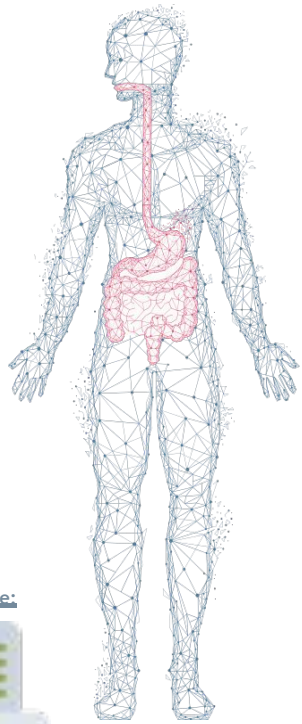
L8:

Biochemistry of vitamin K

GNT Block



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Objectives:

- Identify the types and sources of vitamin K
- Understand the role of vitamin K in blood Coagulation
- Recognize the importance of g-carboxylation of glutamic acid in coagulation proteins
- Understand the role of anticoagulant drugs in affecting vitamin K function
- Discuss the causes and disorders of vitamin K deficiency

Lecture presented by :

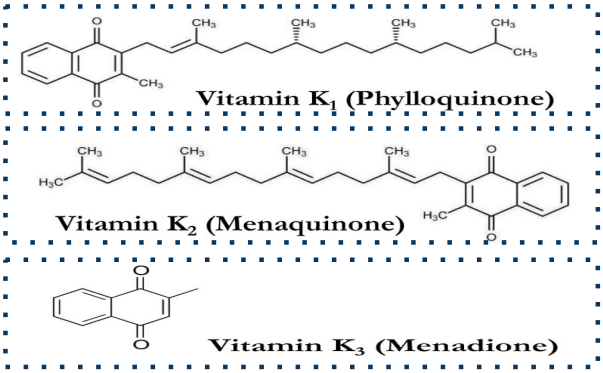
Dr. Sumbul Fatma

Dr. Khalid Alsumaily

Types & Sources

Occurs in several forms:

1. Vitamin K1 (Phylloquinone)
2. Vitamin K2 (Menaquinone)
3. Vitamin K3 (Menadione)



Dietary sources:

→ Cabbage, kale, spinach, egg yolk, liver

Sources of Vitamin K:

1. Phylloquinone: Green leafy vegetables
2. Menaquinone: Intestinal bacteria
   - Intestinal bacterial synthesis meets the daily requirement of vitamin K even without dietary supplement
3. Menadione: synthetic form
   - A precursor of menaquinone
     (toxic as a supplement and not used anymore)

RDA & Functions

RDA stands for recommended daily amount

Children
1-8 years: 30-55 (ug/day)

Woman
(19+): 90 (ug/day)

Upper Limit: Not established

RDA 01 02 03 04 05

Infants
0-1 year: 2-2.5 (ug/day)

Men
(19+): 120 (ug/day)

Pregnancy/Lactation
90/90 (ug/day)

Functions of Vitamin K:

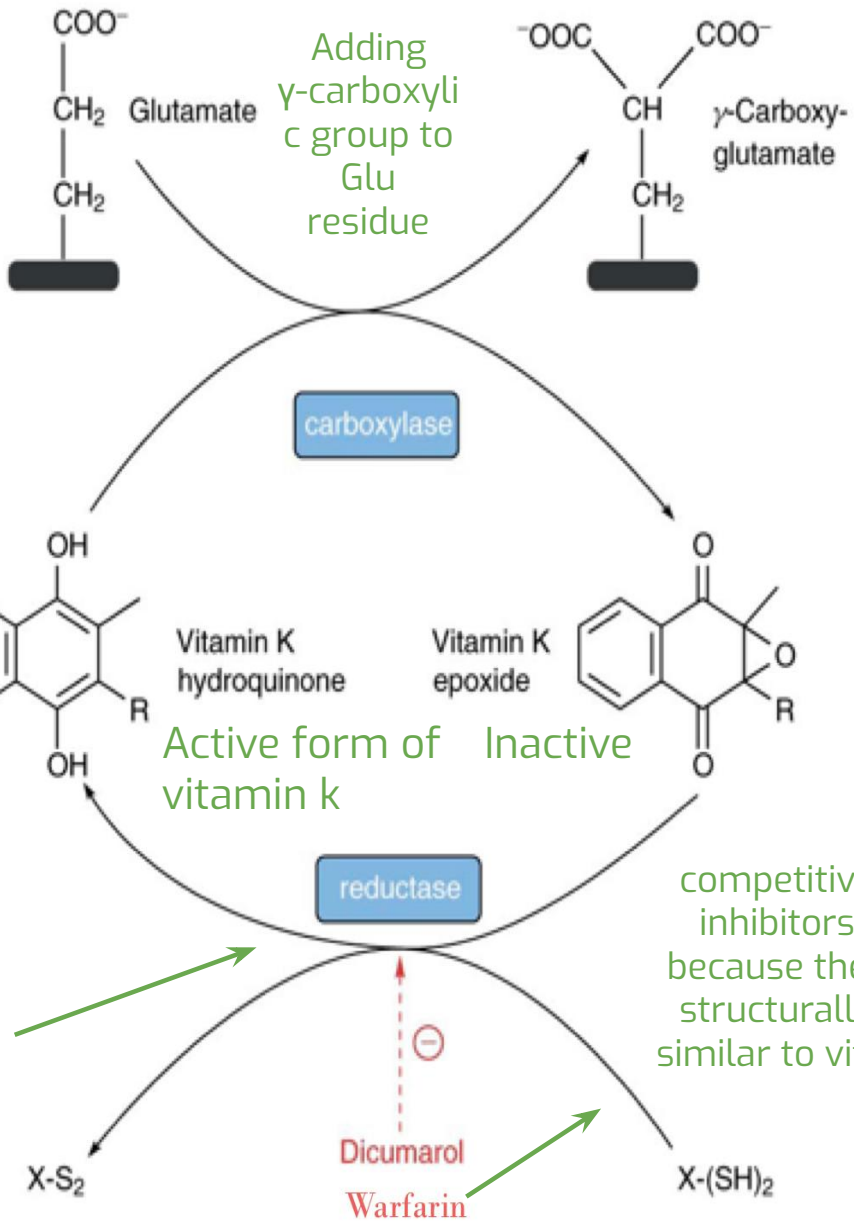
1. **Coenzyme** for the synthesis of **prothrombin** and **blood clotting** factors in the liver.
2. Prothrombin and clotting factors are **protein** in nature.
3. Synthesis of prothrombin, clotting factors II, VII, IX, X require **carboxylation** of their **glutamic acid (Glu) residue**.
4. Mature prothrombin and clotting factors Contain γ-carboxyglutamate (Gla) after carboxylation reaction.
5. Vitamin K is essential for the carboxylase enzyme involved as coenzyme.
6. **Dihydroquinone** form of vitamin K is essential for this reaction.

Functions of Vitamin K

Special thanks to 442

-if the epoxide form doesn't get converted to hydroquinone the coagulation time will increase and this is called "functional deficiency of vitamin K" despite vitamin k is actually abundant

clotting factor protein In inactive form



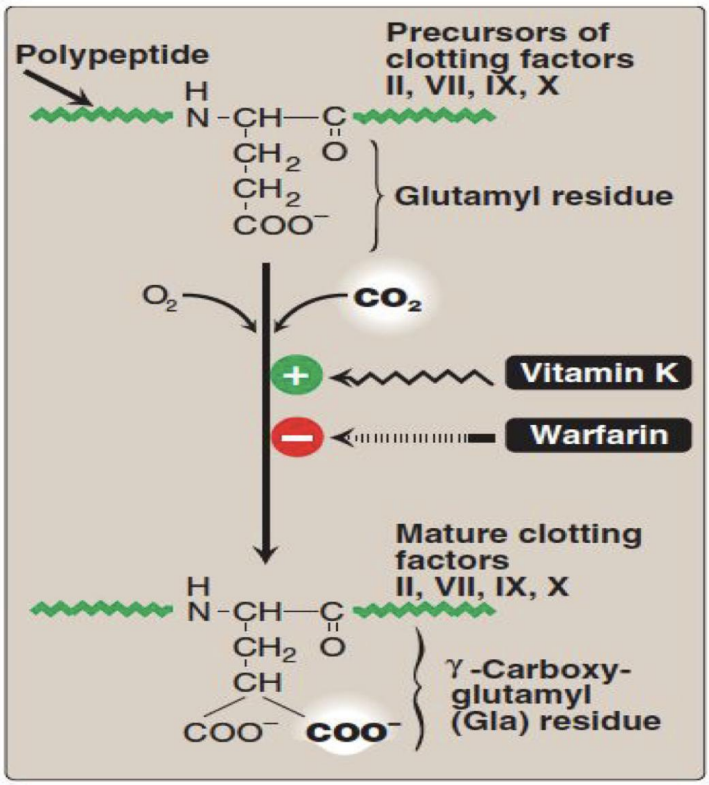
Active form

Anticoagulants Prolong the coagulation by inhibiting reductase

competitive inhibitors because they structurally similar to vit K

Analogs of Vitamin K

- **Anticoagulant drugs**: warfarin and dicoumarol (Structural analogs of vitamin K)
- They inhibit the activation of vitamin K to **hydroquinone** form (inhibiting the reductase enzyme)
- Prothrombin and clotting factors are not carboxylated
- Hence blood coagulation time **increases** upon **injury**



- Carboxylation of glutamate requires vitamin K
- The process is inhibited by warfarin

Function of Vitamin K

Functions of Vitamin K:

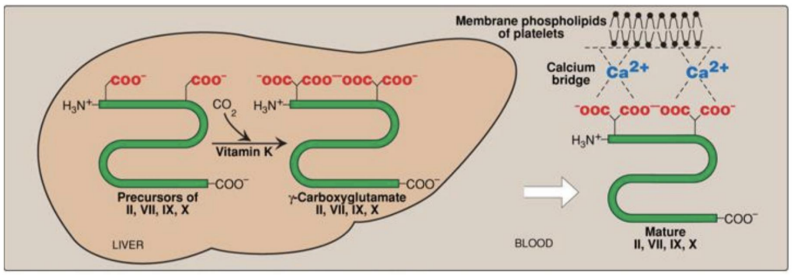
Important

prothrombin - platelet interaction:

- Carboxylated prothrombin contains 2 carboxylate groups (COO^-)
- These groups bind to Ca^{2+}, forming prothrombin-calcium complex
- The complex then binds to phospholipids on the surface of platelets (important for blood clotting)
- Converting prothrombin to thrombin and initiating clot formation

Synthesis of γ-carboxyglutamate in osteocalcin:

- Osteocalcin (Also called Bone Gla Protein "BGP") is a bone turnover protein
- Involved in bone formation, mineralization and resorption
- **γ-Carboxyglutamate** is required for osteocalcin binding to hydroxyapatite (a calcium mineral) in the bone.
- The binding mechanism is similar to that of prothrombin-platelet binding



439 Doctor explanation here!

Deficiency of Vitamin K

- Deficiencies are rare because Vitamin k is synthesized by intestinal bacteria.

Causes of vit K deficiency:

- Lipid malabsorption can lead to vitamin K deficiency
- Some second-generation cephalosporin drugs for long time cause this condition due to 02 warfarin-like effects (antibiotics given with vit. K)
- Prolonged antibiotic therapy Especially in marginally malnourished individuals (eg debilitated geriatric patients)
- Gastrointestinal infections with diarrhea
- Both of the above destroy the bacterial flora leading to vitamin K deficiency

Female Dr: Vit K is vital for Ca binding, so when there is a deficiency of it, people may have high Ca levels in their blood, and it may deposit in their arteries, causing heart problems. matrix gla protein (mgp) prevent the calcification by binding to the Ca. y of Vitamin K

Clinical Manifestations of the Deficiency:

- Mucus membrane hemorrhage
- Hemorrhagic disease of the newborn (called VKBD: vitamin k bleeding deficiency)
- Post-traumatic bleeding / internal bleeding
- Bruising tendency, ecchymotic patches (bleeding underneath the skin)
- Prolonged prothrombin time

Deficiency of Vitamin K

Deficiency most common in newborn infants:

1. Newborns lack intestinal flora
2. Human milk can provide Newborns lack intestinal flora only 1/5th vitamin K lack intestinal flora
3. Supplements are given intramuscularly at birth

vit. k cannot pass the placenta

Effects of Vit K deficiency:

1. Bone growth and mineralization
2. Hypoprothrombinemia: ↑ blood coagulation time

Toxicity of Vitamin K:

- Prolonged supplementation of large doses of menadione can cause:

1. Hemolytic anemia
2. Jaundice

- Due to toxic effects on RBC membrane

how so? Vit.k is important for synthesis which prevents the accumulation of toxic ROS

Take home messages

- Vitamin K is essential for blood coagulation process
- It mediates the process by γ-carboxylation of glutamic acid residues of prothrombin and coagulation factors

Doctor’s explanation 439

- liver synthesizes all the precursors of prothrombin.
- Once the precursors are formed, they’re not in their active form, they contain only one carboxyl group.
- An additional carboxyl group is added by the vitamin k reaction by carboxylase.
- The molecule will have 2 carboxyl groups after the reaction and will go to the circulation and combine with calcium.
- The calcium complex will interact with the membrane phospholipids of the Platelets
- Dr question: why add one more carboxyl group? Because the valency of calcium is 2 so it can bind to 2 cooh (to complete the calcium binding)

Quiz

MCQs

Q1: All the following conditions produce a real or functional deficiency of vitamin K except?

A- Prolonged oral,broad spectrum antibiotic therapy
B- Total lack of red meat in diet
C- Total lack of green leafy vegetables in diet
D- Being a newborn infant

Q2The vitamin that is synthesized by bacteria in the intestine is?

A- D
B- A
C- K
D- C

Q3:Large doses of vitamin K (toxic dose) can cause?

A- Prolonged bleeding
B- Porphyria
C- Bone growth defects
D- Jaundice

Q4:The form of vitamin K that is required for activation of clotting factors is?

A- Dihydroquinone
B- Phylloquinone
C- Menaquinone
D- Menadione

Q5:Vitamin K is required for?

A- Change of prothrombin into thrombin
B- Synthesis of prothrombin
C- Change of fibrinogen to fibrin
D- Formation of thromboplastin

Q6:Vitamin K is a cofactor for?

A- Synthesis of tryptophan
B- Formation of γ-amino butyrate
C- ß-Oxidation of fatty acid
D- γ-carboxylation of glutamic acid residue

Answers:1-B ,2-C ,3-D 4-A ,5-B ,6-D

SAQ

Q1:Carboxylation of glutamate requires what?and its inhibited by?

A. Vitamin K , Inhibited by Warfarin

Q2: Name the sources of Vitamin K?

A.Slide 3

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Team Leaders

Remas Aljeaidi

Raghad Alhamid

Mohammed Alqutub

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- Wafa Alakeel
- Madawi Alhussain
- Leen K Althunayan
- Dana A Alkheliwi
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- Sarah Alajaji
- Waad alqahtani

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Biochemistry.med443@gmail.com