36

Sheet Slides

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Vitamins Introduction

- Vitamins are **organic** molecules which are **vital** and **essential** micronutrients that an organism needs in small quantities for the proper functioning of its metabolism. An essential nutrient is a nutrient required for normal physiological function that **cannot** be synthesized in the body – either at all or in sufficient quantities - and therefore must be obtained through the **diet**.

- The term "naming" is **conditional** both on the organism and on the circumstances. It is called a **vitamin** if:

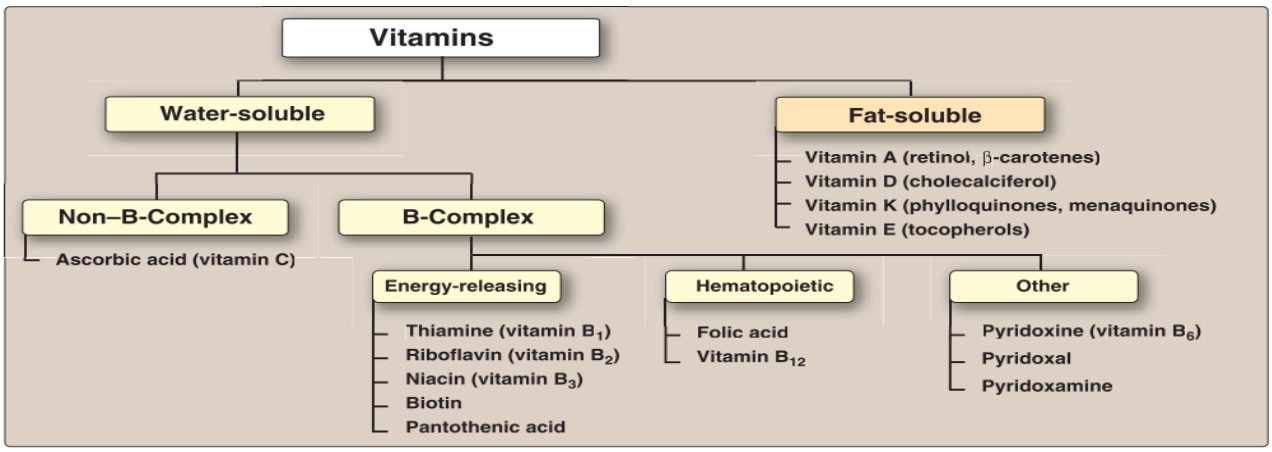
  1- It is **required** in the **diet**, e.g. **ascorbic acid** is **required** in the **human** diet and is called **Vitamin C.** However, in **animals** *(e.g. dogs)* it is **not** required and thus it is termed as **ascorbic acid**. Same for vitamin B and vitamin D which are required in the human diet - *only in certain circumstances* -.

  2- It may be **synthesized** in the organism under **normal** physiological conditions, thus, **not** calling it a vitamin. However, in certain conditions *(e.g. body stops synthesizing)* it may become **vital** and will be considered a **vitamin**.

- The **inability** of an organism to **produce** a certain vitamin doesn't necessarily mean that vitamins are **not** synthesized inside that organism. It means that there is **no** special pathway for producing that vitamin **inside** the organism's **cells**, but it might be synthesized by an **external source** *(e.g. bacteria living inside the human intestine)*

- **Vitamers**, are compounds that are converted to the active form of a vitamin in the body.

- There are **13** vitamins in total, categorized into **fat** and **water-soluble** vitamins:



a- 9 Water-soluble Vitamins *(which we took over the last semester)*

→ Vitamins C and B 1/2/3/5/6/7/9/12

- They are readily **excreted** in the urine.
- They act as **coenzymes** and are **not** stored in the body.
- Toxicity arising due to excess amounts of water-soluble vitamins is **rare**.

Water soluble vitamins

Vitamin	Coenzyme	Consequences of deficiency
Thiamine (B_1)	TPP	
Riboflavin (B_2)	FAD	Angular stomatitis (mouth lesions)
Nicotinic acid (niacin) (B_3)	NAD^+	
Pantothenic acid (B_5)	CoA	
Pyridoxine (B_6)	PLP	
Biotin (B_7)		
Folic acid (B_9)	TH4	Megaloblastic anemia
Cobalamin (B_{12})	5'-Deoxyadenosyl cobalamin	Megaloblastic anemia
Ascorbic acid (C)		Scurvy

b- 4 Fat-soluble Vitamins *(discussed through this sheet)*

→ Vitamins A, D, E, K

- They are **not** readily **excreted** in the urine.
- They have **long chain of carbons** unlike water soluble vitamins.
- They are released, absorbed, and transported with **fats**.
- They are **stored** in the **liver** and **adipose tissue.**
- Overdoses of fat-soluble vitamins may lead to **toxicity.**

Vitamin	Main function	Deficiency
A	Roles in vision, growth, reproduction	Night blindness, cornea damage
D	Regulation of Ca^{+2} & phosphate metabolism	Rickets (children), Osteomalacia (adults)
E	Antioxidant	RBCs fragility
K	Blood coagulation	Subdermal hemorrhaging

- As opposed to water-soluble vitamins, a fat-soluble vitamin has **no single** common defining structure, instead, they're a group of chemically **related** compounds performing a **similar** function.

- Vitamins have diverse biochemical **functions**:

  a- Hormone-like functions (regulators): Regulators of mineral metabolism *(e.g. vitamin D),* or regulators of cell & tissue growth & differentiation *(e.g. vitamin A).*

  b- Vitamins E & C: Anti-oxidants, they fight free radicals which are not stable and tend to hit any unstable molecule to stabilize it.

  c- Vitamin B subclasses: Precursors for enzyme cofactors.

Vitamin A

- Vitamin A is a group of **unsaturated** organic compounds, called **retinoids**, that includes **retinol**, **retinal** and **retinoic acid**.

- Vitamin A has multiple functions: it is important for **growth**, **reproduction**, **maintenance** of the epithelial tissue and **good vision**.

Vitamin A (Retinoids) Sources:

From animal sources → Liver, kidney, cream, butter, and egg yolk.

From plant sources → In the form of β-carotene; a red-orange pigment found in plants and fruits, especially carrots and colorful vegetables.

Vitamin A Structure:

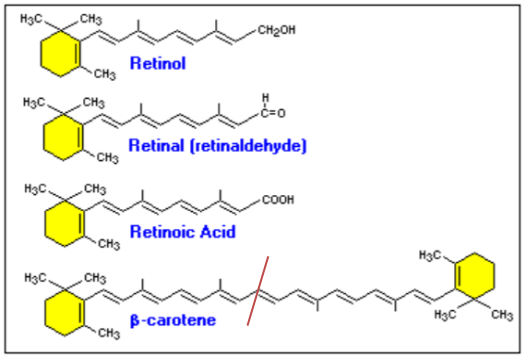
- As mentioned, retinoids can be found in **4 forms**:

1- **Retinol** which is a **primary alcohol.**

2- **Retinal** which is an **aldehyde**.

3- **Retinoic acid** which is a **carboxylic acid.**

4- **β-carotene** which is broken down in the intestines to yield **2 retinal** molecules, which is why β-carotene is also called **provitamin A**.
(as shown in the figure, discussed more later).



- **Retinol** is the form of vitamin A acquired in the diet from animal tissue ingestion, it is a primary **alcohol** and can be **oxidized** to **retinal**. Retinal can be reduced back to retinol, thus they can be **interconvertible**.

- However, **retinal** can be oxidized to **retinoic acid** but it **can't** be reduced back to **retinal** due to the absence of a reductase in our body.

  This indicates that retinol and retinal have **similar** functions in the body that are **different** from the functions of retinoic acid.

  Retinal and Retinol→ For **vision** and **spermatogenesis**.

  Retinoic acid → Mediates **most** of the actions of the retinoids, mainly differentiation and proliferation of cells.

Absorption and Transport of Vitamin A:

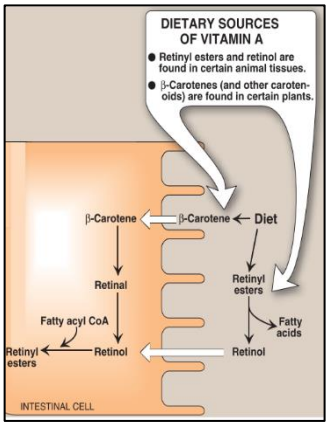
1- Vitamin A can be acquired from the diet as:

A- Retinyl Esters with long FA chains, from animal sources:

→ They are **first** hydrolyzed in the intestinal mucosa, yielding **retinol** and **FA**.

→ Retinol then is **absorbed** by intestinal cells, while long FA chains **can't** be absorbed.

→ Retinol inside the cells is **re-esterified** and Fatty acyl CoA donates FA forming **Retinyl ester** again.



B- β-carotene (provitamin A), from plant sources:

- → It is absorbed by the intestinal cells **without** modification.
- → In the intestinal cells, it is broken down to give **2** molecules of **retinal**.
- → The retinal molecules are **reduced** forming **retinol**.
- → The retinol molecules are then esterified to give **Retinyl esters**.

Both forms end up in forming Retinyl esters.

2- Retinyl esters are then **transported** from the intestinal cells to the **liver**, through the lymphatic system and blood, by **chylomicrons**, where in the liver it can be **stored** as **Retinyl esters**.

3- When in **need** of vitamin A, the Retinyl esters are **hydrolyzed** to give **retinol** which is then transported to **extra hepatic tissue**.

4- Retinol is highly **hydrophobic**, it can't be transported in the blood freely. Thus, they are transported through a Retinol Binding Protein (RBP) named **transthyretin** (TTR); *transported as Retinol-RBP complex.*

(Refering to the figure in the next page would make this much easier)

Mechanism of Action of Vitamin A:

In Tissues: *(refer to a more detailed figure in Lippincot page 384)*

After being transported as **retinol-RBP** and reaching **target tissues**, the complex is **broken** down releasing **retinol** to be absorbed and then **oxidized** to **retinoic acid**.

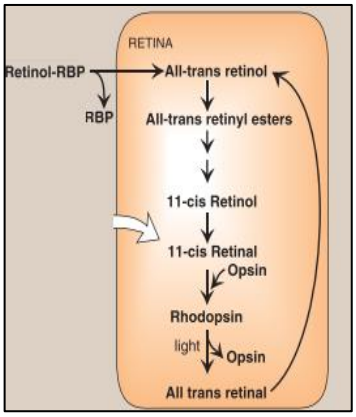
1- **Retinoic acid** then binds with high affinity to specific **nuclear receptors** of target tissues, such as epithelial cells.

2- Activated retinoic acid receptor complex interacts with nuclear chromatin by binds to transcription factors that regulates RNA synthesis, **controlling gene expression**, **stimulating** or **inhibiting** them, *e.g. regulating gene for keratin in most epithelial tissues of the body*.

In the Retina:

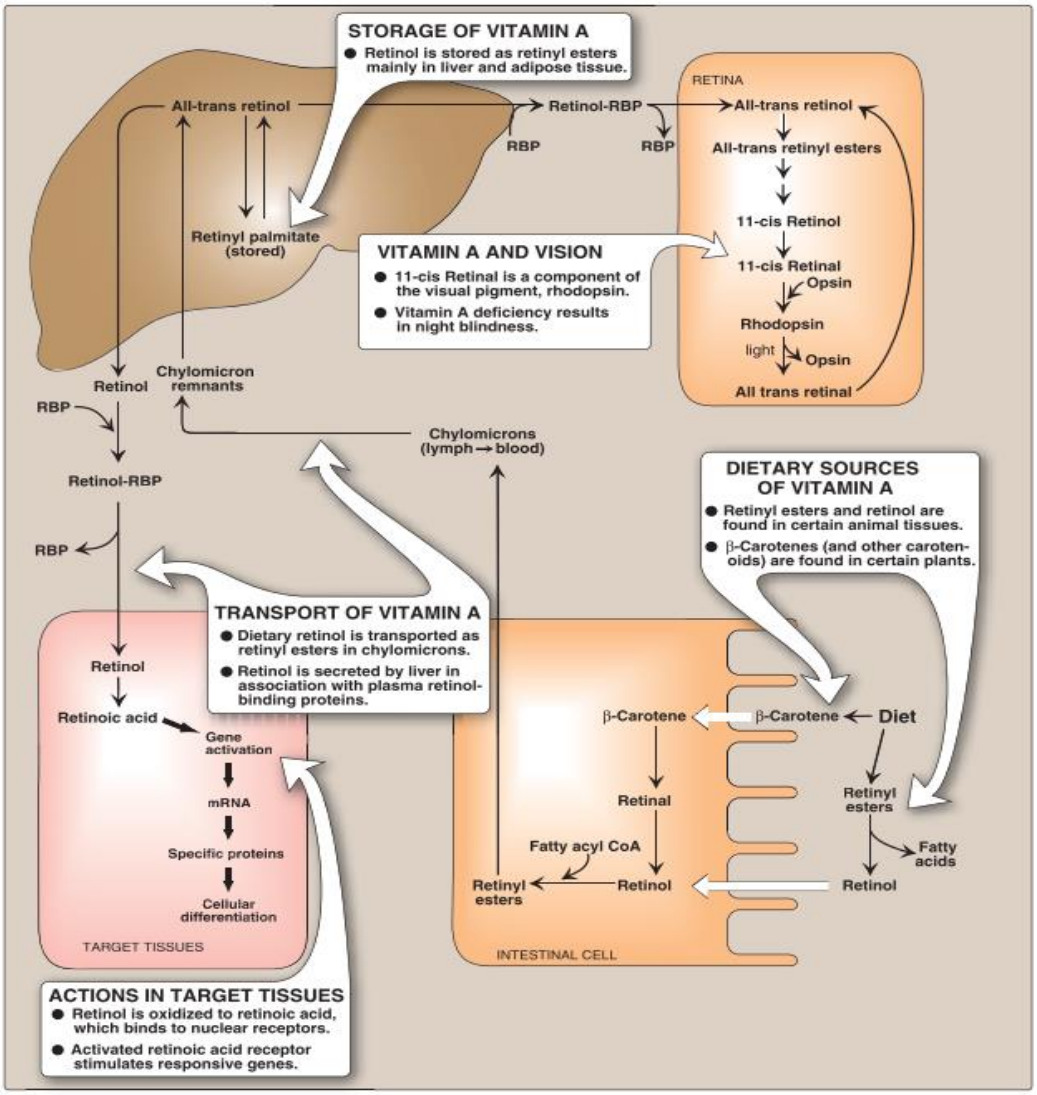
1- Retinol is **oxidized** to retinal, which binds to **opsin**, forming **Rhodopsin** which is the visual pigment of the rod cells in the retina.

2- When rhodopsin is exposed to light, retinal and opsin are released from rhodopsin and this activates a **G-protein** which then triggers a **nerve impulse**.



Note: *Rhodopsin is a biological* ***pigment*** *found in the* ***rods*** *of the retina and is a G-protein-coupled receptor involved in* ***visual phototransduction****. It is extremely* ***sensitive*** *to* ***light****, enabling vision in* ***low-light conditions.***

Summary of Metabolism, absorption and action of Vitamin A



Functions of Vitamin A:

1- **Visual cycle**: 11-cis Retinal specifically binds with the protein opsin forming **rhodopsin**.

2- **Reproduction**: Retinol and retinal (not retinoic acid) are essential for **spermatogenesis** in the male and in preventing **fetal resorption** in the female.

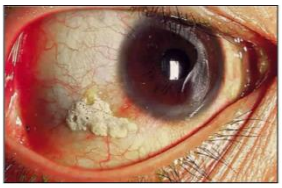
3- **Growth** (retinoic acid): Vitamin A deficiency results in a decreased growth rate and bone development in children.

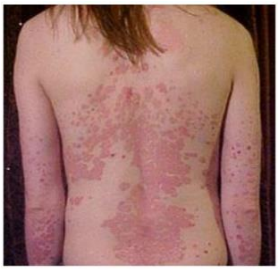
4- **Maintenance of epithelial cells** (retinoic acid): Vitamin A is essential for normal differentiation of epithelial tissues & mucus secretion.

Note: *Animals given vitamin A* ***only*** *as* ***retinoic acid*** *from birth, were* ***blind*** *and* ***sterile****.*

Clinical Indications:

- Vitamin A deficiencies **aren't** usually **fatal**. However, it can cause **severe** symptoms. Deficiency in vitamin A, prevents the eye cells from **maturing** and differentiating normally. Also, it prevents the formation of **rhodopsin**; which is responsible for phototransduction.
  - **a- Mild deficiency:** Causes **night blindness** (nyctalopia) as the visual threshold **increases** from the **decrease** in rhodopsin level.
  - **b- Prolonged deficiency:** Causes **scarring** of the eye which leads to **irreversible** loss of some visual cells.
  - **c- Severe deficiency:** Leads to **Xerophthalmia**, which is the ulceration and dryness of conjunctiva and cornea, followed by scarring and blindness. It affects over 500,000 children worldwide every year.





- Since **Retinoic acid** is a regulator for protein synthesis or **gene expression**, it is prescribed for issues caused by **over expression** which lead to **over production**, such as **dermatologic** problems including **acne** and **psoriasis**.

> ***Note:*** ***Retinol*** *and its precursor are used as* ***dietary*** *supplements, whereas various forms of* ***retinoic acid*** *are useful in* ***dermatology****.*

Toxicity of Retinoids:

- Excessive amounts of **fat-soluble** vitamins may lead to many diseases.
- Excessive intake of any fat-soluble vitamin is termed **hypervitaminosis X**, where X is replaced by the letter of the vitamin, *ex: hypervitaminosis A is excessive vitamin A.*
- **Hypervitaminosis A leads to:**
  - **a- Dry skin,** due to a decrease in keratin synthesis.
  - **b- Enlargement of the liver**, which can become cirrhotic.
  - **c- A rise in the intracranial pressure** in the CNS where it might mimic a brain tumor.
- Pregnant women shouldn't ingest excessive amount of vitamin A as it is **teratogenic**; meaning it might cause congenital malformations in the developing fetus.

Vitamin D

- The D vitamins are a group of **sterols** that have a **hormone-like function**.
- The active form of Vitamin D is: **1, 25-dihydroxycholecalciferol** (1,25-diOH-D3).
- It binds to **intracellular** receptor proteins, interacting with DNA in the nucleus of target cells in a manner similar to that of vitamin A, which **stimulates** gene expression or **represses** gene transcription.
- The most prominent action of 1,25-diOH-D3 is to **regulate the plasma levels of calcium and phosphorus.**

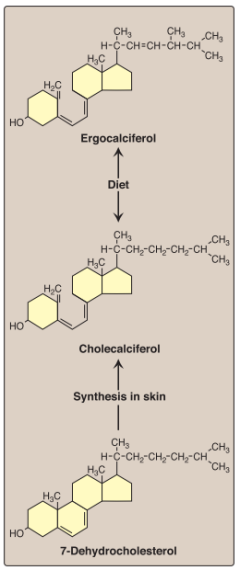
Vitamin D Sources:

1- **Diet (Exogenous): Ergocalciferol** *(vitamin D2),* found in **plants**.
Chole-calci-ferol *(vitamin D3)* → in **animal** tissues.

> ***Note:*** *Ergocalciferol and cholecalciferol differ chemically only in the presence of an additional **double bond** and **methyl** group in the **plant sterol (Vit. D2).***

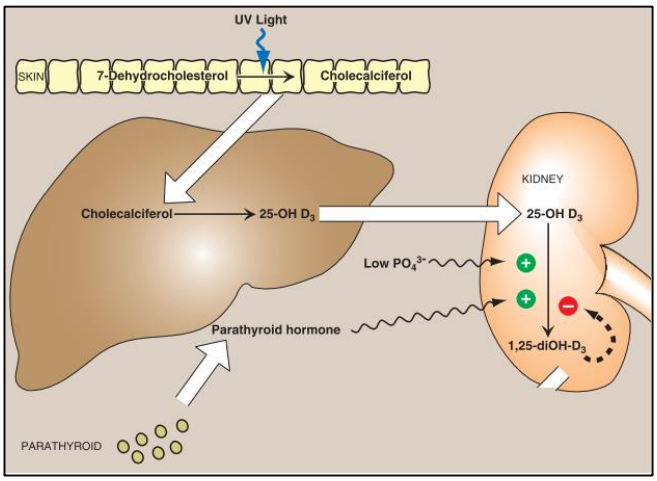
2- **Endogenous**: 7-Dehydrocholesterol, *an intermediate in cholesterol synthesis*, is converted to **cholecalciferol** in the **dermis** and **epidermis** of humans when exposed to **sunlight**.

> ***Note:*** *Vitamin D is a dietary **requirement** only in individuals with **limited exposure to sunlight**.*



Metabolism of vitamin D:

- Vitamins D2 and D3 are **not active**. They are converted to the active form *1,25-diOH-D3* by **two** sequential **hydroxylation** reactions:



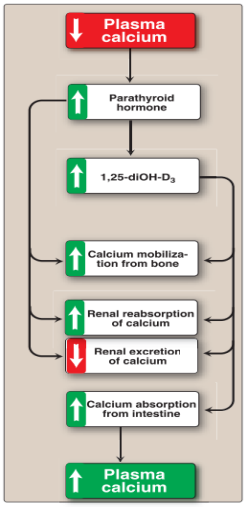
1- **The first hydroxylation** occurs in the **liver** where **cholecalciferol** is hydroxylated at the **25-position**, catalyzed by **cholecalciferol 25-hydroxylase**.

> ***Note:*** *The product of the reaction,* ***25-hydroxy cholecalciferol*** *(25-OH-D3, calcidol) is the* ***predominant*** *form of vitamin D in the* ***plasma*** *and the* ***major storage form*** *of the vitamin.*

2- **The second hydroxylation** reaction occurs in the **kidney** where 25-OH-D3 is further hydroxylated at the **1-position** by 25-hydroxycholecalciferol 1- hydroxylase, resulting in the formation of 1,25-diOH-D3 *(calcitriol).*

- The 1-hydroxylation reaction is **tightly regulated**:
  - **a- Increased directly** by **low levels** of **phosphate** ions present in the serum.
  - **b- Increased indirectly** by **low plasma levels** of **Calcium,** where it stimulates the production of the parathyroid hormone (PTH), which **upregulates** the 1-hydroxylase.
  - **c- Feedback inhibition**, where the **product** (*1,25-diOH-D3),* **inhibits** the 1-hydroxylase.

Functions of vitamin D:



- The overall function of 1,25-diOH-D3 is to **maintain** adequate plasma levels of **calcium**:
  - **a- Increasing** uptake of calcium by the **intestine**.
  - **b- Minimizing** loss of calcium by the **kidney**.
  - **c- Stimulating** resorption of **bone** when necessary.

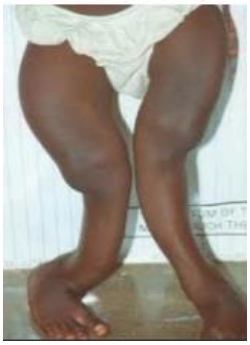
> ***Note:*** *Vitamin D has the* ***same functions*** *as the* ***PTH****. This is why Vit. D is given to people who* ***can't*** *produce PTH.*

Clinical Indications:

1- **Nutritional Rickets**: **Insufficient exposure** to daylight and/or **deficiencies** in vitamin D **consumption** occur predominantly in **infants** and the **elderly**. It leads to the **loss** of calcium ions in the serum *(Recall the functions of Vit. D),* which leads to the **demineralization** of bone.

a- Rickets in children:

→ **Continuous** formation of the collagen matrix of bone with **Incomplete mineralization**. → Soft, pliable bones.



b- Osteomalacia in adults:

→ **Demineralization** of pre-existing bones increasing their susceptibility to **fracture**.

2- **Renal Rickets** *(renal osteodystrophy)*: Chronic renal failure results in decreased ability to form the active form of vitamin D.

> ***Note:*** ***Hypoparathyroidism*** *is the lack of PTH.*

Toxicity of Vitamin D:

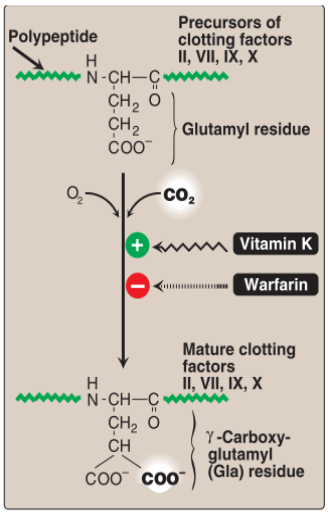
- High doses of vitamin D leads symptoms like **loss** of appetite, **nausea**, **thirst**, and **stupor** *(which is a state of unconsciousness).*
- It can also cause **hypercalcemia**, which leads to calcium deposition in the body, which leads to **atherosclerosis** in the **arteries** and **stones** in **kidneys**.

Vitamin K

- Vitamin K is a group of **quinones** since their structures contain a cyclic **di-ene** molecule.
- Vitamin K is an **exception** to the lipid soluble vitamins; all are **not** coenzymes **except K**.

Vitamin K function:

- Vitamin K is required in the **hepatic synthesis** of **prothrombin** and **blood clotting factors** II, VII, IX, and X.
- Blood clotting factors are synthesized as **inactive** precursor molecules. Vitamin K is needed as a **coenzyme** in the **carboxylation** of certain glutamic acid residues *(present in the precursors of the clotting factors)* forming **mature** blood clotting factors containing γ-carboxyglutamate (**Gla**).



→ More **negative** charges due to carboxylation, allows the **mature** clotting factors to be able to bind to **calcium** ions.

→ Allowing them to bind to **platelets**, leading to **platelet aggregation.**

- The formation of Gla is sensitive to inhibition by **Warfarin.**

Vitamin K exists in several forms:

a- **In plants**: as phylloquinone *(vitamin K1).*

b- **Intestinal bacterial flora** as menaquinone *(vitamin K2).*

c- Present in low concentration in **milk**

Clinical Indications:

1- Deficiency of vitamin K

A true vitamin K deficiency is **unusual**, because adequate amounts are generally produced by **intestinal bacteria** or obtained from the **diet**.

If the bacterial population in the gut is decreased, for example, due to **antibiotics**, the amount of endogenously formed vitamin is **depressed**, and this can lead to **hypoprothrombinemia** *(deficiency in blood prothrombin factor II).*

This condition may require **supplementation** with vitamin K.

2- Deficiency of vitamin K in the newborn

Newborns have **sterile intestines** and so initially **lack** the bacteria that synthesize vitamin K.

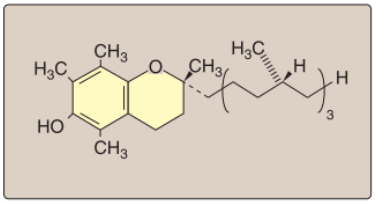
Because human milk provides only about **20%** of the daily requirement for vitamin K, it is recommended that all newborns receive a single **intramuscular dose** of vitamin K as a prophylaxis against hemorrhagic disease.

3- Toxicity of vitamin K

Prolonged administration of large doses of vitamin K can produce **hemolytic anemia** and **jaundice** in the infant, due to toxic effects on the membrane of red blood cells; therefore, it is no longer used to treat vitamin K deficiency.

Vitamin E

- The E vitamins consist of **eight naturally** occurring **tocopherols**, of which **α-tocopherol** is the most active.
- The primary function of vitamin E is as an **antioxidant** against free radicles.



Vitamin E deficiency

- Vitamin E deficiency is **rare** as it is needed in **very small** amounts. It is almost entirely restricted to **premature infants** *(not every premature infant, but only those who are born around the 6th month of pregnancy)*. When observed in adults, it is usually associated with defective lipid absorption or transport.
- The signs of human vitamin E deficiency include sensitivity of erythrocytes to peroxide, and the appearance of abnormal cellular membranes.

"No matter how hard you guys try, we are not going to survive".

Best Wishes ♥