جامعة الملك سعود
King Saud University

"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Biochemistry437

Vitamin K

Biochemistry Team 437

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

GNT block

MED437
KING SAUD UNIVERSITY

Objectives:

Upon completion of this lecture, the Second Year students will be able to:

- 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
- Sources and daily requirements
- **Functions:**
- Synthesis of y-carboxyglutamate in:
  - Prothrombin and blood clotting factors
  - Interaction of prothrombin with platelets
  - Osteocalcin
  - Protein C and S (anticoagulant proteins)
- Deficiency and disorders
- Clinical manifestations

- Coagulation factors are synthesized as zymogens in our body, they require some modifications “Adding a certain molecule” to be activated.
- Vitamin k is used in this reaction, it leads to maturation of clotting factors.

Types and Sources

Occurs in several forms:

- Vitamin K_1 (Phylloquinone)
- Vitamin K_2 (Menaquinone)
- Vitamin K_3 (Menadione) - synthetic form

Dietary sources:

Cabbage, kale, spinach, egg yolk, liver


Cabbage


Kale


Spinach

tip **No need to memorize**

RDA for Vitamin K (mg/day)

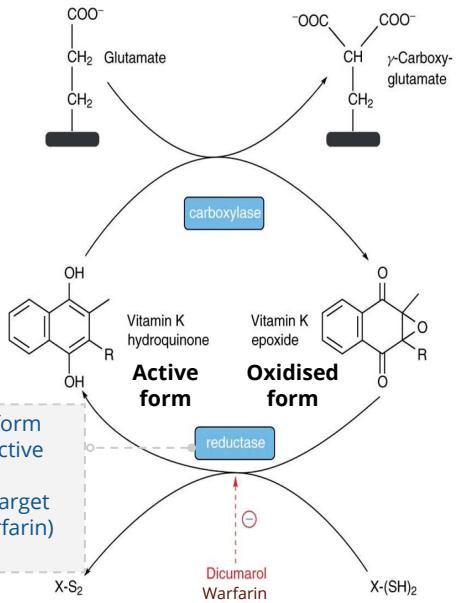
- **Infant (0-1 year):** 2-2.5
- **Children (1-8):** 30-55
- **Men (19+):** 120
- **Women (19+):** 90
- **Pregnancy/lactation:** 90/ 90
- **UL:** Not established **toxicity is rare**

Sources of Vitamin K

Phylloquinone	Menaquinone	Menadione
Green leafy vegetables	**Intestinal bacteria**: Intestinal bacterial synthesis meets the daily requirement of vitamin K even without dietary supplement, it is also stored in the liver, this is the reason why VIT K deficiency is rarely developed.	**Synthetic form:** A precursor of menaquinone. It is small, and very easily absorbed.

Functions of Vitamin K

- Coenzyme for the synthesis of prothrombin and blood clotting factors in the liver:
  - Prothrombin and clotting factors are protein in nature
  - Synthesis of prothrombin, clotting factors II, VII, IX, X require carboxylation of their glutamic acid (Glu) residue[1] by the enzyme carboxylase
- Mature prothrombin and clotting factors contain y-carboxyglutamate (Gla) after carboxylation reaction
- Vitamin K is essential for the carboxylase enzyme involved
- Dihydroquinone form of vitamin K is essential for this reaction



Converts epoxide (inactive form of vit K) to hydroquinone (Active form)
This reductase actually is a target for anticoagulant drugs (warfarin) to block activation Vit K

Figure 28.7. Function of Vitamin K.

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[1] The glutamic acid residues require carboxylation for activation of clotting factors

Functions of Vitamin K

1) The glutamate residue in the clotting factor gets carboxylated to gamma carboxy glutamate by the enzyme carboxylase
2) During this reaction, The hydroquinone form of the vit k "reduced/ active form" gets converted to epoxied "oxidized/inactive form "

Now we have to activate the vit k again , by the enzyme: reductase, this enzyme is the target for anti coagulant drugs like warfarin,

These drugs trap the vitamin K in their inactive form which stops the maturation of the clotting factors causing prolonged prothrombin time.

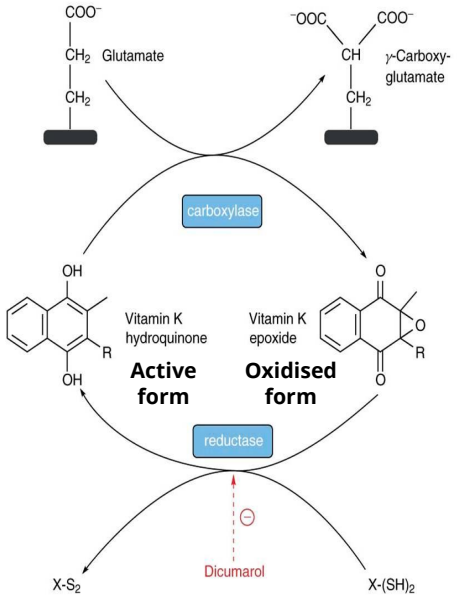

Figure 28.7. Function of Vitamin K.

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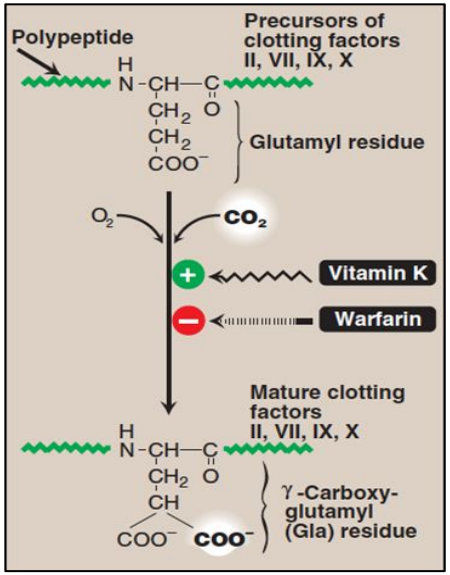
Analogs of Vitamin K

- Anticoagulant drugs: warfarin and dicoumarol (Structural analogs of vitamin K)
- They inhibit the activation of vitamin K to hydroquinone form (inhibiting the reductase enzyme) [1]
- Prothrombin and clotting factors are not carboxylated
- Hence blood coagulation time increases upon injury

[1] By competitive inhibition



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

Functions of Vitamin K

Involved in Prothrombin – platelet interaction:

Carboxylated prothrombin contains two carboxylate groups (COO^-)

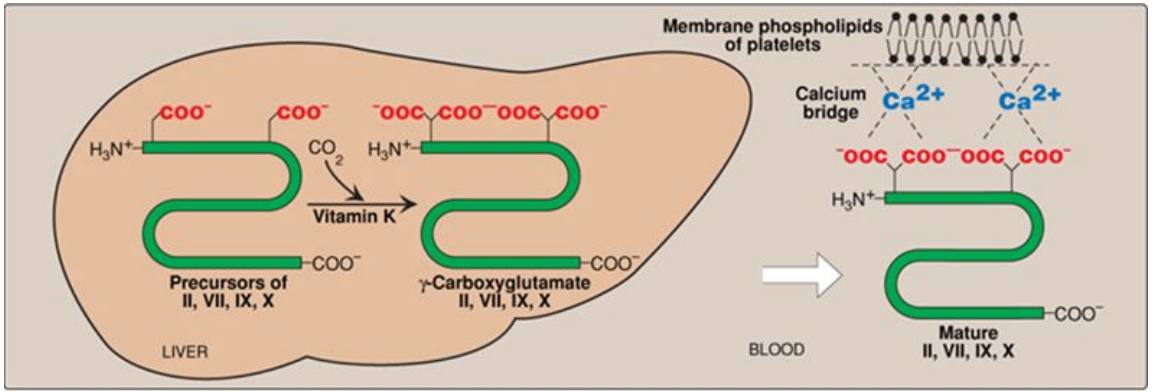
These groups bind to Ca^{2+}, forming prothrombin-calcium complex

The complex then binds to phospholipids on the surface of platelets (important for blood clotting)

Converting prothrombin to thrombin and initiating clot formation

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

Prothrombin – platelet interaction



Prothrombin is transformed into thrombin by a clotting factor known as factor x or prothrombinase, then thrombin acts to transform fibrinogen,into fibrin, which in combination with platelets form a clot in a processes called coagulation

Functions of Vitamin K

The same kind of modification for glutamate happens in the osteoclasts of the bones.

Synthesis of y-carboxyglutamate in osteocalcin:

- Osteocalcin is a bone turnover protein (destroy and rebuild the bone)
- Also called Bone Gla Protein[1] (BGP)
- Involved in bone formation, mineralization and resorption
- y-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
- The exact function is unknown but it was noticed that Vit K deficiency → decrease y-carboxyglutamate (carboxylated osteocalcin) → Osteoporosis

[1]Gla protein: a protein that requires the carboxylation of its glutamate residue to be activated.

Deficiency of Vitamin K

- Deficiencies are rare: it is synthesized by **intestinal bacteria** and stored in the liver
- Hypoprothrombinemia: increased blood coagulation time
- Some second-generation cephalosporin drugs cause this condition due to warfarin-like effects (antibiotics given with vit. K)
- May affect **bone growth** and mineralization
- Lipid malabsorption can lead to vitamin K deficiency "because it is a fat soluble vitamin"

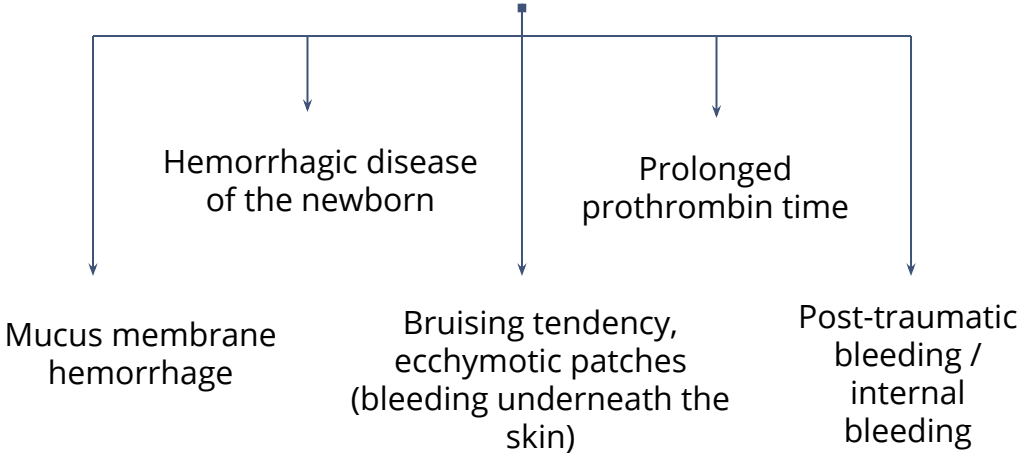
Cause of vit K deficiency:

- **Prolonged antibiotic therapy:** Especially in marginally malnourished individuals (e.g. debilitated geriatric patients)
- Gastrointestinal infections with diarrhea
- Both of the above destroy the bacterial flora leading to vitamin 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

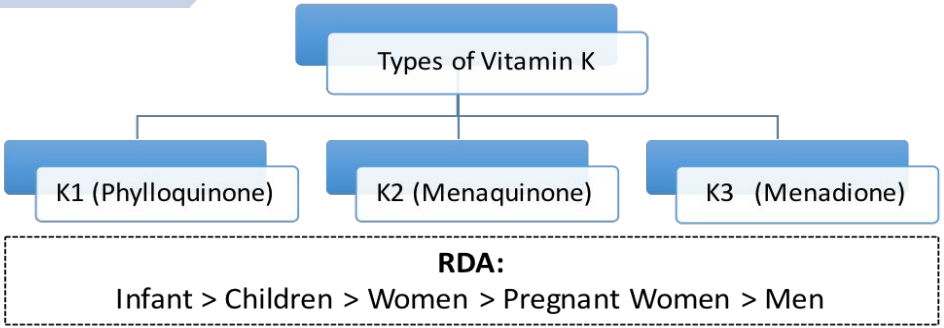
Clinical Manifestations of the Deficiency



Toxicity of Vitamin K

- Prolonged supplementation of large doses of menadione can cause:
  1) Hemolytic anemia; due to inhibition of glutathione system
  2) Jaundice
- Due to toxic effects on RBC membrane
- It's extremely rare but if someone takes supplements at high doses for long term may develop toxicity
- RBCs are mostly targeted by this toxicity

Summary



RDA:

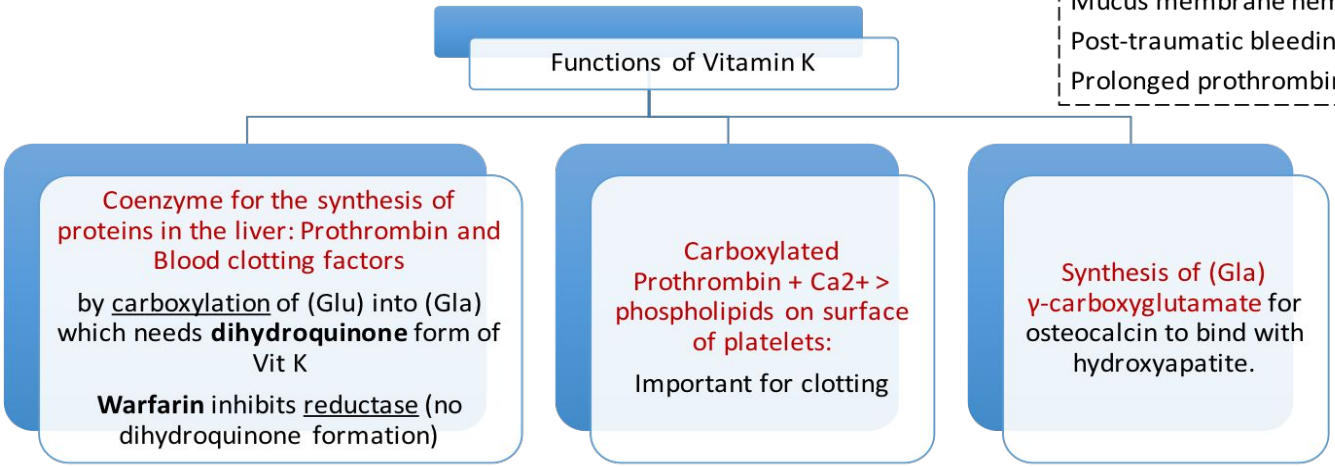
Infant > Children > Women > Pregnant Women > Men

Deficiencies of Vitamin K:

- Lipid malabsorption
- 2nd Gen cephalosporins
- Malnourished ind. using antibiotics
- GI Infections with diarrhea
- Common in antibiotics

Clinical manifestations:

- Hemorrhagic disease of the newborn
- Bruising tendency, ecchymotic patches
- Mucus membrane hemorrhage
- 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

MCQs:

1-The amount of Vitamin K supply (microgram/day) for pregnant women?
A-100 B-120
C-90 D-50

2-Which one of the following can inhibit the formation of hydroquinone (active form of vitamin k):
A- dicumarol B- Aspirin
C- verapamil D- Ritonavir`

3-The clotting factor that is synthesized by vitamin k:
A-VIII B-XII
C-IX D-XIII

4- which of the following is type of Vitamin K produced by the intestinal bacteria:
A-Phylloquinone. B-Menaquinone.
C-Menadione. D- All of the above.

5- The body can get its daily requirement of vitamin K by:
A-Menaquinone alone.
B-Menaquinone + Phylloquinone.
C-Menadione only.
D- Phylloquinone only.

6- Prolonged supplementation of large doses of Menadione can lead to:
A-to toxic effects on RBC membrane
B-Hemolytic anemia
C-Jaundice.
D- All of the above

7- A patient on warfarin get injured by a car accident , he is on risk of which of the following:
A- Increasing of blood coagulation time.
B-Decreasing of blood coagulation time.
C-Prothrombin and clotting factors are normally synthesized.
D- None of the above.

7- A
6- D
5- A
4- B
3- C
2- A
1- C

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