

Aunt Cathy's Guide to:

**Vitamin K --  
New Issues in  
Cardiovascular Health,  
Osteoporosis and Cancer  
of the Liver and Colon  
(Short Version)**



**AUNT CATHY**

Cathy Breedon PhD, RD, CSP, FADA  
Prenatal/Pediatric Nutrition Specialist  
Clinical Nutrition Specialist  
MeritCare Medical Center, Fargo, ND  
and UND School of Medicine

**1. Overview/Summary: Vitamin K Top Ten**

**2. Some Vitamin K Facts and Figures**

**(All the important useful information is on pp. 1-7)**

**3. References from the Scientific Literature:**

**Inadequacy of Vitamin K and:**

- I. Contribution to Unsafe Variability of Anticoagulation Therapy**
- II. Contribution to Cardiovascular Disease and Arterial Calcinosi**
- 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**

**This is the short form of this paper with just the references at the end. Another version is available on line that includes the abstracts 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.

**In particular, individuals using anticoagulant medications like Coumadin/warfarin must not make changes in their vitamin K intake without consulting their physicians.**

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

## Overview/Summary: Vitamin K Top Ten

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 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 K 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.)
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 (K1) and menaquinone (K2) are generally not toxic, and for that reason there is no “Upper Limit of Safety” established for this vitamin.** In contrast, menadione (K3) is potentially harmful and it is 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.** This is even more the case among people chronically on antibiotic therapy.
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**. 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.

**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.

6. **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.
7. **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.**
8. **New roles of vitamin K are being recognized.** For example, failure to activate osteocalcin 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.

**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 possible role of vitamin K inadequacy in **hypertension** (high blood pressure) and **inflammatory diseases** such as **arthritis.**

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 pre-eclampsia, hyperemesis gravidarum, intracranial bleeding in the infant, and excessive blood loss at delivery. Inadequacy in pregnancy resulting in poor nutrient stores in infants is likely a major reason for the recommendation of the American Academy of Pediatrics that we provide vitamin K to newborns. Additionally, breast-fed babies are noted to be at higher risk of inadequacy apparently for the same reason ... maternal vitamin K inadequacy.

[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. **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.**

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

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

**Some Vitamin K Facts and Figures**

<b>Adequate Intake (AI) for Vitamin K</b>			
<b>Life Stage</b>	<b>Age</b>	<b>Males (mcg/day)</b>	<b>Females (mcg/day)</b>
Infants	0-6 months	2.0	2.0
Infants	7-12 months	2.5	2.5
Children	1-3 years	30	30
Children	4-8 years	55	55
Children	9-13 years	60	60
Adolescents	14-18 years	75	75
Adults *	19 years and older	120*	90*
Pregnancy	18 years and younger	-	75
Pregnancy	19 years and older	-	90
Breastfeeding	18 years and younger	-	75
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 may benefit from higher regular intakes than are listed in the AIs.**

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

## Sources

### Food sources

Phylloquinone (vitamin K<sub>1</sub>) is the 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 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. 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 (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.)

Food	Serving	Vitamin K (mcg)
Soybean oil	1 Tablespoon	26.1 – 76 (various refs)
Canola oil	1 Tablespoon	19.7
Mayonnaise	1 Tablespoon	11.9
Corn oil	1 Tablespoon	0 - 6.6 (various refs)
Olive oil	1 Tablespoon	8.0

## Non-Food Sources: Intestinal Bacteria

Bacteria that normally colonize the large intestine synthesize menaquinones (vitamin K<sub>2</sub>), which are an active form of vitamin K. Until recently it was thought that up to 50% of the human vitamin K requirement might be met by bacterial synthesis. Recent research indicates that the contribution of bacterial synthesis is much less than previously thought, although the exact contribution remains unclear. **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<sub>1</sub> is available without a prescription in multivitamin and other supplements in doses that generally range from 10-120 mcg per dose.

(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 products contain none because of the earlier assumptions about the GI sources. Some chewable calcium supplements provide some vitamin K and vitamin D. Again, check the label. A form of vitamin K<sub>2</sub>, menatetrenone (MK-4) has been used to treat osteoporosis in Japan and is currently under study in the U.S National Institutes of Health.

## Vitamin K Nomenclature

Older nomenclature	IUPAC (abbreviation)	IUNS (abbreviation)
K1	Phylloquinone (K)	Phytolmenaquinone (PMQ)
K <sub>2(n)</sub>	Menaquinone-n (MK-n)	Prenylmenaquinone-n (MQ)
K <sub>2(4)</sub>	Menatetrenone (MK-4)	
K <sub>2(35)</sub>	Menaquinone-7 (MK-7)	Prenylmenaquinone-7 (MQ-7)
K3	Menadione	Menaquinone

From Machlin, L.J. 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<sub>1</sub>), or menaquinone (vitamin K<sub>2</sub>) 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<sub>3</sub>) 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 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.

# References by Topic:

(A version with abstracts of these references is also available.)

## **I. Inadequacy of Vitamin K: Contribution to Unsafe Variability of Anticoagulation Therapy**

### **2009**

J Manag Care Pharm. 2009 Apr;15(3):244-52. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States.

Blood Coagul Fibrinolysis. 2009 Apr 3. Erythrocyte folate and 5-methyltetrahydrofolate levels decline during 6 months of oral anticoagulation with warfarin.

### **2008**

Hamostaseologie. 2008 Feb;28(1-2):44-50 New insight in therapeutic anticoagulation by Coumarin Derivatives.

J Thromb Haemost. 2008 Jul;6(7):1226-8. Vitamin K epoxide reductase complex subunit 1 (VKORC1 ) polymorphism influences the anticoagulation response subsequent to vitamin K intake: a pilot study

Vitam Horm. 2008;78:265-79 Vitamin K and thrombosis.

### **2007**

J Thromb Haemost. 2007 Oct;5(10):2043-8..Daily vitamin K supplementation improves anticoagulant stability.

Thromb Haemost. 2007 Jul;98(1):120-5. Vitamin K: The coagulation vitamin that became omnipotent.

INRJ Thromb Thrombolysis. 2007 Feb 24; Prospective study of supplemental vitamin K therapy in patients on oral anticoagulants with unstable international normalized ratios.

J Am Diet Assoc. 2007 Nov;107(11):2022. Vitamin K: what are the current dietary recommendations for patients taking coumadin?

Curr Opin Clin Nutr Metab Care. 2007 Jan;10(1):1-5. Dietary vitamin K intake & anticoagulation in elderly patients.

### **2006**

Blood. 2006 Nov 16 Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin.

Int J Vitam Nutr Res. 2006 Mar;76(2):65-74. Dietary vitamin K variability affects International Normalized Ratio (INR) coagulation indices.

### **2004-2005**

Pharmacotherapy. 2005 Dec;25(12):1746-51. Low-dose vitamin K to augment anticoagulation control.

Am J Cardiovasc Drugs. 2004;4(1):43-55. The use of vitamin K in patients on anticoagulant therapy: a practical guide.

## **II. Inadequacy of Vitamin K: Contribution to Cardiovascular Disease: Arterial Calcinosi s, Renal Calcinosi s, Diabetes, Inflammation and Hypertension**

### **2009**

- J Thromb Haemost. 2009 Sep 28. Warfarin use and the risk of valvular calcification.
- Int J Artif Organs. 2009 Feb;32(2):67-74. Coagulation meets calcification: The vitamin K system.
- J Bone Miner Res. 2009 Vitamin k and bone: past, present, and future.
- Br J Nutr. 2009 Apr 1:1-16 Minerals and vitamins in bone health: the potential value of dietary enhancement.
- Osteoporos Int. 2009 Mar 12 Prior treatment with vitamin K(2) significantly improves the efficacy of risedronate.
- J Bone Miner Metab. 2009;27(3):333-40. Short-term menatetrenone therapy increases gamma-carboxylation of osteocalcin with a moderate increase of bone turnover in postmenopausal osteoporosis: a randomized prospective study.
- Bioorg Med Chem Lett. 2009 Feb 15;19(4):1054-7. Elucidation of the mechanism producing menaquinone-4 in osteoblastic cells.
- J Bone Miner Res. 2009 Jun;24(6):983-91. Vitamin k treatment reduces undercarboxylated osteocalcin but does not alter bone turnover, density, or geometry in healthy postmenopausal north american women.
- J Mal Vasc. 2009 Apr 2. Origin of the mediocalcosis in kidney failure.

### **2008**

- Am J Clin Nutr. 2008 Jul;88(1):210-5. Phylloquinone intake, insulin sensitivity, and glycemic status in men and women.
- Atherosclerosis. 2008 Jul 19 Thromb Res. 2008;122(3):411-7. High dietary menaquinone intake is associated with reduced coronary calcification. Effects of the blood coagulation vitamin K as an inhibitor of arterial calcification.
- J Vasc Res. 2008 Apr 10;45(5):427-436. The Circulating Inactive Form of Matrix Gla Protein (ucMGP) as a Biomarker for Cardiovascular Calcification.
- Arterioscler Thromb Vasc Biol. 2008 Apr;28(4):771-6. Vitamin K epoxide reductase complex subunit 1 (VKORC1) polymorphism and aortic calcification: the Rotterdam Study.
- Am J Epidemiol. 2008 Feb 1;167(3):313-20. Vitamin K and vitamin D status: associations with inflammatory markers in the Framingham Offspring Study.
- Clin J Am Soc Nephrol. 2008 May 21. Vitamin K-dependent Proteins, Warfarin, and Vascular Calcification.
- Am J Clin Nutr. 2008 Jul;88(1):210-5. Phylloquinone intake, insulin sensitivity, and glycemic status in men and women.
- Cell Cycle. 2008 Jun;7(11):1575-9. Does the absence of ABCC6 (multidrug resistance protein 6) in patients with Pseudoxanthoma elasticum prevent the liver from providing sufficient vitamin K to the periphery?
- J Pharm Pharmacol. 2008 Jul;60(7):889-93. Mechanisms underlying the biphasic effect of vitamin K1 (phylloquinone) on arterial blood pressure.
- Curr Opin Lipidol. 2008 Feb;19(1):39-42. Vitamin K intake and atherosclerosis.

### **2007**

- J Atheroscler Thromb. 2007 Dec;14(6):317-24. Treatment with vitamin k(2) combined with bisphosphonates synergistically inhibits calcification in cultured smooth muscle cells.

- Nat Clin Pract Nephrol. 2007 Oct;3(10):522-3. Vascular calcification in chronic kidney disease: the role of vitamin K.
- Rhinology. 2007 Sep;45(3):208-13. Vitamin D3, vitamin K2, and warfarin regulate bone metabolism in human paranasal sinus bones.
- Thromb Haemost. 2007 Jul;98(1):120-5. Vitamin K: The coagulation vitamin that became omnipotent.
- Exp Anim. 2007 Jul;56(4):273-8. Vitamin K Deficiency of Germfree Mice Caused by Feeding Standard Purified Diet Sterilized by gamma-Irradiation. .
- Nutr Metab Cardiovasc Dis. 2007 Jan;17(1):58-62. Phylloquinone intake and risk of cardiovascular diseases in men.

### **2005-2006**

- Blood. 2006 Nov 30; Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats.
- Am J Health Syst Pharm. 2005 Aug 1;62(15):1574-81 Vitamin K in the treatment and prevention of osteoporosis and arterial calcification
- Eur J Clin Nutr. 2005 Feb;59(2):196-204 Phylloquinone intake as a marker for coronary heart disease risk but not stroke in women.
- Nutr Res. 2009 Apr;29(4):221-8. High-dose vitamin K supplementation reduces fracture incidence in postmenopausal women: a review of the literature.

## **III. Inadequacy of Vitamin K:**

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

#### **2009**

- Nutr Res. 2009 Apr;29(4):221-8. High-dose vitamin K supplementation reduces fracture incidence in postmenopausal women: a review of the literature.
- Br J Nutr. 2009 May 19;111(5):811-8. The effect of menaquinone-7 (vitamin K2) supplementation on osteocalcin carboxylation in healthy prepubertal children.
- J Nutr Sci Vitaminol (Tokyo). 2009 Feb;55(1):15-21. Effect of low dose vitamin K2 (MK-4) supplementation on bio-indices in postmenopausal Japanese women.

#### **2008**

- Calcif Tissue Int. 2008 Aug;83(2):121-8. Effects of vitamin k(2) and risedronate on bone formation and resorption, osteocyte lacunar system, & porosity in the cortical bone of glucocorticoid-treated rats.
- Ann Rheum Dis. 2008 Jul 14 Vitamin K in hand osteoarthritis: results from a Randomized Clinical Trial.
- Bone. 2008 Aug;43(2):230-7. Uptake of postprandial lipoproteins into bone in vivo: Impact on osteoblast function.
- Br J Nutr. 2008 Feb 18;103(2):1-7. Vitamin K status is associated with childhood bone mineral content.
- J Bone Miner Metab. 2008;26(3):260-4. Response of serum carboxylated and undercarboxylated osteocalcin to alendronate monotherapy and combined therapy with vitamin K2 in postmenopausal women.
- Am J Clin Nutr. 2008 May;87(5):1513-20. Vitamin K1 intake is associated with higher bone mineral density and reduced bone resorption in early postmenopausal Scottish women: no evidence of gene-nutrient interaction with apolipoprotein E polymorphisms.

- J Pharmacol Sci. 2008 Apr;106(4):530-5. Pharmacological topics of bone metabolism: recent advances in pharmacological management of osteoporosis.
- Proc Nutr Soc. 2008 May;67(2):163-76. Importance of calcium, vitamin D and vitamin K for osteoporosis prevention and treatment.
- J Biol Regul Homeost Agents. 2008 Jan-Mar;22(1):35-44. Vitamin K and D association stimulates in vitro osteoblast differentiation of fracture site derived human mesenchymal stem cells.
- Arch Pediatr. 2008 Mar;15(3):301-12. Recommendations for the management of bone demineralization in cystic fibrosis
- J Clin Endocrinol Metab. 2008 Apr;93(4):1217-23. Effect of vitamin K supplementation on bone loss in elderly men and women.
- Clin Calcium. 2008 Feb;18(2):224-32. Genomic approaches to bone and joint diseases. New insights into molecular mechanisms underlying protective effects of vitamin K on bone health
- Eur J Epidemiol. 2008;23(3):219-25. Association of hip fracture incidence and intake of calcium, magnesium, vitamin D, and vitamin K.
- J Cyst Fibros. 2008 Jul;7(4):307-12. Undercarboxylated osteocalcin and bone mass in 8-12 year old children with cystic fibrosis.
- J Nutr. 2008 Jan;138(1):172S-177S. The balance of bone health: tipping the scales in favor of potassium-rich, bicarbonate-rich foods.
- J Bone Miner Metab. 2008;26(1):79-85. Low plasma phylloquinone concentration is associated with high incidence of vertebral fracture in Japanese women.
- J Bone Miner Metab. 2008;26(1):9-12. Steroid and xenobiotic receptor mediates a novel vitamin K2 signaling pathway in osteoblastic cells.
- Br J Nutr. 2008 Jan;99(1):198-205. Nutrition and bone health projects funded by the UK Food Standards Agency: have they helped to inform public health policy?
- Clin Exp Rheumatol. 2008 May-Jun;26(3):484-91. Extremes in vitamin K status of bone are related to bone ultrasound properties in children with juvenile idiopathic arthritis.

## 2007

- Mayo Clin Health Lett. 2007 Nov;25(11):4. Vitamin K linked to bone strength.
- Pediatr Res. 2007 Mar;61(3):366-70. Pronounced elevation of undercarboxylated osteocalcin in healthy children.
- J Nutr Sci Vitaminol (Tokyo). 2007 Dec;53(6):464-70. Vitamin K content of foods and dietary vitamin K intake in Japanese young women.
- J Nutr Sci Vitaminol (Tokyo). 2007 Oct;53(5):419-25. Nutritional effects of gamma-glutamyl carboxylase gene polymorphism on the correlation between the vitamin K status and gamma-carboxylation of osteocalcin in young males.
- Clin Calcium. 2007 Nov;17(11):1752-60. Experience of vitamin K2 in Thailand
- Clin Calcium. 2007 Nov;17(11):1709-16. Clinical application of undercarboxylated osteocalcin
- Clin Calcium. 2007 Nov;17(11):1702-8. Measurement of serum undercarboxylated osteocalcin by ECLIA with the "Picolumi ucOC" kit.
- Osteoporos Int. 2007 Jul;18(7):963-72. Vitamin K2 supplementation improves hip bone geometry and bone strength indices in postmenopausal women.
- Int J Cardiol. 2007 Jun 12;118(3):338-44. Fracture risk in users of oral anticoagulants: a nationwide case-control study.
- Thromb Haemost. 2007 Jul;98(1):120-5. Vitamin K: The coagulation vitamin that became omnipotent.
- Curr Rheumatol Rep. 2007 Apr;9(1):85-92. Not just calcium and vitamin D: other nutritional considerations in osteoporosis.
- Curr Opin Clin Nutr Metab Care. 2007 Jan;10(1):20-3. Vitamin K status in the elderly.
- Int J Cardiol. 2007 Jun 12;118(3):338-44. Fracture risk in users of oral anticoagulants: a nationwide case-control study.

Comp Biochem Physiol B Biochem Mol Biol. 2007 May 29; Vitamin K deficiency inhibits mineralization & enhances deformity in vertebrae of haddock (*Melanogrammus aeglefinus* L.)  
Br J Nutr. 2007 Apr;97(4):661-6. Serum percentage undercarboxylated osteocalcin, a sensitive measure of vitamin K status, and its relationship to bone health indices in Danish girls.  
Exp Anim. 2007 Apr;56(2):103-10. Additive effect of vitamin K2 and risedronate on long bone mass in hypophysectomized young rats.  
J Bone Miner Metab. 2007;25(1):46-53. Effect of vitamin K2 and growth hormone on the long bones in hypophysectomized young rats: a bone histomorphometry study.  
Am J Kidney Dis. 2007 Mar;49(3):432-9. Subclinical vitamin K deficiency in hemodialysis patients.  
J Nutr Sci Vitaminol (Tokyo). 2007 Jun;53(3):219-24. vitamin K2 (menaquinone-4) on intestinal alkaline phosphatase activity in rats.

### 2006

Curr Drug Saf. 2006 Jan;1(1):87-97 Role of vitamin K2 in the treatment of postmenopausal osteoporosis.  
Clin Calcium. 2006 Sep;16(9):106-14 and Nutrition. 2006 Jul-Aug;22(7-8):845-52. (same article in both journals) Protective effects of vitamin K against osteoporosis and its pleiotropic actions  
J Nutr Sci Vitaminol (Tokyo). 2006 Oct;52(5):307-15. Beneficial effect of pretreatment and treatment continuation with risedronate and vitamin K2 on cancellous bone loss after ovariectomy in rats: a bone histomorphometry study.  
Arthritis Rheum. 2006 Apr;54(4):1255-61. Low vitamin K status is associated with osteoarthritis in the hand and knee.  
Calcif Tissue Int. 2006 Nov;79(5):318-25. Synergistic effect of vitamin K2 and prostaglandin E2 on cancellous bone mass in hypophysectomized young rats.  
Clin Calcium. 2006 Dec;16(12):2017-25. Present knowledge in nutritional aspects of fracture.  
Am J Clin Nutr. 2006 Feb;83(2):380-6. Vitamin K status of healthy Japanese women: age-related vitamin K requirement for gamma-carboxylation of osteocalcin.  
Int J Vitam Nutr Res. 2006 Nov;76(6):385-90. A preliminary assessment of vitamin K1 intakes and serum undercarboxylated osteocalcin levels in 11-13 year old Irish girls.  
Br J Nutr. 2006 May;95(5):982-8 Phylloquinone (vitamin K1) intakes and serum undercarboxylated osteocalcin levels in Irish postmenopausal women.

### 2004-2005

Am J Health Syst Pharm. 2005 Aug 1;62(15):1574-81 Vitamin K in the treatment and prevention of osteoporosis and arterial calcification.  
Curr Pharm Des. 2004;10(21):2557-76. Effects of vitamin K2 on osteoporosis.

## IV. Inadequacy of Vitamin K:

### Cancer: Liver, Colorectal, Prostate, Ovarian, Pancreatic and Cancer Risk in General

### 2008

Am J Clin Nutr. 2008 Apr;87(4):985-92. Dietary intake of vitamin K and risk of prostate cancer in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg).  
Biol Pharm Bull. 2008 Jun;31(6):1270-3. An attempt to evaluate the effect of vitamin K3 using as an enhancer of anticancer agents.

Vitam Horm. 2008;78:435-42 Hepatocellular carcinoma and vitamin K.

Am J Clin Nutr. 2008 Apr;87(4):985-92. Dietary intake of vitamin K and risk of prostate cancer in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg).

Cancer Sci. 2008 May;99(5):1040-8. DNA polymerase gamma inhibition by vitamin K3 induces mitochondria-mediated cytotoxicity in human cancer cells.

Cancer Lett. 2008 May 8;263(1):53-60. Vitamin K2 suppresses malignancy of HuH7 hepatoma cells via inhibition of connexin 43.

Anticancer Res. 2008 Jan-Feb;28(1A):45-50. The utility of vitamin K3 (menadione) against pancreatic cancer.

J Clin Pathol. 2008 Apr;61(4):537-40. A study of the prevalence of vitamin K deficiency in patients with cancer referred to a hospital palliative care team and its association with abnormal haemostasis.

J Cancer Res Clin Oncol. 2008 Jul;134(7):803-12. Induction of apoptosis in PA-1 ovarian cancer cells by vitamin K(2) is associated with an increase in the level of TR3/Nur77 and its accumulation in mitochondria and nuclei.

## 2007

Hepatogastroenterology. 2007 Oct-Nov;54(79):2073-7. Effect of vitamin K2 on the recurrence in patients with hepatocellular carcinoma.

Clin Calcium. 2007 Nov;17(11):1693-9. Clinical application of vitamin K for hepatocellular carcinoma.

Int J Mol Med. 2007 Dec;20(6):801-8. Vitamin K2-induced cell growth inhibition via autophagy formation in cholangiocellular carcinoma cell lines.

Int J Oncol. 2007 Aug;31(2):323-31. Vitamins K2, K3 and K5 exert antitumor effects on established colorectal cancer in mice by inducing apoptotic death of tumor cells.

Hepatol Res. 2007 Sep;37 Suppl 2:S303-7. Potential role of vitamin K(2) as a chemopreventive agent against hepatocellular carcinoma.

Hepatol Res. 2007 Sep;37 Suppl 2:S299-302. Chemoprevention of liver carcinogenesis with retinoids: Basic and clinical aspects.

World J Gastroenterol. 2007 Jun 21;13(23):3259-61. Combined treatment of vitamin K(2) and angiotensin-converting enzyme inhibitor ameliorates hepatic dysplastic nodule in a patient with liver cirrhosis.

Intern Med. 2007;46(11):711-5. Hepatocellular carcinoma with peritoneal dissemination which was regressed during vitamin K2 and vitamin E administration.

Am J Surg. 2007 Apr;193(4):431-7. A review of the prognostic factors in patients with recurrence after liver resection for hepatocellular carcinoma.

J Gastroenterol Hepatol. 2007 Apr;22(4):518-22. Preventive effects of vitamin K on recurrent disease in patients with hepatocellular carcinoma arising from hepatitis C viral infection.

Int J Oncol. 2007 Aug;31(2):323-31. Vitamins K2, K3 and K5 exert antitumor effects on established colorectal cancer in mice by inducing apoptotic death of tumor cells.

Cancer Sci. 2007 Mar;98(3):431-7. Synergistic growth inhibition by acyclic retinoid and vitamin K2 in human hepatocellular carcinoma cells.

Clin Cancer Res. 2007 Apr 1;13(7):2236-45. Menatetrenone, a vitamin K2 analogue, inhibits hepatocellular carcinoma cell growth by suppressing cyclin D1 expression through inhibition of nuclear factor kappaB activation.

J Gastroenterol Hepatol. 2007 Apr;22(4):518-22. Preventive effects of vitamin K on recurrent disease in patients with hepatocellular carcinoma arising from hepatitis C viral infection.

## 2006

Clin Calcium. 2006 Sep;16(9):106-14 and Nutrition. 2006 Jul-Aug;22(7-8):845-52. (same article in both journals) Protective effects of vitamin K against osteoporosis and its pleiotropic actions  
Cancer. 2006 Feb 15;106(4):867-72. The effect of menatetrenone, a vitamin K2 analog, on disease recurrence & survival in patients with hepatocellular carcinoma after curative treatment: a pilot study.

### Miscellaneous

#### **Vitamin K Deficiency Associated with Intestinal Malabsorption Problems**

Pediatrics. 2008 Nov;122(5):1014-20. Prevalence of low bone mass and deficiencies of vitamins D and K in pediatric patients with **cystic fibrosis** from 3 Canadian centers.

J Cyst Fibros. 2008 May 27. Efficacy of high dose phylloquinone in correcting vitamin K deficiency in **cystic fibrosis**.

Arch Pediatr. 2008 Mar;15(3):301-12. Epub 2008 Mar 5. Recommendations for the management of bone demineralization in **cystic fibrosis**

J Cyst Fibros. 2008 Jul;7(4):307-12. Undercarboxylated osteocalcin and bone mass in 8-12 year old children with **cystic fibrosis**.

Nutrition. 2008 Apr;24(4):330-9. Nutrient intake from habitual oral diet in patients with severe **short bowel syndrome** living in the southeastern United States.

Tohoku J Exp Med. 2007 Jul;212(3):335-9. Vitamin K-deficient intracranial hemorrhage as the first symptom of **cytomegalovirus hepatitis with cholestasis**.

Masui. 2007 Feb;56(2):181-5. Suspicious case of epidural hematoma due to coagulopathy caused by vitamin K deficiency associated with **antibiotics**.

J Hum Nutr Diet. 2007 Dec;20(6):605-10. Vitamin K prescribing patterns and bone health surveillance in UK children with **cystic fibrosis**.

Bone. 2007 Dec;41(6):965-72. **Shwachman-Diamond syndrome** is associated with low-turnover osteoporosis.

Adv Ther. 2007 Nov-Dec;24(6):1286-9 **Celiac disease** with diffuse cutaneous vitamin K-deficiency bleeding.

J Child Neurol. 2007 Jan;22(1):114-5. Cerebral hemorrhage as the initial manifestation of **cystic fibrosis**.

Gastroenterol Clin Biol. 2007 Jun;31(6-7):614-5. Severe vitamin K deficiency during a drug wash-out procedure with **cholestyramine**.

Adv Ther. 2006 May-Jun;23(3):469-74. Evaluation of vitamin K deficiency in children with acute and **intractable diarrhea**.

Pediatr Neurosurg. 2006;42(6):362-7 Intracranial hemorrhage and vitamin K deficiency associated with **biliary atresia**: summary of 15 cases and review of the literature.

### Odds and Ends:

Prenat Diagn. 2008 Jan;28(1):59-61. Vitamin K deficiency in **hyperemesis gravidarum** as a potential cause of fetal intracranial hemorrhage and hydrocephalus.

**Preeclampsia** is associated with low concentrations of protein Z. J Matern Fetal Neonatal Med. 2007 Sep;20(9):661-7.

- Am J Med Genet A. 2007 Jan 15;143(2):200-4. Gray matter heterotopias and brachytelephalangi chondrodysplasia punctata: a complication of **hyperemesis gravidarum** induced vitamin K deficiency?
- Neurology. 2007 Dec 11;69(24 Suppl 3):S10-6. Importance of monotherapy in women across the reproductive cycle. [**Seizure Medications**]
- J Am Diet Assoc. 2007 Dec;107(12):2091-9. Poor nutrient intakes during 1-year follow-up with community-dwelling older adults with **early-stage Alzheimer dementia** compared to cognitively intact matched controls.
- Eur J Pediatr. 2008 Feb;167(2):165-9. Incidence of late **vitamin K deficiency bleeding** in newborns in the Netherlands in 2005: evaluation of the current guideline.
- Pediatrics. 2008 Apr;121(4):e857-63. **Prevention of vitamin K deficiency bleeding in breastfed infants**: lessons from the Dutch and Danish biliary atresia registries.
- Arch Dis Child. 2007 May 23; Vitamin K deficiency bleeding: the readiness is all.
- N Engl J Med. 2007 Jan 11;356(2):174-82. Case records of the Massachusetts General Hospital. Case 1-2007. A 40-year-old woman with epistaxis, hematemesis, and altered mental status.
- Arch Dis Child. 2007 May 30; Vitamin K deficiency bleeding in the Great Britain and Ireland; British Paediatric Surveillance Unit Surveys, 1993 - 94 and 2001 - 02.
- Pediatrics. 2006 Dec;118(6):e1657-66. Vitamin K prophylaxis for preterm infants: a randomized, controlled trial of 3 regimens.

### **Some Basic Science References: some recent study topics.**

- Bioelectrochemistry. 2008 May 12. Direct and indirect methods for the determination of vitamin K(3) using differential pulse polarography and application to pharmaceuticals
- Biochemistry. 2008 Jun 17;47(24):6301-10. Transmembrane domain interactions and residue proline 378 are essential for proper structure, especially disulfide bond formation, in the human vitamin K-dependent gamma-glutamyl carboxylase.
- J Biol Chem. 2008 Jun 27;283(26):17991-8001. Periostin, a member of a novel family of vitamin K-dependent proteins, is expressed by mesenchymal stromal cells.
- Vitam Horm. 2008;78:185-209. Vitamin K-dependent actions of Gas6.
- Vitam Horm. 2008;78:131-56. Vitamin K-dependent carboxylation.
- Vitam Horm. 2008;78:103-30. Structure and function of vitamin K epoxide reductase.
- Vitam Horm. 2008;78:85-101. Quinone oxidoreductases and vitamin K metabolism.
- Bioorg Med Chem Lett. 2007 Nov 15;17(22):6383-6. Effects of quinones on free-radical processes of oxidation and fragmentation of hydroxyl-containing organic compounds.
- Vitam Horm. 2008;78:63-84. Structure, function, and mechanism of cytosolic quinone reductases.
- Vitam Horm. 2008;78:35-62. The vitamin K cycle.
- Vitam Horm. 2008;78:23-33. VKORC1 and the vitamin K cycle.
- Vitam Horm. 2008;78:1-22. Determinants of vitamin K status in humans.
- Vitam Horm. 2008;78:XIX-XX. Vitamin K. Preface.
- Methods Mol Biol. 2008;446:85-94. gamma-Glutamate and beta-hydroxyaspartate in proteins.
- J Nutr. 2008 Mar;138(3):492-6. Age and dietary form of vitamin K affect menaquinone-4 concentrations in male Fischer 344 rats.
- J Biol Chem. 2008 Apr 25;283(17):11270-9. Conversion of phylloquinone (Vitamin K1) into menaquinone-4 (Vitamin K2) in mice: two possible routes for menaquinone-4 accumulation in cerebra of mice.