

→ Vitamins are organic compounds that cannot be synthesized in adequate quantities by humans and therefore must be supplied through diet.

Classification:

Based on relative solubility

- Water soluble vitamins.
- Fat soluble vitamins.

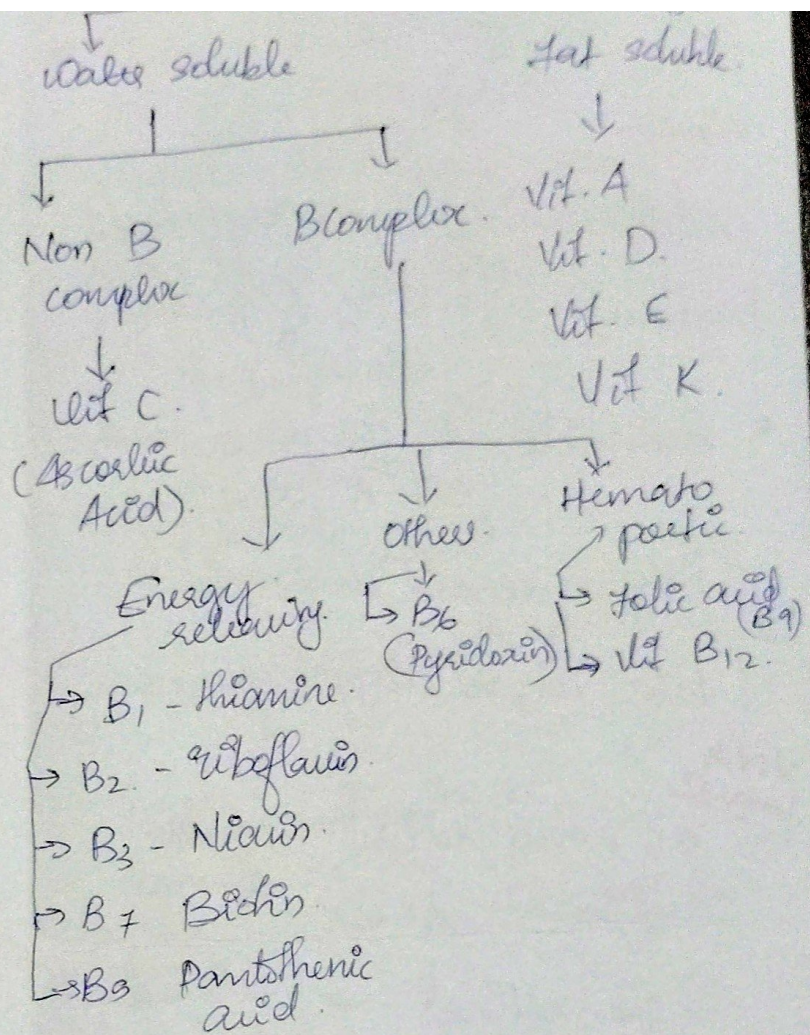
Differences:

Fat soluble vitamins

- Soluble in fat, insoluble in water.
- Absorbed along with lipids, require bile salts.
- Carrier proteins required for transport and stored in liver.
- Deficiency manifests when stores get depleted.
- Hypervitaminosis → toxicity.

Water soluble vitamins

- Soluble in water, insoluble in fat.
- Simple absorption.
- No carrier proteins and no storage in the body.
- Manifests rapidly as there is no storage.
- Excess is excreted.



Vit. A, D, C → essay.

FAT SOLUBLE VITAMINS

Vitamin A

- Pro vitamin A - Beta carotene (plants) (mark)

Sources: yellow and dark green vegetables and fruits are good sources of carotenes.
animal sources → milk, butter, cream, egg yolk, fish liver oils.

Men 450 - 1000 $\mu\text{g/day}$.
 Women 460 $\mu\text{g/day}$.
 Children 400 - 600 $\mu\text{g/day}$.
 Pregnancy 1000 $\mu\text{g/day}$.

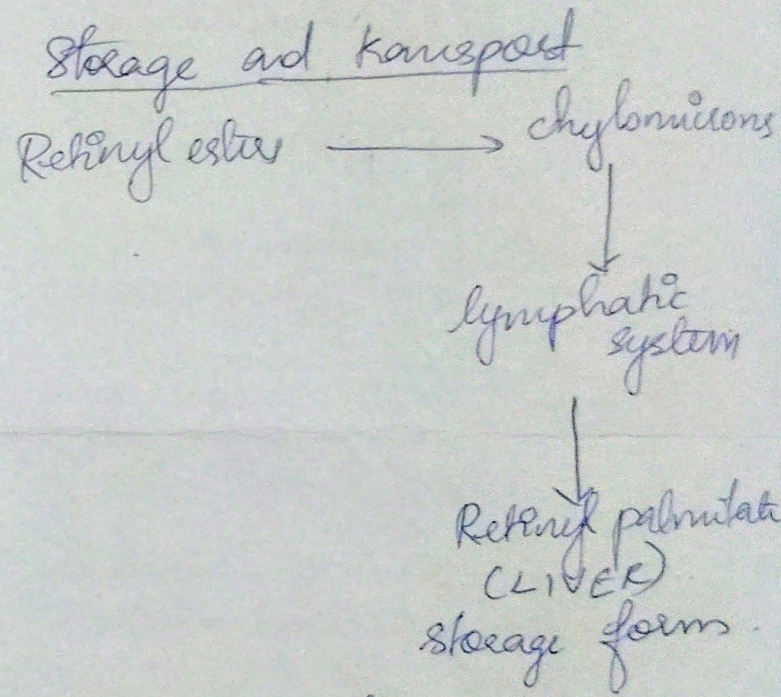
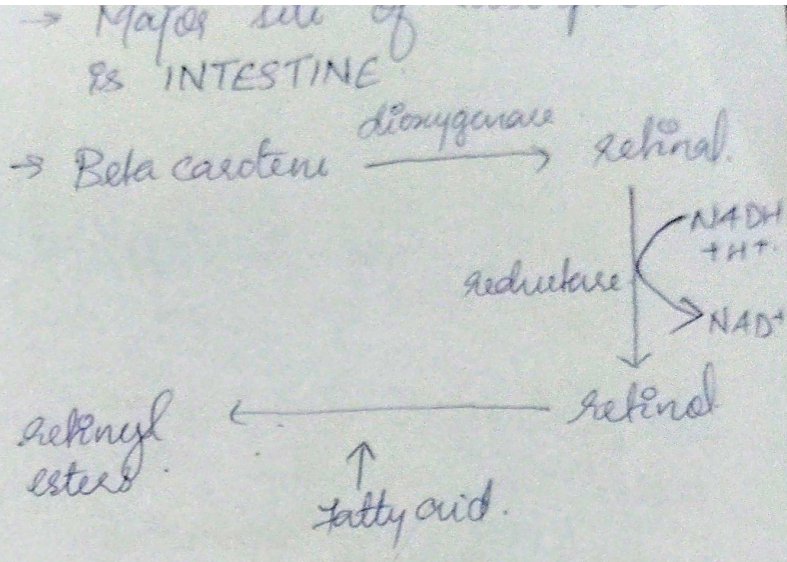
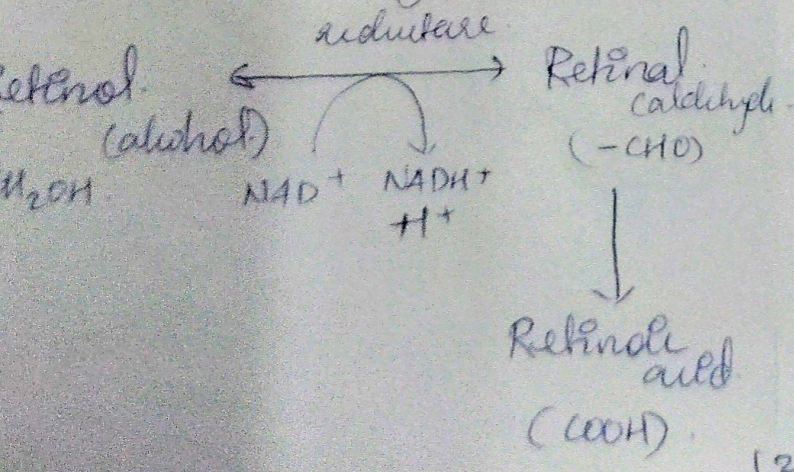
Retinoids - compounds with vit. A ~~activity~~ activity.
 Polyisoprenoid compounds + beta ionone ring (cyclohexenyl).

Vitamin A
 all trans retinal $\rightarrow$ most common vit A1

11 cis retinal $\rightarrow$ biologically active form

compounds with vit A activity -
 Retinol (Vit. A alcohol)
 Retinal (Vit. A aldehyde)
 Retinoic acid (Vit. A acid).

Interconversion of vit. A molecules



Release from liver
 Retinol.

Retinol binding protein (RBP)
 $\rightarrow$ Extra hepatic tissues.

Uptake by Tissues
 Retinol RBP complex $\rightarrow$ receptors (on surface of cells of peripheral tissues)

Retinol $\rightarrow$ Retinoic acid $\rightarrow$ cytoplasm $\downarrow$ nucleus

- vision.
- growth and differentiation of tissues.
- reproduction.
- maintenance of epithelium and skin.
- antioxidant.
- preventing heart attacks.

Role in Division (4 mark)

(Wald's vision cycle).

- It is a component of visual pigments of rod and cone cells.
- Rhodopsin is the visual pigment in rod cells (dark vision).
- Conopsin is responsible for color vision in ~~rod~~ cone cells.

Rhodopsin $\rightarrow$ membrane protein.

↓
photoreceptor cells
of retina (rod cells)

- Rhodopsin is made up of Opsin (protein) and 11-cis retinal.

- when rhodopsin, a G protein receptor is exposed to light, series of isomerizations take place.

- This will activate G protein, transducin.
- Transducin triggers nerve impulse, transmitted by optic nerve to brain.

Single photon

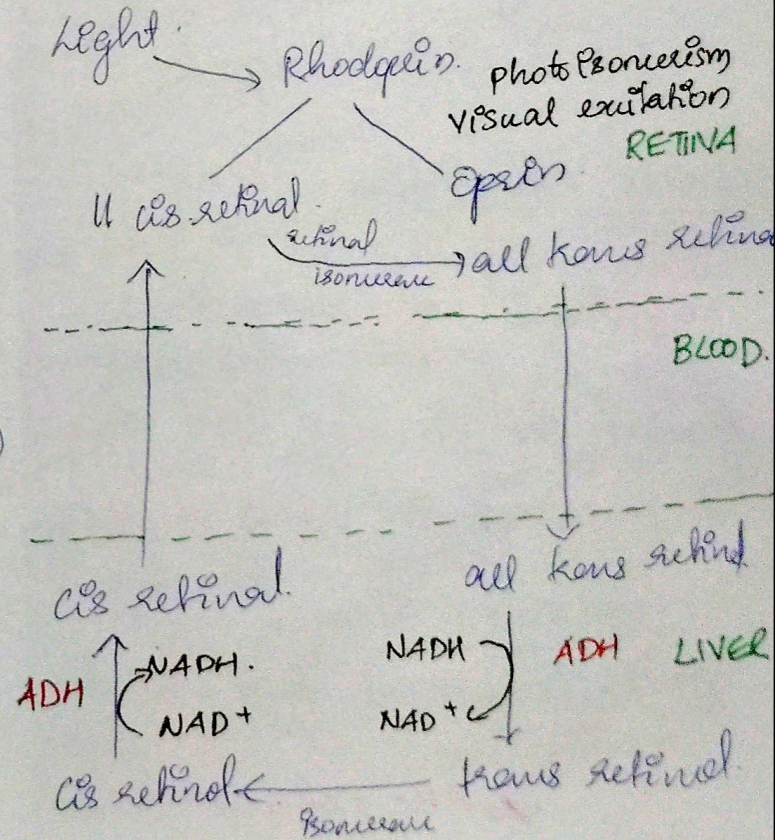
Rhodopsin

Batho rhodopsin

Meta ↓ rhodopsin 1.

Mela - rhodopsin 2

Open $\downarrow$ + all cones retinal.



unpaired receptors
transducin - G protein in
retina

hooking of 11-cis retinal
with opsin.

↓
critical for pigment's catalytic
activity.

Activated rhodopsin.

↓ rhodopsin kinase.

phosphorylation of serine residue
in rhodopsin

↓
Betas-arrestin binds

↓
inactivated rhodopsin.

Dark adaptation time:

Time required for the
resynthesis of rhodopsin,
when a person shifts suddenly
from bright to dim light area.

It increases in vit A deficiency.

Stargardt's disease.

All have retinal from retinal
epithelium.

* ABC protein.

↓
then

• deficiency of ABC protein (4)

blindness.

Deficiency manifestations.

- Ocular manifestations.
- Skin and mucous membrane
lesions.

Ocular manifestations include:

- Night blindness (Nyctalopia)
- Xerophthalmia.
- Bitot's spot
- Keratomalacia.

Nyctalopia (night blindness)

→ vision diminished in dim
light.

→ dark adaptation time increased

→ Deficiency of vit A (11-cis
retinal).

Xerophthalmia

- conjunctiva becomes
dry, thick and wrinkled.
- gets ~~less~~ keratinised.
- Normal transparency is lost.
- cornea becomes glossy and
lustrous due to ~~less~~
keratinisation of corneal
epithelium.

Bitot's spot

Increased thickness of
conjunctiva in some areas
→ greyish-white triangular
plaques in conjunctiva

→ These 3 are completely reversible on supplementation of vit A.

Keratomalacia

- softening of cornea.
- degeneration of corneal epithelium.
- corneal epithelium gets vascularised.
- Bacterial infections lead to corneal ulceration.
- Perforation of cornea.
- Total blindness.

Causes of vit A deficiency

- decreased intake.
- defective absorption (obstructive jaundice)
- reduced synthesis of RBP (carriers of liver)
- severe malnutrition - amino acids not available for RBP synthesis.
- RBP involved in urea - chronic nephrosis.

Hypervitaminosis A

- Dermatological manifestations
- Keratinisation of epithelium of
- Respiratory tract.
 - Gastrointestinal tract.
 - Genitourinary tract.
- Increased occurrence of infections. (anti-inflammatory vitamin)
 - formation of urinary calculi.

- Anorexia.
- headache, ~~and~~ irritability.
- vomiting and diarrhoea.
- peeling of skin.
- swelling over long bones. (long exostosis)
- Enlargement of liver in children (hepatomegaly)

Isotretinoin (1 mark)

- synthetic variant of vit A.
- reduces sebaceous secretions → prevents acne formation.

(1 mark) ESKIMOS refrain from eating liver of polar bear due to high vit A content.

Cellular death.

higher conc: of retinol releases lysosomal enzymes leading to cellular death.

VITAMIN K

- K - German word
Koagulation vitamins.

→ Naphthoquinone derivatives.
It has long isoprenoid side chain.

Vitamin K₁ - Phylloquinone
(20 C side chain)

Vit. K₂ - Menaquinone (30 C side chain)

Menadiolone - water soluble
synthetic vitamin.

Dietary sources

Green leafy vegetables are good sources.

→ Intestinal bacteria can meet daily requirement.

RDA

50 - 100 µg/day (normal diet)

→ Absorption.

site: intestine

Bile salts and chylomicrons.

→ Storage and transport

site: liver.

transport → liver lipoproteins
↓
plasma

→ Functions

- Blood coagulation
- Functional activity of osteocalcin.
- Structural proteins of lungs, kidney and spleen

Role in coagulation (4/8 mark)

→ Post-translational modification

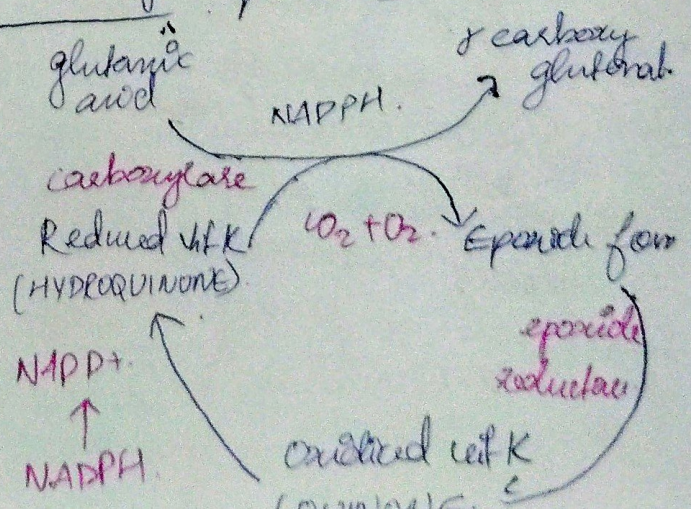
↓
gamma carboxylation

↓
glutamic acid residues
(binding site of Ca).

↓
clotting factors II, VII, IX and X

→ Vitamin K dependent carboxylase enzyme.

- is a microsomal enzyme.
- contains O₂, NADPH and CO₂.
- substrate required for this is reduced vit K (Hydroquinone)



Deficiency ~~man~~ manifestations

- Unusual in adults.
- Newborns have skull fracture.

↓
single intramuscular dose of vit. K.

↓
prophylaxis (to prevent congenital hemorrhagic diseases).

→ Antibiotics can decrease bacterial ~~for~~ production.

- Bruising tendency, ecchymotic patches.
- Hemorrhage, post-traumatic bleeding.
- Internal bleeding.
- Prolonged prothrombin time.
- Delayed clotting time.

Causes of deficiency

- dietary deficiency rare
- malabsorption of lipids
 - cystic fibrosis
 - chronic pancreatitis, sprue.
- prolonged antibiotics.
- gastrointestinal infections (diarrhea).

Mark Warfarin and Dicoumarol.
(structurally similar to vit E)
(Antivitamin).

Epoxide structure ~~X~~

↓
gamma carboxylation.

Anticoagulation (therapeutic purposes).

WARFARIN → synthetic analogue of vit K.

DICOUMAROL → natural anti-coagulant in spoiled sweet clover.

Hypervitaminosis K

- Hemolysis
- Hyperbilirubinemia.
- Kernicterus and brain damage.

Vitamin E

→ chromane ring + isoprenoid side chain.

→ Vit E → 8 naturally occurring tocopherols.

Biologically active form
↳ α -tocopherol.

Other names

- Anti-infertility vitamin.
- Most potent biological antioxidant.

Sources

- vegetable oils - rich sources
- liver and eggs → moderate

RDA

- males → 10mg/day
- females → 8mg/day
- pregnancy → 10mg/day
- lactation → 12mg/day

Biochemical Roles

- Scavenger of free radicals
- prevent RBC's from hemolysis
- Prevents lipid peroxidation
- Keeps structural integrity of cells
- Immune response
- Reduce risk of atherosclerosis

Metabolism

- Absorbed with the help of bile salts
- Transported as chylomicrons
- Stored in adipose tissue
- Excreted in bile after conjugation with glucuronic acid
- Normal level in blood - 0.6 - 1 mg/dL

Mineral Relation

- Selenium $\longleftrightarrow$ Vit E.
balance each other.
→ glutathione peroxidase

Deficiency manifestations

- Almost entirely restricted to pre-mature infants.
- Symptoms rare in adults
- Sensitivity of erythrocytes to peroxide, appearance of abnormal cellular membranes
- Muscular weakness

Hypervitaminosis

- Least toxic of fat-soluble vitamins
- Tendency to hemorrhage (above 1000 IU/day)
- 10 → International units

Vitamin D (ESSAY)

- Vitamin D is a generic term and indicates a molecule of the general structure shown for rings A, B, C and D with different side chain structures.

→ The A, B, C and D ring structure is derived from the cyclopentanoperhydrophenanthrene ring structure for steroids.

→ Technically vitamin D is classified as a seco-steroid.

→ Seco-steroids are those in which one of the rings has been broken; in vitamin D, the 9,10 carbon-carbon bond of ring B is broken.

→ Vitamin D₂ = ergocalciferol (found in plants).

- completely synthetic form produced by the irradiation of the plant steroid ergosterol.

→ Vitamin D₃ = cholecalciferol (found in animal tissues)

- Produced photochemically by the action of sunlight or ultraviolet light from the precursor sterol 7-dehydrocholesterol.

— Vitamin D = calciferol.

→ Endogenous vitamin D precursors

pro vitamin D

7-dehydrocholesterol.
an intermediate in cholesterol synthesis is converted to cholecalciferol in the dermis and epidermis of humans exposed to sunlight.

Sources:

good sources → Exposure to sunlight.
fish, egg yolk, fish liver oil.

Moderate amount → milk.

RDA

→ children → 10 µg/day.

→ Adults → 5 µg/day

→ Pregnancy } 10 µg/day
lactation }

Above 60 years — 20 µg/day.

Metabolism of vit D.

Formation of CALCITRIOL.

→ humans and animals can produce vit D inside their bodies from cholesterol.

→ cholesterol is converted to 7-dehydrocholesterol (7DH) which is a precursor of vitamin D₃.

→ Exposure to the ultraviolet rays in the sunlight

convert 7DC to cholecalciferol.
* Vit D₂ and D₃ are not biologically active.

→ 25-HCC binds to VDB
(Vit D Binding protein, an α -2 globulin).

- converted in vivo to the active form (calcitriol)
- Includes two hydroxylation reactions.
one in liver and another in kidney.

cholesterol.

↓

7-Dehydrocholesterol

↓ sunlight.

cholecalciferol. (inactive).

LIVER. ↓ 25-hydroxylase.

25-Hydroxycholecalciferol.

KIDNEY. ↓ 1, 25 Dihydroxylase
or 1 α -hydroxylase.

1,25 Dihydroxycholecalciferol
(Calcitriol).

→ 1,25 DHL acts as a hormone rather than a vitamin.

→ Hepatic 25-hydroxylase → microsomal mono oxygenase.
requires cytochrome P-450.
(CYP450) and NADPH.

→ 25-HCC → Major storage form. (10)

→ 1 α Hydroxylase - located in mitochondria of PCT.
Requires CYP P-450, NADPH and ferredoxin (Fe-S protein).

→ CALCITRIOL - Active form of Vit D.

3 Sites of Action

→ Intestinal epithelial cells.

→ Bone osteoblasts

→ Kidney DTC

Intestine

→ promotes the absorption of Ca and P from the intestine

→ 1,25-(OH)₂D binds to vitamin D receptors (VDR) in nucleus.

→ Induces the synthesis of Calbindin (Ca-binding protein)
↳ required for absorption of Ca in intestine.

Bone

→ ↑ activity of osteoblast.
→ ↑ mineralisation of bone.
→ Osteoblast secrete alkaline phosphatase

- Hydrolyses phosphate ester bonds
- Releases phosphorus.

Kidney

- Increases reabsorption of Ca and P by renal tubules.

Other functions of Calcitriol.

- Immune system - important for cell mediated immunity and coordination of immune response.
- Cell differentiation.
- reduces risk of cancer and coronary vascular diseases.

Vitamin D

- Increases the calcium release from bone
- Increases calcium absorption from intestine.

Regulation of Calcitriol

• Factors regulating Calcitriol Production

- Ca, P, PTH. (Parathyroid H)
- feedback control.

Parathyroid Hormone

- Calcium-sensor protein in the thyroid gland
- detects low plasma

calcium concentration.

- Effects of parathyroid hormone
- stimulates $1-\alpha$ hydroxylase activity in the kidney



Plasma Ca ↓

↓
PTH ↑

↓
Calcitriol ↑

↓
Ca mobilization from bone, renal reabsorption of Ca ↑

↓
Renal excretion of Ca ↓

↓
Ca absorption from intestine ↑

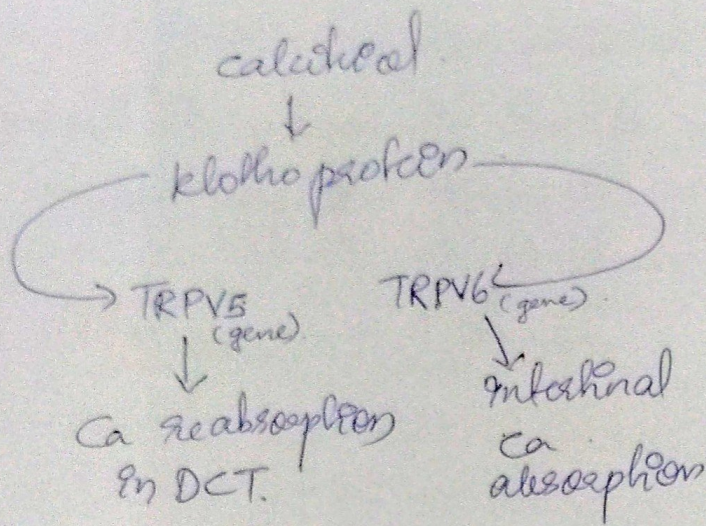
↓
Plasma Ca ↑
(9-11 mg/dL)

Plasma Ca level increases

↑ Ca level / adequate Vit D

↓
Hydroxylation at the 24th position (kidney)

↓
formation of 24,25 DCC
is less active.



- Gastrointestinal diseases.
- Antiepileptic.
- Glucocorticosteroids.

5) Defective absorption of vit D
Obstructive jaundice
Steatorrhea
High phytate content in diet

Serum Vitamin D3

- Reference levels of serum 25 (OH) D3 is 30 ng/mL (75 nmol/L).
- level less than 10 ng/mL is the mark of severe vitamin D deficiency

Vitamin D deficiency.

- Rickets in children.
- Osteomalacia in adults.

Anti Rachitic Vitamin.

- 1) Lack of sunshine.
- 2) Dietary deficiency of vit D.

Breast milk	0 - 10 IU/100mL.
Cow's milk	0.3 - 4 IU/100mL.
Egg yolk	25 IU/average yolk.

3) Improper Ca and P ratio.

- 4) Diseases and drug:
- Liver diseases, renal diseases - affecting activation of vit D

Rickets (Rachitis)

→ Rickets is a systemic disease with skeletal involvement most, but the nervous system, muscular system and other systems are also involved.

Clinical features:

- Seen in children.
- Bones become soft & pliable.
- Inefficient mineralization of bones.
- Bone deformities, knock-knee, legs.
- Bow legs, rickety rosary, pigeon chest.
- Harrison's sulcus (transverse depression from costal cartilage to axilla)

Vitamin D - anti rachitic vitamin.

Types:

- Classical vit D deficiency rickets.
- Renal rickets (renal osteodystrophy).

- Hypophosphatemic rickets
- Vit D resistant rickets
- End organ refractoriness

Classical vit D deficiency rickets

- limited exposure to sunlight
- Renal rickets
 - chronic renal failure
 - ↓ formation of calcitriol
 - administration of calcium calcitriol is effective.

→ Hypophosphatemic rickets

- ↓ renal tubular reabsorption of phosphate.
- Supplementation of phosphate with vitamin D.

→ Vit D resistant rickets

- Symptoms similar to Fanconi's syndrome.
- Reabsorption of phosphate, glucose, amino acids, bicarbonates - defective.

- End organ refractoriness
- decrease in the no. of cystolic receptors.
- structurally abnormal receptors

→ Hypoparathyroidism

Lack of PTH → hypocalcemia
hypophosphatemia

Supplementation

- any form of vit D along with PTH.

Osteomalacia

Clinical features:

- Term derived from Greek, *ostion* (bone) and *malakia* (softness).
- Demineralisation of pre-existing bones.

↓
↑ susceptibility of fractures (pathological)

Abnormalities

- Hypocalcemia, hypophosphatemia (severe hypocalcemia not produced. Tetany not manifested).
- Serum ALP increased.

Hyper vitaminosis D

- Above 1500 units/day.
- Loss of appetite, thirst.
- Nausea, stupor, hypertension, weight - loss.
- Hypercalcemia → deposition of Ca → arteries and kidneys (metastatic calcification or calcinosis).