

28/09/2024
Tuesday

VITAMINS

- Dr. Sanoop Sir

CA, D, C

- Definition

Vitamins are chemically unrelated organic comp. that generally cannot be synthesised by the body and must be supplied through the diet in small amounts necessary for health, growth and reproduction.

- * Present in small quantities in natural foods
- * Plants & bacteria synthesise vitamins on their own.
- termed micronutrients.

* Endogenously synthesised vitamins

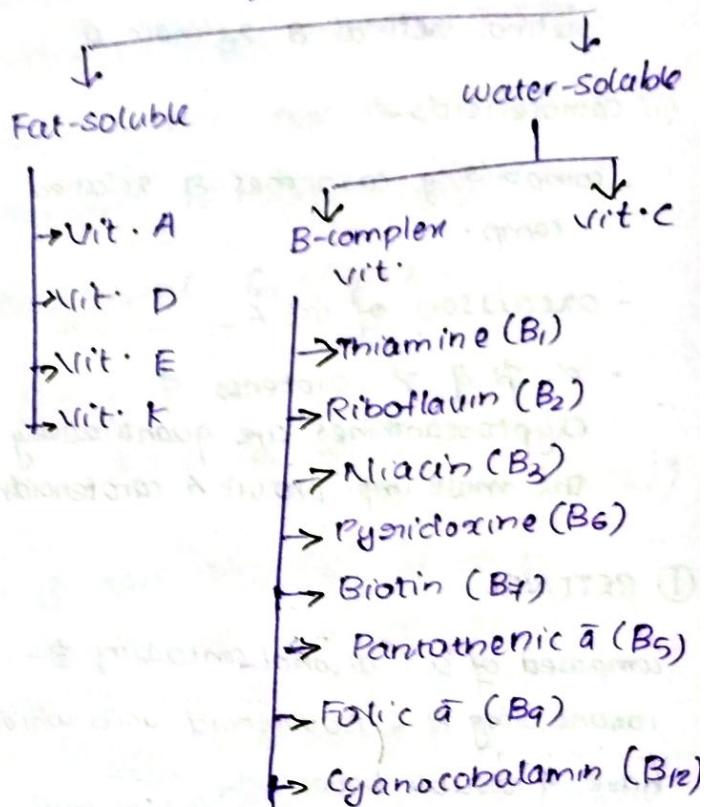
Vitamin D
niacin
Vitamin K
Biotin,
Riboflavin,
Panthoic a.

by intestinal
bacterial
flora.

Fat soluble

- Absorption is along with lipids requiring bile salts
- Stored in liver & adipose tissue
- Excreted through bile & lost through faeces
- Not readily excreted in urine & hence excess intake of these vit leads to their accumula. & result in toxic effects
- Rx of def: single large doses may prevent def.
- Do not act as coenzymes (except Vit K)

Vitamins



Water soluble.

- Absorption is simple (except Vit B12)
- No storage in large quantity (except Vit B12) hence must be continuously supplied through diet.
- readily excreted through urine
- Regular dietary supply is req.
- Do not act directly but fn through their respective coenzyme.

Vitamin - A [sure question]

- fat soluble vitamin
- 2 groups of compounds have vit A activity.

(i) Retinoids -

retinol, retinal & retinoic acid

(ii) Carotenoids -

- comprising carotenes & related comp.
- precursors of vit A
- α , β & γ carotenes & cryptoxanthins are quantitatively the most imp. provit A carotenoids.

① RETINOL

composed of a 1° alcohol containing β -ionone ring & 2 isoprenoid units which have 4 double bonds.

② RETINAL

Aldehyde form of vit A.

Vertebrate animals ingest retinal directly from meat $\rightarrow$ by intestinal dioxygenase enz.

③ RETINOIC ACID

: produced by oxidn of retinal in the body.

- cannot be reduced in the body so cannot give rise to retinal/retinol.

④ β CAROTENE & other provit A carotenoids

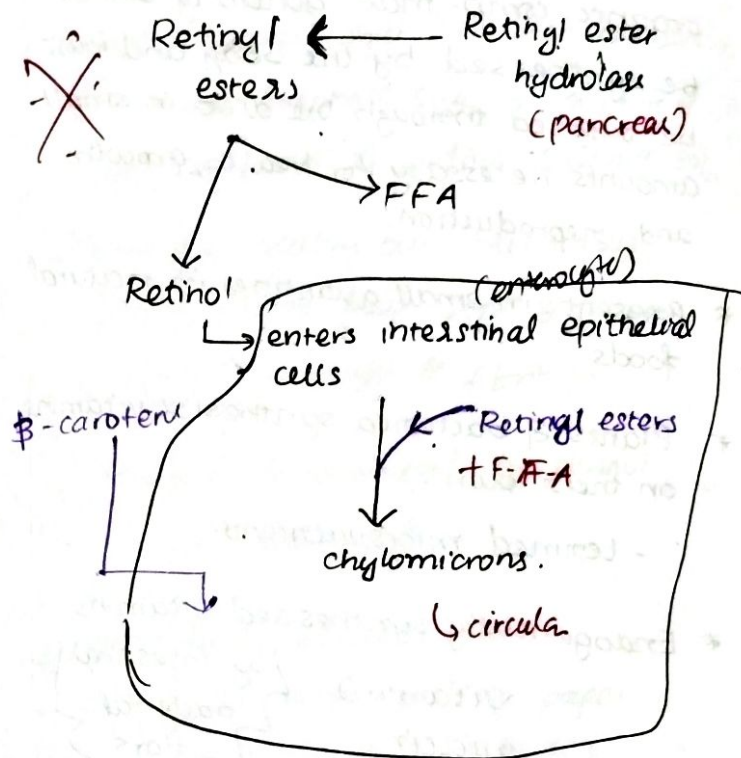
600 $\rightarrow$ nature

50 $\rightarrow$ can be conv. to vit A.

β -carotene is predominant carotene in human diet. (green leafy veg., carrots & some fruit) with vit A activity.

β -carotene $\rightarrow$ 2 Retinal $\rightarrow$ Retinol

Absorption of Vit A



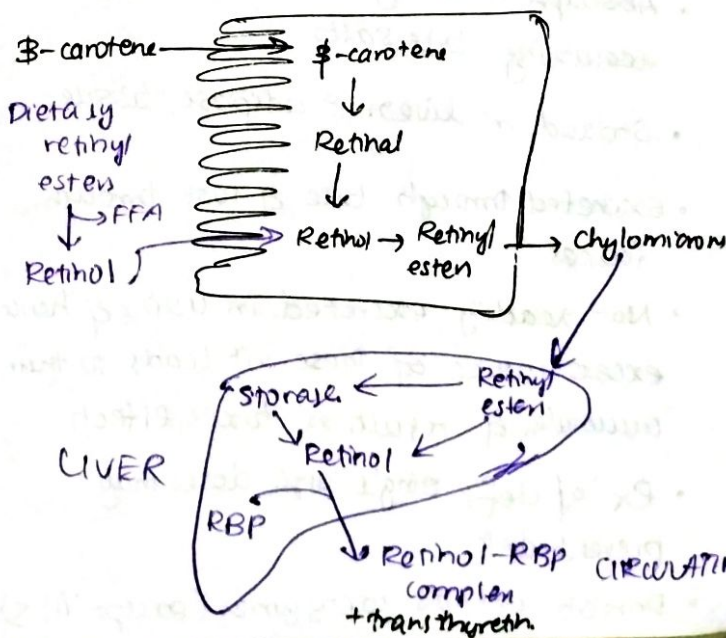
* carotene will enter directly to the intestinal epithelial cells.

Carotene $\xrightarrow{\text{carotene dehydrogenase}}$ Retinal $\xrightarrow{\text{Retinal reductase}}$ Retinol $\rightarrow$ Retinylester $\Rightarrow$ chylomim

GIUT LUMEN

ENTEROCYTE

LYMPH



Transport & metabolism of Vit A

Storage of vit A

- in the liver perisinusoidal stellate (Ito) cells as retinyl ester (retinyl palmitate)

Excretion

- of vit A is via the bile, reaches the intestine & lost through feces.

03/02/2023

Dietary sources

Animal foods:

- liver, whole milk, eggs, butter, cheese, fish & meat.
- fish (cod or shark) liver oils are the richest source of vit A
- Halibut liver oil

Plant foods

Among the best sources are green leafy veg. such as spinach & amaranthus, which are available in all seasons.

The darker the green leaves, the higher is its carotene content.

Vit A also occurs in veg & fruits such as papaya, pumpkin & mango. Carrot is also a good source of vit A.

Recom. daily allowance

RDA of vit A

Children - 400 - 600 $\mu\text{g/day}$

Men - 750 - 1k Hg/day 900 RAE

Women - 750 Hg/day 700 RAE

1 RAE = 1 Hg retinol

12 Hg β carotene

24 Hg of other carotenoids

Prevention of vit A def

- single massive dose of 2,00,000 IU to children (1-6 yr) once in 6 months
- single massive dose to 1 lakh IU to children (6 months - 1 yr)

Biochemical fn of vit A

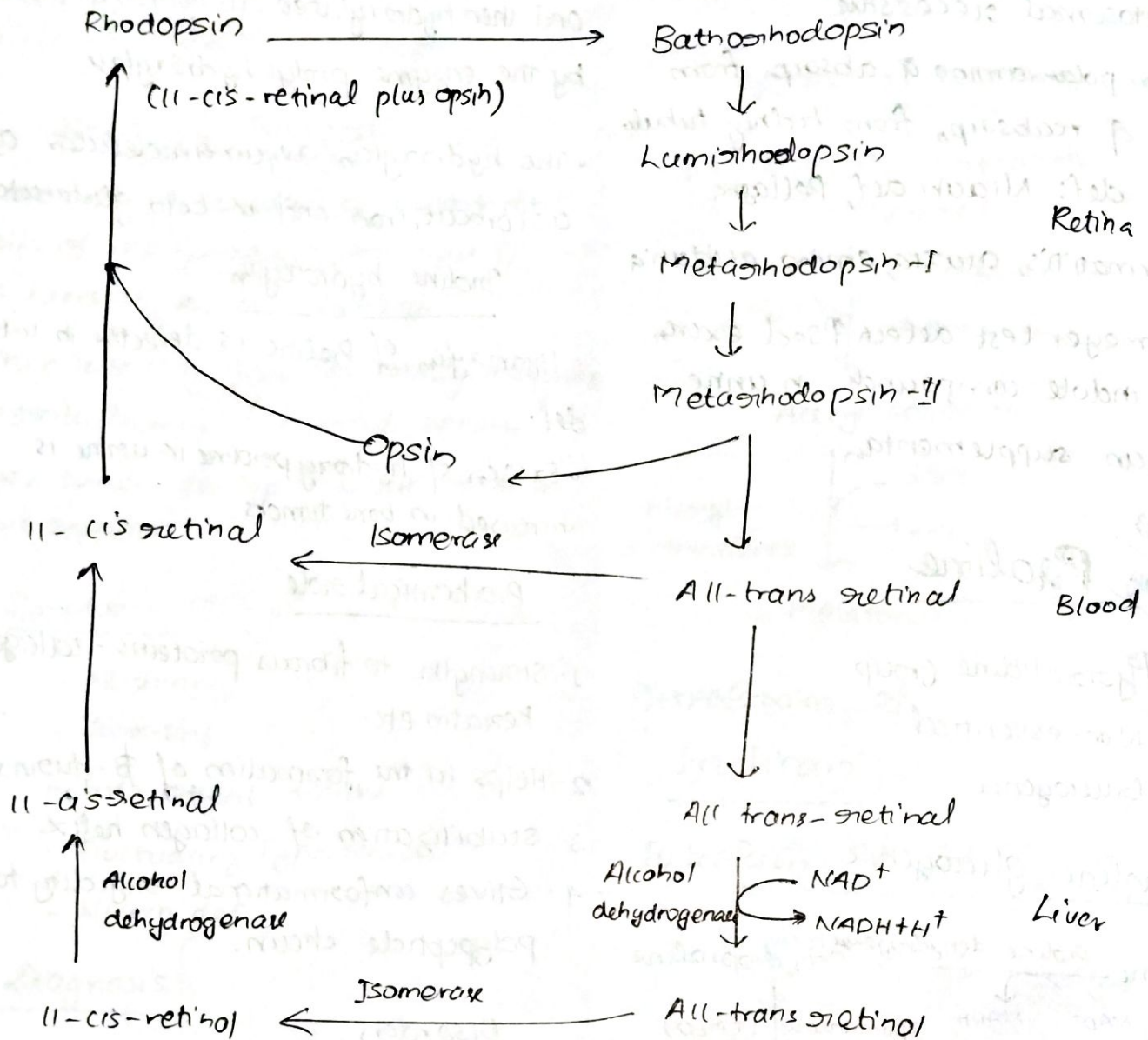
① Role in vision

discovered by G. Wald
(Nobel prize - 1967)

In a dark room, vision can only be supplied by rods; $\therefore$ they have greater sensitivity than cones, during the exposure to bright light, Rhodopsin of rods are completely activated & cannot fully respond again, until it is restored to its original state, which takes a few minutes.

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Light (Photons)



Metarhodopsin-II $\rightarrow$ Transducin $\rightarrow$ phosphodiesterase

cGMP $\rightarrow$ 5'GMP

(conc of cGMP $\downarrow$)

closure of Na^+ channels

Hyperpolarisation of Rod cell

closure of gated Ca^{2+} channels

↓
 stoppage of release of glutamate
 ↓
 stimulation of bipolar cells & ganglion cells
 ↓
 optic n. & thalamus → visual cortex

② cellular growth & differentiation

Retinoic acid is implicated in cellular growth & differentiation by regulating the expression of several genes

③ Vit A is required for normal reproduction.

- retinoic acid has a role in spermatogenesis.

④ Vit A is req. for maintaining of healthy epithelial tissue

- it maintains moist & pliable epithelium by inhibiting the synthesis of excess keratin (responsible for horny surface)
 - retinol & retinoic acid downregulate keratin synthesis.

⑤ Glycoprotein synthesis

- retinoyl phosphate synthesised from retinoic acid participates in glycoprotein synthesis (involving dolichol)

- glycoproteins are important constituents of mucus.

- In Vit A def. lack of mucus secretion results in drying of epithelial tissue.

⑥ Role in immunity

Vit A def. causes keratinisation of the mucosal lining of the respiratory, GI & genitourinary tracts making them susceptible to freq. infection.

⑦ Retinol & retinoic acid are essential for the synthesis of transferrin (the iron transport protein).

- Iron def. anemia may occur in Vit A def.

⑧ Antioxidant property

there is evidence that β -carotene has a beneficial effect in preventing certain types of cancers & MI.

Deficiency manifestations

Vit A can be 1° (dietary) or 2° - fat malabsorption.

- failure to synthesise chylomicrons.

- failure to cleave β -carotene

- impaired storage in hepatic cells

- failure to synthesise retinol binding protein (RBP)

- clinical signs of Vit A def. mostly involve the eye

- Vit A def. is the most common cause of preventable blindness.

Eyes

- the earliest sign of def. is a loss of sensitivity to green light.

↳ followed by impairment to adapt to dim light followed by night blindness (nyctalopia)

- more prolonged def. leads to xerophthalmia & night blindness

Xerophthalmia

night blindness if left untreated causes dryness of the conjunctiva & cornea. The conjunctiva becomes thick & wrinkled, the cornea loses its mucosal cells & become dull, hazy due to keratinisation & loses its transparency. These changes are described as xerophthalmia.

Bitot's spots

Triangular white patches on the conjunctiva on either side of cornea - usually bilateral.

Keratomalacia

If the condition progresses beyond xerophthalmia there is ulceration & necrosis of cornea, which results in total blindness.

② Skin & mucous membranes

- follicular hyperkeratosis of the skin (also called phrynoderma) occurs due to increased keratin formation in follicle & lead to coarse, rough & dry skin.
- Infections of the skin & mucous membranes are more common due to abnormal skin & mucous surface
- keratinisation of respiratory, genitourinary tracts & intestinal mucosa leads to frequent infection.
- urinary bladder mucosa involvement may promote stone formation.

③ Failure of bone remodelling

occurs leading to thick, solid bones in skull especially in infants & children. This leads to ↑sed CSF pressure leading to hydrocephalus.

Both osteoblasts (bone building cells) and osteoclasts (bone breakdown cells) are influenced by vit A.

④ Gonadal dysfunction

decreased spermatogenesis & ↑sed abortions are known in vit A def.

Assessment of vit A def.

(a) Dark adaptation test

(b) plasma vit A levels - decreased

normal - 30 - 80 µg/dl

(c) RBP - ↓sed in vit A def.

- normal → 3 - 6 mg/dl

Hypervitaminosis

plasma vit A > 140 µg/dl

- after liver storage of retinol & its esters exceeds > 3000 µg/g tissue
- after ingestion of vit A > 30,000 µg/day for months or years.
- organelle damaged in hypervitaminosis is lysosomes
- acute toxicity; ~~pseud~~ pseudotumor cerebri (headache, dizziness, vomiting, stupor & blurred vision) & exfoliative dermatitis

hepatomegaly & hyperlipidemia

Chronic toxicity: If intake of $> 50,000$ IU/day for more than 3 months.

wt loss, anorexia, nausea, vomiting, bone exostosis, bone & jt pain, decreased cognition, hepatomegaly, cirrhosis.

VITAMIN-D $\times$ Imp

Group of sterols having a hormone like function.

Ergocalciferol - Vit D₂ (plant source)

cholecalciferol - Vit D₃ (animal source)

Chemistry

* Vit-D₂ - Ergocalciferol - commercial vit D obtained from fungus, ergot.

* Vit D₃ - cholecalciferol - endogenous synthesis from dehydrocholesterol both are equally active (after conversion) and have similar biological actions.

Sources of vit D

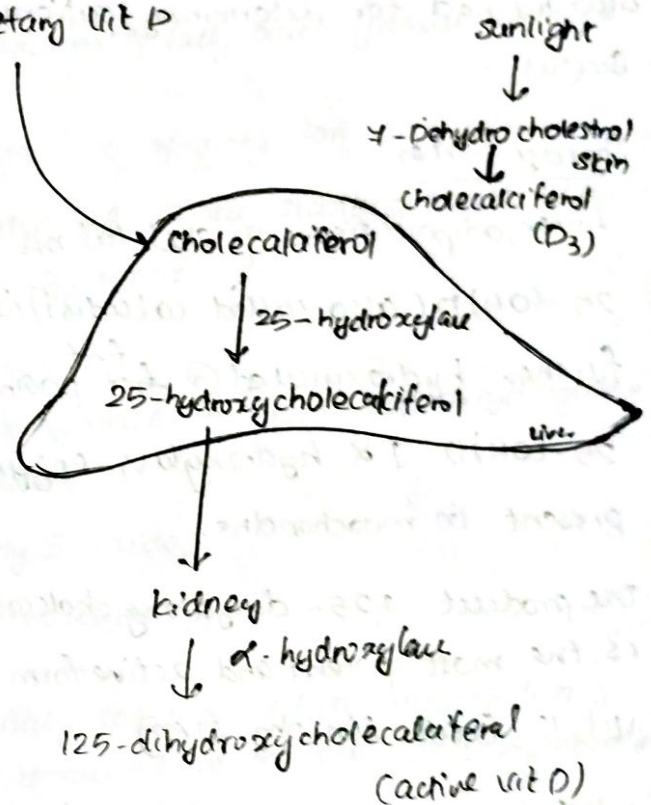
major source of vit D for humans -

endogenous synthesis in the skin by photochemical conversion of a precursor, 7-dehydrocholesterol to cholecalciferol (vit D₃) via the energy of solar or artificial UV light in the range of 290 nm to 315 nm (UVB radiation) in the stratum corneum of epidermis of skin.

Dietary sources

- fish liver oils, egg yolk, liver, milk
 - ergosterol, a fungal sterol in yeast, on UV exposure similarly produces 7-ergocalciferol, the vit D₂.
- This is also the method used for commercial vit D production.

Dietary vit D



Route of excretion

via the bile into the faeces

Active form of vit D

1,25 dihydroxy cholecalciferol or calcitriol both dietary vit D₃ & vit D₂ (absorbed with lipids) & the vit D₃ synthesised in the skin are

- transported to liver in blood in combination with α_2 globulin transport prot called vit D binding prot.

- Both vit D₂ & vit D₃ are converted to 25-hydroxycholecalciferol (25-(OH)D)

in the liver by a specific

most abundant circulatory form of

Vit D is $25-(OH)D$.

$t_{1/2}$ of $25-(OH)D$ is 2-3 weeks

The measurement of $25-(OH)D$ is the

std. method for determining patient's
Status

Storage sites

Liver, adipose tissue & skeletal m.

$25-(OH)D$ (also called calcidiol) is

further hydroxylated @ ^{first} posn by

$25-(OH)D$ 1 α hydroxylase enzyme,
present in mitochondria.

The product 1,25-dihydroxy cholecalciferol
is the most potent and active form of
vit D. (rate limiting step)

Kidney - major source of $1,25-(OH)_2D$

colon, prostate, breast, brain, β -

cells of pancreas, vascular smooth muscles

& the macrophages - can produce

$1,25-(OH)_2D$

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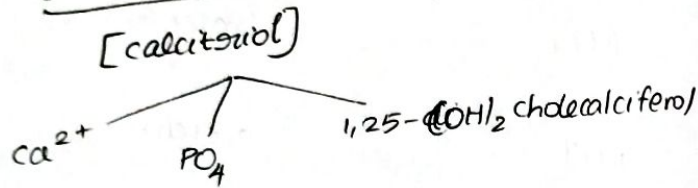
Vitamin (cont.)

Vitamin-D

Assessment of vit-D

→ 25-Hydroxycholecalciferol is tested / assessed

Regulation of synthesis of $1,25-(OH)_2 D$



(i) Ca^{2+} (indirectly)

low plasma calcium stimulates the secretion of PTH

→ ↑ses the 1α hydroxylase activity which in turn enhances the synthesis of $1,25(OH)_2 D$

(ii) Phosphate (directly)

low plasma phosphate (though not as strong as hypocalcemic effect)

directly ↑ses the activity of 1α -hydroxylase high plasma phosphate level & high plasma Ca^{2+} levels lowers the levels of $1,25(OH)_2 D$.

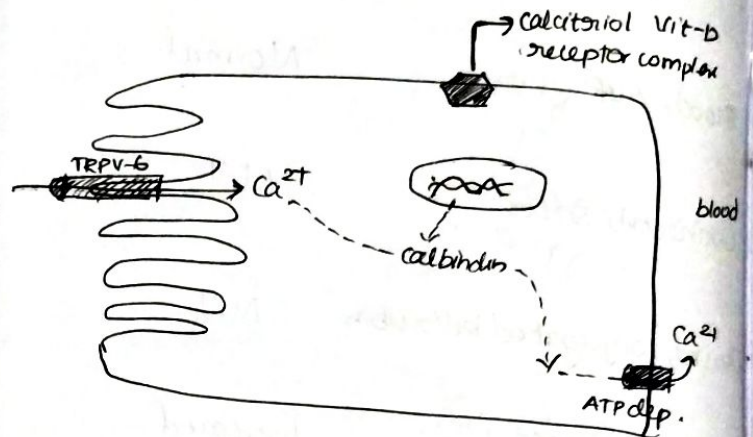
(iii) $1,25-(OH)_2 D$ (feedback regulation)

↑levels of $1,25-(OH)_2 D$ inhibit renal 1α hydroxylase & stimulate 24 -hydroxylase to produce the inactive metabolite $24,25-(OH)_2 D$ excreted through urine

Functions of vit-D

1) Regulation of Ca^{2+} & Phosphorous homeostasis

(a) Action on the intestine.



Vit D ↑ Ca^{2+} absorption by 2 mechanisms

(i) calcitriol binds to a receptor inside the cell → calcitriol receptor complex



enters the nucleus & interacts with DNA



expression of a specific gene leading to synthesis of a calcium binding protein — calbindin



calbindin promotes the Ca^{2+} uptake across the intestinal cell mem

(ii) It also ↑ses the transcription of TRPV6 (a member of Transient Receptor Potential Vanilloid family) which encodes a critical calcium transport channel. This ↑ses Ca^{2+} absorption from duodenum. PO_4^{2-} transport accompanies Ca^{2+} transport by an independent mechanism

(b) Action on kidney

Vit D increases Ca^{2+} & P reabsorption

PTH & calcitriol work together to prevent loss of Ca^{2+} .

PTH increases Ca^{2+} influx in distal tubule of kidney through the expression of TRPV5 another member of transient receptor potential vanilloid family.

(c) Action on bone

Bone is composed of collagen & crystals of $\text{Ca}_5(\text{PO}_4)_3\text{OH}$ (hydroxyapatite) acts on 2 types of bone cells - osteoblasts & osteoclasts.

(a) $1,25-(\text{OH})_2\text{D}$ stimulates Ca^{2+} uptake in osteoblasts depositing it as $\text{Ca}_5(\text{PO}_4)_3\text{OH}$ [hydroxyapatite] & enhances mineralisation.

(b) when blood Ca^{2+} is low, $1,25-(\text{OH})_2\text{D}$ & PTH stimulates bone resorption by ↑ the expression of RANKL (receptor activator of NF- κB ligand) on osteoclasts.

RANKL binds to its receptor located on preosteoclasts, inducing the differentiation of these cells into mature osteoclasts.

They dissolve bone (bone resorption) & release Ca^{2+} & P into the circulation

[demineralisation]

(2) Immunomodulatory & antiproliferative effects

prevent infection by mycobacterium TB.
 $1,25-(\text{OH})_2\text{D}$ level less than 20 ng/mL is associated with increased incidence of colon cancer, breast cancer and prostate cancer.

(3) Mineralisation of bone

Vit D contributes to mineralisation of osteoid matrix of epiphyseal cartilage in both flat & long bone.

$1,25-(\text{OH})_2\text{D}$ stimulates Ca^{2+} uptake in osteoblasts depositing it as Ca^{2+}

Recommended Daily Allowance (RDA)

children - $10\text{ }\mu\text{g/day}$ (400 IU)

Adults - $5\text{ }\mu\text{g/day}$ (200 IU)

pregnancy / lactation - $10\text{ }\mu\text{g/day}$ (400 IU)

Vit D - deficiency

Normal range for circulating $25(\text{OH})\text{D}$

- $20-100\text{ ng/mL}$

< 20 ng/mL

> 150 ng/mL

Vit D deficiency causes inadequate mineralisation of bone osteoid before closure of epiphysis - Rickets in children.
after closure of epiphysis - osteomalacia

Rickets

"softening & weakening of bones in children, usually coz of an extreme & prolonged vit D def."

Rare inherited problems also can cause rickets.

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Clinical features

• failure to thrive, protruding abdomen, muscle weakness, fractures

head - craniotables, frontal bossing, delayed fontanel closure, delayed dentition, anier, craniosynostosis
↳ closed cranium

Chest

• Rachitic rosary - bead like prominence @ costochondral jn.

• Harrison groove - Horizontal groove at lower border of thorax

• respiratory infection & atelectasis

Spine

scoliosis, kyphosis, lordosis

↓
inward curvature of lumbar spine

Extremities

- enlargement of the wrists & ankles
- valgus or varus deformities
- windswept deformity
- ant. bowing of tibia & femur
- coxa vara
- leg pain

Types of rickets

Nutritional rickets Vit-D def

[Nutritional rickets]

most common cause

Serum Ca^{2+}

- need not be always low

Serum $1,25-(OH)_2 D$

- need not be always low

PTH
bring up
calcitonin
&
calcitriol
level

Serum P

- remains low

Serum PTH

- high

Serum $25-(OH) D$

- low

Vit-D dependent rickets Type I

[Pseudo Vit-D - resistant rickets]

- mutation in the gene encoding 1α hydroxylase

- autosomal recessive disorder

- prevent conversion of $25-(OH) D$ to $1,25-(OH)_2 D$

- even with high PTH, $1,25-(OH)_2 D$ is low

- usually present in first 2 yrs of life

Serum PTH -
high

Serum $1,25-(OH)_2 D$ -
low

Vitamin D dependent rickets - Type 2
(resistant to calcitriol)

due to mutations in the gene ^{en}coding the Vit D receptor causing end organ resistance to active vit D

- autosomal recessive disorder

- presents in infancy

- serum $1,25-(OH)_2 D$ -
very high



01/06/2023
Theirschen

Cont: of Vitamins

X-linked hypophosphatemic rickets (vit D resistant rickets)

- most common hypophosphatemic rickets
- x-linked dominant disorder
- defective gene is called PHEX gene (phosphate regulating gene with homology to endopeptidases on the X chromosome)
- mutation of PHEX gene lead to ↑ level of FGF-23.

Lab findings -

in
uride

Serum Ca^{2+} -
normal

Serum P -

low

Serum PTH -

normal

spasm
tany

Serum $1,25-(OH)_2 D$ -

low or normal

Autosomal dominant hypophosphatemic rickets

mutation in gene encoding FGF 23 which prevents the degradation of FGF 23 by proteases

ventan

Lab findings

same as in x linked hypophosphatemic

Autosomal recessive hypophosphatemic rickets

very rare

Uly

due to mutation in the gene encoding dentin matrix protein 1 which results in elevated level of FGF 23.

Hereditary Hypophosphatemic Rickets with Hypercalcaemia (HHRH)

- autosomal recessive disorder
- due to mutation in the gene for sodium phosphate cotransporter in the proximal renal tubule
- hypophosphatemia stimulates production of $1,25-(OH)_2D$ cause increased intestinal absorption of Ca^{2+}

Chronic renal failure (Renal rickets)

- decreased activity of 1α hydroxylase in the kidney leading to diminished prodn of $1,25-(OH)_2D$
- unlike other cause of vit D def, here patients have hyperphosphatemia.

Beneficial effects of vit D

- protective against Ca prostate, colorectal cancer, prediabetes & metabolic syndrome.

Hypervitaminosis D

- doses above 10,000 units per day for long periods.

Symptoms -

weakness, polyuria, intense thirst, hypertension & weight loss
hypercalcaemia can lead to constriction of blood vessels, $\uparrow$ BP & calcinosis (calcification of soft tissues)

Osteomalacia

- is softening of bone as a result of demineralisation.
- seen in adults (after the growth plates have fused)
- most common cause is vit D def.
- other causes are renal dysfunction, abnormalities of osteoblasts.

Rickets is characterised by continued formation of the osteoid matrix & cartilage but incomplete mineralisation resulting in soft, pliable bones. Occur in children

- Osteomalacia can be differentiated from the most common osteoporosis by the fact that osteoid matrix remains intact in the former but not in the latter.

Vitamin C

- chemical name is ascorbic acid
- antiscorbutic factor
- most animals synthesise vit C from glucose by uronic acid pathway
- humans & higher primates cannot due to absence of gulonolactone oxidase.

Chemistry

- ascorbic acid structurally similar to a monosaccharide
- it is a strong reducing agent
- water soluble
- easily destroyed by heat, alkali & storage
- in the process of cooking, 70% of vit C is lost

2 forms of vit C - L ascorbic acid & in oxidised form, dehydroascorbic acid, are biologically active and are interconvertible

D-ascorbic acid is inactive

vit C is not destroyed by freezing & steaming

benedict's test will be positive

ascorbic acid is excreted in urine unchanged or as its metabolites, diketoglu

diketogulonic acid & oxalic acid

ascorbic acid & the amino acid glycine are the major contributors of oxalates in urine

low serum levels of vit C is seen in smokers, women taking oral contraceptive pills etc.

Absorption & Storage

is absorbed from the small intestine by a carrier mediated process at the luminal surface that requires a Na^+ gradient.

ascorbic acid is by sodium dependent transporter

Dehydroascorbic acid via facilitated diffusion glucose transporters

body pool - 2g

$t_{1/2}$ = 16 days

normal plasma levels - 0.7 - 1.2 mg/dl

found in glandular tissue such as pituitary, adrenal cortex, copper luteum, & thymus have the highest amount

High amount can also be seen in WBC, lens of eye, retina, brain & in healing wounds.

Dietary sources

fresh fruits & green leafy vegetables, citrus fruit, Indian gooseberry, guava, cabbage, spinach, germinating pulses

RDA

75 mg/day (equivalent to 50 ml orange juice)

90 mg/day for males

MPR = 10 mg/day

Function of vit C

(1) Collagen form

hydroxylation of proline & lysine residues requires ascorbic acid besides molecular O_2 & Fe^{2+} .

(2) Antioxidant

Strong natural antioxidant

along with other antioxidants, such as vit E & β carotene, it prevents the development of heart d/s, cancer & slows down the process of aging

it inhibits nitrosamine formation from dietary nitrite & nitrate in the intestine.

SIC-582
Glu d

(3) Role in amino acid metabolism

ascorbic acid is essential for the formation of 5-OH tryptophan from tryptophan. 5-OH tryptophan is the decarboxylated to serotonin

Tyrosine
↓
para-hydroxy phenyl pyruvate
↓ vit C
homogentisic acid
↓ vit C
maleylacetoacetic acid → fumarate + malonate

④ Role in lipid metabolism

required for the formation of carnitine,
a transporter of LCFA into the mitochondria,
during β -oxidation

(for the hydroxylation of α -ketoglutarate to
carnitine)

• fatigue observed in vit C def. may be
due to decreased carnitine levels.

vit C is required for synthesis of bile acid
from cholesterol.

(7 α hydroxylation of cholesterol requires vit C
& NADPH as coenz.)

⑤ Role in iron metabolism

vit C reduces ferric to ferrous form of
iron, this facilitates the absorption of iron.

• it also has a role in the formation of ferritin.
(storage form of iron) & in the mobilization
of iron from it.

⑥ Role in hemoglobin metabolism.

The degradation of Hb to bile pigments &
reconversion of methemoglobin