FAT SOLUBLE VITAMINS
(VITAMIN A,D,E,K)

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VITAMIN D

Vitamin D is a derivative of cholesterol.

It can be produced in skin. UV light when falls on skin (epidermis and dermis), activates certain enzymes which convert **7-Dehydrocholesterol** molecule into **cholecalciferol** (also known as **Vitamin D_3**), which is inactive form of Vitamin D.

For activation, cholecalciferol needs to be modified. It should be hydroxylated first at carbon No. 25, and then at carbon No. 1

First hydroxylation is done in liver in hepatocytes. An enzyme in the liver named **25-hydroxylase** hydroxylate carbon No. 25 on cholecalciferol and is converted into **25-hydroxy-calciferol.**

Vitamin D can also be taken in diet from plants and animal sources e.g. egg yolk and liver. Vitamin D from plants is called **Ergocalciferol (Vitamin D_2)** while Vitamin D from animal sources is called **cholecalciferol (Vitamin D_3).** Ergocalciferol is eventually converted into cholecalciferol in the body.

The calciferol from diet also moves to liver and is hydroxylated at 25^{th} carbon.

The 25-hydroxy-calciferol (also called **pro-Vitamin D** or **calcidiol**) is still inactive. It is activated by enzyme called **1-α-hydroxylase** present in proximal convoluted tubules of kidney. This enzyme convert 25-hydroxy-calciferol into **1,25-Dihydroxy cholecalciferol (calcitriol)** which is active form of Vitamin D.

The 1-α-hydroxylase is a very well regulated enzyme. It is regulated by levels of calcium and phosphate. Phosphate (PO_4) directly influence activity of 1-α-hydroxylase. Whenever phosphate level in blood goes down, 1-α-hydroxylase is stimulated and production of 1,25-Dihydroxy cholecalciferol is increased.

When calcium level in blood goes down, it stimulate the release of parathormone. Parathormone stimulates 1-α-hydroxylase which convert pro-Vitamin D into active Vitamin D.

HOW VITAMIN D MAINTAINS LEVELS OF CALCIUM AND PHOSPHATE

Vitamin D:

1. Act on GIT to absorb more calcium and phosphate
2. Mobilize calcium and phosphate from the bone
3. Re-absorb more calcium from the renal tubules

ACTION OF VITAMIN D

1,25 Dihydroxy cholecalciferol when enter into mucosal cells of GIT binds with intracellular receptors (which serves as transcription factor), change the configuration of receptors into active receptors and form Vitamin D-Receptor complex. This complex translocates to nucleus. Inside the nucleus, this complex acts on specific genes and express them. These genes produce mRNA which produce specific proteins that helps in absorption of calcium. These proteins are called calcium-binding proteins. These calcium-binding proteins move to membrane and helps to transfer calcium from GIT to blood. With the absorption of calcium, phosphate is also absorbed.

Vitamin D (along with parathormone) also acts on bone and mobilize calcium and phosphate.

Vitamin D also re-absorb calcium from distal convoluted tubules of kidenys in same manner as it absorbs from GIT.

If in blood, calcium level is high and phosphate level is low; calcium phosphate will not deposit on bone.

If both calcium and phosphate levels are low; still calcium phosphate will not deposit on bones.

For deposition of minerals on bone; both the levels of calcium as well as phosphate should be high.

CLINICAL PROBLEMS RELATED WITH VITAMIN D DEFICIENCY

1. NUTRITIONAL RICKETS AND OSTEOMALACIA

Develop due to prolonged deficiency of Vitamin D.
(FIY: white skin makes 5 times more Vitamin D in same amount of sun than black skin)

Deficiency of Vitamin D may be due to:

1. Limited exposure to sun
2. Low intake of Vitamin D in diet
3. Problems with digestion and absorption of fat which may be due to problems in bile system or deficiency of pancreatic lipases or problems with ileum of small intestine.

DIFFERENCE BETWEEN RICKETS AND OSTEOMALACIA:

Rickets is deficiency of Vitamin D in childhood while osteomalacia is deficiency of Vitamin D in adults.

Our bones are in constant turnover i.e. new bones being made and old bones being destroyed.

In children, bones are in growing phase. Initially un-mineralized collagen is made, which is called osteoid. This osteoid should rapidly mineralize if there is enough calcium and phosphate in the blood. In the absence of calcium and phosphate, children will keep making osteoid but they are unable to mineralize this osteoid and hence develop weak bones which bend easily under pressure.

In adults, the deficiency of Vitamin D will prevent re-mineralization of bones (even though they have been mineralized at childhood). So bone will become brittle at multiple points and with little pressure, it will fracture.

2. RENAL RICKETS

- Occurs in patients who have chronic renal failure
- In proximal convoluted tubules, 1-α-hydroxylase is not present in sufficient amount and hence there is chronic deficiency of active form of Vitamin D which leads to poor mineralization of bone.
  To treat renal rickets, active form of Vitamin D also called **calcitriol** is injected in patients.

3. TOXICITY OF VITAMIN D

- When Vitamin D supplements taken in high doses for long duration of time
- Calcium and phosphate level goes high. Phosphate is usually lost in urine so the patient develops hypercalcemia, hypercalciuria and high phosphate level in urine.
- Anorexia, nausea, vomiting
- Patients are more thirsty. High level of calcium damage the ADH channels in distal convoluted tubules and hence less water is re-absorbed so patient will have polyuria due to which patient will feel thirsty.
- Stupor

(TO REMEMBER) **HIGH CALCIUM LEVELS IN BODY**

- Bones
- Stones
- Abdominal Groans
- Psychic Moans

VITAMIN A

VITAMIN A FUNCTIONS

1. Helps in growth and maturation
2. Aids vision in dim light
3. Retinoic acid Helps maintain healthy skin i.e. reduce acne
   Retinoic acid should not be prescribed in pregnancy
4. Reproductive function i.e. Spermatozoic development in males
5. Helps in development of placenta i.e. helps in pregnancy in females. Either deficiency or excess of Vitamin A, both are teratogenic.

RETINOIDS

Three forms:

1. **Retinol** – ring structure + unsaturated chain with –OH group at the end of the chain
2. **Retinal** – on oxidation, retinol converts into retinal.
   Instead of OH group, aldehyde group is present.
3. **Retinoic acid** – On oxidation, retinal converts into retinoic acid
   Retinoic acid have COOH group

The conversion of retinol to retinal is reversible.

However, retinoic acid cannot convert back to retinal.

Retinoic acid doesnot play a role in visual function and neither in reproduction. So only retinoic acid is not enough for body needs.

SOURCES OF VITAMIN A

ANIMAL SOURCES – liver oil, butter, milk, cheese, egg yolk

PLANT SOURCES – in the form of provitamin carotene, tomatoes, carrots, spinach etc.

Vitamin A is present in plants as carotene. Two molecules of retinol makes β-carotene.

ROUTE OF VITAMIN A INSIDE BODY

Retinol from animal sources is attached with long chain fatty acids i.e. they are in esterified form. Once retinol is absorbed, the long chain fatty acid is removed by pancreatic enzymes. Retinol is then absorbed in GIT.

The β-carotene also gets absorbed in GIT and converts into retinal and eventually into retinol.

Long chain fatty acid is again added to retinol and this re-esterified product move to blood along with chylomicrons. Chylomicrons are lipid-loaded particles moving from GIT into blood.

The esterified retinol along with chylomicrons move to liver. In the liver, retinol is separated from its long chain fatty acid. The retinol is either stored in liver or moved to blood for its target function.

VITAMIN A AND VISION

When Vitamin A is released into blood, it forms a Retinol-protein complex with special proteins.

The rod cells of eye have a receptor for this retinol-protein complex which helps retinol moves inside the rod cells. The retinol-binding proteins move back to liver and bind with other proteins. Hence retinol-binding proteins transport retinol molecules from liver to tissue.

In the rod cells, retinol is converted into retinal.

If side chain of retinol is straight, it is **all-trans retinol**. The all-trans retinol and retinal is converted into **11-cis-retinal**. After the 11-cis-retinal is loaded with **opsin**, it is called **Rhodopsin.**

When light falls on rhodopsin, opsin is released and all-trans configuration is restored.

When light hits rhodopsin, opsin is released, which triggers action potential in optic pathway. Rods and cones undergo ionic changes and action potential is triggered. The molecule goes back to all-trans configuration and the cycle continues.

In severe deficiency of Vitamin A, there is not enough rhodopsin and hence the person cannot see clearly in dim light and person suffers with night blindness.

VITAMIN A FUNCTION IN DEVELOPMENT

The retinol goes to epithelial cells with the help of retinol-binding-proteins. The epithelial cells requiring Vitamin A have receptors for retinol. Retinol enters inside cell and is converted into retinal. The retinal is further oxidized into retinoic acid. The molecules of retinoic acid binds with its receptors present inside the nucleus and these receptors are able to interact with DNA which activate certain genes that produce specific proteins. These proteins will eventually lead to other functions of Vitamin A.

e.g. in epithelial cells gene for keratin is activated and keratin proteins are synthesized and they help in development of epithelial cells and mucous membrane.

VITAMIN A DEFICIENCY CAUSES

1. Impaired growth
2. Under-developed skin
3. Night blindness may occur but if severe vitamin A deficiency is prolonged rods and cones may undergo degeneration
4. Xerophthalmia

RETINOIC ACID FOR ACNE

For acne retinoic acid can be applied topically as all-trans retinoic acid (along with benzoyl peroxide and some antibiotics)

In case of severe acne, Vitamin A is given orally. All-trans retinoic acid is never given orally as it is very toxic. In our body, all-trans retinoic acid is made within cells in small amount.

For oral treatment, 13-cis retinoic acid is prescribed. (not prescribed in pregnant women)

Name of Drugs

All-trans retinoic acid → Tretinoin

13-cis retinoic acid → Isotretinoin

EXCESS OF VITAMIN A

1. Skin becomes dry and pruritic (itchy)
2. Too much Vitamin A deposits on liver and damage the liver
3. Excessive amount of Vitamin A for long time cause high intracranial pressure

VITAMIN K

VITAMIN K FORMS

- From plants → Phylloquinone (Vitamin K_1)
- Produced by bacteria in GIT → Menaquinone (Vitamin K_2)
- Synthetic Vitamin K → Vitamin K_3

SOURCES

- Plants → cabbage, cauliflower, spinach
- Animals → liver, egg yolk
- Microbes in GIT

VITAMIN K AND BLOOD CLOTTING

Genes for coagulation factors are regulated in hepatocyte nuclei. mRNA are produced and after translation, proteins called **coagulation factors** are produced. **Glutamic acid** having α, β, γ carbons are present in coagulation factors. Normally glutamic acid on γ carbon has one carboxyl (COO^-) group.

Mature coagulation factors should have two γ-carboxylations at glutamic acid.

Vitamin K helps enzyme i.e. γ-Glutemyl-carboxylase to lead to **γ-carboxylation of glutamic acid residues**. Coagulation factors II, VII, IX, X and proteins C and S undergo post-translational modification i.e. Vitamin K dependent γ-carboxylation of glutamic acid residues.

Calcium (Ca^{+2}) binds mature coagulation factor to negatively charged phospholipids on platelets. Calcium then binds two mature coagulation factors together. In this way coagulation factors can bind to each other and coagulation cascade can begin.

In severe deficiency of Vitamin K, coagulation factors can be produced but γ-carboxylation of coagulation factors does not take place.

The enzyme γ-Glutemyl-carboxylase is dependent on Vitamin K (hydroquinone). Hydroquinone itself convert into Vitamin K epoxide after carboxylation. Vitamin K epoxide is converted back into hydroquinone by enzyme Vitamin K epoxide reductase. **Warfarin** is a drug which inhibits the enzyme Vitamin K epoxide reductase.

DEFICIENCY OF VITAMIN K

1. In adults, Vitamin K deficiency can occur if microbial flora is killed which usually occurs when broad spectrum antibiotics are taken.
2. Antibiotics like cephalosporin work like warfarin and inhibits Vitamin K Epoxide reductase and produce functional deficiency of Vitamin K
3. New born have tendency of Vitamin K defieciency due to
   a) Low vitamin K intake from maternal source
   b) GIT in new born is sterile

TOXICITY OF VITAMIN K

Toxicity of Vitamin K is rare and less common but may lead to damage to RBCs and hemolysis. In hemolysis, lots of bilirubin is produced which leads to some degree of jaundice.