

VITAMIN K.

* Please check out [this link](#) to know if there are any changes or additions.

Revised by

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Color index: **Important** | **Doctors notes** | Further explanation.

OBJECTIVES:

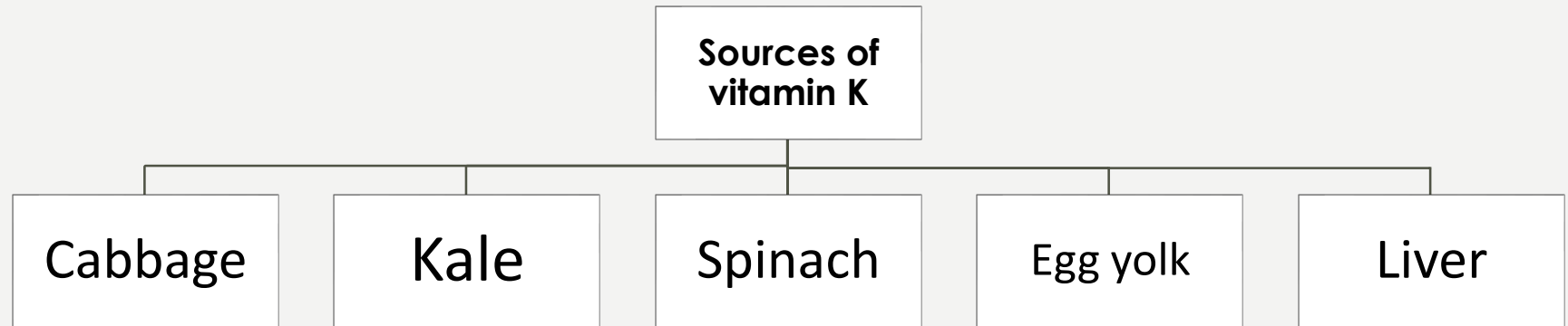
- ✓ Identify the types and sources of vitamin K
Understand the role of vitamin K in blood coagulation.
- ✓ Recognize the importance of γ -carboxylation of glutamic acid in coagulation proteins.
- ✓ Understand the role of anticoagulant drugs in affecting vitamin K function.
- ✓ Discuss the causes and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

Vitamin K.

Occurs in several forms:			
Form:	Vitamin K ₁	Vitamin K ₂	Vitamin K ₃
Another name:	Phylloquinone	Menaquinone	Menadione
Source:	Green leafy vegetables (plants)	Intestinal bacteria Intestinal bacterial synthesis meets the daily requirement of Vitamin K even without dietary supplement.	Synthetic form (Precursor of menaquinone)

RDA for Vitamin K (mg/day):
You don't have to memorize them

- 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



Functions of vitamin K

Formation of γ -carboxyglutamate

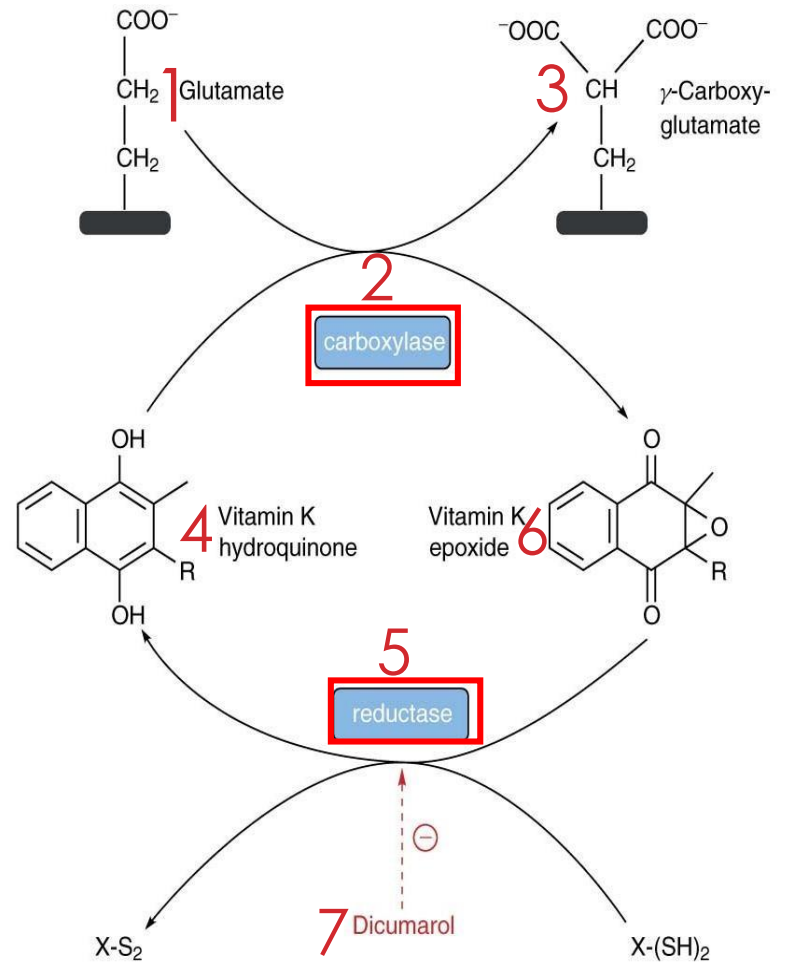
Prothrombin platelets interactions

Formation of γ -carboxyglutamate
In osteocalcin

Prothrombin and blood clotting factors Synthesis

“Explanation”:

- 1 Non-functional clotting factor with a **glutamic acid residue**.
- 2,3 **Carboxylase** converts the glutamic residue to gamma-carboxyglutamate (Gla) residue
- 4 **Dihydroquinone** (Active \ Reduced form) of vitamin K works as a co-enzyme for carboxylase. “Di-hydro = 2 hydrogen”
- 5,6 Vitamin K form (**epoxide**) cannot be used for carboxylation so it requires **Reductase** to be converted into **Dihydroquinone**
- 7 **Reductase** can be inhibited by vitamin K analogs. Ex: anticoagulant drugs: **warfarin, Dicumarol**.



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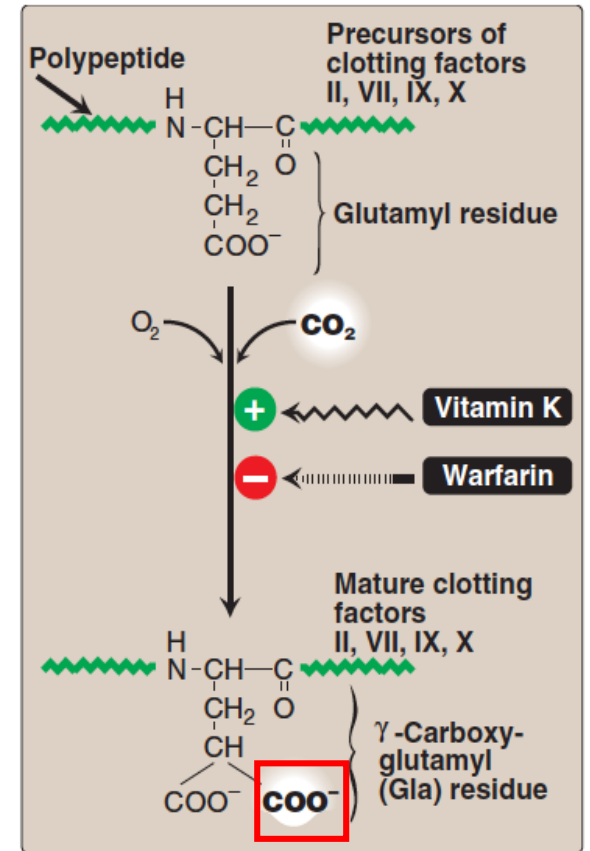
Formation of γ -carboxyglutamate In osteocalcin

Prothrombin and blood clotting factors Synthesis:

Site of formation:	in the liver
Coenzyme:	Vitamin K (Dihydroquinone form). "Reduced form"
Reaction:	Synthesis of mature prothrombin and clotting factors VII, IX, X requires carboxylation of their glutamic acid residues (Glu) .
Products:	Mature prothrombin and clotting factors contain γ-carboxyglutamate (Gla) due to carboxylation reaction.

Analogs of vitamin K:

Analogs:	Anticoagulant drugs: warfarin and dicoumarol .
How they act?	They inhibit the activation of vitamin K to hydroquinone form (inhibiting the reductase enzyme), so Prothrombin and clotting factors are NOT carboxylated. "cause the required co-enzyme (Vit, K) is inactive"
Effect:	blood coagulation time increases upon injury



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

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Prothrombin platelets interactions:

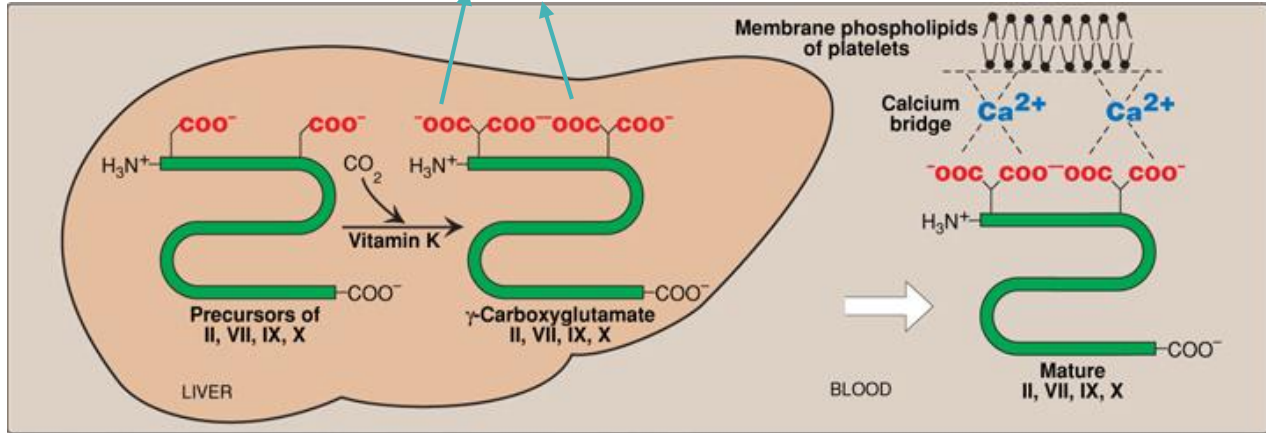
Carboxylated prothrombin contains two carboxylate groups (COO^-)

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

The new carboxyl groups after carboxylation and now it is mature prothrombin



Prothrombin synthesized in liver and has already carboxyl groups, so why carboxylation?

Because one Calcium ion needs two carboxyl groups to bind with, for better and tight interaction.

But what's the purpose of carboxylation generally ?

Carboxyl groups are negatively charged and the phospholipid membrane of platelets are also negative, they need positive ion in between to help in binding. in this case carboxylation is needed so calcium (Positive ion) bind to the carboxyl groups and act as a bridge to bind to phospholipid membrane of platelets

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Formation of γ -carboxyglutamate
In osteocalcin

❖ What is Osteocalcin?

- it is a bone turnover protein.
- **also called:** Bone Gla Protein (**BGP**)

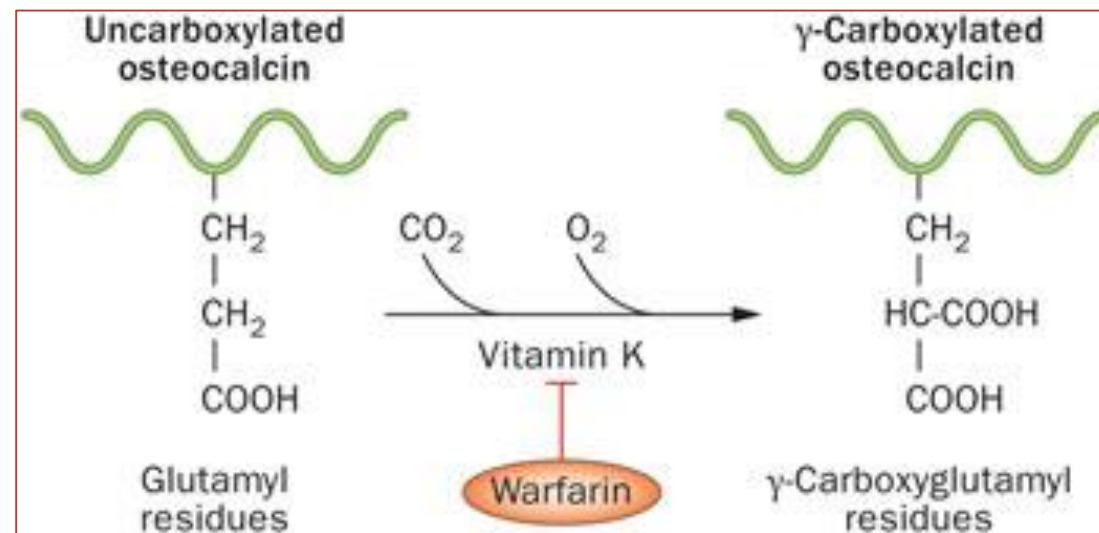
❖ Involved in:

- bone formation, mineralization and resorption.

❖ γ -Carboxyglutamate is **required for** osteocalcin binding to **hydroxyapatite** (a calcium mineral) in the bone.

❖ The binding mechanism:

- **Similar** to that of prothrombin-platelet binding.



Extra picture



[Vitamin k2 and bone metabolism](#) (2:29)

Note: Uncarboxylated osteocalcin is associated with increased risk of bone fracture

Deficiency of Vitamin K

❖ It is unusual and rare . WHY?

- Adequate amounts are synthesized by **intestinal bacteria** or obtained from diet.

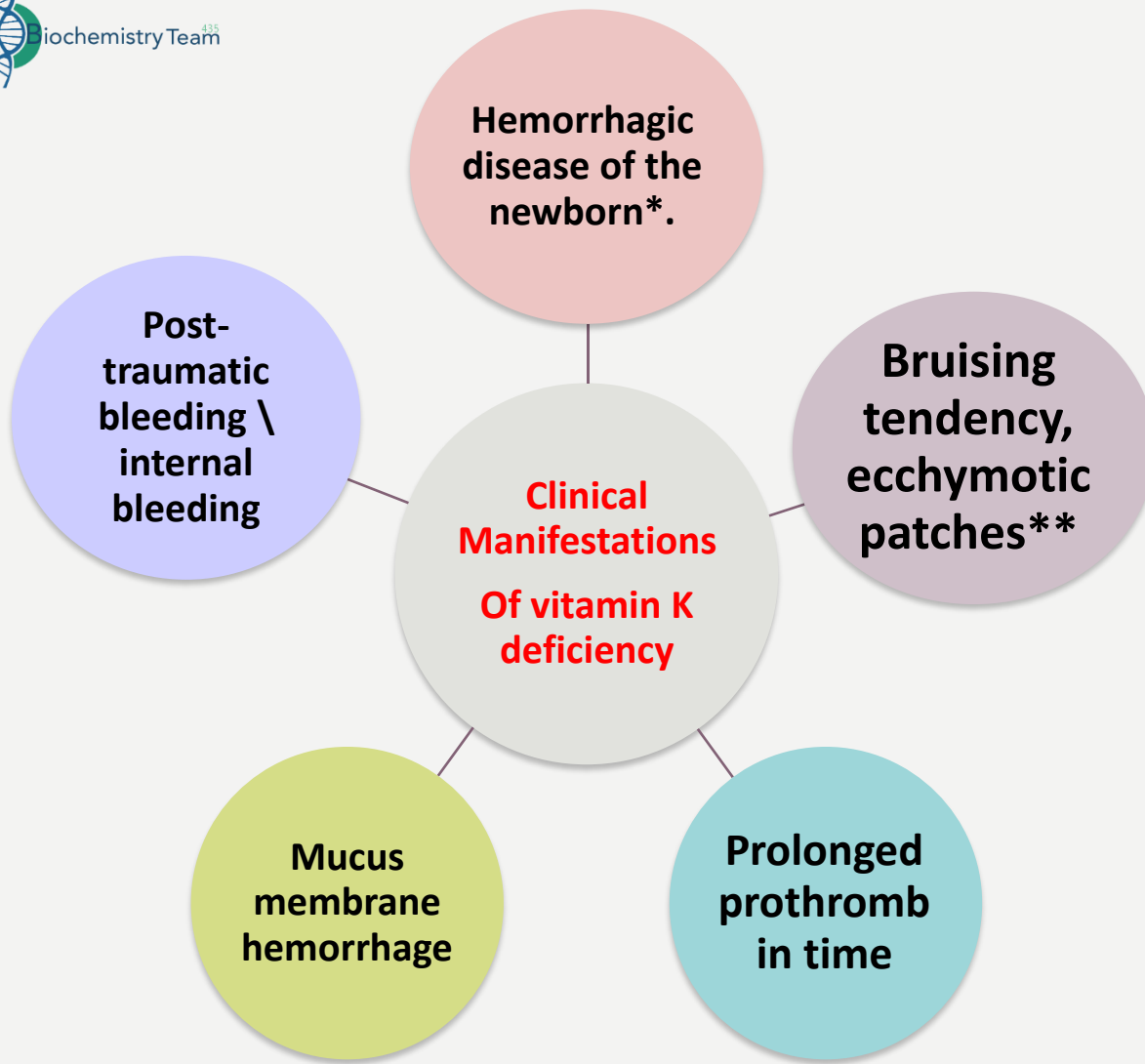
❖ Effects:

1. **Hypoprothrombinemia**: increased blood coagulation time
2. May affect bone growth and mineralization.

Causes of vitamin K deficiency:

Lipids malabsorption	In the newborn infants "most common"	Gastrointestinal infection with diarrhea	Prolonged use of antibiotic
vitamin K is fat soluble. فأي شيء يؤثر على امتصاص الليبيدز ييأثر على امتصاصه.	1. Newborns lack intestinal flora . 2. Human milk can provide only 1/5th vitamin K. - Supplements are given intramuscularly (IM) at birth.	- Destroys the bacterial flora leading to vitamin K deficiency.	- Some second-generation cephalosporin drugs cause this condition due to warfarin-like effects (antibiotics given with vit. K) - Especially in marginally malnourished individuals (e.g. debilitated geriatric patients) - It also destroys the bacterial flora leading to vitamin K deficiency

أغلب فايتمن كاي يتم انتاجه بواسطة بكتيريا الأمعاء ، معدة حديثي الولادة بتكون خالية من النورمل فلورا وبيكون المصدر الوحيد لهم هو الحليب.. علشان كذا ممكن انهم يعانون من نقص فايتمن كاي



Toxicity of Vitamin K

Prolonged supplementation of large doses of **menadione**
“Vit. K3 (synthetic form)”



toxic effects on RBC membrane



Hemolytic anemia
+
Jaundice

*Babies often have a low level of vitamin K for a variety of reasons. Vitamin K does not move easily across the placenta from the mother to the baby. As a result, a newborn does not have much vitamin K stored up at birth. Also, the bacteria that help make vitamin K are not yet present in a newborn's gastrointestinal tract. Finally, there is not much vitamin K in mother's milk. The most common areas of bleeding include:

A boy's penis “if he has been circumcised” - Belly button area - Gastrointestinal tract - Mucus membranes “such as the lining of the nose and mouth”

**bleeding underneath the skin.

Check your understanding!

Q1: 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.

Q2: the body can get its daily requirement of vitamin K by :

- A. Menaquinone alone.
- B. Menaquinone + Phylloquinone.
- C. Menadione only.
- D. Phylloquinone only.

Q3: vitamin K is required for which of the following clotting factors

- A. II.
- B. VII.
- C. A+B.
- D. Non of the above.

Q4: the active form of vitamin K is :

- A. Coenzyme for Synthesis of prothrombin.
- B. The reduced form.
- C. vitamin K hydroquinone.
- D. all of the above.

Q5: the function of the Vitamin K Analogs is :

- A. Inhibiting the activation of vitamin K.
- B. inhibiting the reductase enzyme.
- C. Inhibiting the carboxylation of prothrombin.
- D. All of the above.

Q6: 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 increases.
- B. Decreasing of blood coagulation time.
- C. Prothrombin and clotting factors are normally synthesized.
- D. Non of the above.

Check your understanding!

Q7: which one of the following is a co-enzyme of γ -carboxyglutamate for the synthesise of prothrombin?

- A. Vi A
- B. Vi K
- C. Vi E
- D. Vi D

Q8: baby born came to the ER with bleeding from he's belly button area. which one of the vitamin deficiency caused that?

- A- Vitamin A
- B- Vitamin K
- C- Vitamin D
- D- Vitamin E

Q9: which type of malabsorption could lead to vitamin K deficiency:

- A. Lipid malabsorption
- B. Protein malabsorption
- C. Carbohydrate malabsorption

Q10: 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.

Done by:

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- جواهر الحربي.
- عاصم الوهيبي.
- ابراهيم الشايع.
- دلال الحزيمي.

Resources:

- 435's slides and notes.
- Lippincott's illustrated reviews: Biochemistry – sixth edition.
- [New born belly button bleeding: Health line website](#)



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