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NUTRITION IN DERMATOLOGY

An Evidence-Based Guide



Editors
Aseem Sharma
Abhishek De

JAYPEE

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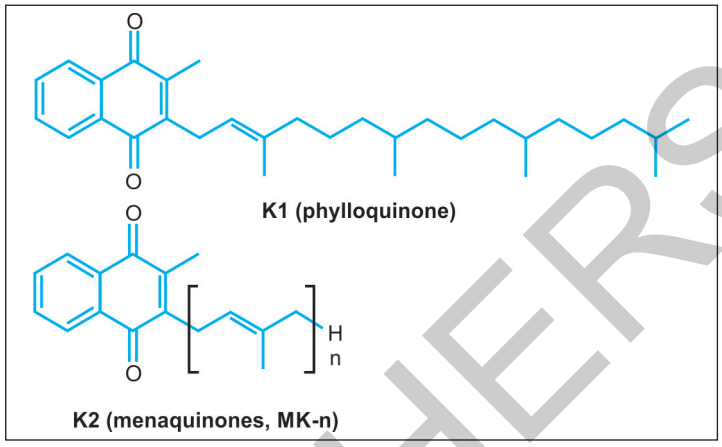

Phylloquinone, Menaquinones

Vitamin K

Sachin Varma

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- OXIDATIVE STRESS
- PEDIATRIC ATOPIC DERMATITIS
- PSEUDOXANTHOMA ELASTICUM (PXE)
- WOUND HEALING

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Nutrient Snapshot

▶ REQUIREMENT IN THE INDIAN CONTEXT

- Vitamin K is a fat-soluble, "multitasking" vitamin that was originally identified for its role in the activation of vitamin K-dependent coagulation factors.[1] Naturally, vitamin K appears as two variants—vitamin K1 is known as phylloquinone and vitamin K2 refers to a family of molecules called menaquinones (MKs).[2] Other than coagulation, vitamin K-dependent proteins are involved in tissue renewal and cell growth control. Other functions of vitamin K are mainly ascribed to vitamin K2 including the support of bone mineralization, calcium homeostasis and endothelial integrity, and inhibiting vessel wall calcification.[2,3]

- A deficiency of vitamin K is uncommon in healthy adults, due to its homeostatic control and it is widespread in food.[1] Vitamin K1 is found in green leafy vegetables and some plant oils, which is why it is more abundant in our diet. However, it is less bioactive than vitamin K2, especially compared to MK-7.

- Vitamin K2 forms are usually found in cheese, animal products, and certain fermented foods,[2] and tend to be lower in the Indian diet.[4] Although vitamin K2 is produced by the microbiota of the large intestine, our diet is its principal source, as it is absorbed in the small intestine.[5-7]

- Our body prioritizes the use of vitamin K for essential, life-sustaining, vitamin K-dependent proteins (e.g., the activation of blood coagulation proteins). The remaining vitamin K1 is converted to vitamin K2. However, vitamin K2 is thought to be insufficient for a number of other vitamin K-dependent proteins, nonessential for survival, that promote immune, cardiovascular, skeletal, and neuromuscular health.[4]

- From a dermatological perspective, vitamin K is not given much importance. It's topical application shows beneficial effects, such as suppression of pigmentation and alleviation of bruising, and promoting wound healing. It is also used prophylactically to limit the acneiform side effects in patients receiving the monoclonal antibody cetuximab. However, its photodegradation and phototoxicity limit its topical use.[8]

- From a supplement perspective, a case can be made for vitamin K2 insufficiency. Its ability to promote vascular health may benefit aging factors with a vascular component, including the appearance of undereye dark circles, hair loss, varicose veins, and bruising.

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▶ ACTIVE FORMS

ACTIVE FORMS	SUPPLEMENT SOURCES	SALIENT FEATURES
Vitamin K1 (phylloquinone)	Plant based extraction or synthetic[9]	Vitamin K1 is well absorbed but has a shorter shelf-life.[10,11]
Vitamin K2 (menaquinones; MKs)	Bacterial fermentation synthetic	Menaquinone is analogous to ubiquinone in function as ubiquinone is used as an electron carrier in electron transport chain by bacteria.[12] K2-MK7 has a longer half life and thus is stable in serum.[10]
Vitamin K3 (menadione)	Synthetic	Vitamin K3 is not allowed for human consumption as per the FSSAI, and is usually used in animal feeds.

▶ SAFETY AND DOSAGE

GENERAL REQUIREMENTS	
Indian recommendations	RDA 2020: 55 µg/day, TUL: N/A
Global recommendations and limits	Adequate intake, NIH: Male—120 µg, Females—90 µg/day TUL: Not established.[13]
	EFSA AI: 70 µg/day for phylloquinone[14] NOAEL: Not established.
Notes:	Because of the lack of data to estimate an average requirement, an adequate intake (AI) is given. Vitamin K needs to be taken after a meal as it is a fat soluble vitamin.

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▶ CLINICAL CONDITIONS

EVIDENCE LEVEL	CONDITION OR USE CASE	DOSAGE	BENEFIT OR MECHANISM OF ACTION
+++	Collagen metabolism	Rats were injected with Vikasol solution (converts to vitamin K2) for 10 days or pelentan (anticoagulant) by mouth for 15–20 days, or both preparations together for 20 days. Rats getting pelentan suffered from avitaminosis; they were started with Vikasol for 8 days.	In avitaminosis-K rats, the total collagen content in the skin was reduced. There was a parallel increase in the rate of its hydrolysis and in the level of free hydroxyproline, suggesting an increase in catabolism of collagen.[15]
+++++	Wound healing	N/A (meta-analysis)	According to various studies, vitamin K has shown to increase the rate of wound healing in animal models.[16]
+	Pseudoxanthoma elasticum (PXE)—calcium accumulation in elastin fibers	N/A (observational study)	The serum levels of vitamin K in patients with PXE were lower than the controls.[17]
++	Oxidative stress	Human embryonic kidney cells were treated with vitamin K (in vitro).	Cell viability under conditions of no induced oxidative stress was increased by the presence of vitamins K1 and K2 but not ubinquinone-10 and was specifically dependent on VKORC1L1 expression. Intracellular oxidative damage to membrane intrinsic proteins was inversely dependent on VKORC1L1 expression and the presence of vitamin K1.[18]

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▶ CLINICAL CONDITIONS (*Continued*)

EVIDENCE LEVEL	CONDITION OR USE CASE	DOSAGE	BENEFIT OR MECHANISM OF ACTION
++	Aging-related proinflammatory factors	Vitamin K2-MK7 was added in cell culture human monocyte derived macrophages (hMDMs) for 30 hours (in vitro).	MK-7 was able to modulate immune and inflammatory reactions by a dose-dependent inhibition of TNF-α, IL-1α, and IL-1β gene expression and protein production in healthy hMDMs.[19]
+++	Pediatric atopic dermatitis	Peripheral blood mononuclear cells of children with and without atopic dermatitis were collected and treated with vitamin K2.	Vitamin K2 attenuated activated T-cell immunity in atopic dermatitis patients through the inhibition of mitogen activated protein kinase (Mek1), extracellular signal-regulated kinases (ERK 1/2), and stress activated protein kinase (SAPK) or c-Jun N-terminal kinase (JNK) signaling pathway.[20]

▶ SUPPLEMENTATION

	BASIS	WHAT TO LOOK OUT FOR
Supplementation form	Vitamin K1 (phylloquinones) Vitamin K2-MK7 (menaquinones) Both K1 and K2-MK7 are well absorbed but K2-MK7 has a longer half life.[10,11] Vitamin K2 can be supplemented, as vitamin K1 is plenty in the Indian diet.	The form of vitamin K is stated on the nutritional table or in ingredients of the product packaging.
Administration form	Capsules, tablets, softgels, powders, gummies	N/A
Purity considerations	Vitamin K normally has >99% purity.	N/A
Patient considerations	Vitamin K is a fat soluble vitamin, and thus should be taken after meals.	
Safety considerations	There are no severe side effects from vitamin K supplementation.[13,21]	N/A

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▶ SUPPLEMENTATION (*Continued*)

	BASIS	WHAT TO LOOK OUT FOR
Other considerations	Individuals on warfarin and other blood thinners should be careful while taking vitamin K supplements as it acts as an antagonist and might reduced the effect of warfarin.[21]	Most of the multivitamin formulations will have vitamin K.
	Prolonged use of antibiotics accompanied with low vitamin K intake may require vitamin K supplementation. A multivitamin formulation with vitamin K can be given.[13]	

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▶ INTRODUCTION

Carboxylation is a post-translational modification of proteins that converts specific glutamate residues (Glu) to γ-carboxyglutamate residues (Gla). It is catalyzed by γ-glutamyl carboxylase (GGCX), which utilizes the reduced form of vitamin K as a cofactor. Both vitamin K1 and K2 can function as cofactors for blood coagulation proteins. With the discovery of new vitamin K-dependent proteins, we now know that vitamin K2 is involved in bone metabolism and other important physiological processes.[22]

The body stores very small amounts of vitamin K, which is probably why the body recycles it through a process called the vitamin K-epoxide cycle. Briefly, vitamin K hydroquinone (reduced form; KH_2) is oxidized to vitamin K epoxide (oxidized form; KO). An enzyme called vitamin K-oxidoreductase (VKOR) converts KO to vitamin K and back to KH_2. The anticoagulant drug warfarin acts as a vitamin K antagonist by inhibiting this enzyme and preventing vitamin K recycling **(Figure 1)**.[23]

▶ DIGESTION, ABSORPTION AND STORAGE

Digestion and Absorption

- Vitamin K1 is absorbed in the intestine via active transport in the jejunum, whilst vitamin K2 is absorbed in the small intestine by diffusion. Bile salts and products of pancreatic lipase are required for optimal absorption.[6]
- Vitamin K1 is metabolized and more than half the amount is excreted by the organism, while vitamin K2 is transported by LDL to extrahepatic tissue.[23]
- Bioavailability and pharmacokinetics vary widely amongst the different forms. Some of them have very short half-life, like vitamin K1, are found in the circulation from 4-10 hours after ingestion, whilst others, like vitamin K2 MK-7, are present for more than 96 hours.[6] Typically, longer chain MKs, such as MK-7, MK-8 and MK-9, have a longer half-life in circulation in comparison to K1. However, MK-9, being even more lipophilic, has a very long half-life, but is poorly absorbed. That's why MK-7, providing high bioavailability and a long half-life, is frequently used in supplements.[3]

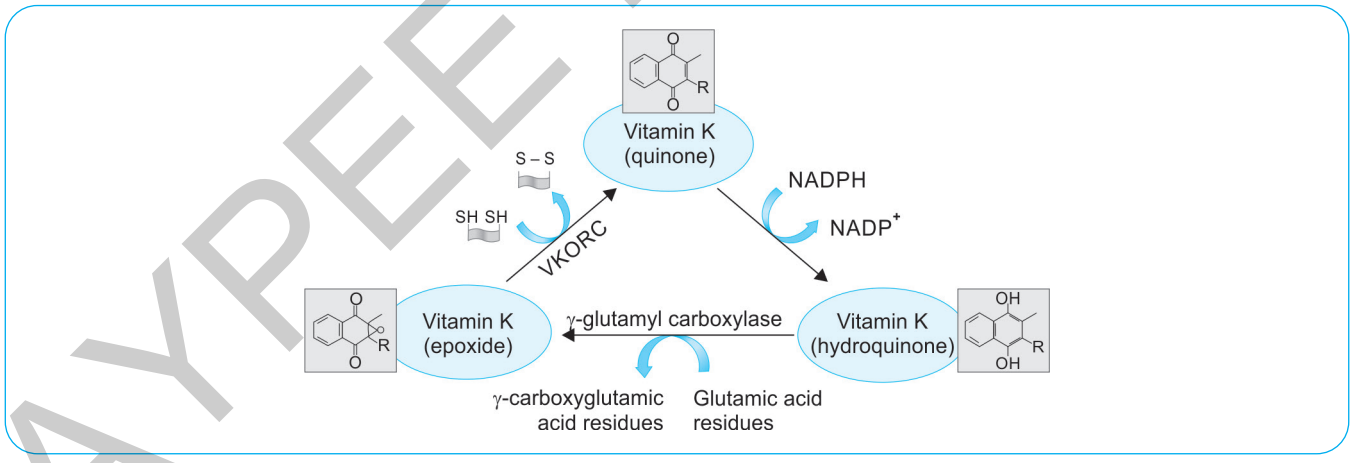

Figure 1: *Metabolic redox-cycle of vitamin K.*
(VKORC: vitamin K-dependent epoxide reductase complex)
Source: *Adapted from Ivanova.*

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Storage

- As a fat-soluble vitamin, vitamin K is stored mainly in adipose tissue. Vitamin K1 is stored in the liver and vitamin K2 accumulates in many tissue.[3]

- With limited vitamin K storage capacity, the body reuses it by recycling it in the vitamin K oxidation-reduction cycle.

▶ MECHANISM OF ACTION

01 | Antioxidant Activity

Vitamin K's reduced form, KH_2, has been recognized as a potent biological antioxidant, nearly 10- to 100-fold higher than any other known antioxidants, such as α-tocopherol and coenzyme Q10.[3,24]

Both vitamin K1 and K2 have shown to increase survival of oxidatively stressed cells caused by depleted glutathione levels. They have been recognized to be important for limiting oxidative damage to membrane proteins.[18,25]

02 | Regulation of Cellular Function

Vitamin K-dependent signaling pathways in osteogenic cells have been long established. Due to its ability to bind to the intranuclear receptor SXR (steroid and xenobiotic receptor), which activates several genes, vitamin K2 is being called a hormone.[26]

Similar to coenzyme Q10, vitamin K2 has been reported to facilitate ATP production and rescue mitochondrial dysfunction.[27] Decline of mitochondrial activity is a result of cellular aging, and has been implicated in conditions such as female pattern hair loss.[28]

Vitamin K has been shown to be cytotoxic to cancer cells via redox mechanisms involving cell growth arrest and suppression of proliferation. This has been exploited for cancer suppression and preventing bacterial growth during wound healing.[16,23]

03 | Immunoregulation

Vitamin K has shown to reduce the expression of pro-inflammatory markers, TNF-α, IL-6, IL-1α and IL-1β, via the inactivation of the NF-κB signaling pathway.[19,29] This is one of the reasons for its use in managing type 2 diabetes.[29]

Other than blood clotting, in wound healing, vitamin K is thought to promote the expression of transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF), but the exact mechanism is still unclear.[16]

Vitamin K2 can also modulate T-cell function. This has been shown in vitro, where it suppressed the proliferation of T-cell mitogen-activated peripheral blood mononuclear cells acquired from atopic dermatitis patients.[20,30]

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NUTRITION IN DERMATOLOGY
An Evidence-Based Guide

This comprehensive guide delves into the applications of nutrients within dermatology practice, tailored specifically to meet the needs of practitioners in the Indian context. Drawing from extensive scientific research conducted by a team of 10 distinguished dermatologists, this book provides a detailed examination of nutrient requirements, supplemental forms, and dose-dependent effects—both beneficial and adverse. Edited by the esteemed Dr Aseem Sharma and Dr Abhishek De, this evidence-based resource is indispensable for dermatologists and healthcare professionals.



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