Vitamin K and thrombosis

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The role of the fat soluble vitamin K (VK) in thrombosis is getting more clear every day. VK plays a major role in the coagulation cascade. VK deficiency can occur in any age group, but is encountered most often in infancy. The body needs VK to use calcium to build bone. Low levels of VK may be associated with a higher risk of osteoarthritis. VK improves bone health and reduces the risk of bone fractures, particularly in postmenopausal women who are at risk for osteoporosis.

Our research in the physiology, role in thrombosis and uses of VK tell us that VK is one of the very important vitamins in life. Although use of warfarin is gradually going down due to the discovery of NOAC's, warfarin is there to stay, and therefore we know that vitamin K is going to stay.

Introduction

Following the discovery of warfarin, a Vitamin K Antagonist (VKA), the importance of Vitamin K has become more apparent. The "K" in Vitamin K originated from the German word, "koagulation". Millions of patients who take warfarin for atrial fibrillation, DVT, PE, and prosthetic cardiac valves. The wide use of warfarin, an agent with a very narrow therapeutic index, has resulted in significant risk for major bleeding. Vitamin K serves as one of the major reversing agents for patients over-anticoagulated with warfarin.

We at GTF took a challenge of researching the physiology of vitamin K and its role in thrombosis.

History of development of vitamin K

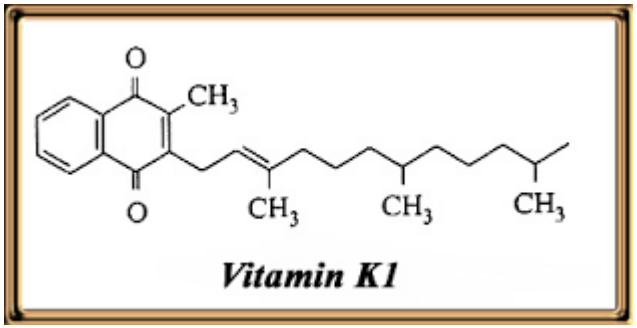
1. Discovered in the 1930s during cholesterol metabolism experiments in chickens.

2. A fat-soluble vitamin occurring in naturally in plants as phylloquinone (Vitamin K1), produced by gram-negative bacteria in the human gastrointestinal tract as menaquinone (Vitamin K2).

3. Found to be essential for normal functioning of hemostasis.

4. Number of clinical conditions (hemorrhagic disease of the newborn, obstructive jaundice, and malabsorption syndromes) have vitamin K deficiency as the underlying pathophysiologic problem.

Chemical structure of Vitamin K



Physiology of Vitamin K

Vitamin K is an essential factor to a hepatic gamma-glutamyl carboxylase that adds a carboxyl group to glutamic acid residues on factors II, VII, IX and X, as well as Protein S, Protein C and Protein Z. Vitamin K epoxide reductase (VKORC) reduces vitamin K back to its active form. VKORC is a target for warfarin, causing a deficiency of reduced vitamin K by blocking VKORC, thereby inhibiting maturation of clotting factors. Vitamin K is required in the synthesis of 4 clotting factors in the liver: factors II,VII, IX, and X. It is also essential in the production of protein C and S, which are anticoagulant proteins. Vitamin K is very

important in blood coagulation, a deficiency in the nutrient will lead to problems with blood clotting. For someone who does not have a clotting factor, a small cut on the finger, or even a bruise, can prove to be fatal. Vitamin K helps in the formation of blood clot.

Coagulation Cascade

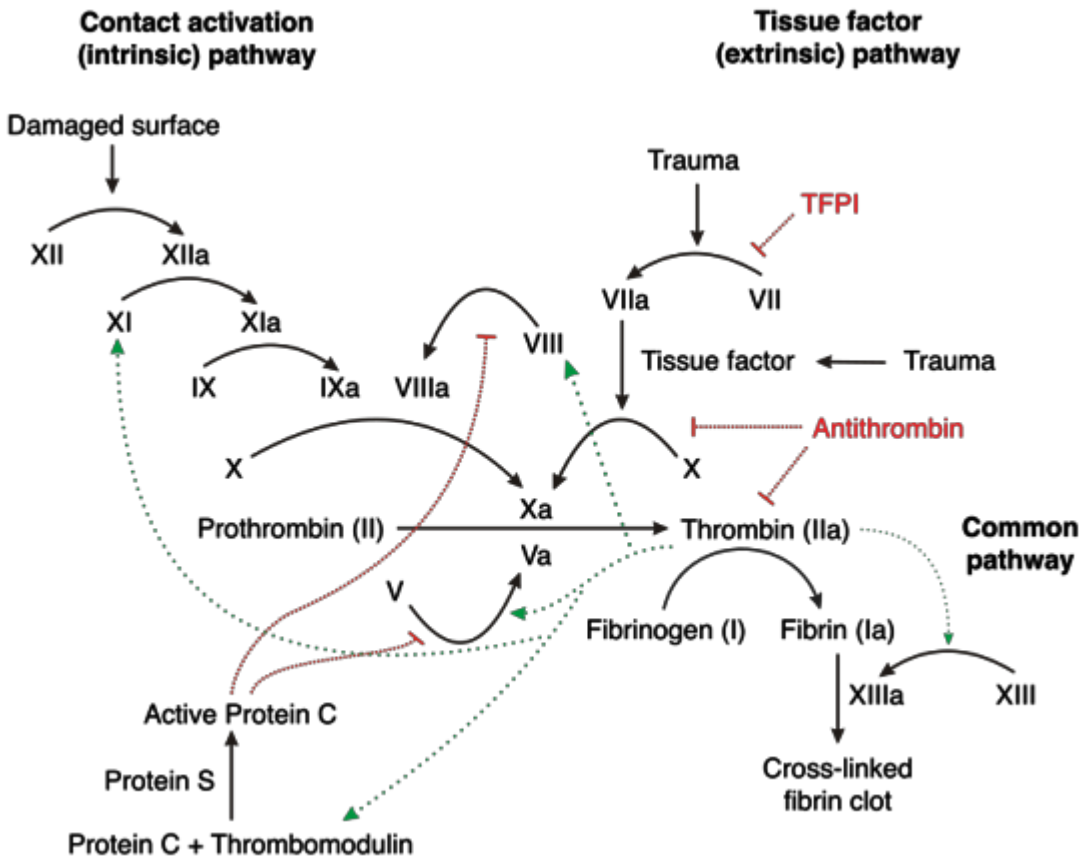
Blood clotting (coagulation) works in two different stages. Platelets gather at the spot of the broken vessel. They begin to adhere to the walls around the vessel and then pile on top of one another to form a plug.

After the plug is formed, proteins (clotting factors) work together to create fibrin that finalizes the clot.

Fibrin serves as a mesh material that ties together the platelet pile to make a secure clot.

The clot won’t protect the blood vessel properly until the fibrin web has solidified it.

Warfarin works against vitamin K, making blood clot more slowly.



Role of Vitamin K in Coagulation Cascade

Vitamin K is vitally important to blood clotting because the proteins that create the fibrin webbing in the second part of the clotting process depend on this vitamin. Vitamin K is needed for the clotting proteins to be activated and start the final part of the clotting process. When vitamin K is not present in the necessary amount, the clotting process can take longer and is not as effective.

Interaction between various agents and vitamin K

Warfarin inhibits vitamin K epoxide reductase and vitamin K1 reductase, resulting in an accumulation of vitamin KO and depletion of vitamin KH2.

γ-carboxylation of the vitamin K-dependent coagulant proteins (prothrombin, factors VII, IX and X) and anticoagulant proteins (proteins C and S) is limited,

resulting in production of acarboxylated proteins which are unable to bind calcium.

What is INR?

INR stands for International Normalized Ratio. INR is a laboratory measurement that provides information about how long it takes blood to clot. Originally created in 1983, INR provides a universal method of reporting the effects of oral anticoagulants such as warfarin. Prior to INR, blood clotting was measured by prothrombin time (PT).

INR is calculated as:

1. Prothrombintest / Prothrombincontrol)ISI

2. A normal INR ranges between 0.9 to 1.1. Patients on warfarin should have the INR adjusted between 2 to 3.5.

Vitamin K (VK) deficiency

VK, an essential, lipid-soluble vitamin that plays a vital role in the production of coagulation proteins, is found in green, leafy vegetables and in oils, such as soybean, cottonseed, canola, and olive oils. VK is also synthesized by colonic bacteria. VK deficiency can occur in any age group, but is encountered most often in infancy.

Infants with VK deficiency are at risk for hemorrhagic conditions, caused by a lack of VK reaching the fetus across the placenta, the low level of VK in breast milk, and low colonic bacterial synthesis.

Vitamin K deficiency bleeding (VKDB) in infants is a serious condition.

1. Early (<24 hours after birth)
2. Classic (first week after birth)

3. Late (between 1 week and 6 months after birth).

In adults, VK deficiency is uncommon because of the intake of a wide variety of vegetables and other foods, the body's ability to recycle VK, and adequate gut flora production of VK.

Bleeding in response to minor or trivial trauma is the major symptom.

Ecchymosis, petechiae, hematomas, and oozing of blood at surgical or puncture sites are observed.

Minimum Daily Requirement (MDR) for Vitamin K is 100-200 mcg/day.

Vitamin K and Bleeding

Vitamin K is used to reduce the risk of bleeding in liver disease. All newborns receive vitamin K injections to prevent the possibility of bleeding, particularly in the brain.

Babies are born without any bacteria in their intestines and do not get enough vitamin K from breast milk to tide them over until their bodies are able to make it. Even though vitamin K deficiency in newborns is very rare, it is dangerous enough that doctors give the injections. Newborns at greatest risk for vitamin K deficiency are premature or those whose mother had to take seizure medications during pregnancy.

Osteoporosis

The body needs vitamin K to use calcium to build bone. People who have higher levels of vitamin K have greater bone density, while low levels of vitamin K have been

found in those with osteoporosis. Low levels of vitamin K may be associated with a higher risk of osteoarthritis. Vitamin K improves bone health and reduces the risk of bone fractures, particularly in postmenopausal women who are at risk for osteoporosis.

Dietary Sources

Foods that contain a significant amount of vitamin K include beef liver, green tea, turnip greens, broccoli, kale, spinach, cabbage, asparagus, and dark green lettuce. Chlorophyll is the substance in plants that gives them their green color and provides vitamin K. Freezing foods may destroy vitamin K, but heating does not affect it.

Uses of Vitamin K

Vitamin K is most commonly used to reverse the effects of warfarin. It is also used to prevent clotting problems in

newborns who don't have enough vitamin K. Vitamin K is also given to treat and prevent vitamin K deficiency.

Laboratory conducting Vitamin K research

There are several laboratories that conduct research on Vitamin K, of which Human Nutrition Research Center on Aging in Boston is a major one.

Conclusion

1. Our research in the physiology, role in thrombosis and uses of vitamin K tell us that vitamin K is one of the very important vitamins in life.

2. Although use of warfarin is gradually going down due to the discovery of NOAC’s, warfarin is there to stay, and therefore we know that vitamin K is going to stay.

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