Vitamin K

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Editing File

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

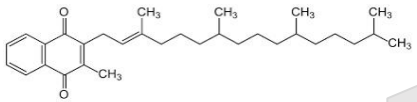
Overview:

- Types, chemistry and sources of vitamin K
- Functions:
  - Synthesis of γ-carboxyglutamate in:
  - Prothrombin and blood clotting factors
  - Interaction of prothrombin with platelets
  - Osteocalcin
  - Protein C and S (anticoagulant proteins)
- Sources and daily requirements
- Deficiency and disorders
- Clinical manifestations

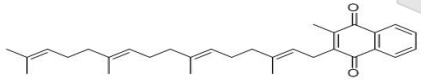
Types and Sources

Occurs in several forms:

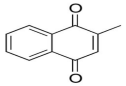
- Vitamin K_1 (Phylloquinone) — Chemistry



- Vitamin K_2 (Menaquinone) — Chemistry



- Vitamin K_3 (Menadione) — Chemistry



RDA for Vitamin K (mg/day)

- **Infant (0-1 year):** 2-2.5
- **Children (1-8):** 30-55
- **Upper limit:** Not established
- **Men (19+):** 120
- **Pregnancy / lactation:** 90
- **Women (19+):** 90

01 **Phylloquinone**: Green leafy vegetables

02 **Menaquinone**: Intestinal bacteria
- Intestinal bacterial synthesis meets the daily requirement of vitamin K even without dietary supplement

03 **Menadione**[1]: Synthetic form
- A precursor of menaquinone (look at the chemistry for both of them)

1- No more use as supplement, because of ↑ in toxicity and now we use phylloquinone for supplementation

Dietary sources:

Cabbage, kale, spinach, egg yolk, liver


Cabbage


Kale


Spinach

Functions of Vitamin K

Coenzyme for the synthesis of prothrombin and blood clotting factors in the liver

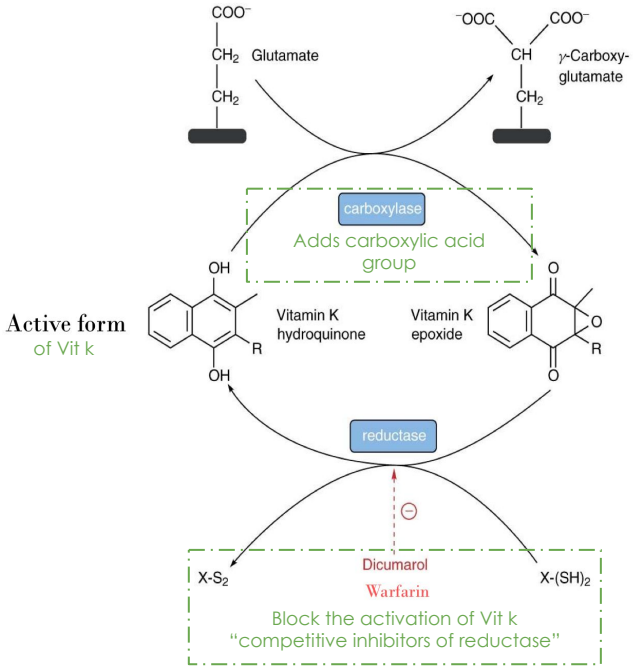
Prothrombin[1] and clotting factors are protein in nature.

Synthesis of prothrombin[1], clotting factors II, VII, IX, X require carboxylation of their glutamic acid (Glu) residue.

Mature prothrombin and clotting factors contain g-carboxyglutamate (Gla) after carboxylation reaction.

Vitamin K is essential for the carboxylase enzyme involved.

Dihydroquinone form of vitamin K is essential for this reaction.



- If Vit K is in it's epoxide form and can't get back to it's hydroquinone form → decrease clotting factors and increase prothrombin time.
- Quinone form epoxide isn't active so even vit K needs to get activated by being reduced again into hydroquinone "active form" with the help of the enzyme reductase.
- Carboxylase enzyme is also called epoxidase since it turns vit k to epoxide form.

1- Prothrombin = coagulation factor II

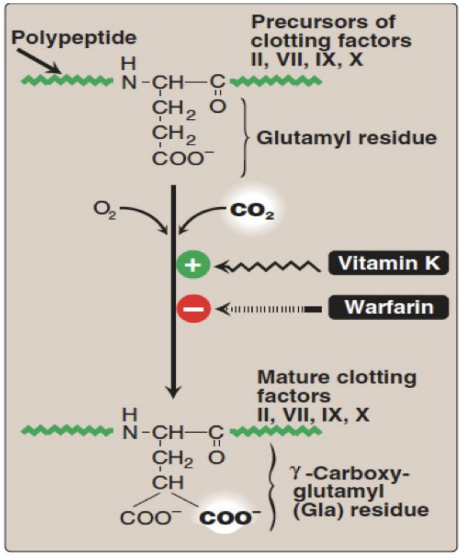
Analogs of Vitamin K

- 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

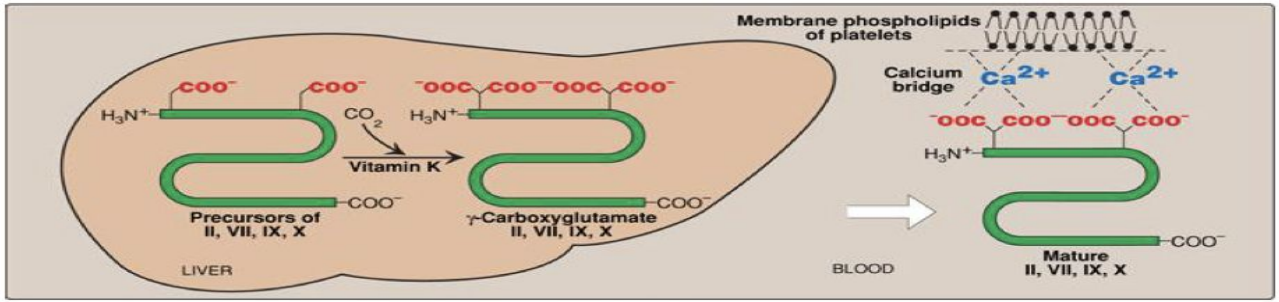
- The process is inhibited by warfarin

Functions of Vitamin K

Prothrombin – platelet interaction:

1. Carboxylated prothrombin contains two carboxylate groups (COO–)
2. These groups bind to Ca2+, forming prothrombin-calcium complex
3. The complex then binds to phospholipids on the surface of platelets (important for blood clotting)
4. Converting prothrombin to thrombin and initiating clot formation

Prothrombin > Thrombin > Clot formation



So the calcium works as a bridge between the clotting factors and membrane of platelets

Functions of Vitamin K

Synthesis of γ-carboxyglutamate in osteocalcin:

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

The exact function is unknown but it was noticed that Vit K deficiency → decrease γ-carboxyglutamate (carboxylated osteocalcin) → Osteoporosis and another thing that vit K deficiency lead to decrease ca absorption so ca increase in circulation and lead to calcification in arteries and soft tissue which increase risk of CVD

Deficiency of Vitamin K

Deficiencies are rare: Vitamin k is synthesized by intestinal bacteria (normal flora) and stored in the liver

Causes of vit K deficiency:

- Lipid malabsorption can lead to vitamin K deficiency "because it is a fat soluble vitamin"
- Prolonged antibiotic therapy → killing normal flora → Vit K deficiency
  Especially in marginally malnourished individuals (e.g. debilitated geriatric patients)
- Some second-generation cephalosporin drugs cause this condition due to warfarin-like effects (antibiotics given with vit. K)
- Gastrointestinal infections with diarrhea → loss of normal flora → Vit K deficiency

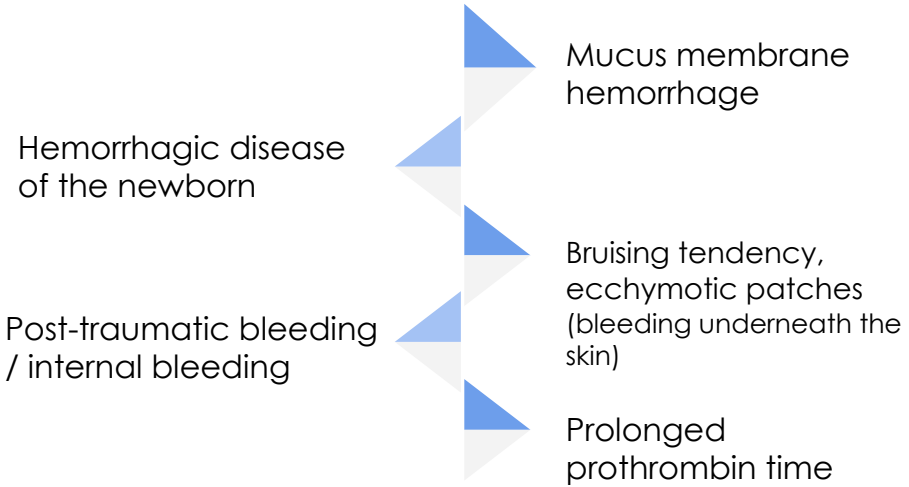
Deficiency most common in newborn infants

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

Affects of Vit K deficiency:

- Hypoprothrombinemia:
  ↑ blood coagulation time
- Bone growth and mineralization

Clinical Manifestations of the Deficiency



Toxicity of Vitamin K

01

Prolonged supplementation of large doses of menadione can cause:

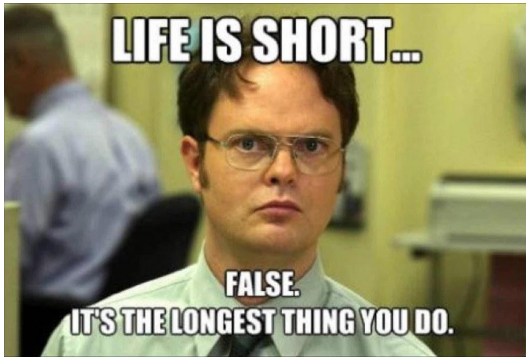
- Hemolytic anemia
- Jaundice

02

Due to toxic effects on RBC membrane

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**



Summary

Vitamin K

Types

- K1 (Phylloquinone)
- K2 (Menaquinone)
- K3 (Menadione)

Function

Coenzyme for the synthesis of proteins in the liver:
Prothrombin and Blood clotting factors by carboxylation of (Glu) into (Gla) which needs dihydroquinone form of Vit K.
Warfarin inhibits reductase (no dihydroquinone formation)

Synthesis of (Gla) γ-carboxyglutamate for osteocalcin to bind with hydroxyapatite.

Carboxylated Prothrombin + Ca2+ > phospholipids on surface of platelets:
(Important for clotting)

Deficiency

- Lipid malabsorption
- 2nd Gen cephalosporins (given antibiotic + vit k due to warfarin-like effects)
- Prolonged antibiotic therapy
- GI Infections with diarrhea
- last two destroy normal flora → Vit k deficiency because Vit k is synthesized by intestinal bacteria (normal flora)

Clinical Manifestations

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

Toxicity

Prolonged large intake of menadione for a long time > toxic effects on the RBC membrane which leads to:
- Hemolytic anemia
- Jaundice

Quiz

MCQs :

Q1: All factors and proteins in blood clotting are synthesized in
a) Pancreas **b)** Liver **c)** Kidney **d)** Spleen

Q2: The form of vitamin K that is required for activation of clotting factors is:
a) Menaquinone **b)** Menadione **c)** Phylloquinone **d)** Hydroquinone

Q3: Which of the following is type of vitamin K is produced by the intestinal bacteria?
a) Phylloquinone **b)** Menaquinone **c)** Menadione **d)** Hydroquinone

Q4: The clotting factor that is synthesized by vitamin k is:
a) VI **b)** V **c)** XII **d)** IX

Q5: Which one of the following can be inhibited by Dicumarol?
a) Glutamate **b)** Vit K Epoxide
c) Vit K hydroquinone **d)** γ-Crboxy-glutamate

Q6: What type of malabsorption could lead to vitamin K deficiency?
a) Lipid malabsorption **b)** Protein malabsorption
c) Carbohydrate malabsorption **d)** B & C

SAQs :

Q1: Mention the dietary sources of Vitamin K

Q2: A patient on warfarin get injured by a car accident, he is on risk of:

Q3: Write 3 causes of Vit K deficiency

Q4: Prolonged supplementation of large doses of Menadione can lead to:

★ **MCQs Answer key:**

1) B 2) D 3) B 4) D 5) C 6) A

★ **SAQs Answer key:**

1) Cabbage, kale, spinach, egg yolk, liver

2) Increasing of blood coagulation time.

3) Prolonged antibiotic therapy , lipid malabsorption , destroy the bacterial flora

4) Hemolytic anemia, Jaundice

Team members

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★ **Learn from yesterday,live for today,hope for tomorrow,The important thing is not to stop questioning**

438 BIOCHEMISTRY TEAM

We hear you