Sanford Medical Center

Aunt Cathy's Guide to:

Vitamin K --New Issues in Cardiovascular Health, Renal Health, Osteoporosis, Liver & Colon Cancer, Diabetes, Pregnancy & Varicose Veins (Short Version)

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1. **Overview/Summary: Vitamin K Top Ten**
2. **Some Vitamin K Facts and Figures**

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3. **<u>References from the Scientific Literature</u>:**

Inadequacy of Vitamin K and:

I. **Contribution to Cardiovascular Disease and Arterial and Renal Calcinosis**

II. **Contribution to Unsafe Variability of Anticoagulation Therapy**

III. **Contribution to Osteoporosis and Osteoarthritis and Rheumatoid Arthritis**

IV. **Potential Issues in Liver Cancer and Colorectal Cancer**

V. **Miscellaneous Health Issues: Non-warfarin-related hemorrhage, cholestasis, diarrhea, celiac disease, cystic fibrosis, short bowel syndrome, pregnancy, and odds and ends**

<u>This is the short form</u> of this paper with <u>just the references</u> at the end. Another version is available that includes the <u>abstracts</u> of the referenced articles. As always, this paper is a review of new issues in the scientific literature and not intended to take the place of your personal health care provider.

<u>In particular, individuals using anticoagulant medications like Coumadin/warfarin must not make changes in their vitamin K intake without consulting their physician/PA/NP</u>.

A separate paper for health professionals is available that discusses this issue in more detail.

Overview/Summary: Vitamin K Issues

1. Vitamin K has been found to be **involved in carboxylation reactions in various tissues**. As a result, it is now recognized as playing a critical role in bone health, growth, diabetes, pregnancy, cardiovascular health, renal health, and certain cancers, in addition to its well-known role in blood coagulation. **Allowing (or inducing) vitamin K deficiency for any reason is clearly not benign.**

2. Foods that are generous in vitamin K1 are also excellent sources of beneficial antioxidant phytochemicals. This includes lutein, a pigment in leafy greens that appears to have an additional unique potential benefit in the prevention or the slowing of the progression of blindness due to macular degeneration. These foods are also very low in calories and rich in other vitamins and minerals as well. However, **many Americans eat very few of these foods** and as a result, relative vitamin K inadequacy is not at all uncommon when it is actually checked. (It is currently only very rarely checked.) The most generous dietary vitamin K_2 sources include bacterially fermented foods. One of the richest is natto … a strong flavored soy bean product popular in Japan but considerably less so in the US.

3. **Elderly people appear to require a regular intake of vitamin K above the 2001 "Adequate Intake" (AI) level in order to assure adequacy.** Note that the recommended amounts for everyone (AIs, RDI, RDA, etc.) were set at a time when it was assumed that intestinal bacteria provided about half of one's requirements. As this source has been found to be more unreliable than was thought, it is very reasonable to aim toward an intake that is generous. People using the drug Coumadin need to discuss this issue with their physician as described below in #6 and #8 because of a drug/nutrient interaction. However**, except for this well-known drug/nutrient interaction, there is no upper level of safety for vitamin K and foods rich in vitamin K are rich in many other nutrients as well.**

4. **Vitamin K as phylloquinone (K_1) and menaquinone (K_2) are not toxic, and for that reason there is no "Upper Limit of Safety" established for this vitamin.** In contrast, menadione (K_3) is potentially harmful and it is generally no longer used as a vitamin K supplement. It was previously assumed that about half of a person's vitamin K requirements were met via production by intestinal bacteria. It is now clear that **healthy people are in fact MUCH more dependent on vitamin K from foods and/or supplements to assure adequacy than we thought.**

5. **Misunderstanding about recommendations for vitamin K intake for people on anticoagulant therapy has resulted in many people avoiding all sources of vitamin K** (instead of taking in a CONSISTENT but ADEQUATE amount of vitamin K as recommended by the drug manufacturers.) One result, for example, is the association seen between anticoagulant use and **increased risk of osteoporosis and cardiac and renal calcification** . Initially it was thought to be due to the drug itself, but it turned out to be related to the far too common inappropriate excessive restriction of vitamin K.

6. **It appears that dangerous VARIABILITY of blood clotting among some patients taking anticoagulants can be controlled significantly by assuring a consistent daily intake of an adequate amount of vitamin K.** Coagulation variability is a much greater problem among patients whose usual vitamin K status is low. Those are the people most greatly affected by fluctuations in vitamin K content of diet or supplements. Persons with a reliable adequate intake level are far less affected by additional intake in vitamin K.

7. **Vascular calcification, a known cardiovascular risk factor, is another side effect related to the problem of inducing low vitamin K status** in patients on anticoagulants and among the population at large. Failure to activate the hormone osteocalcin because of inadequate vitamin K results in failure to move calcium from the bloodstream into bone. Instead, calcium is deposited inappropriately in other tissues, such as blood vessel walls and the kidneys. **This results in arteriocalcinosis (an independent risk factor for cardiovascular disease.) It also results in renal** calcinosis because increased calcium needs to be excreted.

8. **Vitamin K inadequacy is now being identified even among healthy children** when vitamin K status is evaluated …however, at present it is only very rarely evaluated. People with **conditions that result in malabsorption** are at very high risk of deficiency. This includes conditions like **cystic fibrosis, poorly controlled celiac disease, Crohn's disease (inflammatory bowel disease or IBD,) biliary atresia, short bowel syndrome and intractable diarrhea.**

Others at particular risk of inadequacy of vitamin K include people using drugs that interfere with vitamin K such as **salicylates** (e.g. aspirin) and many **seizure-control medications.** Similarly, some renal medications used to bind phosphate in the intestine (e.g. **sevelamer-HCl**) can greatly impair vitamin K absorption. [Metal ion and vitamin adsorption profiles of phosphate binder ion-exchange resins. Clin Nephrol. 2010 Jan;73(1):30-5.

Assuring vitamin K adequacy in **pregnant and breast-feeding women** is an important new focus. Vitamin K inadequacy in pregnancy has recently been identified as a risk factor for **pregnancy complications** like hyperemesis gravidarum, pre-eclampsia, intracranial bleeding in the infant, and excessive blood loss at delivery. Although vitamin K transfer across the placenta is noted to be poor, relative inadequacy in pregnancy can also contribute to poor nutrient stores in infants.

Whether more generous maternal stores of vitamin K might enhance the transfer to the fetus has not been evaluated. The recommendation of the American Academy of Pediatrics is to provide vitamin K to newborns. Additionally, breast-fed babies are noted to be at higher risk of inadequacy apparently for the same reason … low vitamin K content of mother's milk. Again, whether relative maternal vitamin K inadequacy is a factor in the breastmilk vitamin K content has not been evaluated yet.

[American Academy of Pediatrics Policy Statement: Controversies Concerning Vitamin K and the Newborn Committee on Fetus and Newborn Pediatrics Vol. 112 No. 1 July 2003, pp. 191-192]

9. **New roles of vitamin K are being recognized.** For example, failure to activate osteocalcin because of inadequate vitamin K appears to have a negative effect on **energy metabolism, including insulin metabolism**. A possible role of vitamin K inadequacy in **diabetes and obesity** is just beginning to be examined. This is in addition to the cardiovascular, bone, and renal health issues.

   Assuring vitamin K adequacy appears to be a factor in some aspects in the prevention or treatment of cancers of the liver, colon/rectum, prostate, pancreas and ovaries. Other recent areas of investigation include a role of vitamin K inadequacy in **hypertension** (high blood pressure) and **inflammatory diseases** such as **arthritis**. Dietary vitamin K appears to have a role in **sulfatide metabolism, myelin structure and behavior functions.**

10. All of the health concerns described above are made less severe by the same intervention:

Assure adequacy of vitamin K status for everyone from foods and/or supplements. (Do not ASSUME adequacy.)

If a person is on the anticoagulant medication Coumadin*, assure that the vitamin K is administered in a consistent manner each day and that the physician has approved any adjustments of vitamin K intake.

Remember that inducing a vitamin K deficiency is common in this context, makes the drug use more dangerous, and causes damage to the cardiovascular system, the renal system, bone health and increases risk of certain cancers.

*Note that many anticoagulants do not involve vitamin K in their function as Coumadin does, so it makes even less sense to restrict vitamin K with these medications.

Adjust intake recommendations to compensate for conditions associated with malabsorption and the effects of aging.

Some Vitamin K Facts and Figures

Adequate Intake (AI) for Vitamin K		
Life Stage	**Age**	**mcg/day**
Infants	0-6 months	2.0
Infants	7-12 months	2.5
Children	1-3 years	30
Children	4-13 years	55
Adolescents	14-18 years	75
Adults *	19 years and older	Males 120 Females 90
Pregnancy or Breastfeeding	18 years and younger	75
Pregnancy or Breastfeeding	19 years and older	90

Food and Nutrition Board, Institute of Medicine. Vitamin K. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington D.C.: National Academy Press; 2001:162-196.

***Older adults [for sure] may benefit from higher regular intakes than are listed in the the Advisable Intakes (AIs.)** These were developed with the assumption that intestinal production of usable vitamin K provided a more significant amount. Current AIs for other age groups have not been re-evaluated since the discovery that the intestinal bacterial sources are far less available than was believed, so it is not just the elderly who may be at risk. The rest have not been checked yet.

Vitamin K status in the elderly. Curr Opin Clin Nutr Metab Care. 2007 Jan;10(1):20-3.

Sources

Leafy Vegetable Food Sources

Phylloquinone (vitamin K_1) is a major dietary form of vitamin K, and the major food source is leafy green vegetables. Not all green vegetables are good sources . . . it's the darker leafy ones that have the most! Additional benefits of these foods are the extremely low calories and the generous provision of other vitamins (such as vitamin C and vitamin A as beta carotene) and potent antioxidant phytochemicals such as lutein.

There are many excellent reasons to include these foods in one's diet. This is also true for people using anticoagulation medications like Coumadin (warfarin.) As described earlier, the goal is to assure both an adequate intake of vitamin K and a consistent level of intake. No one benefits from vitamin K deficiency.

Food	**Serving**	**Vitamin K_1 (mcg)**
Seaweed, dulse dried	100g (3.5 oz)	1700
Kale, raw	1 cup (chopped)	547
Broccoli, cooked	1 cup (chopped)	420
Parsley, raw	1 cup (chopped)	324
Swiss chard, raw	1 cup (chopped)	299
Green tea, dried	1 oz (28 g)	199
Spinach, raw	1 cup (chopped)	120
Leaf lettuce, raw	1 cup (shredded)	118
Iceberg lettuce	1 leaf (20 g)	22
Watercress, raw	1 cup (chopped)	20-85 (various refs)

Pennington, JA. Bowes & Church's Food Values of Portions Commonly Used, Ed. 16 Phil: Lippincott Co., 1994

Some is available in vegetable oils as shown on the next page, but they contribute far less vitamin K than leafy green vegetables. And, it is fairly impractical and also unwise to suggest that people attempt to meet their vitamin K requirements by increasing fat intake substantially. Additionally, hydrogenation of vegetable oils may decrease the absorption and biological effect of dietary vitamin K.

(Effects of a hydrogenated form of vitamin K on bone formation and resorption. Am J Clin Nutr. 2001;74(6):783-790.)

Oil Food Sources:

Food	Serving	Vitamin K_1 (mcg)
Soybean oil	1 Tablespoon	26 – 76 (various refs)
Canola oil	1 Tablespoon	20
Mayonnaise	1 Tablespoon	12
Corn oil	1 Tablespoon	0 - 7 (various refs)
Olive oil	1 Tablespoon	8

Animal Food Sources:

Food	Serving	Vitamin K_1 (mcg)
Meat	3.5 oz	4
Raw Beef Liver (others less)	3.5 oz	104
Milk	8 oz	10
Egg Yolk	1 large	25

Fermented Food Sources:

Food	Serving	Vitamin K_2 (mcg)
Natto (fermented soybeans)	1 oz	245
Curd Cheese	1 oz	20

Non-Food Sources: Intestinal Bacteria

Bacteria that normally colonize the large intestine synthesize menaquinones (vitamin K_2), which are active forms of vitamin K. Until recently it was thought that up to 50% of the human vitamin K requirement might be met by this bacterial synthesis. Recent research

indicates that the contribution of intestinal bacterial synthesis is much less than previously thought, although the exact contribution remains unclear. Most of our menaquinones we actually make ourselves from phylloquinone. **The likelihood is that even healthy people are more dependent on food sources of vitamin K than we previously believed.** Individuals taking chronic antibiotics are far more dependent on food or supplement sources, of course, because these "friendly" colonic bacteria are killed by the medication as well.

(Suttie JW. The importance of menaquinones in human nutrition. Annu Rev Nutr. 1995;15:399-417.)

Non-Food Sources: Supplements

In the U.S. vitamin K_1 is available without a prescription in multivitamin and other supplements in doses that generally range from 10-120 mcg per dose. Vitamin K_2 supplements are also available now.

(PDR for Nutritional Supplements. Montvale: Medical Economics Company, Inc; 2001.)

The amount of vitamin K associated with a decreased risk of hip fracture in the Framingham Heart Study was about 250 mcg/day. This can be obtained from a little more than 1/2 cup of chopped broccoli or a large salad of mixed greens every day. **A multivitamin with minerals that provides at least the AI level of vitamin K would also be an excellent idea, and the label should be checked closely because vitamin K is notoriously variable between various products.**

Many vitamin supplement products contain none because of the earlier assumptions about the GI bacterial sources providing a significant amount. Some chewable calcium supplements provide some vitamin K and vitamin D. Again, check the label. A form of vitamin K_2, menatetrenone (MK-4) has been used to treat osteoporosis in Japan and is currently under study in the U.S National Institutes of Health. K2 as MK-7 is the form produced in natto.

Many earlier references state that vitamin K inadequacy is extremely unusual in adults. Testing for vitamin K inadequacy is also generally rare because inadequacy is assumed to not be a problem. Traditionally testing involves measuring prothrombin time. However, it appears that this hematological manifestation of inadequacy may not reflect adequacy of vitamin K for other functions. For example, newer studies use **undercarboxylated osteocalcin** or other measures as a marker of vitamin K inadequacy in bone and cardiovascular applications in particular.

Vitamin K adequacy has not been in the public health radar … or the radar of health care professionals. Consider, for example, the mypyramid.gov guidelines*, which are an effort to help people achieve an advisable intake of all nutrients over two weeks in 2000 kcals/day. **Vitamin K is simply not included in the analysis**. Vitamin D is missing as well. Apparently these nutrients are assumed to be adequate because "you can make your own." In the case of vitamin D, this assumed adequacy is now being discarded because of the overwhelming evidence that vitamin D deficiency is actually a huge but previously unrecognized public health problem. It is possible that the assumption of vitamin K adequacy may turn out to be

similarly suspect. **In any case, with the clear safety of generous vitamin K in normal circumstances, it would be advisable to simply assure adequacy rather than to assume it.**
*(http://www.mypyramid.gov/downloads/sample_menu.pdf)

Vitamin K Nomenclature

Older nomenclature	IUPAC (abbreviation)
K_1	Phylloquinone (K)
$K_{2(n)}$	Menaquinone-n (MK-n)
$K_{2(4)}$	Menatetrenone (MK-4)
$K_{2(35)}$	Menaquinone-7 (MK-7)
K_3	Menadione

From Machlin, LJ. Handbook of Vitamins: Nutritional, Biochemical and Clinical Aspects. New York: Marcel Dekker, Inc.,1984

Toxicity Issues

There is no known toxicity associated with high doses of phylloquinone (vitamin K_1), or menaquinone (vitamin K_2) forms of vitamin K.

No tolerable upper level (UL) of intake of these forms of vitamin K has been established.

(Food and Nutrition Board, Institute of Medicine. Vitamin K. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington DC: National Academy Press; 2001:162-196.)

The same is not true for menadione (vitamin K_3) and its derivatives. Menadione can interfere with the function of glutathione, one of the body's natural antioxidants, resulting in oxidative damage to cell membranes. Menadione given by injection has induced liver toxicity,

jaundice, and hemolytic anemia (due to the rupture of red blood cells) in infants, and is no longer used for treatment of vitamin K deficiency.

Contrary to popular belief, the fat-soluble status of vitamin K does NOT make it more likely to be toxic than water soluble vitamins.

The toxicity traditionally ascribed somewhat globally to the fat soluble vitamins is in fact due to the fact that two of them (vitamins A and D) have actual hormonal messenger roles in the body. For this reason, relative inadequacy or excess of the active hormonal form of these two vitamins can actually induce metabolic changes to occur. The other two fat soluble vitamins (E and K) and the water soluble vitamins (C and the B vitamins) are much less likely to be toxic because they exert no hormonal influence on tissues.

The fact that a substance dissolves in butter is not a measure of its potential toxicity, although most of us were taught that it is. This is an important big change in our understanding

Mnemonic Devices:

I always find it hard to keep these kinds of terms and numbers straight, so I usually make up a little mnemonic device to help me out. Here's the one I use for remembering which form of vitamin K comes from which source, and which is K_1 and which is K_2 (Feel free to disregard this section and make up your own if you find these unhelpful. ☺)

Phylloquinone starts with a **P** … as in "**P**lants."

("Leafy greens" vitamin K is **P**hylloquinone)

I think of the kind made in people's intestines by bacteria or made in man from phylloquinone is **menaquinone** … that is, the kind made **"in men."**

(The kind of vitamin K made in **men** is **men**aquinone. Wo**men** too, of course.)

Because we convert phylloquinone to menaquinone for many of its uses, I think of **phylloquinone** (the spinach one) coming <u>first</u> **(K_1)** and **menaquinone** (the kind made in man out of K_1) as coming along <u>second</u>arily **(K_2)**

References by Topic:

(A version with <u>abstracts</u> of these references is also available.)

I. Inadequacy of Vitamin K:

Contribution to Cardiovascular Disease: Arterial Calcinosis, Renal Calcinosis, Diabetes, Inflammation and Hypertension

2010

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II. Inadequacy of Vitamin K:

Contribution to Unsafe Variability of Anticoagulation Therapy

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III. Inadequacy of Vitamin K:

Contribution to Osteoporosis, Osteoarthritis, Bone Development, Rheumatoid Arthritis, and Related Conditions

2010

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