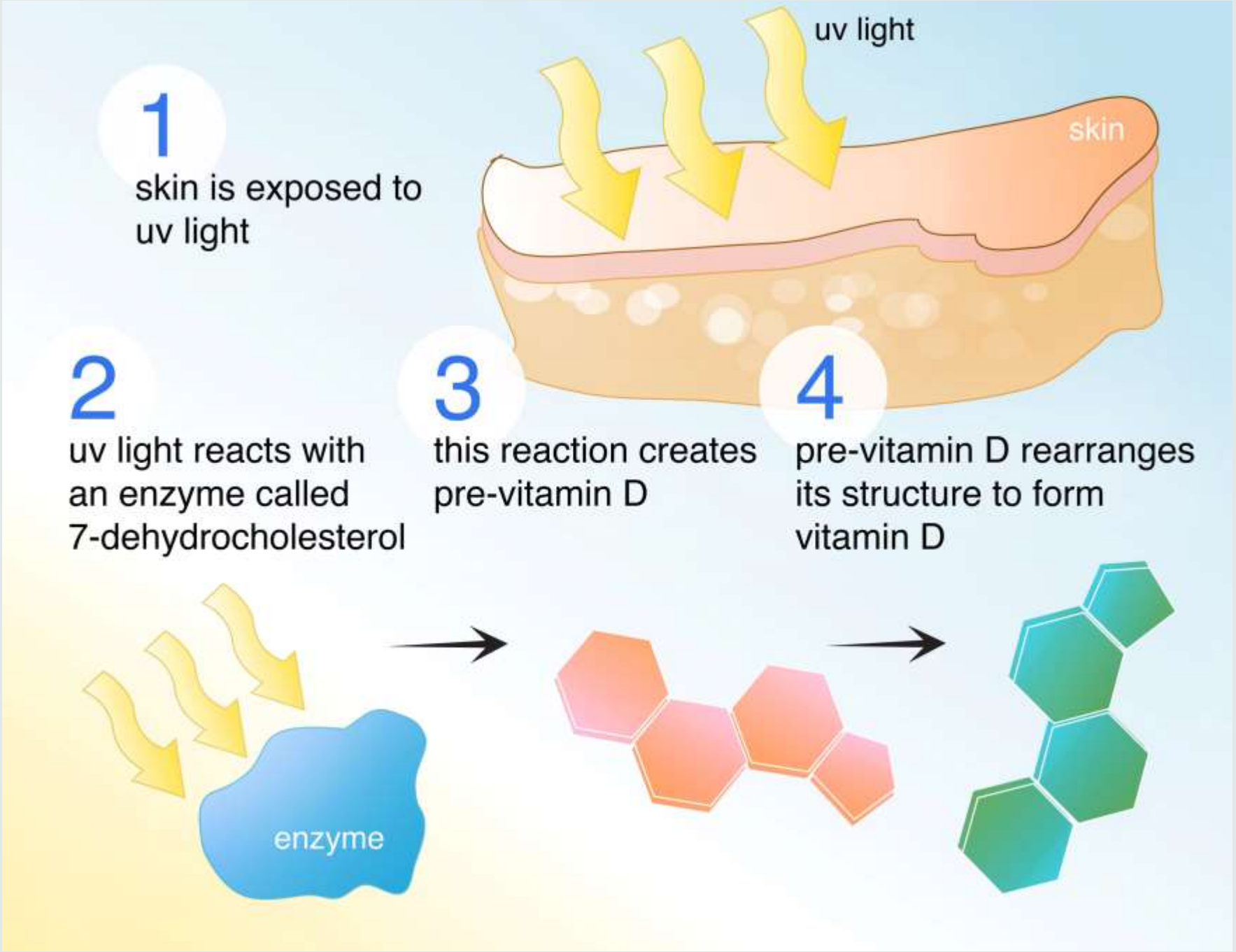
Sources

1- Food :

2- UV light?

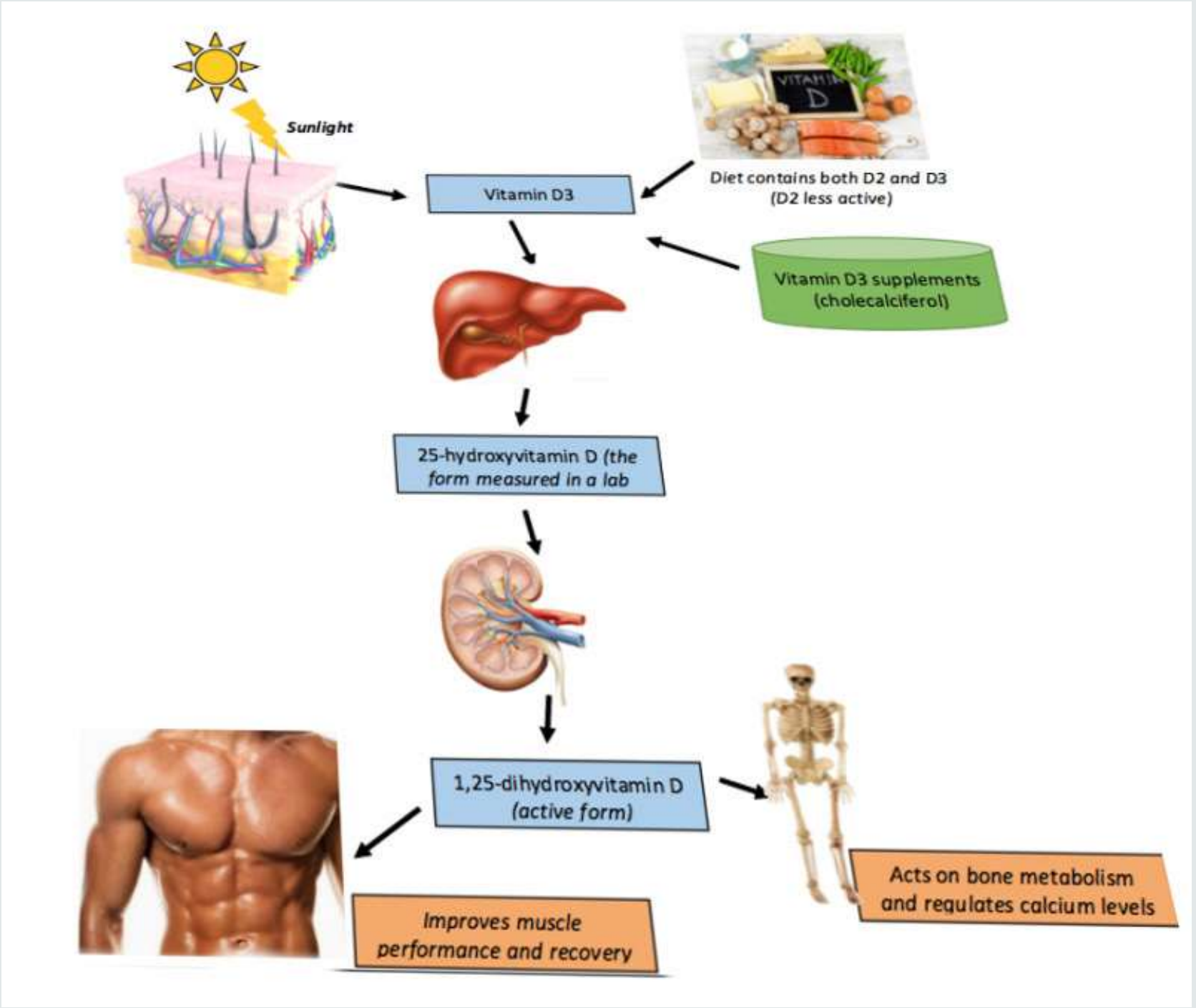
- Endogenous source need UV light….how?

- Keratinocytes in the epidermis of skin contain a precursor called **7-dehydrocho-lesterol** which is converted to **previtamin D3** when exposed to UV light
- Then previtamin D3 spontaneously transforms to vitamin D3 (cholecalciferol)

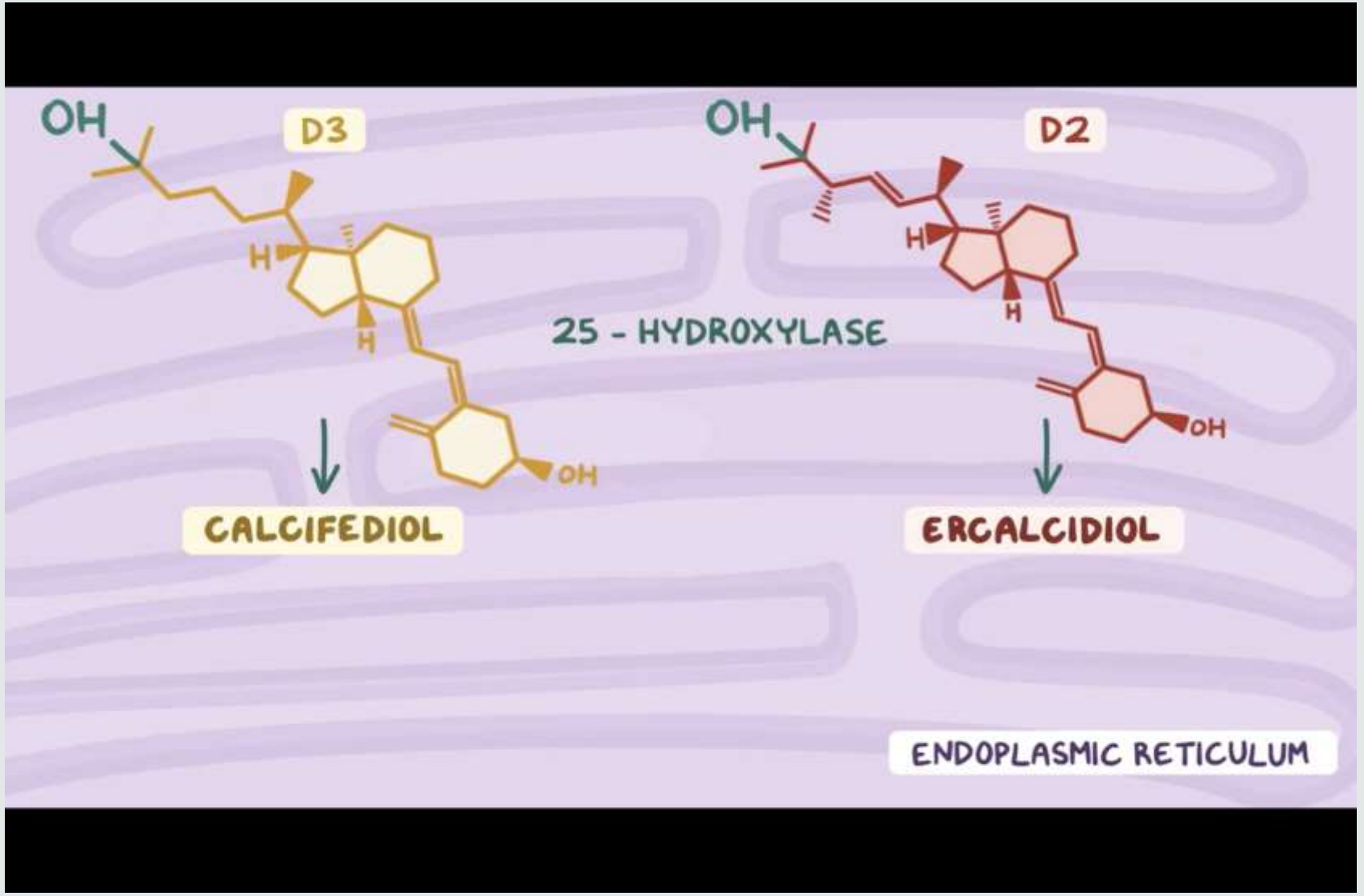

1
skin is exposed to uv light
uv light
skin
2
uv light reacts with an enzyme called 7-dehydrocholesterol
3
this reaction creates pre-vitamin D
4
pre-vitamin D rearranges its structure to form vitamin D
enzyme

Activation of vitamin D

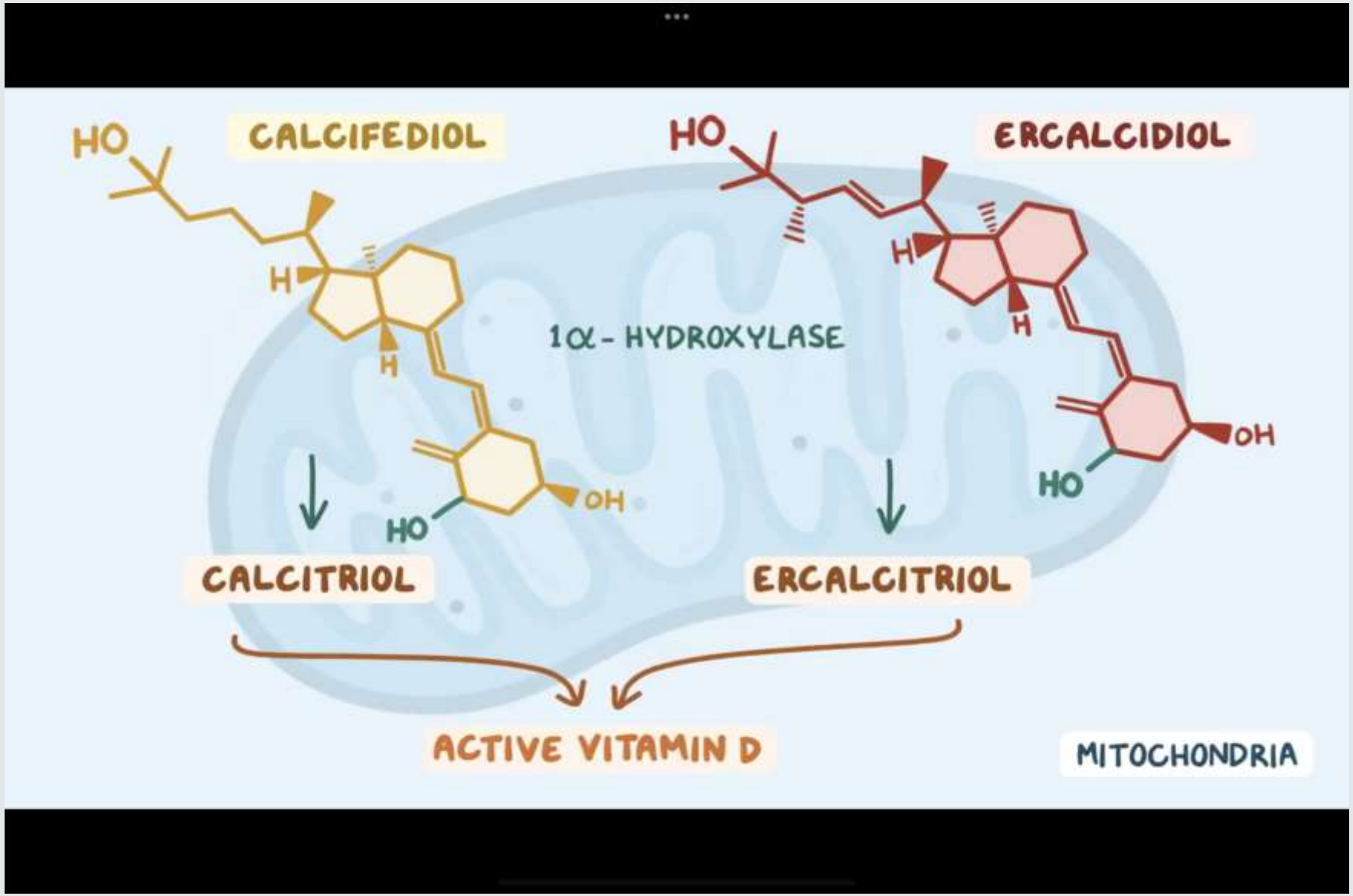
- Both vitamin D2 and D3 endogenously or from food must be activated first by **hydroxylation** before the active form can perform its functions
- The hydroxylation is done by **2 steps**; first one occurs in the **liver** by the enzyme **25-hydroxylase**, and the product is **25-hydroxyvitamin D**
- The second step happens in the **kidney** by the enzyme **1α-hydroxylase**, the product is **1,25-dihydroxyvitamin D** (active form) which is also called **calcitriol**


Sunlight
Diet contains both D2 and D3
(D2 less active)
Vitamin D3
Vitamin D3 supplements
(cholecalciferol)
25-hydroxyvitamin D (the
form measured in a lab
1,25-dihydroxyvitamin D
(active form)
Improves muscle
performance and recovery
Acts on bone metabolism
and regulates calcium levels

In the liver


OH
D3
H
H
OH
25 - HYDROXYLASE
CALCIFEDIOL
OH
D2
H
H
OH
ERGALCIDIOL
ENDOPLASMIC RETICULUM

In the kidneys



Mechanism of action

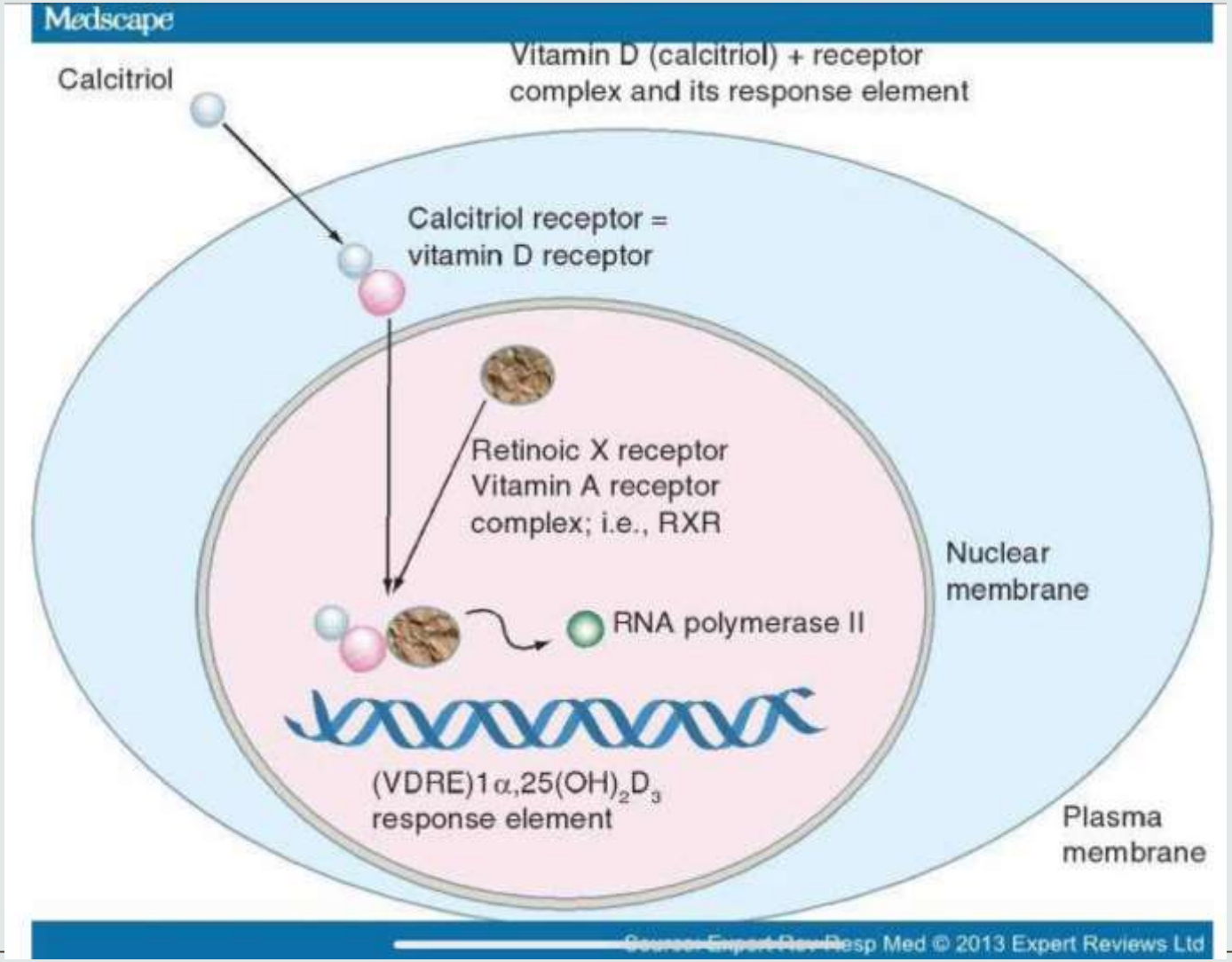
mohammed Abushanab

How does the vitamin D work?

the dihydroxycholecalciferol has receptor protein in target cells then it binds to

Vitamin D response element in the

nuclear DNA. This leads to regulation of transcription of specific genes in the target cells thus controlling the synthesis of specific proteins



Calcium homeostasis

- The normal serum calcium (ca^{2+})range is **(8.5 to 10.6 mg/dl)**
- The normal phosphate levels: (**3.0 to 4.5 mg/dl)**

THE DISTRIBUTION OF CALCIUM AND PHOSPHATE IN THE BODY

* Calcium : note: adult body contains about 1Kg of calcium 99% of it is stored in skeleton,

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)biologically inactive

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

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

Both 2 & 3 are diffusible with tissues .

CALCIUM AND PHOSPHATE FUNCTION

Calcium	Phosphate
Contraction of skeletal ,cardiac and smooth muscles	Energy production
Blood clotting	Part of nucleic acid
Transmission of nerve impulses	Part of cell membrane

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

1- Albumin :

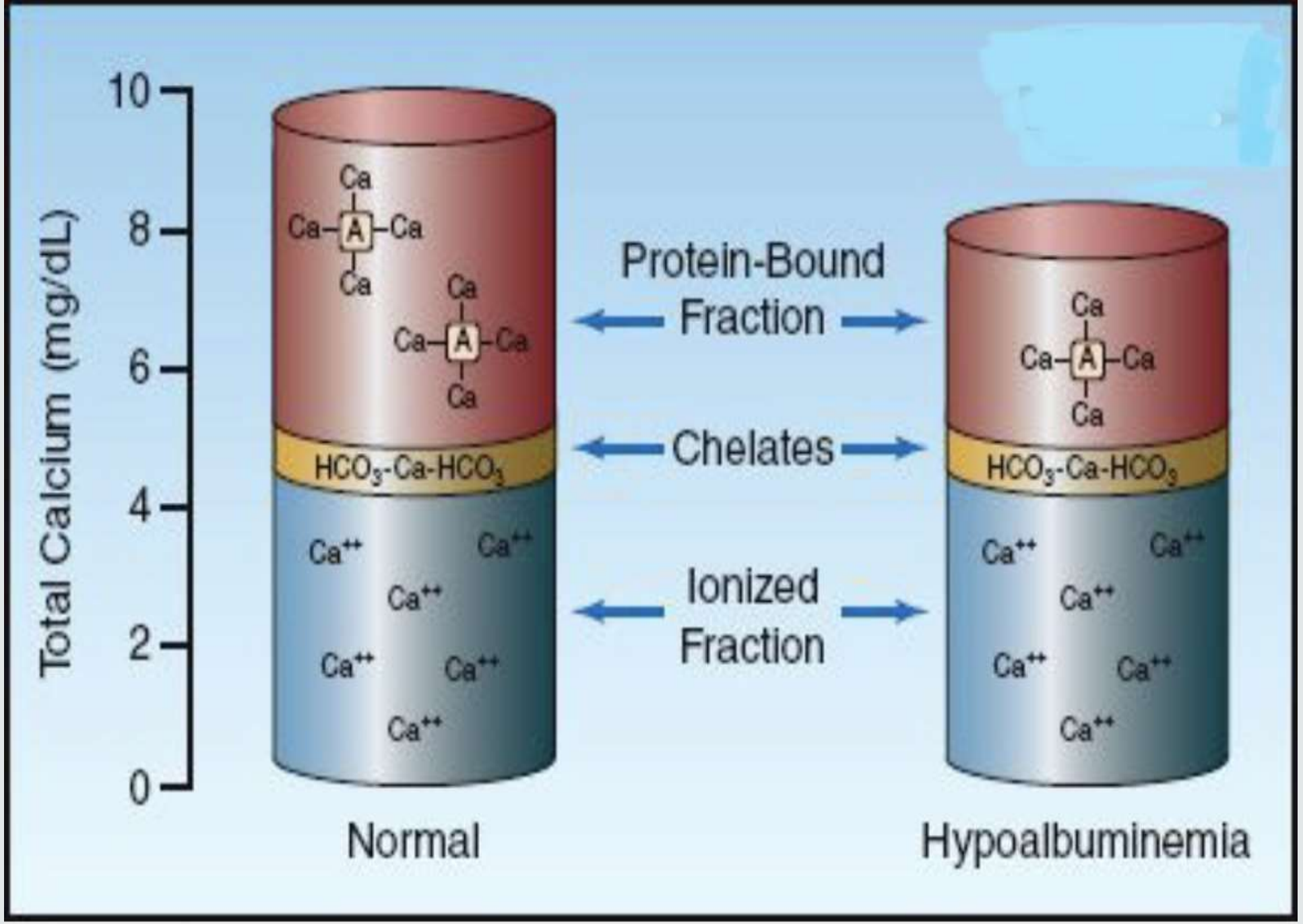
protein - bound form : most calcium ions are bound to albumin, so the total calcium concentration fluctuates with the protein (albumin) concentration.

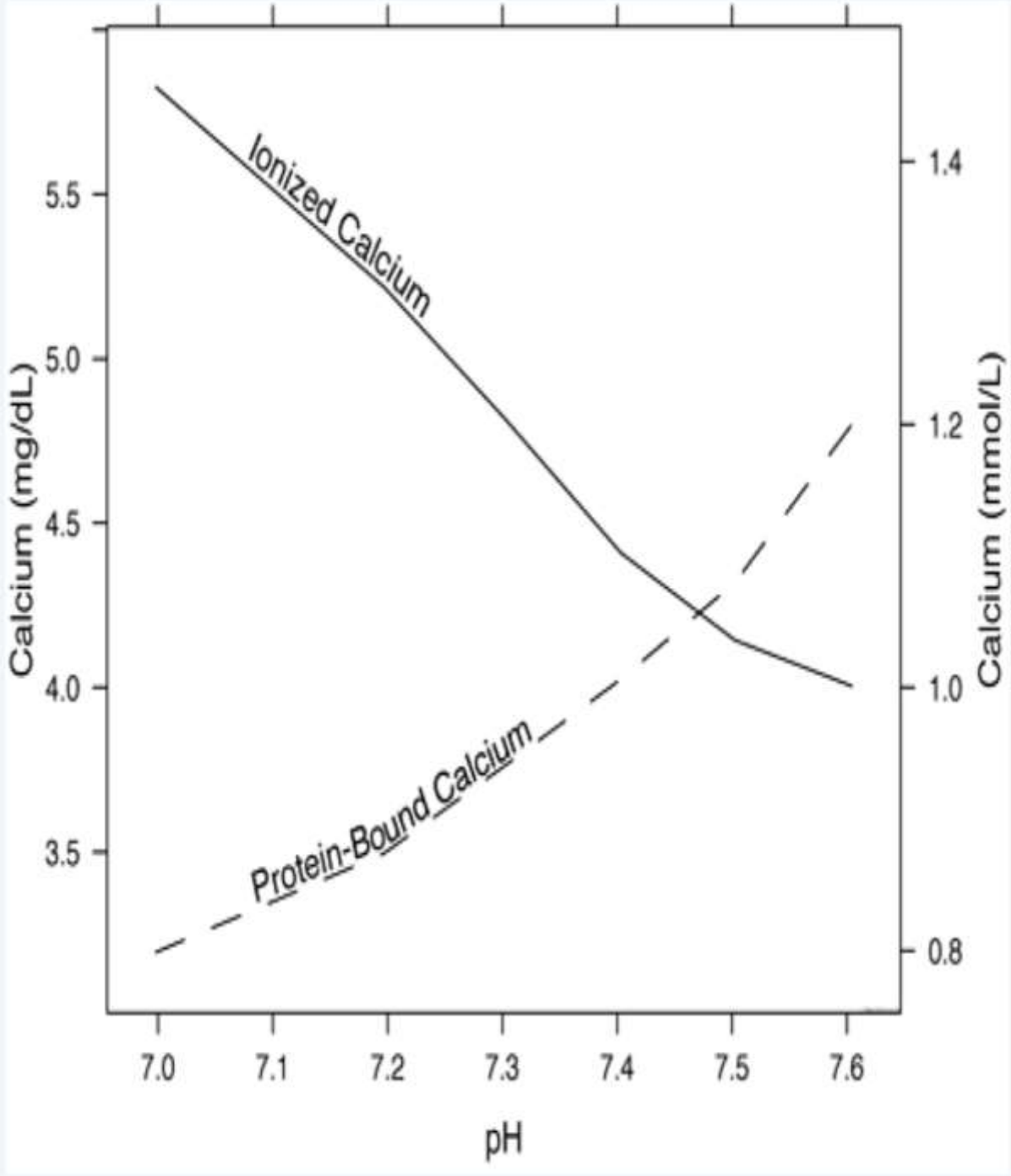
Free ionized form: physiologically active fraction; under tight hormonal control (PTH), independent of albumin levels.

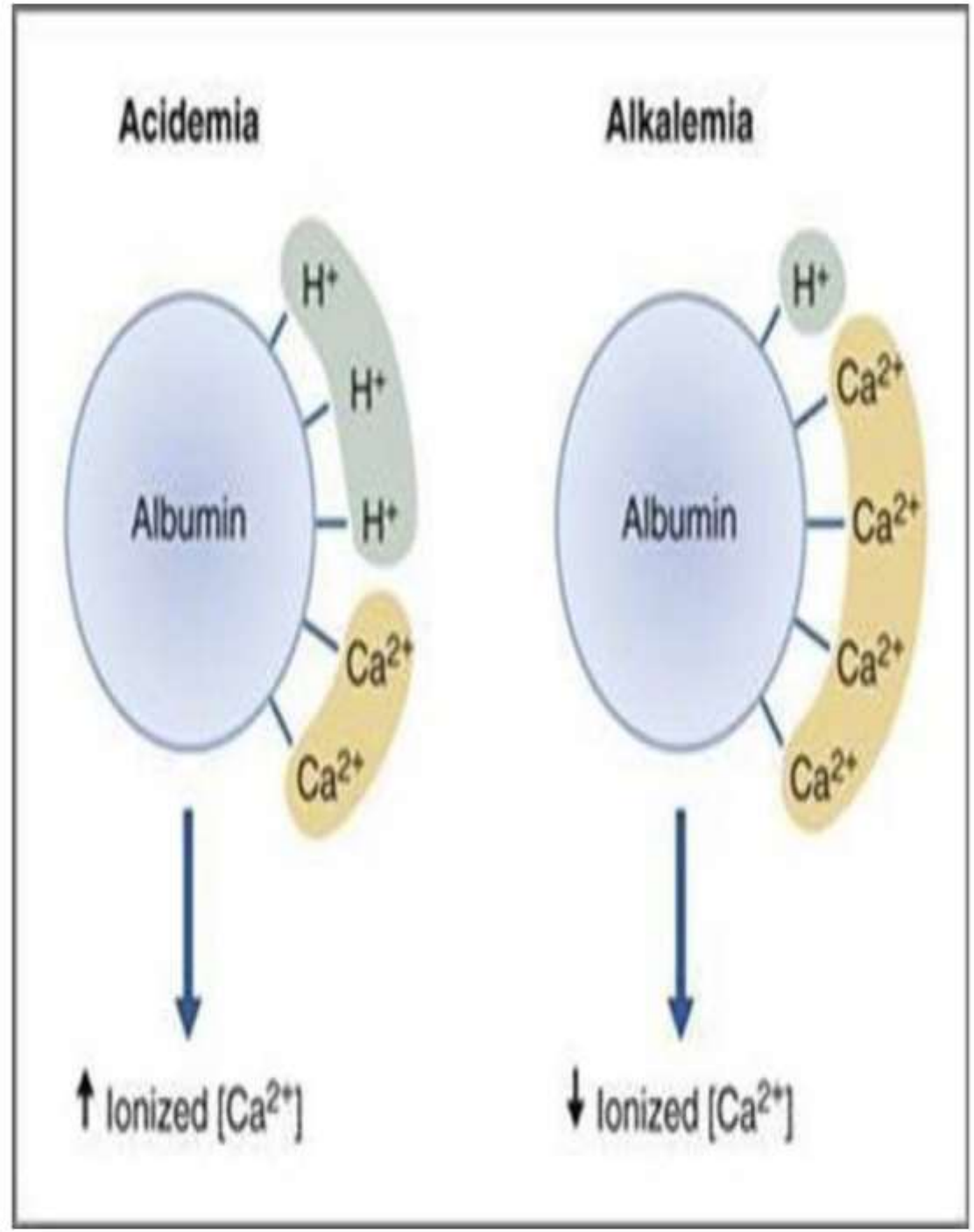
In hypoalbuminemia the total calcium is low, but ionized calcium is normal which gives falsely low total serum calcium level.

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

Alkalosis promotes calcium binding to plasma proteins which decrease free calcium(ionized form) levels and vice versa.


Total Calcium (mg/dL)
10
8
6
4
2
0
Ca
Ca–A–Ca
Ca
Ca
Ca–A–Ca
Ca
HCO3-Ca-HCO3
Ca++
Protein-Bound Fraction
Chelates
Ionized Fraction
Ca
Ca–A–Ca
Ca
HCO3-Ca-HCO3
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
H+
H+
H+
Ca2+
Ca2+
Albumin
H+
Ca2+
Ca2+
Ca2+
Ca2+
↑ Ionized [Ca2+]
↓ Ionized [Ca2+]

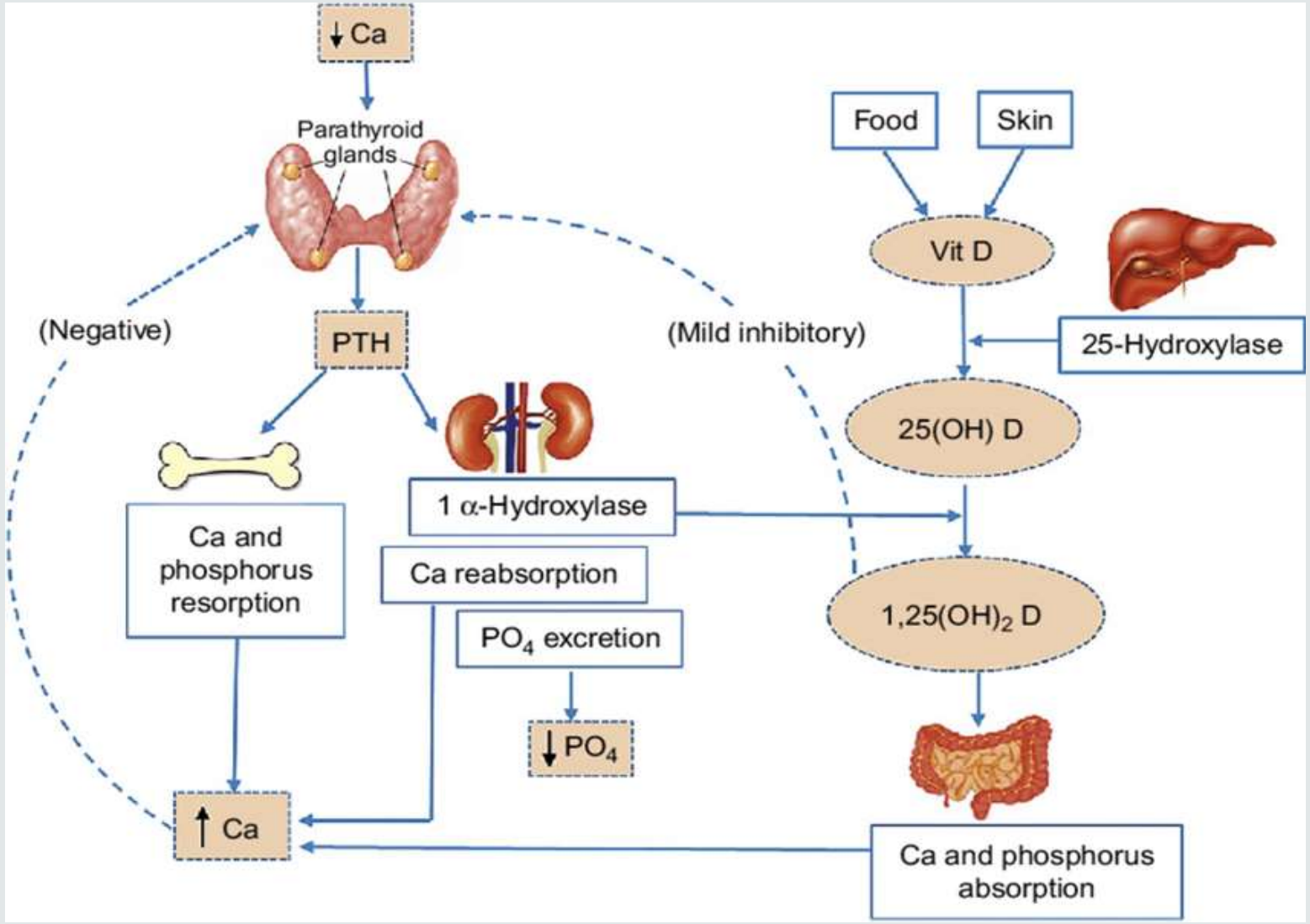
CALCIUM AND PHOSPHATE HOMEOSTASIS

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 [Ca2+] binding to Ca2+-sensing receptors in the parathyroid cell membrane.

Decreased serum [Ca2+] increases PTH secretion, whereas increased serum Ca2+ decreases PTH secretion.

- Mild decreases in serum [Mg2+] stimulate PTH secretion.

- Severe decreases in serum [Mg2+] 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.

note:Active form of vit D will increase expression of calcium transporters on the brush borders of intestinal cells which enhance calcium absorption in the gut.

PTH AND BONE

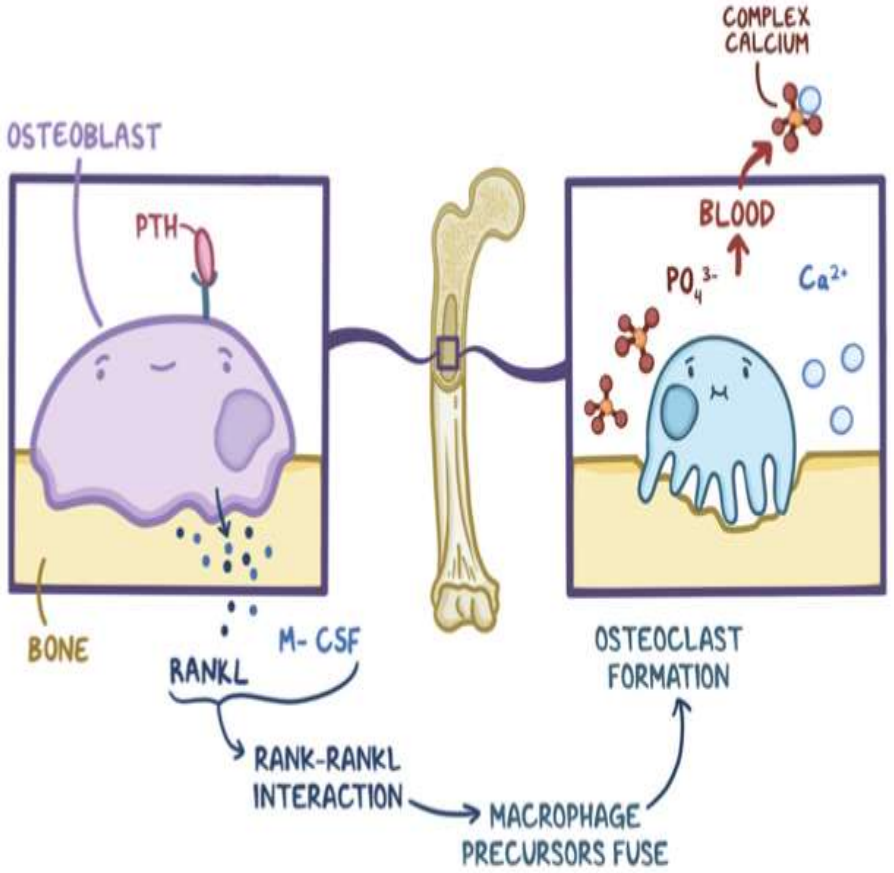


Figure 35.5 One way PTH increases extracellular calcium levels is by stimulating osteoclast formation in bone.

PTH AND KIDNEY

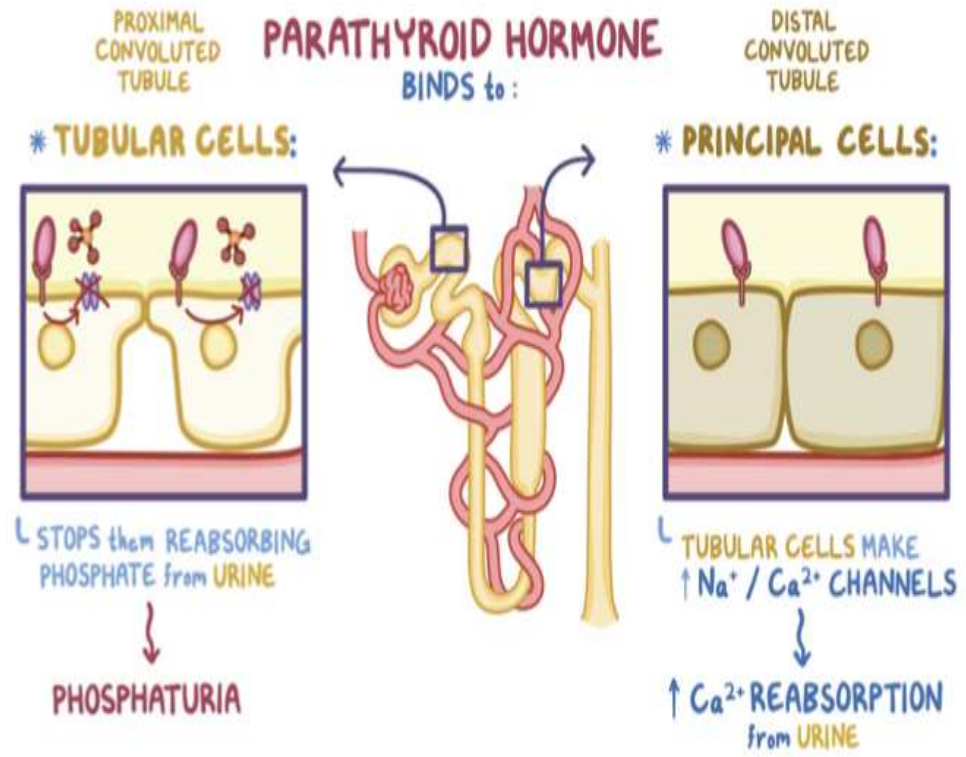


Figure 35.6 The second way PTH increases extracellular calcium levels is by ↑ urinary phosphate excretion and ↑ calcium reabsorption from urine.

PTH AND INTESTINE

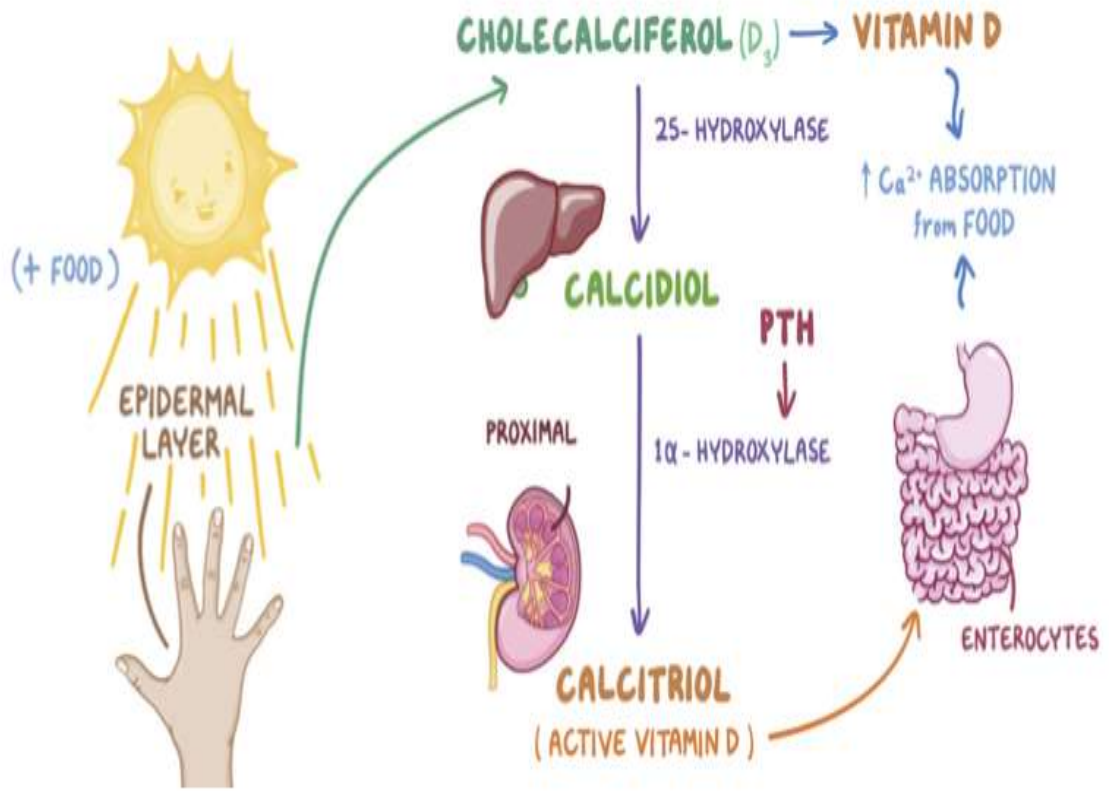


Figure 35.7 The third way PTH increases extracellular calcium levels is by helping convert cholecalciferol into vitamin D. It does so by upregulating enzyme 1α-hydroxylase.

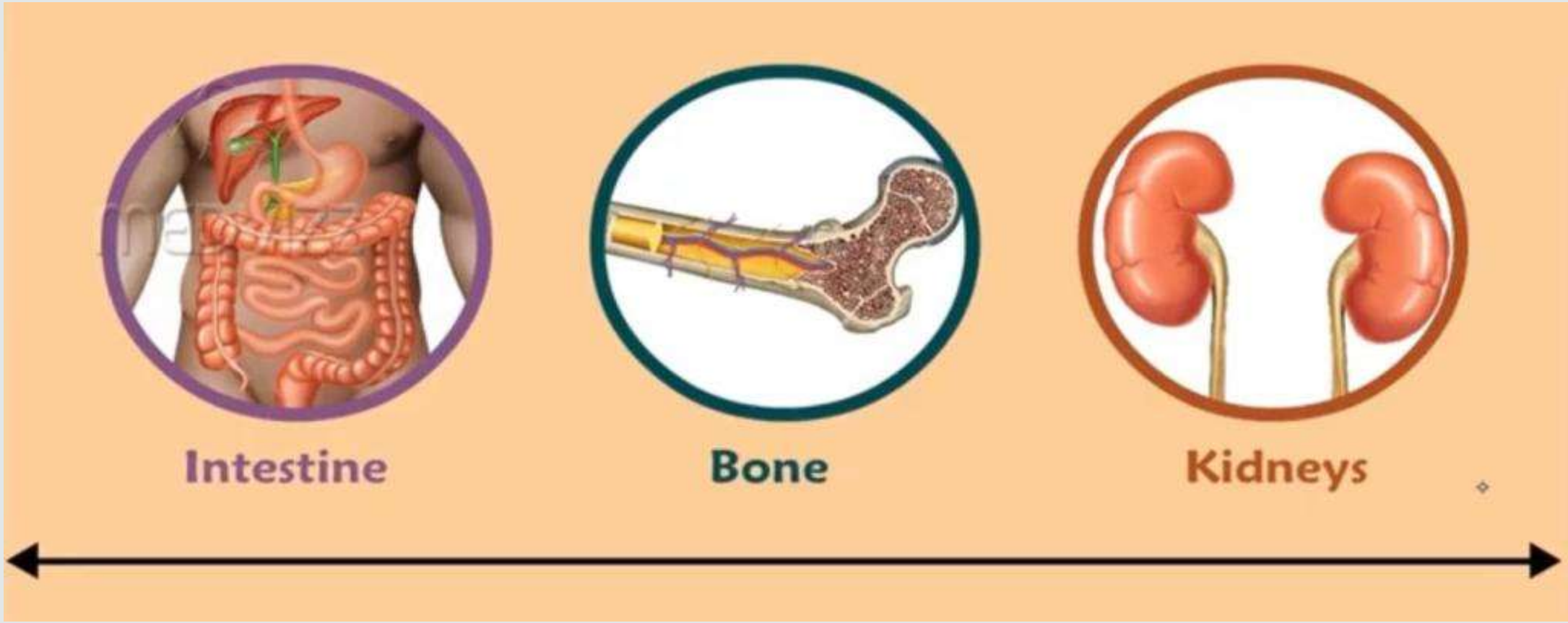
CALCITONIN

- 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 Ca2+ 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 Ca2+ receptor on the parafollicular cells. Elevations in plasma Ca2+ 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.

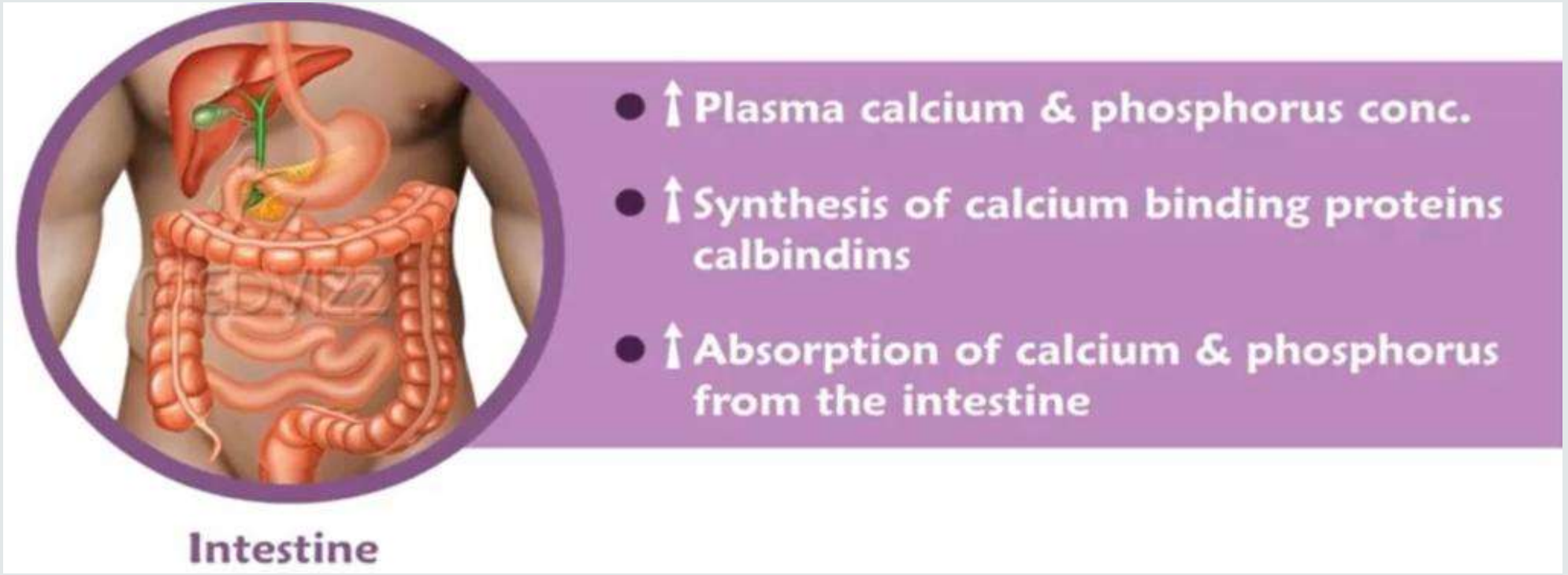
Functions

Farer Alsaidi

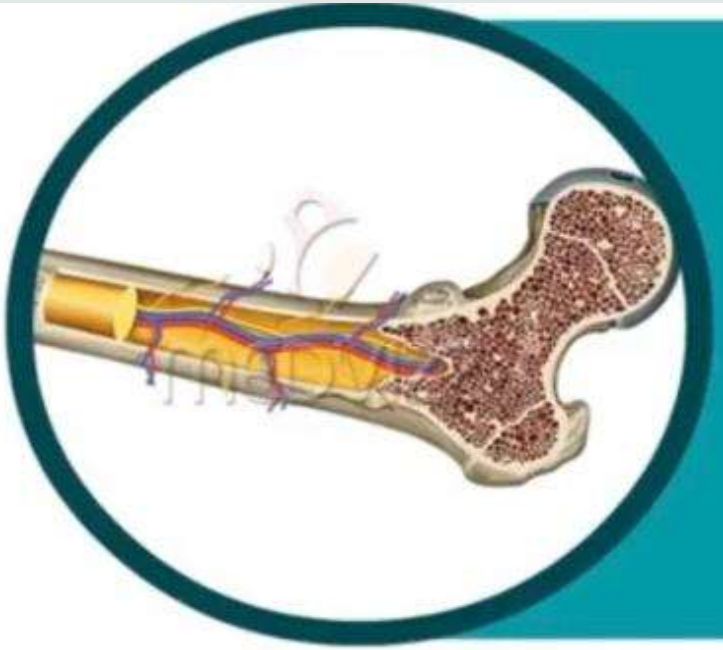
1) It plays an essential role as a hormone in the regulation of calcium & phosphorus metabolism by acting on ….



A) Action of vit.D on intestine



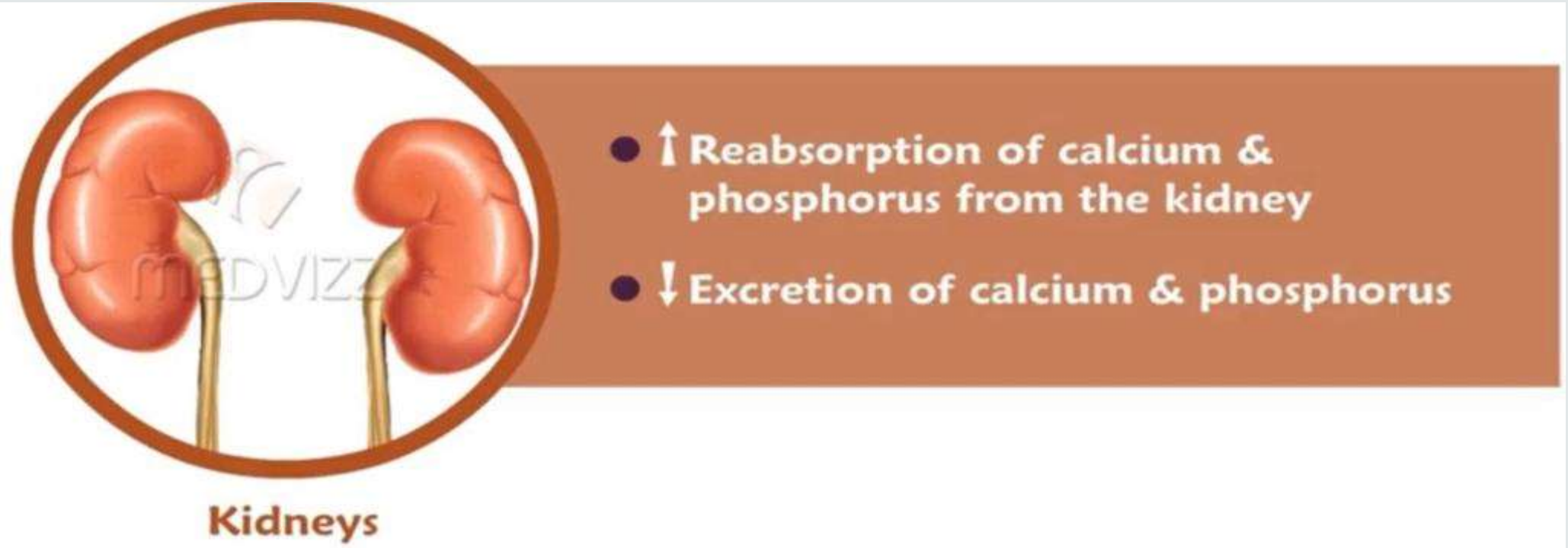
B) Action of vit.D on bone



Bone

- It is believed that calcitriol has both anabolic & catabolic role on bone
- It promotes the mineralization of bones (Anabolic)
- D_3 along with PTH stimulates the mobilization of calcium & phosphorus from bone (Catabolic)

C) Action of vit.D on kidneys



2) vitamin D is also used therapeutically for many other conditions including ;

- Diabetes
- Autoimmune disease
- Dementia
- Cardiovascular disease

Regulation

- Formation of 1, 25-Dihydroxycholecalciferol is regulated by :

1) Parathyroid gland :

A- hypocalcemia lead to stimulates PTH secretion which increase 1 alpha-hydroxylase that stimulates 1, 25-Dihydroxycholecalciferol

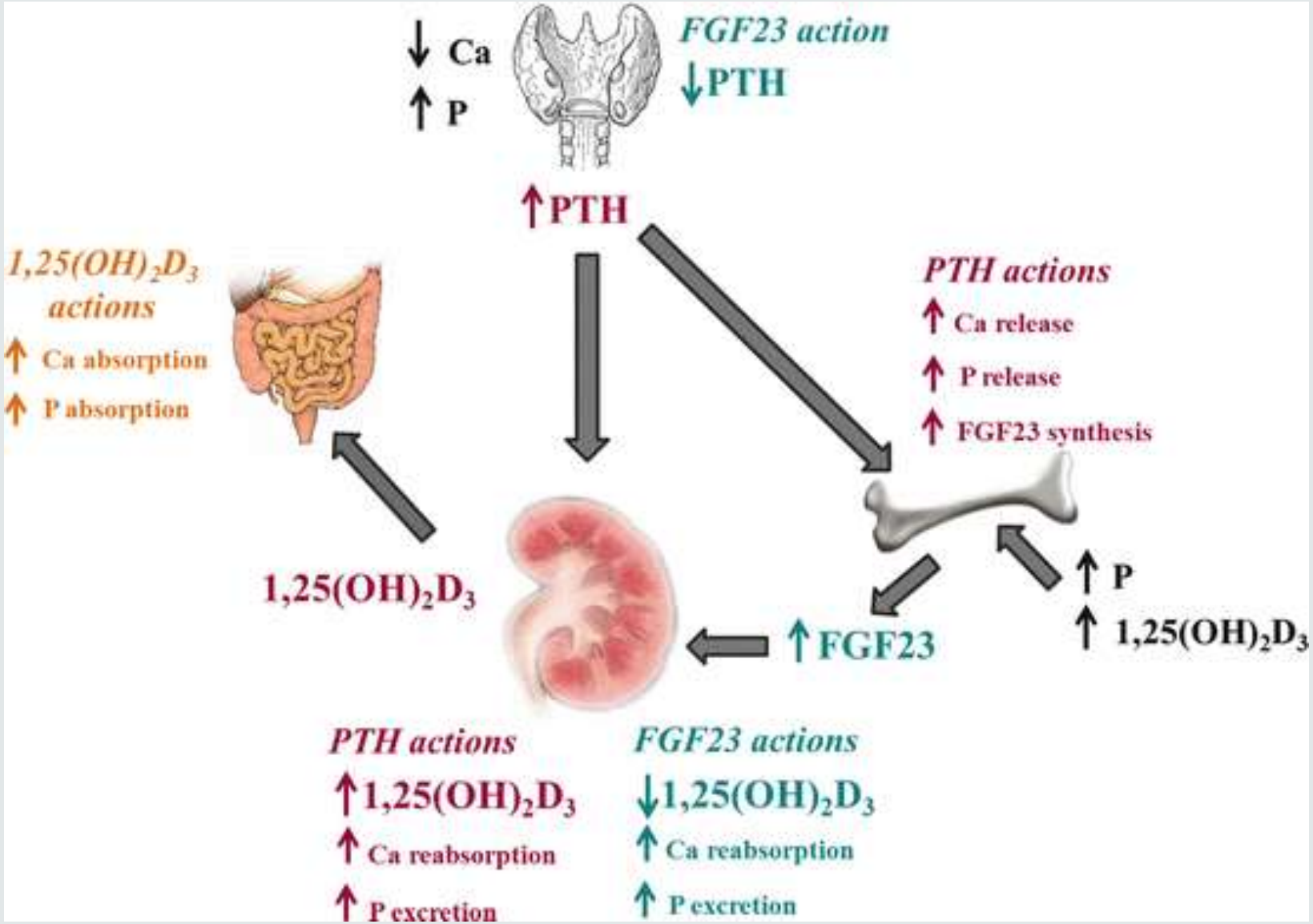
B- hypercalcemia lead to inhibit PTH secretion which decrease 1, 25-Dihydroxycholecalciferol

2) 24-hydroxylase :

When 1, 25-Dihydroxycholecalciferol Increase it activated 24-hydroxylase from liver to convert it to 1,24,25-trihydroxycholecalciferol that excretion by bile

3) FGF-23 :

Hyperphosphatemia stimulate FGF-23 that inhibit 1, 25-Dihydroxycholecalciferol


↓ Ca
↑ P
FGF23 action
↓PTH
↑PTH
1,25(OH)2D3 actions
↑ Ca absorption
↑ P absorption
PTH actions
↑ Ca release
↑ P release
↑ FGF23 synthesis
1,25(OH)2D3
↑FGF23
↑ P
↑ 1,25(OH)2D3
PTH actions
↑1,25(OH)2D3
↑ Ca reabsorption
↑ P excretion
FGF23 actions
↓1,25(OH)2D3
↑ Ca reabsorption
↑ P excretion

Vitamin D deficiency causes

Tamim Altamimi

Mechanisms

Main mechanisms:

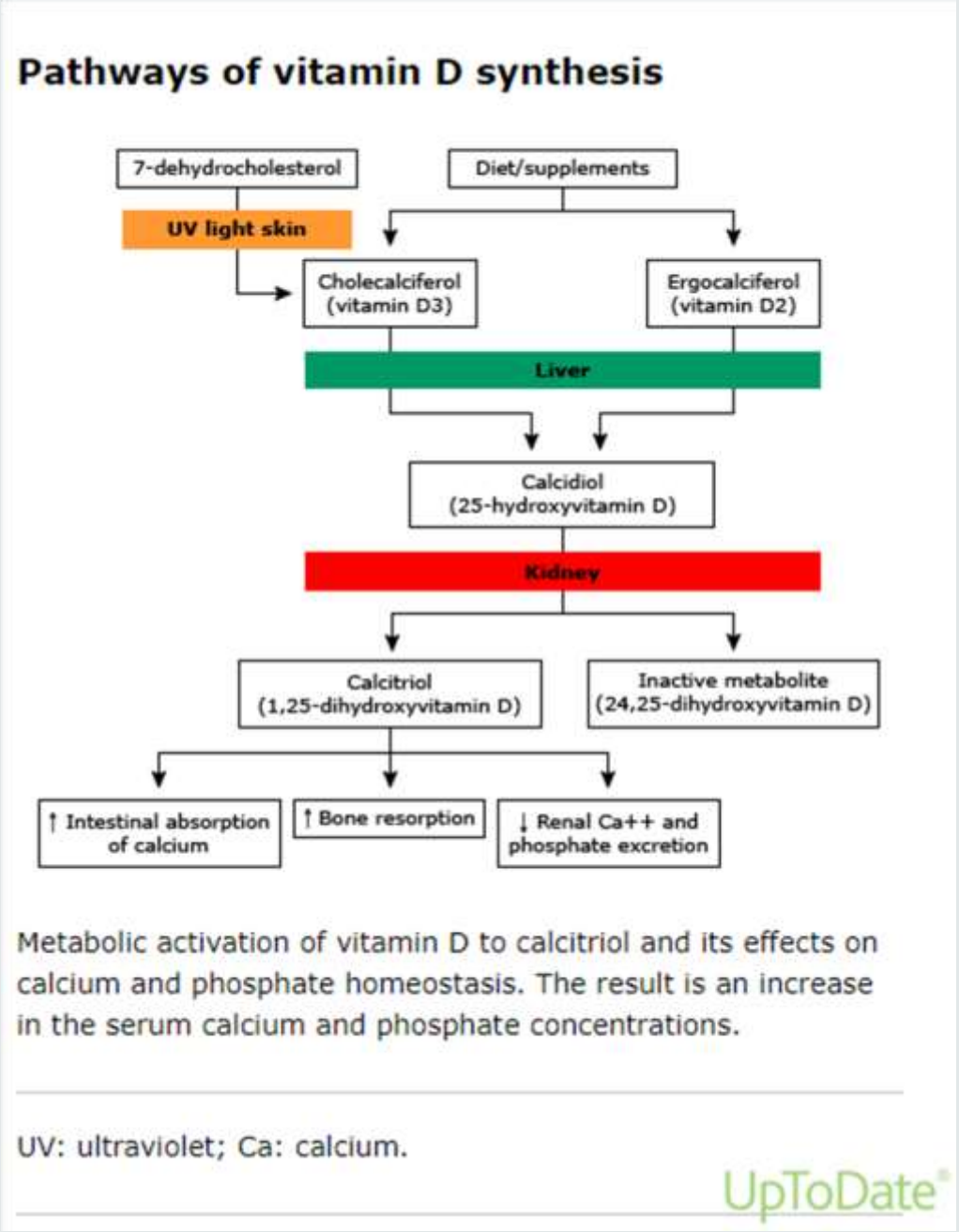
- Impaired availability of vitamin D, secondary to inadequate dietary vitamin D, malabsorptive disorders, and/or diminished cutaneous synthesis.
- Impaired hydroxylation by the liver to produce 25-hydroxyvitamin D (25[OH]D).
- Increased hepatic catabolism of 25(OH)D.
- Impaired kidney production of 1,25-dihydroxyvitamin D.
- Renal loss of vitamin D and vitamin D-binding proteins.
- End-organ insensitivity (resistance) to vitamin D metabolites is rare. Hereditary vitamin D-resistant rickets (HVDRR) is associated with end-organ resistance to calcitriol due to variable mutations in the gene encoding the vitamin D receptor.

Nutritional deficiency and reduced cutaneous synthesis

Nutritional: most vitamin D is derived from foods that are rich in the vitamin (fatty fishes) or fortified with the vitamin (milk and related products and cereals).

Synthesis: The remainder is synthesized in the skin from 7-dehydrocholesterol under the influence of ultraviolet light

Note that Vitamin D that is synthesized in the skin, and under most conditions this is the major source of the vitamin. Only when sunlight exposure is inadequate is a dietary source required



Nutritional deficiency and reduced cutaneous synthesis

- Vitamin D deficiency due to:

1- Reduced vitamin D intake

2- Reduced absorption

3- Reduced cutaneous production

Nutritional deficiency and reduced cutaneous synthesis

- Special patient groups:
- Elderly patients (most prone); multiple mechanisms:

1- Cutaneous vitamin D production and vitamin D stores decline with age (especially in winter)

2- Vitamin D intake is often low in older adults

3- Age-dependent resistance to calcitriol

Nutritional deficiency and reduced cutaneous synthesis

- Children; multiple mechanisms:

1- Dietary vitamin D deficiency.

The prevalence varies considerably among different countries and subpopulations because of differences in risk factors, especially skin pigmentation, sun exposure, and dietary vitamin D intake

Nutritional deficiency and reduced cutaneous synthesis

- **Healthy adults in the winter**; decrease sun exposure, maybe affected with RF
- **Hospitalized patients**; decreased sun exposure and dietary intake.
- **Chronic renal disease;** Patients with chronic kidney disease (CKD) have 1,25-dihydroxyvitamin D (calcitriol) deficiency due to impaired metabolism. Especially in patients on dialysis and in patients with stages 3 and 4 CKD predialysis.

Nutritional deficiency and reduced cutaneous synthesis

- Gastrointestinal malabsorption:

1- Steatorrhea of any cause

2- Celiac disease

3- Gastric bypass (Bariatric surgery, Gastrectomy)

- Others:
  - **Cystic fibrosis**; due to pancreatic exocrine insufficiency
  - **Extensive burns**; In patients with a history of extensive burn injuries, vitamin D synthesis in skin is below normal, even with sun exposure

Deficiency related to abnormal synthesis and catabolism

- Main mechanisms:

1- Decreased synthesis in the liver,

2- Increased catabolism

3- Renal loss of calcidiol bound to vitamin D-binding protein

4- Renal Failure

5- others

Deficiency related to abnormal synthesis and catabolism

1- Decreased synthesis in the liver

Physiologically, vitamin D is hydroxylated in the liver by hepatic 25-hydroxylase (CYP2R1, 11p15.2) to produce calcidiol (25-hydroxyvitamin D [25(OH)D])

- Patients with **severe parenchymal or obstructive hepatic disease** (The majority of the liver must be dysfunctional before calcidiol synthesis is reduced, thus very rare)
- **Gain-of-function variants in CYP3A4**, the gene encoding a vitamin D catabolic enzyme, cause increased degradation of both 25OHD and the active 1,25(OH)2D metabolite

Deficiency related to abnormal synthesis and catabolism

2- **Increased catabolism**; via increasing P450 enzyme activity, which metabolizes calcidiol to inactive vitamin D metabolites

Certain drugs can increase vitamin D catabolism,

Phenytoin, phenobarbital, carbamazepine, oxcarbazepine, isoniazid, theophylline, and rifampin

++++Glucocorticoids have multiple mechanisms

Deficiency related to abnormal synthesis and catabolism

3- **Renal loss**

Most of the calcidiol in serum is bound to vitamin D-binding protein. Patients with the **nephrotic syndrome** can excrete enough vitamin D-binding protein (with calcidiol bound to it) to become vitamin D deficient

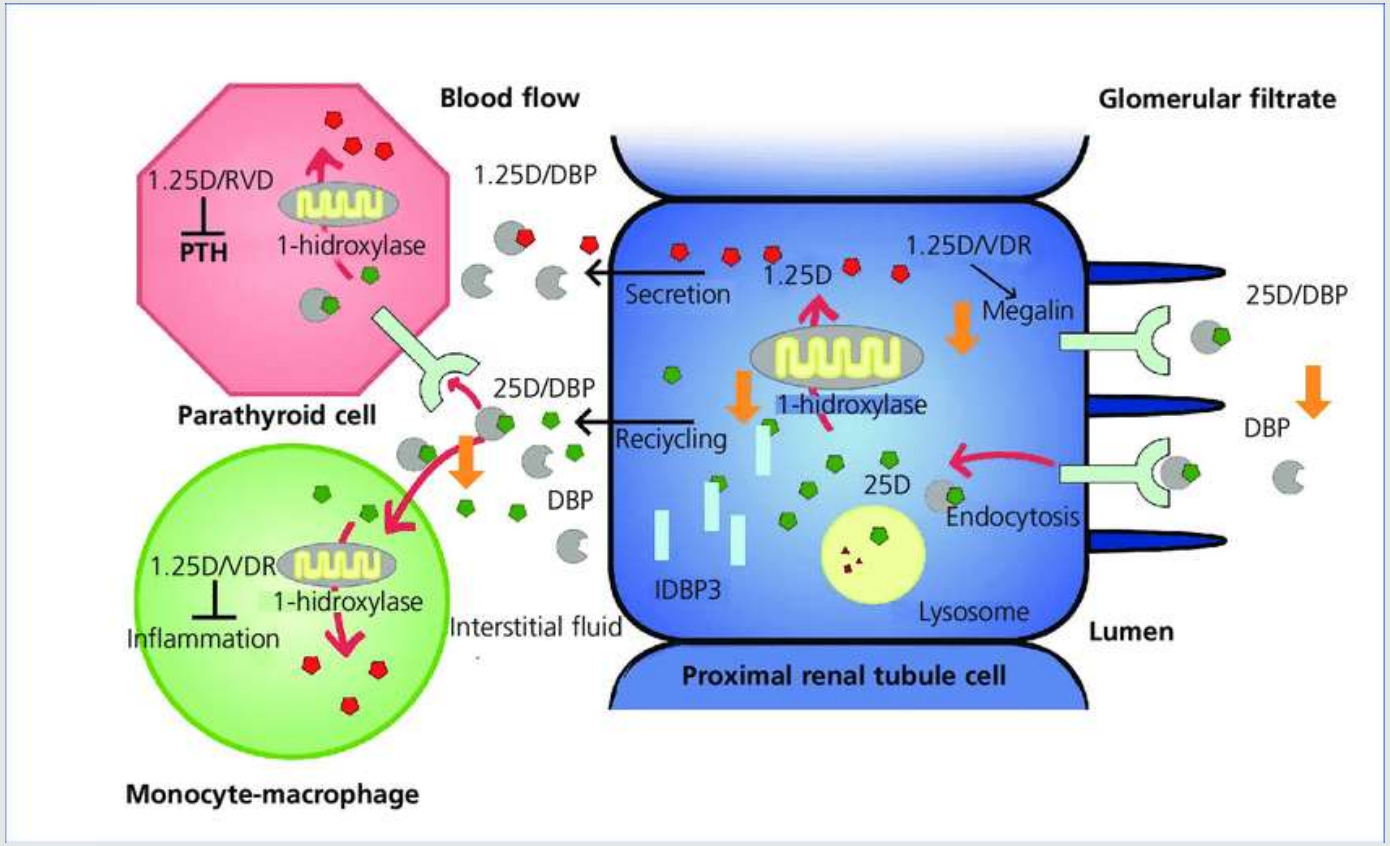
Deficiency related to abnormal synthesis and catabolism

4- Renal failure; mechanisms:

1- diminished glomerular filtration

2- limited availability of the substrate - for calcitriol production, secondary to decreased protein (megalin)-mediated reabsorption of glomerular-filtered 25(OH)D in renal proximal tubular epithelial cells

3- the loss of the 1-alpha-hydroxylase enzyme secondary to structural renal compromise and suppression of enzyme activity as a consequence of hyperphosphatemia and resultant increased circulating FGF23 levels.



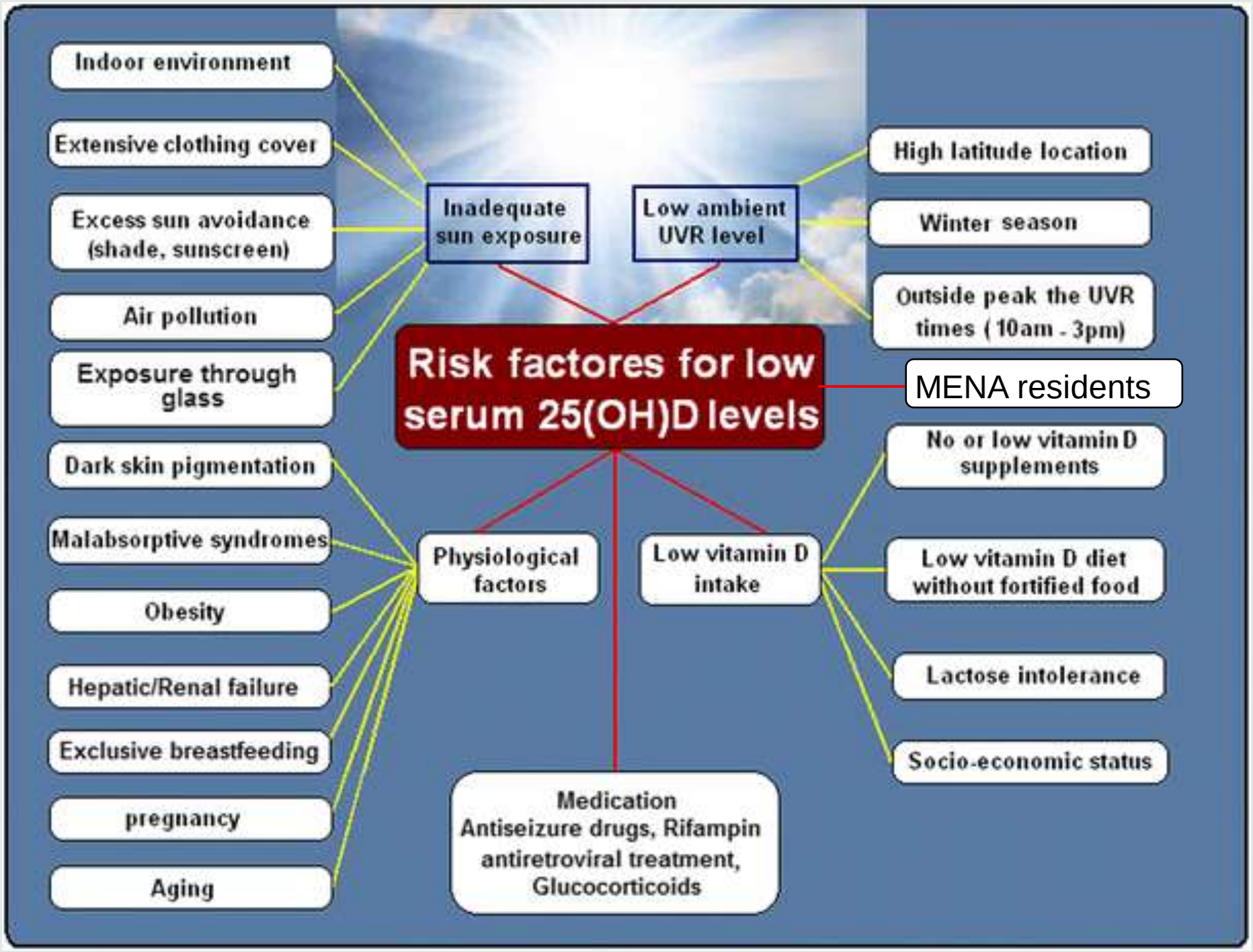
Proximal convoluted tubules

Deficiency related to abnormal synthesis and catabolism

- Vitamin D-dependent rickets type 1 (dz of children!)
- Mutation in the 1α-hydroxylase gene
- Leads to impaired conversion of inactive vitamin D to the active form, 1,25-dihydroxyvitamin D3 (calcitriol).
- Characterized by **early onset of rickets**, muscle weakness, failure to thrive, hypotonia, and pathological fractures
- Similar presentation to dietary deficiency; but earlier (3-4 months of age)

Vitamin d resistance

- AKA Vitamin D-dependent rickets type 2 (dz of children!)
- Mutation in the vitamin D receptor gene causes end-organ resistance to vitamin D.
- Characterized by early onset of rickets, failure to thrive, and alopecia
- Extremely rare; only 120 cases reported!!!


Indoor environment
Extensive clothing cover
Excess sun avoidance (shade, sunscreen)
Air pollution
Exposure through glass
Dark skin pigmentation
Malabsorptive syndromes
Obesity
Hepatic/Renal failure
Exclusive breastfeeding
pregnancy
Aging
Inadequate sun exposure
Low ambient UVR level
High latitude location
Winter season
Outside peak the UVR times (10am - 3pm)
Risk factores for low serum 25(OH)D levels
MENA residents
Physiological factors
Low vitamin D intake
No or low vitamin D supplements
Low vitamin D diet without fortified food
Lactose intolerance
Socio-economic status
Medication
Antiseizure drugs, Rifampin
antiretroviral treatment,
Glucocorticoids

Clinical features and complications

Sohaib Shalaan

- Symptoms when vitamin D is low

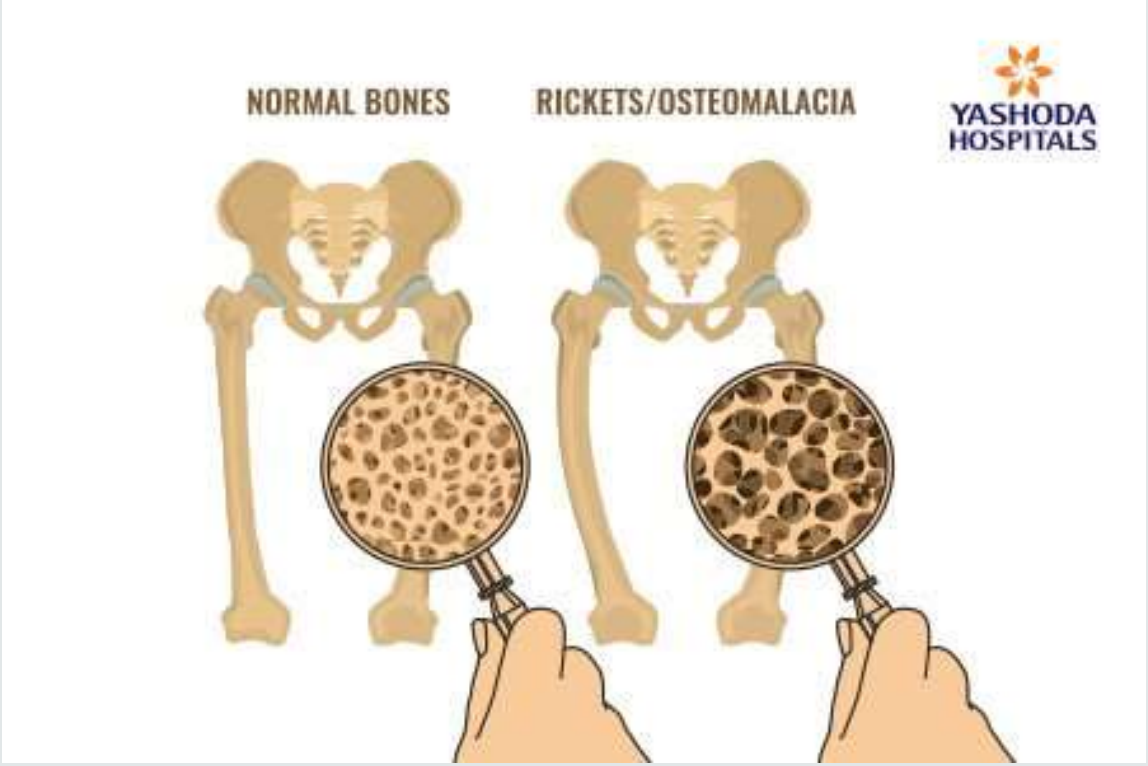
Most people with vitamin D deficiency are asymptomatic. However, if you're exhausted, your bones hurt, you have muscle weakness or mood changes, that's an indication that something may be abnormal with your body.

- **Symptoms of vitamin D deficiency may include:**

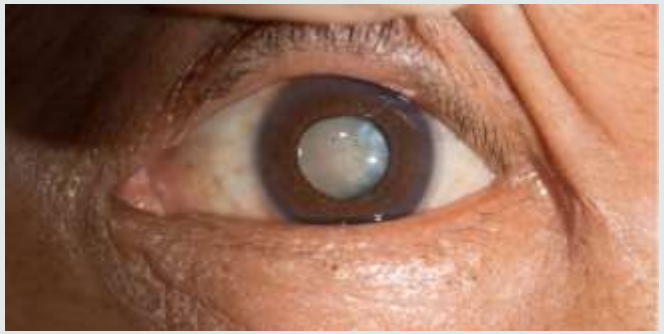
1. Fatigue
2. Not sleeping well
3. Bone pain or achiness
4. Depression or feelings of sadness
5. Hair loss
6. Muscle weakness
7. Loss of appetite
8. Increased susceptibility to infections.
9. Pale skin

The most serious complications of vitamin D deficiency are:

- Hypocalcemia.
- Hypophosphatemia.
- Rickets.
- Osteomalacia.



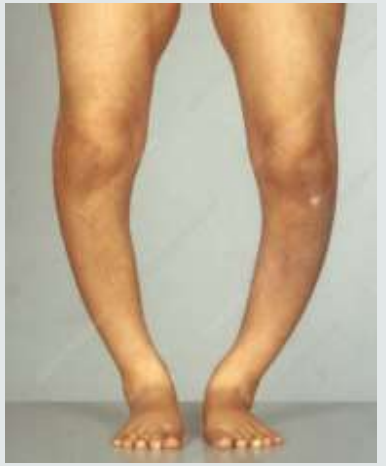
1- Hypocalcemia



Hypocalcemia results in increased neural hyperexcitability such as seizures, tetany, circumoral numbness, and tingling of the extremities.

- Arrhythmias may develop because of a prolonged QT.
- Cataracts develop for unclear reasons.

2- Rickets



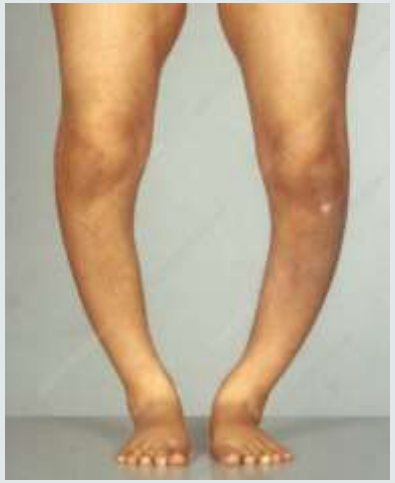
- Rickets is the softening and weakening of bones in children, usually because of an extreme and prolonged vitamin D deficiency. Rare inherited problems also can cause rickets

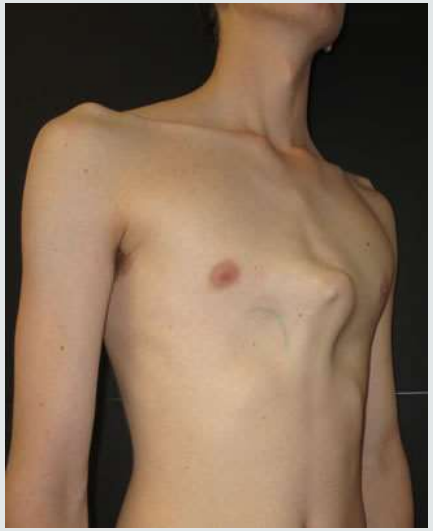
- Vitamin D helps your child's body absorb calcium and phosphorus from food. Not enough vitamin D makes it difficult to maintain proper calcium and phosphorus levels in bones, which can cause rickets.

Signs and symptoms of rickets can include:

- Delayed growth
- Delayed motor skills
- Pain in the spine, pelvis and legs
- Muscle weakness

Because rickets softens the areas of growing tissue at the ends of a child's bones (growth plates), it can cause skeletal deformities such as:





- Bowed legs or knock knees
- Thickened wrists and ankles
- Pectus carinatum

Factors that can increase a child's risk of rickets include:

- ***Dark skin***. Dark skin has more of the pigment melanin, which lowers the skin's ability to produce vitamin D from sunlight.

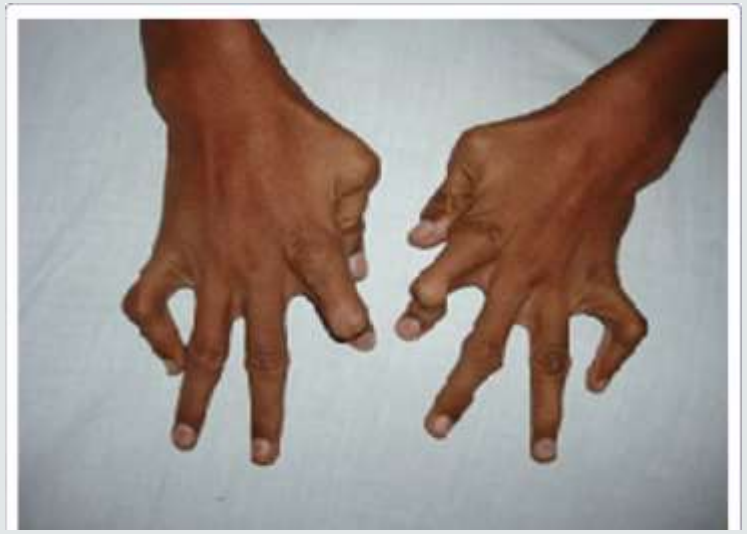
- ***Mother's vitamin D deficiency*** during pregnancy. A baby born to a mother with severe vitamin D deficiency can be born with signs of rickets or develop them within a few months after birth.

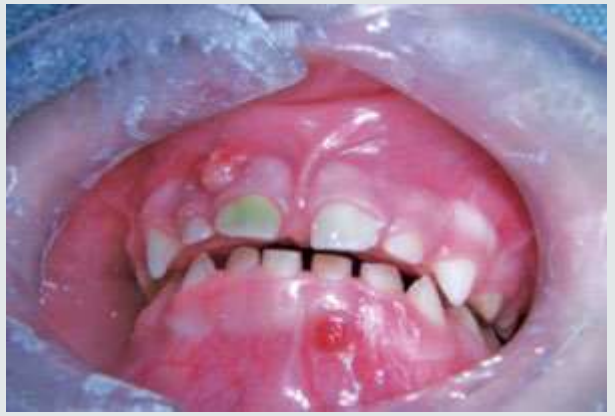
- ***Northern latitudes***. Children who live in geographical locations where there is less sunshine are at higher risk of rickets.
- ***Premature birth***. Babies born before their due dates tend have lower levels of vitamin D because they had less time to receive the vitamin from their mothers in the womb.

- ***Medications***. Certain types of anti-seizure medications and antiretroviral medications, used to treat HIV infections, appear to interfere with the body's ability to use vitamin D.
- ***Exclusive breast-feeding***. Breast milk doesn't contain enough vitamin D to prevent rickets. Babies who are exclusively breast-fed should receive vitamin D drops.

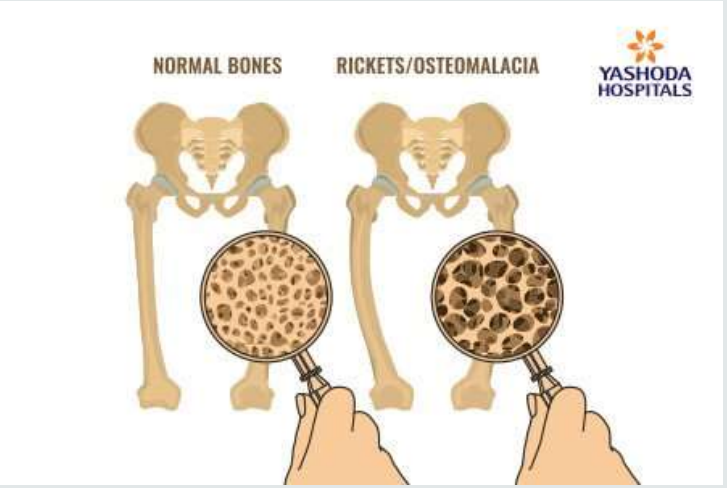
Left untreated, rickets can lead to:

- Failure to grow
- An abnormally curved spine
- Bone deformities
- Dental defects
- Seizures





3- Osteomalacia



- Is softening of the bones. It most often occurs because of a problem with vitamin D, which helps your body absorb calcium. it is a disorder of decreased mineralization, which results in bone breaking down faster than it can re-form.

- In children, the condition is called rickets.

✳osteomalacia can cause:

- ***Pain*** felt in the bones and joints, **Bone pain is felt most often in the legs, groin, upper thighs and knees. It's sometimes felt in the feet when you stand, walk or run.**

- ***muscle pain***, cramps and weakness, particularly following exerciseThe **weakness tends to affect muscles in the thighs, shoulders and main part of the body – the trunk. This can make it difficult to climb stairs in very severe cases, get out of bed.**

- Increased susceptibility to ***fractures***, particularly bones in the hips, lower back and feet.

- Bones can break more easily from falls or simple knocks that wouldn’t normally cause a fracture. This is often how people find out they have osteomalacia.

- difficulty walking and a change in how you walk – possibly with a waddle.

Vitamin D deficiency and depression

- Researchers have found that many people who have depression also have low circulating levels of vitamin D in their blood, so it is possible that the two factors are related

- Some small, high quality studies have noted that various groups of people experience improvements in symptoms of depression after they start taking vitamin D supplements, Because findings are so mixed, more research is needed to determine how vitamin D deficiency and depression may be linked

Vitamin D deficiency and immunogenecity

- As the vitamin D receptor is expressed on immune cells (B cells, T cells and antigen presenting cells), Vitamin D can modulate the innate and adaptive immune responses.
- Deficiency in vitamin D is associated with increased autoimmunity as well as an increased susceptibility to infection.

Diagnosis and imaging of vitamin D deficiency

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Who Should Be Tested For Vitamin D Deficiency?

- Although vitamin D deficiency is prevalent, measurement of serum 25(OH)D levels is **expensive**, and universal screening is not supported.
- However, vitamin D testing may benefit those **at risk for severe** deficiency or those with **laboratory or radiographic findings** commonly associated with vitamin D deficiency
- In these patients, knowledge of the 25(OH)D blood level provides an accurate assessment of vitamin D body stores, helps identify the need for vitamin D therapy, and may help to determine an effective dose.

Who is considered at risk for severe deficiency?

- **Decreased intake**
  1. Inadequate oral intake
  2. Malnutrition (poor oral intake)
  3. Limited sun exposure
- **Gastrointestinal Malabsorption** (eg, short bowel syndrome, pancreatitis, inflammatory bowel disease, amyloidosis, celiac sprue, and malabsorptive bariatric surgery procedures)
- **Hepatic**
  1. Some antiepileptic medications (increased 24-hydroxylase activity)
  2. Severe liver disease or failure (decreased 25-hydroxylase activity)
- **Renal Aging** (decreased 1-α hydroxylase activity)
- Renal insufficiency
- Nephrotic syndrome decreased levels of vitamin D binding proteins

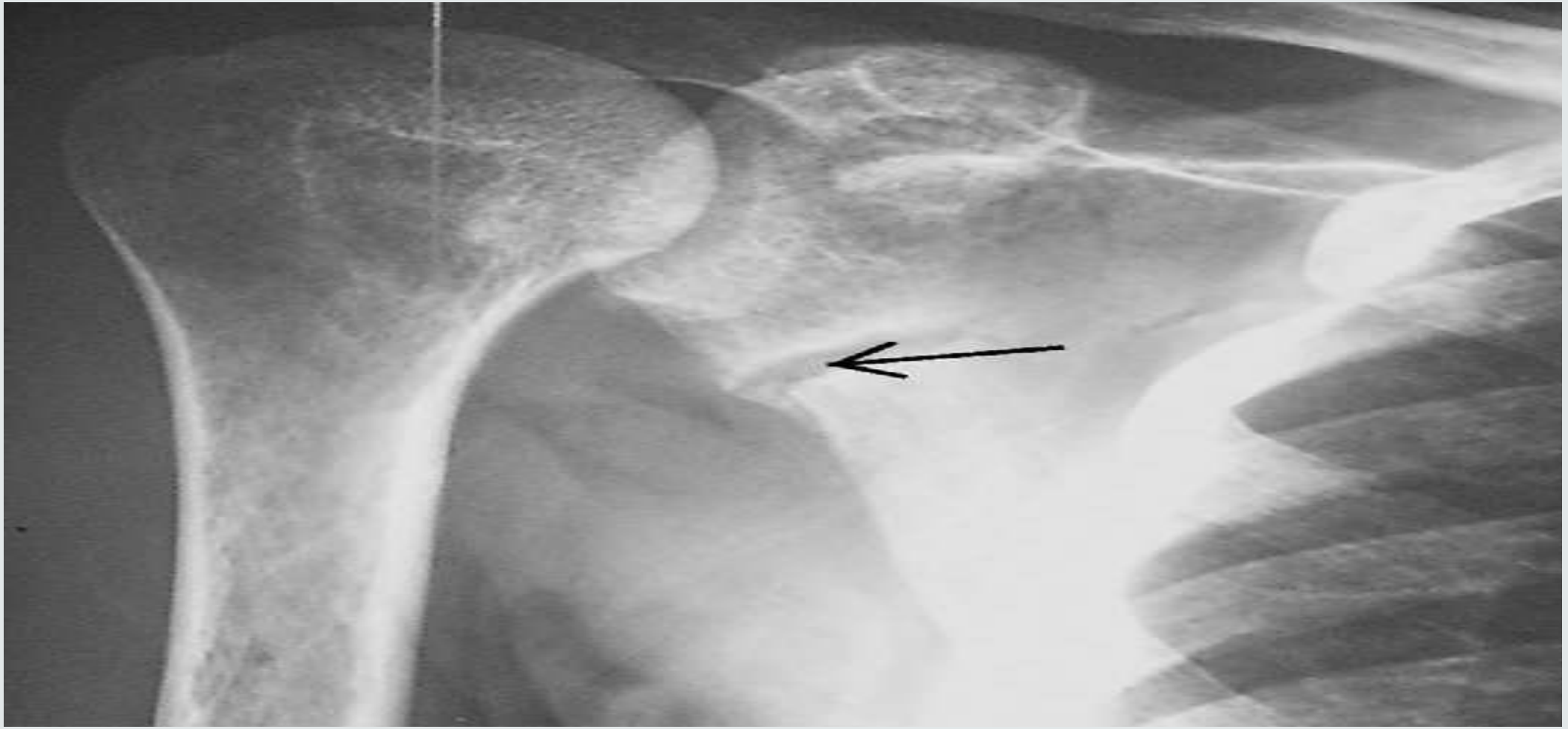
Laboratory and Radiographic Findings That Suggest Possible Vitamin D Deficiency

- **Laboratory**

1. Low 24-hour urine calcium excretion (in the absence of thiazide use)
2. Elevated parathyroid hormone level
3. Elevated total or bone alkaline phosphatase level
4. Low serum calcium and/or serum phosphorus level

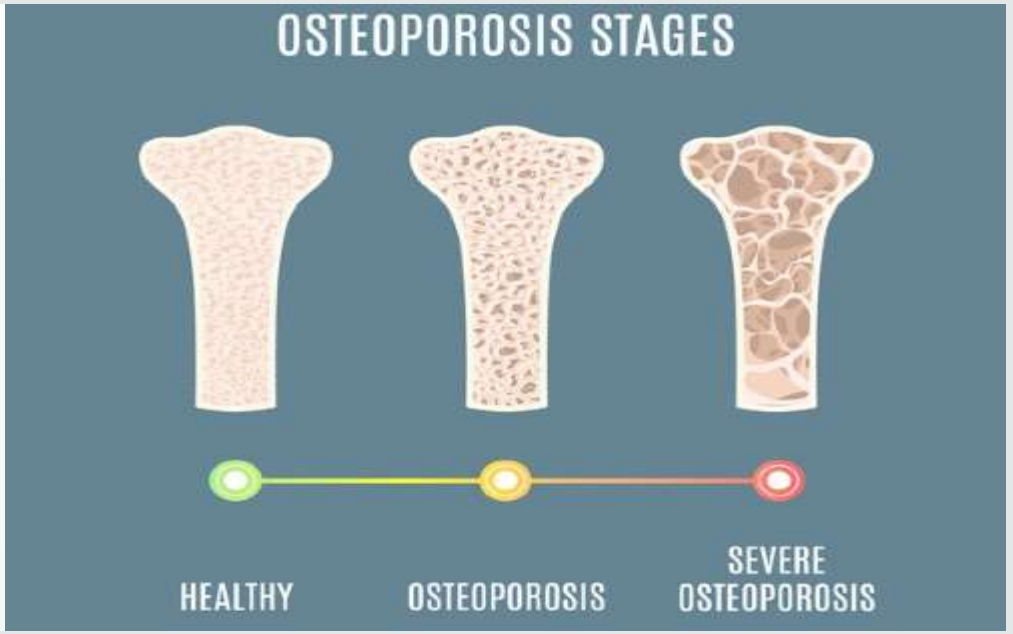
- **Radiographic**

1. Decreased bone mineral density (osteopenia or osteoporosis)
2. Nontraumatic (fragility) fracture
3. Skeletal pseudofracture



Looser zones, also known as **cortical infractions**, **Milkman lines** or **pseudo fractures**, are wide, transverse lucencies with sclerotic borders traversing partway through a bone, usually perpendicular to the involved cortex, and are associated most frequently with **osteomalacia and rickets.**

A fragility fracture is a fracture resulting from a fall from standing height or less. These fractures, which most commonly occur at the hip, spine, or wrist, are an indication that the body's bones have been weakened by an underlying illness mostly being osteoporosis.



The DXA machine sends a thin, invisible beam of low-dose x-rays with two distinct energy peaks through the bones being examined. One peak is absorbed mainly by soft tissue and the other by bone. The soft tissue amount can be subtracted from the total and what remains is a patient's bone mineral density.

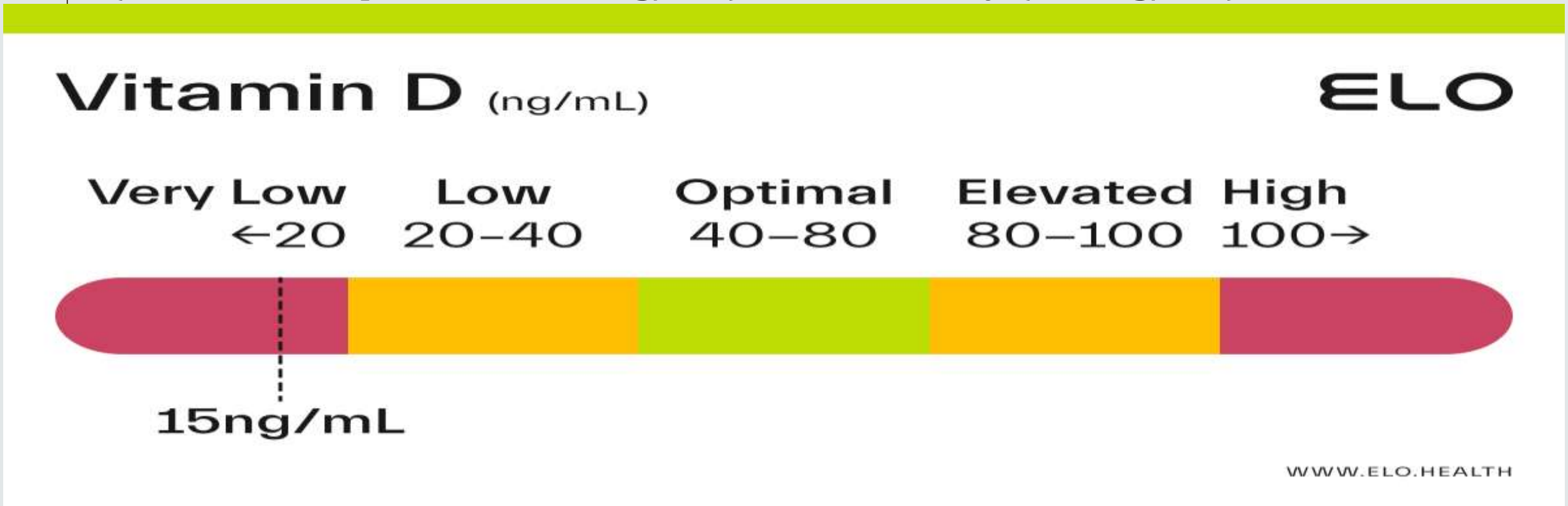
- It has been suggested that clinicians should routinely test for hypovitaminosis D in patients with musculoskeletal symptoms, such as bone pain, myalgias, and generalized weakness, because these symptoms are often associated with hypovitaminosis D and might be misdiagnosed as fibromyalgia, chronic fatigue, age-related weakness, or even depression
- Alternatively, **empiric vitamin D supplementation** without testing can be justified for patients who have *no* evidence of deficiency but are thought to have inadequate sun exposure or dietary intake.

Which Test Best Measures Vitamin D Status?

- Ingested and cutaneously produced vitamin D is rapidly converted to 25(OH)D, but in serum only a fraction of 25(OH)D is converted to its active metabolite $1,25(OH)_2D$. Thus, measurement of the **total 25(OH)D** level is the best test to assess body stores of vitamin D. The total 25(OH)D level allows for the diagnosis and monitoring of vitamin D deficiency, whereas **quantification of $25(OH)D_2$ and $25(OH)D_3$ fractions** may facilitate treatment monitoring.
- Clinicians should not measure $1,25(OH)_2D$ levels to diagnose hypovitaminosis D. Doing so can lead to an erroneous interpretation of vitamin D status because calcitriol levels are often normal or even elevated in patients with vitamin D deficiency as a result of elevated PTH levels.

What Is an Optimal 25(OH)D Level?

- A wide “optimal” range for 25(OH)D is reported (25-80 ng/mL), and differences of opinion exist as to the definitions of vitamin D insufficiency (sometimes reported as <30 ng/mL) and deficiency (<20 ng/mL).



Vitamin D2 vs. D3: What's the Difference?

Vitamin D comes in two main forms:

- Vitamin D2 (**ergocalciferol**)
- Vitamin D3 (**cholecalciferol**)

>>>The two forms of vitamin D differ depending on their food sources.

- Vitamin **D3** is only found in **animals**, while vitamin **D2** comes from **plant-sourced** foods. So since vitamin D2 is cheaper to produce, it's the most common form in fortified foods.
- Vitamin D3 is also produced in your skin when you spend time in the sun. In contrast, vitamin D2 is produced by plants and mushrooms exposed to sunlight.

- **Vitamin D2 and D3 are not equal when it comes to raising your vitamin D status.**

> Both are effectively absorbed into the bloodstream. However, the liver metabolizes them differently.

- The liver metabolizes vitamin D2 into 25-hydroxyvitamin D2 and vitamin D3 into 25-hydroxyvitamin D3. These two compounds are collectively known as **calcifediol**.
- Calcifediol is the **main circulating form** of vitamin D, and its blood levels reflect your body's stores of this nutrient.
- For this reason, your health care provider can estimate your vitamin D status by measuring your levels of calcifediol. However, vitamin D2 seems to yield less calcifediol than an equal amount of vitamin D3.
- For example, one study in 32 older women found that a single dose of vitamin D3 was nearly twice as effective as vitamin D2 at raising calcifediol levels

How is vitamin D deficiency treated?

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- The goals of treatment and prevention for vitamin D deficiency are the same: to reach and then maintain an adequate vitamin D level in your body.

- Both D2 (ergocalciferol) and D3 (cholecalciferol) are available as dietary supplements. The relative efficacy of D2 vs D3 in humans continues to be debated, although both appear to be effective for preventing or treating disease, provided that an adequate total 25(OH)D blood level is obtained

- The variable efficacy of D2 vs D3 may relate primarily to differences in serum half-life and is clinically relevant for dosing and monitoring frequency. A single dose of 50,000 IU of D2 or D3 produces a similar increase in the total 25(OH)D concentration, but the apparent longer half-life of D3 suggests that less frequent dosing may be needed

- However, a recent study comparing 1600 IU of D2 once daily vs 1600 IU of D3 once daily vs 50,000 IU of D2 once monthly vs 50,000 IU of D3 once monthly suggested that D3 is superior in that it showed slightly higher levels of 25(OH)D3 at the end of 1 year

- It is recommended that both D2 and D3 be taken with a meal containing fat to ensure maximum absorption
- We recommend the use of D3 , particularly if dosing is infrequent
- One situation in which D2 may be preferred is a vegetarian or vegan diet

TABLE 4. **Mayo Medical Laboratories Reference Ranges for Total Serum 25-hydroxyvitamin D [25(OH)D][a]**

Severe deficiency[b]	<10 ng/mL
Mild to moderate deficiency[c]	10-24 ng/mL
Optimal[d]	25-80 ng/mL
Possible toxicity	>80 ng/mL

How Much Is Enough ?

Vitamin D Level	Treatment	Follow-Up
<20 ng/ml	Ergocalciferol 50,000 iu/week x 16 weeks + Cholecalciferol 3,000 iu/day	Recheck Vitamin D 25,OH on week 17 • < 30 → continue the same treatment for another 16 weeks – recheck level again on week 17. If level still <30 address possible non-compliance • ≥ 30 → maintain on Cholecalciferol 3000 iu/daily
20-25 ng/ml	Ergocalciferol 50,000 iu/week x 16 weeks + Cholecalciferol 2000 iu/day	Recheck Vitamin D 25,OH on week 17 • < 30 → continue the same treatment for another 16 weeks – recheck level again on week 17. If level still <30 address possible non-compliance • ≥ 30 → maintain on Cholecalciferol 2000 iu/daily
25-30 ng/ml	Cholecalciferol 2000 iu/day	Recheck Vitamin D 25,OH prior to next visit
<30 ng/ml	Ergocalciferol (Drisdol) 8,000 iu/week x 16 weeks + Drink milk No daily supplement needed	Recheck level at next office visit
≥ 40	If on supplement and Vitamin D ≥ 40, continue 800 IU daily	Recheck prior to next office visit

- Special mention is needed for patients who have malabsorption or require tube feeding or parenteral nutrition. Patients receiving tube feeding (but without malabsorption) have vitamin D dosing requirements similar to persons with oral intake

- Special mention is needed for patients who have malabsorption or require tube feeding or parenteral nutrition. Patients receiving tube feeding (but without malabsorption) have vitamin D dosing requirements similar to persons with oral intake

- tablets contain D3 in powder form and can be used without clogging the feeding tube

- Patients with malabsorption often require larger maintenance dosing of vitamin D. For example, patients with malabsorptive gastric bypass procedures may require 50,000 IU of D2 or D3 maintenance dosing from once weekly to as frequently as daily to maintain sufficiency
- In extreme malabsorptive states, UVB exposure (ie, sunlight or phototherapy) can be effective for those who do not respond to large oral doses.

Vitamin D Benefits

- Higher serum levels of vitamin D are associated with reduced injury rates and improved sports performance
- It strengthens the immune system
- It boosts your mood
- It can lower the risk of rheumatoid arthritis
- It can help lower blood pressure
- It might reduce the risk of heart disease

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