Overview of vitamin K

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INTRODUCTION — Vitamins are a number of chemically unrelated families of organic substances that cannot be synthesized by humans but need to be ingested in the diet in small quantities to prevent disorders of metabolism. They are divided into water-soluble and fat-soluble vitamins (table 1).

More than 50 years ago, Henrik Dam of Denmark discovered an "antihemorrhagic factor" that was capable of reversing dietary-induced bleeding disorders in chicks [1]. The name "K" comes from the German/Danish word koagulationsvitamin (clotting vitamin) [2].

In 1930, vitamin K was first isolated by Doisy and his colleagues, as well as by Dam, from alfalfa sprouts [3]. Until the 1980s, when chromatographic techniques were used, the mainstay of vitamin K isolation was through using chick bioassay [2].

This topic review will focus on vitamin K. Overviews of the other fat-soluble vitamins, minerals and water-soluble vitamins are available elsewhere. (See "Overview of vitamin A" and "Overview of vitamin D" and "Overview of vitamin E" and "Overview of dietary trace minerals" and "Overview of water-soluble vitamins" and "Vitamin supplementation in disease prevention".)

SOURCES — Dietary vitamin K1 (phylloquinone or phytonadione) is found in green vegetables like spinach and broccoli (table 2) [4]. Gut micro-flora synthesizes vitamin K2 (menaquinones, including menatetrenone), which provides a portion of the dietary requirement of vitamin K [4]. Vitamin K2 has approximately 60 percent of the activity of vitamin K1, by weight, but bioavailability of both forms varies substantially depending on other intraluminal nutrients [5].

CHEMISTRY — Vitamin K and its derivatives contain a 2-methyl-1, 4, naphthoquinone nucleus with a lipophilic side chain (figure 1).

METABOLISM — Vitamin K absorption requires intact pancreatic and biliary function and fat absorptive mechanisms. Dietary vitamin K is protein-bound and is liberated by the proteolytic action of pancreatic enzymes in the small intestine. Bile salts then solubilize vitamin K into micelles for absorption into enterocytes, where it is incorporated into chylomicrons, thereby facilitating absorption into the intestinal lymphatics and portal circulation for transport to the liver [6].

ACTIONS — Vitamin K has a major role in coagulation pathways because it is a cofactor required for the activity of several key proteins containing carboxyglutamic acid residues. Several other proteins within the body (eg, osteocalcin) also contain carboxyglutamate residues and depend upon vitamin K for their activity (table 3). (See "Vitamin K and the synthesis and function of gamma-carboxyglutamic acid".)

Coagulation pathway — Vitamin K is essential for activity of several carboxylase enzymes within hepatic cells, and therefore is necessary for the activation of coagulation factors VII, IX, X, and prothrombin. These factors contain carboxyglutamic acid, which is carboxylated by gamma-glutamyl carboxylase, an endoplasmic enzyme found in mammalian cells (figure 2) [2]. Vitamin K is the active coenzyme in this process, providing energy for the reaction through oxidation [7]. After carboxylation, these proteins gain affinity for the negatively charged phospholipids on the surface of platelets and promote coagulation [8].

Antithrombotic effects of proteins C and S — The natural anticoagulants, proteins S and C also require vitamin K for their activity. Protein C, following its activation by thrombin, inactivates factors Va and VIIIa, thus inhibiting excess generation of thrombin (see "Protein C deficiency", section on 'Pathophysiology'). Protein S also helps prevent excessive coagulation through its action as a cofactor for activated protein C [9]. (See "Protein S deficiency".)

Mechanism of action of the coumarin-like family — Coumarin-like anticoagulants, which are similar in structure to vitamin K (figure 1), interrupt the vitamin K dependent carboxylation cycle by blocking reduction of the inactive vitamin K 2,3 epoxide to the active form of the vitamin (figure 2) [4]. Vitamin K administration is one of the methods used to reverse the effects of coumarin. (See "Management of warfarin-associated bleeding or supratherapeutic INR", section on 'Treatment'.)

Bone formation — Vitamin K is a cofactor for some proteins involved in bone mineralization, including osteocalcin (bone Gla protein) and matrix Gla protein (see "Normal skeletal development and regulation of bone formation and resorption", section on 'Biochemistry of bone mineral matrix'). Clinical trials have examined the use of vitamin K1 (phylloquinone) or vitamin K2 for the treatment of osteoporosis, with conflicting results which are discussed separately. (See "Overview of the management of osteoporosis in postmenopausal women", section on 'Therapies not recommended'.)

DEFICIENCY

Symptoms — Clinical signs and symptoms of vitamin K deficiency include easy bruisability, mucosal bleeding, splinter hemorrhages, melena, hematuria, or any other manifestations of impaired coagulation. Vitamin K deficiency in an otherwise healthy adult is rare. This is largely due to the wide distribution of phylloquinone in plants, menaquinone production by gut micro-flora, and because vitamin K is easily recycled within cells (figure 2). However, an acquired deficiency can occur secondary to drugs such as antibiotics. Patients on total parenteral nutrition or those on long-term antibiotics are prone to develop vitamin K deficiency and require supplementation. Prolonged fasting or starvation also decreases vitamin K levels. Such patients are more sensitive to treatment with coumarin-based anticoagulants [10]. (See 'Daily value' below and "Beta-lactam antibiotics: Mechanisms of action and resistance and adverse effects", section on 'Hematologic reactions'.)

Laboratory evaluation — The coagulation abnormalities caused by vitamin K deficiency are manifested as prolonged prothrombin time (PT) and International Normalized Ratio (INR). When the deficiency is mild, only the PT may be prolonged, due to a predominant effect on factor VII. In severe vitamin K deficiency, both the PT and partial thromboplastin time (PTT) may be affected. Levels of PIVKA-II (Proteins induced in vitamin K absence) are more sensitive than PT in detecting vitamin K deficiency and may be helpful in monitoring patients with diseases predisposing to vitamin K deficiency. Vitamin K levels also can be measured directly but are impractical for clinical use. (See "Clinical use of coagulation tests", section on 'Prothrombin time (PT) and INR'.)

Causes — Vitamin K is a fat-soluble vitamin, thus any cause of fat malabsorption may result in vitamin K deficiency. Fat malabsorption may be caused by disorders of bile or pancreatic secretion, or by extensive disease or resection of the intestinal mucosa. As examples, patients with the following conditions are at risk for fat-soluble vitamin deficiencies and usually require supplementation and monitoring, as discussed in the corresponding topic reviews:

- Cystic fibrosis. (See "Cystic fibrosis: Nutritional issues", section on 'Vitamin K'.)
- Primary biliary cholangitis. (See "Overview of the treatment of primary biliary cholangitis (primary biliary cirrhosis)", section on 'Deficiencies of fat-soluble vitamins'.)
- Primary sclerosing cholangitis. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Steatorrhea and vitamin deficiency'.)
- Biliary atresia (See "Biliary atresia", section on 'Fat-soluble vitamin supplements'.)
- Familial intrahepatic cholestasis and other inherited disorders associated with cholestasis. (See "Inherited disorders associated with conjugated hyperbilirubinemia".)
- Intestinal diseases associated with malabsorption, such as active celiac disease, inflammatory bowel disease, or short bowel syndrome, may be associated with vitamin K deficiency. This is particularly true if the terminal ileum is involved because this can cause maldigestion of the fat-soluble vitamins by reducing the bile salt pool. (See "Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults" and "Nutrient deficiencies in inflammatory bowel disease" and "Chronic complications of short bowel syndrome in children".)
- Liver failure – Because the vitamin-K dependent coagulation factors are synthesized in the liver, severe parenchymal liver disease also may lead to deficiencies of these factors. In patients with severe liver disease and coagulation abnormalities, measurement of factors V and VII can help to distinguish between liver parenchymal dysfunction and vitamin K malabsorption. (See "Hemostatic abnormalities in patients with liver disease".)

Medications that may contribute to vitamin K deficiency include antibiotics and high doses of vitamins E or A. Antibiotics can contribute to vitamin K deficiency by affecting intestinal bacteria, and also through direct effects on vitamin K activation in the liver. Most of the ingested vitamin K is absorbed in the distal small intestine. A number of microorganisms, which colonize the colon and distal ileum, synthesize absorbable vitamin K (vitamin K2, menaquinone). Many broad-spectrum antibiotics diminish this population of bacteria, limiting menaquinone production [11]. Second and third generation cephalosporin antibiotics are associated with hypoprothrombinemia and have a weak coumarin-like effect in patients with low vitamin K stores [12]. They cause vitamin K deficiency by inhibiting the function of vitamin K epoxide reductase enzyme in the liver, therefore impairing the recycling of vitamin K (figure 2) [12].

Extremely high doses of vitamin E and A antagonize vitamin K [13]. Hypervitaminosis A appears to reduce absorption of vitamin K, as suggested by the observation that the parenteral infusion of vitamin A (retinoic acid) does not increase the vitamin K requirement [14]. Very high doses of vitamin E also cause vitamin K deficiency, but do not appear to affect absorption [15].

Vitamin K deficient bleeding in newborns and young infants — Vitamin K deficiency is common in the newborn, and if vitamin K is not replaced, the infant is at risk for vitamin K deficient bleeding (VKDB), previously known as hemorrhagic disease of the newborn. It is characterized by cutaneous bruising or bleeding from mucosal surfaces, the gastrointestinal tract, umbilicus or circumcision site, and/or intracranial hemorrhage (ICH).

- Early-onset VKDB develops within the first 24 hours of life, and is usually associated with maternal medications that block vitamin K action (eg, anticonvulsants). It is associated with ICH in about 25 percent of affected infants [16].
- Classic VKDB develops between one and four weeks of life, and is largely prevented by administration of vitamin K at birth.

- Late-onset VKDB typically develops between three weeks and eight months of age. There is a high frequency of ICH in affected infants (eg, 50 percent in some series), and associated central nervous system symptoms such as vomiting or seizures may be the primary presenting symptoms [17]. Of note, late-onset VKDB and associated ICH appear to be increasing in the United States, and these cases are associated with the parental refusal of vitamin K prophylaxis at birth, followed by exclusive breast feeding [18-20]. It can also be precipitated by fat malabsorption due to gastrointestinal or hepatobiliary disease, such as biliary atresia, in infants who are not given parenteral vitamin K prophylaxis at birth, or by coumarin poisoning [17,21]. One study documented ICH due to VKDB in 21 Egyptian infants despite standard parenteral vitamin K prophylaxis at birth; risk factors included exclusive breast feeding, diarrhea, and antibiotic consumption [22].

Newborn infants are at risk for vitamin K deficiency because their immature liver does not efficiently utilize vitamin K. In addition, they tend to have low vitamin K stores because of the low vitamin K content of breast milk, a sterile gut, and poor placental transfer of vitamin K [23]. In infants, the plasma concentrations of all vitamin K dependent factors are about 20 percent of the adult values. Within a month after birth, the levels rise to within normal limits [24]. The risk of developing VKDB is further increased by maternal ingestion during pregnancy of warfarin or other coumarin-like anticoagulants, certain antibiotics (ie, cephalosporins), and some anticonvulsants [23].

To prevent VKDB, the American Academy of Pediatrics recommends administration of parenteral vitamin K at birth, and supplementation of infant formulas with vitamin K [25]. (See "Overview of the routine management of the healthy newborn infant" and 'Prevention of vitamin K deficient bleeding in newborns' below.)

EXCESS — Vitamin K toxicity is very rare, and a tolerable upper limit for consumption has not been defined (table 4). Menadione, a synthetic water-soluble form of vitamin K, can cause hemolytic anemia, hyperbilirubinemia, jaundice, and kernicterus in infants [26]. Menadione has been used in premature or low-birth-weight newborns and it may precipitate kernicterus only in high doses [27]. However, this form of vitamin K supplementation is not widely available.

REQUIREMENTS

Daily value — The primary source of vitamin K in the diet is from leafy green vegetables (table 2). The dietary requirement, expressed as adequate intake (AI) is 90 micrograms daily in women and 120 micrograms daily in men (table 4) [28].

Parenteral nutrition — Patients on total parenteral nutrition require vitamin K supplementation. Vitamin K is included in most brands of standard multivitamin mix added to the parenteral nutrition solution. A typical daily dose of adult injectable multivitamins for parenteral nutrition includes 150 mcg of vitamin K1 (phytonadione). For patients on warfarin, daily intake of 150 mcg of vitamin K1 has not been associated with a requirement for excessive doses of warfarin, or sub-therapeutic anticoagulation, as long as the anticoagulation regimen is appropriately monitored and doses are adjusted as needed. Nonetheless, for patients on warfarin, some providers select a brand of multivitamin mix that does not contain vitamin K (eg, MVI-12).

Interference with oral anticoagulant therapy — In a study of healthy subjects stably anticoagulated with the vitamin K antagonist (VKA) acenocoumarol, use of food supplements providing up to 100 micrograms/day of vitamin K1 did not significantly interfere with treatment [29]. The threshold dose of vitamin K1 causing a statistically significant lowering of the INR in these subjects was 150 micrograms/day, an amount easily exceeded following the ingestion of one-half cup of kale (table 2).

Treatment of coagulopathy — Depending upon the cause of deficiency, vitamin K can be administered in doses of one to 25 mg via oral, intramuscular, subcutaneous, or intravenous routes. When vitamin K deficiency

occurs in patients who are also receiving coumarin-like anticoagulants, doses of vitamin K should be minimized in order to prevent refractoriness to further anticoagulation. (See "Management of warfarin-associated bleeding or supratherapeutic INR", section on 'Vitamin K dose, route, formulation'.)

Vitamin K status can be determined indirectly by measuring vitamin K-dependent factors (ie, prothrombin, factors VII, IX, X, or protein C). In patients who are vitamin K deficient, levels of these factors often are less than 50 percent of normal [23]. Measurement of des-gamma-carboxyprothrombin (DCP) in plasma is another more sensitive way of determining vitamin K deficiency. In normal subjects, DCP is zero; it is elevated in vitamin K deficiency from whatever cause and/or liver disease [30].

Prevention of vitamin K deficient bleeding in newborns — There is general consensus that all babies should receive vitamin K. Standard treatment is with vitamin K (0.5 to 1 mg IM) administered at birth. For healthy, exclusively breastfed, term infants, an alternative strategy may be oral vitamin K1 (2 mg orally with the first feed and at one, four, and eight weeks of age). However, oral supplements may be less effective in preventing late-onset vitamin K deficient bleeding in infants, and no approved oral preparation is available in the United States. (See "Overview of the routine management of the healthy newborn infant".)

Administration of a second "booster" dose of vitamin K to selected infants has been suggested as a possible approach to prevent intracranial hemorrhage (ICH) due to late-onset vitamin K deficient bleeding (VKDB). Further studies are needed to determine the efficacy of this approach and selection factors. (See 'Vitamin K deficient bleeding in newborns and young infants' above.)

The Adequate Intake for vitamin K, as defined by the Food and Nutrition Board is not increased for lactating mothers. However, one study suggests that exclusively breast-fed infants often have low plasma vitamin K concentrations, and that this can be prevented by supplementation of the mothers' diet with 5 mg of vitamin K1 (phylloquinone) throughout the first 12 weeks of life [31,32]. No studies have evaluated whether maternal supplementation with vitamin K has any clinically important benefits.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Warfarin (Coumadin) (Beyond the Basics)")

SUMMARY

- Dietary vitamin K1 (phylloquinone or phytonadione) is found in green vegetables like spinach and broccoli (table 2). The dietary requirement, expressed as adequate intake (AI) is 90 micrograms daily in women and 120 micrograms daily in men (table 4). Gut micro-flora synthesizes vitamin K2 (menaquinones, including menatetrenone), which provides a portion of the dietary requirement of vitamin K. Vitamin K absorption requires intact pancreatic and biliary function and fat absorptive mechanisms. (See 'Sources' above and 'Metabolism' above.)

- Vitamin K is essential for activity of several carboxylase enzymes within the hepatic cells and therefore is necessary for the activation of coagulation factors VII, IX, X, and prothrombin. The natural anticoagulants proteins S and C also require vitamin K for their activity. (See 'Actions' above.)

- Coumarin-like anticoagulants are similar in structure to vitamin K (figure 1) and interrupt the vitamin K dependent carboxylation cycle. Vitamin K administration is one of the methods used to reverse the effects of coumarin. Patients with severely impaired liver function do not respond well to vitamin K supplementation, and coumarin-induced coagulopathy is not as easily reversed. (See 'Mechanism of action of the coumarin-like family' above.)

- Vitamin K is a cofactor for some proteins involved in bone mineralization. Clinical trials have examined the use of vitamin K1 (phylloquinone) or vitamin K2 for the treatment of osteoporosis, with conflicting results. (See 'Bone formation' above and "Overview of the management of osteoporosis in postmenopausal women", section on 'Therapies not recommended'.)

- Clinical signs and symptoms of vitamin K deficiency include easy bruisability, mucosal bleeding, splinter hemorrhages, melena, hematuria, or any other manifestations of impaired coagulation. Vitamin K deficiency in an otherwise healthy adult is rare. Patients at risk for vitamin K deficiency include those on long-term broad-spectrum antibiotics or those with fat malabsorption for a variety of reasons, including disorders of bile or pancreatic secretion, or extensive disease or resection of the intestinal mucosa. (See 'Causes' above.)

- Vitamin K deficiency is common in the newborn because of immature liver function and low transfer of vitamin K through the placenta or breast milk. If vitamin K is not replaced, the infant is at risk for vitamin K deficient bleeding (VKDB), previously known as hemorrhagic disease of the newborn. This disorder is associated with cutaneous, gastrointestinal, and intracranial bleeding in neonates, typically developing within the first week of life. To prevent VKDB, standard treatment is with vitamin K1 (0.5 to 1 mg IM) administered at birth. (See 'Vitamin K deficient bleeding in newborns and young infants' above and 'Prevention of vitamin K deficient bleeding in newborns' above.)

- Vitamin K deficiency causes prolonged prothrombin time (PT) and International Normalized Ratio (INR). In more severe vitamin K deficiency, the partial thromboplastin time (PTT) also may be affected. Levels of PIVKA-II (proteins induced in vitamin K absence) are more sensitive than PT in detecting vitamin K deficiency and may be helpful in monitoring patients with diseases predisposing to vitamin K deficiency. (See 'Laboratory evaluation' above.)

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Topic 2624 Version 26.0

GRAPHICS

Clinical symptoms of selected vitamin deficiencies

Vitamin	Deficiency syndrome
Water-soluble vitamins	
Vitamin B1 (thiamine)	Beriberi – Congestive heart failure (wet beriberi), aphonia, peripheral neuropathy, Wernicke encephalopathy (nystagmus, ophthalmoplegia, ataxia), confusion, or coma
Vitamin B2 (riboflavin)	Nonspecific symptoms including edema of mucous membranes, angular stomatitis, glossitis, and seborrheic dermatitis (eg, nose, scrotum)
Niacin (nicotinic acid)	Pellagra – Dermatitis on areas exposed to sunlight; diarrhea with vomiting, dysphagia, mouth inflammation (glossitis, angular stomatitis, cheilitis); headache, dementia, peripheral neuropathy, loss of memory, psychosis, delirium, catatonia
Vitamin B6 (pyridoxine, pyridoxal)	Anemia, weakness, insomnia, difficulty walking, nasolabial seborrheic dermatitis, cheilosis, stomatitis
Vitamin B12 (cobalamin)	Megaloblastic anemia (pernicious anemia), peripheral neuropathy with impaired proprioception and slowed mentation
Folate	Megaloblastic anemia
Biotin	Nonspecific symptoms including altered mental status, myalgia, dysesthesias, anorexia, maculosquamous dermatitis
Pantothenate	Nonspecific symptoms including paresthesias, dysesthesias ("burning feet"), anemia, gastrointestinal symptoms
Vitamin C (ascorbate)	Scurvy – fatigue, petechiae, ecchymoses, bleeding gums, depression, dry skin, impaired wound healing
Fat-soluble vitamins	
Vitamin A (retinol, retinal, retinoic acid)	Night blindness, xerophthalmia, keratomalacia, Bitot spot, follicular hyperkeratosis
Vitamin D (cholecalciferol, ergocalciferol)	Rickets, osteomalacia, craniotabes, rachitic rosary
Vitamin E (tocopherols)	Sensory and motor neuropathy, ataxia, retinal degeneration, hemolytic anemia
Vitamin K (phylloquinone, menaquinone, menadione)	Hemorrhagic disease

Graphic 63827 Version 11.0

Amount of vitamin K in different foods

Food name	Serving size	Vitamin K (micrograms)
High vitamin K foods		
Brussels sprouts, fresh (cooked, drained)	1/2 cup	110
Brussels sprouts, frozen (cooked, drained)	1/2 cup	150
Greens, beet, fresh (cooked, drained)	1/2 cup	350
Greens, collard, frozen (cooked, drained)	1/2 cup	530
Greens, collard, fresh (cooked, drained)	1/2 cup	365
Greens, mustard, fresh (cooked, drained)	1/2 cup	415
Greens, turnip, fresh (cooked, drained)	1/2 cup	265
Greens, turnip, frozen (cooked, drained)	1/2 cup	425
Kale, fresh (cooked, drained)	1/2 cup	530
Kale, frozen (cooked, drained)	1/2 cup	565
Spinach, fresh (cooked, drained)	1/2 cup	444
Spinach, frozen (cooked, drained)	1/2 cup	514
Spinach, fresh (raw)	1 cup	150
Medium vitamin K foods		
Asparagus, frozen (cooked, drained)	1/2 cup	72
	4 spears	48
Asparagus, fresh (cooked, drained)	4 spears	30
Beans, green or yellow, fresh (cooked, drained)	1/2 cup	10
Broccoli, fresh (cooked, drained)	1 spear	26
Broccoli, frozen (cooked, drained)	1/2 cup	80
Broccoli, raw	1/2 cup	45
Cabbage (cooked, drained)	1/2 cup	80
Cabbage, Chinese bok choy (cooked, drained)	1/2 cup	28
Cabbage, green (raw)	1/2 cup	26
Cabbage, red (raw)	1/2 cup	14
Cabbage, Savoy (raw)	1/2 cup	24
Calcium soft chews (brand name Viactiv with D) see note below about other vitamin pills	1 chew	40
Carrots, fresh or frozen (cooked, drained)	1/2 cup	10
Cauliflower, fresh or frozen (raw or cooked, drained)	1/2 cup	10
Celery, raw	1/2 cup	17
Coleslaw (fast food-type)	1/2 cup	37
Endive	1/2 cup	60
Lettuce (butterhead, Boston, Bibb)	1/2 head	80
Lettuce (iceberg, crisphead)	1/2 head	65
Lettuce (romaine, cos)	1 cup	57
Lettuce (green leaf)	1 cup	97

Oil, canola	1 tablespoon	17
Okra, fresh (cooked, drained)	1/2 cup	32
Okra, frozen (cooked, drained)	1/2 cup	44
Peas, frozen, with pod (cooked, drained)	1/2 cup	24
Peas, fresh, with pod (cooked, drained)	1/2 cup	20
Peas, green, frozen (cooked, drained)	1/2 cup	18
Pickle relish, sweet	1 tablespoon	13
Pickles, cucumber dill or kosher dill	1 pickle	25
Sauerkraut, canned	1/2 cup	56
Vegetables, mixed frozen or canned (cooked, drained)	1/2 cup	20
Low vitamin K foods		
Avocado	1 ounce	All of these foods have less than 10 micrograms of vitamin K per serving
Bananas	1 banana	
Chickpeas (garbanzo beans)	1/2 cup	
Corn	1/2 cup	
Fruit (fresh, frozen or canned including apples, nectarines, peaches, watermelon)	Whole piece of fresh fruit, 1 wedge of watermelon, or 1/2 cup	
Mayonnaise	1 tablespoon	
Oil, olive	1 tablespoon	
Oil, other (including peanut, sesame, safflower, corn, sunflower, soybean)	1 tablespoon	
Peppers, green or red	1/2 pepper or 1/2 cup	
Potatoes	1 potato or 1/2 cup	
Seaweed, kelp (raw)	1 tablespoon	
Tomatoes	1 tomato or 1/2 cup	
Foods very low in vitamin K, but have been occasionally implicated in warfarin or other drug interactions		
Cranberry juice	4 ounces juice	We suggest limiting the amount of these to one or two servings per day
Grapefruit	4 ounces juice	
	1/2 grapefruit	
Green tea, brewed	4 ounces	

The goal is to take in similar amounts of vitamin K daily rather than to eliminate sources of high vitamin K intake. Note that vitamins, herbs, and supplements such as calcium soft chews may contain vitamin K.
A separate version of this table with additional information specifically for patients is available in UpToDate. Refer to patient information on medicines to prevent blood clots (warfarin) and the table included.

Data from: US Department of Agriculture, Agricultural Research Service. 2013. USDA Nutrient Database for Standard Reference, Release 25. Nutrient Data Laboratory Home Page, http://www.ars.usda.gov/nutrientdata. Accessed August 7, 2013.

Graphic 78708 Version 4.0

Biochemical similarity between vitamin K and warfarin molecules

Graphic 66755 Version 1.0

Known gamma-Carboxyglutamic acid-containing proteins

Blood clotting and regulatory proteins
Prothrombin
Factor VII
Factor IX
Factor X
Protein C
Protein S
Protein Z
Other proteins
Gas6
PRGP1
PRGP2

Bone proteins
Osteocalcin
Matrix Gla protein
Conopeptides
Conantokin G
Conantokin T

Data reproduced with permission from Furie, B, et al. Blood 1999; 93:1798.

Graphic 60052 Version 1.0

Biosynthetic pathway for vitamin K-dependent production of gamma-carboxyglutamic acid

It has been hypothesized that a free cysteine residue in the carboxylase converts vitamin KH2 into a "strong base" of sufficient basicity to abstract a hydrogen from the gamma-carbon of glutamic acid (shown in red). However, the role of a free cysteine in the carboxylation reaction is uncertain. Subsequently, CO2 is added to the gamma-carbon of glutamic acid to form gamma-carboxyglutamic acid. The activated vitamin K species collapses into vitamin K epoxide and is recycled back to vitamin KH2, following the action of two vitamin K reductases, one of which is inhibited by warfarin.

Data redrawn from Furie, B, Bouchard, BA, Furie, BC. Blood 1999;93:1798.

Graphic 61632 Version 2.0

Dietary reference intakes for fat-soluble vitamins

Nutrient	Age group	RDA*/AI¶	UL$^{\Delta}$	Adverse effects of excess
Vitamin A				
1 mcg retinol activity equivalent = 3.3 unit vitamin A		**Micrograms daily**	**Micrograms daily**	Ataxia, alopecia, hyperlipidemia, hepatotoxicity, bone and muscle pain; teratogenic
	Infants			
	0 to 6 months	400¶	600	
	7 to 12 months	500¶	600	
	Children			
	1 to 3 years	300	600	
	4 to 8 years	400	900	
	Males			
	9 to 13 years	600	1700	
	14 to 18 years	900	2800	
	≥19 years	900	3000	
	Females			
	9 to 13 years	600	1700	
	14 to 18 years	700	2800	
	≥19 years	700	3000	
	Pregnancy			
	<18 years	750	2800	
	≥19 years	770	3000	
	Lactation			
	<18 years	1200	2800	
	≥19 years	1300	3000	
Vitamin D				
(calciferol) 1 mcg calciferol = 40 int. unit		**Micrograms daily**	**Micrograms daily**	Hypercalcemia, hypercalciuria, polydipsia, polyuria, confusion, anorexia, vomiting, bone demineralization
	Infants			
	0 to 12 months	10 (400 int. unit)¶	0 to 6 months: 25 (1000 int. unit)	
			6 to 12 months: 37.5 (1500 int. unit)	
	Children and adolescents			
	1 to 18 years	15 (600 int. unit)	1 to 3 years: 62.5 (2500 int. unit)	
			4 to 8 years: 75 (3000 int. unit)	
			9 to 18 years: 100 (4000 int. unit)	
	Males and females (including pregnancy and lactation)			
	19 to 50 years	15 (600 int. unit)	100 (4000 int. unit)	
	50 to 70 years	15	100	
	>70 years	20 (800 int. unit)	100	
Vitamin E				
(alpha-tocopherol) 1 mg = 1.47 int. unit "natural source" vitamin E,		**Milligrams daily**	**Milligrams daily**	Increased risk of bleeding; possibly increased risk of
	Infants			
	0 to 6 months	4¶	ND	

or 2.2 int. unit synthetic vitamin E	7 to 12 months	5¶	ND	necrotizing enterocolitis in infants
	Children			
	1 to 3 years	6	200	
	4 to 8 years	7	300	
	Males and females (including pregnancy)			
	9 to 13 years	11	600	
	14 to 18 years	15	800	
	>18 years	15	1000	
	Lactation			
	≤18 years	19	800	
	>19 years	19	1000	
Vitamin K				
		Micrograms daily	**Micrograms daily**	No adverse effects associated with vitamin K consumption from food or supplements have been reported; however, data are limited
	Infants			
	0 to 6 months	2¶	ND	
	7 to 12 months	2.5¶	ND	
	Children			
	1 to 3 years	30¶	ND	
	4 to 8 years	55¶	ND	
	Males			
	9 to 13 years	60¶	ND	
	14 to 18 years	75¶	ND	
	>19 years	120¶	ND	
	Females (including pregnancy and lactation)			
	9 to 13 years	60¶	ND	
	14 to 18 years	75¶	ND	
	>19 years	90¶	ND	

Vitamin A doses given as retinol activity equivalents (RAE). 1 RAE = 1 mcg retinol, 12 mcg beta-carotene, 14 mcg alpha-carotene, or 24 mcg beta-cryptoxanthin.

RDA: recommended dietary allowance; AI: adequate intake; UL: upper tolerable level.
* Values in this column represent the recommended dietary allowance (RDA) unless otherwise indicated. The RDA is the level of dietary intake that is sufficient to meet the daily nutrient requirements of 97 percent of the individuals in a specific life stage group.
¶ These values represent an adequate intake (AI). The AI represents an approximation of the average nutrient intake that sustains a defined nutritional state, based on observed or experimentally determined values in a defined population.
Δ The UL is the maximum level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals in the specified life-stage or gender group.

Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Otten JJ, Hellwig JP, Meyers LD (Eds), The National Academies Press, Washington, DC 2006. pp.530-541. Modified with permission from the National Academies Press, Copyright © 2006, National Academy of Sciences.
Sources: Dietary reference intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Panthothenic acid, Biotin, and Choline (1998); Dietary reference intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); Dietary Reference Intake reports of the Food and Nutrition Board, Institute of Medicine (2010). These reports may be accessed via www.nap.edu.

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