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Foundation for the  
Advancement of  
Science, Inc.

# VitalLongevity™

Logo: Life's blood flows through the hourglass; the stopcock represents the alteration of aging and disease as biomedical research progresses.

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www.orentreich.org

## Vitamin K

The K in Vitamin K comes from the Germanic word *koagulation*, for its ability to clot blood and prevent hemorrhage. Although discovered in the early 1930s, vitamin K remains one of the least understood vitamins. The history of its discovery is intriguing, if not as blood-curdling as that of insulin, when potential Nobel Laureates literally fought over recognition. The Danish and American biochemists Henrik Dam and Edward Doisy shared the 1943 Nobel Prize: Dam for appreciating the existence of a factor essential for the coagulation of blood and Doisy for elucidating Vitamin K's structure. A US team at Berkeley attempted to publish a paper with evidence of this new vitamin several years earlier; it was rejected, and university politics prevented submission of further timely reports—glory narrowly missed.

Dam and others noticed certain clues pointing to a blood clotting factor: bleeding disorders suffered by cows eating moldy sweet clover hay and by chicks fed experimental, simplified fishmeal diets. It turns out that molds acting on sweet clover hay produce dicoumarin, a vitamin K antagonist. The fishmeal was lacking a factor that could be compensated for with concentrated extract of alfalfa meal, now known as rich source of vitamin K.

### Structure and Activity

Today we know that vitamin K is fat-soluble (like vitamins A, D, and E) and that it has several forms (Fig. 1). Vitamin K1 (phylloquinone) is made by plants (phytonadione is identical to K1 but is synthesized commercially). Vitamin K2 or MK-n (menaquinone-n, a variously sized molecule depending on the number (n) of repeating 5-carbon units) is made by intestinal bacteria. K2 production by bacteria provides only a minor fraction of our daily needs since it is made mostly in the large intestine and colon where it is poorly absorbed. Therefore, dietary K1 is very important. The body stores about an 8-day supply of vitamins K1 and K2, primarily in the liver, but also in the brain, pancreas, and bones.

Vitamin K takes part in what is called the vitamin K cycle (Fig. 2) by assisting enzymes (vitamin K-dependent carboxylases) that control the activation of several key coagulation factors including prothrombin (II), proconvertin (VII), and Christmas factor (IX). The result is the addition of carbon dioxide (carboxylation) to glutamic acid residues (Glu) in these proteins, converting them to their calcium-

binding, pro-coagulation forms (Gla). Vitamin K then gets recycled back to its usable form through the actions of two reductase enzymes.

Blood thinning medications such as Coumadin® (a coumarin anti-coagulant) do not interfere with the carboxylation reaction but block the enzymes that reactivate vitamin K, thus preventing its reuse. In 2004, the gene for one of the reductase enzymes (VKOR) was cloned, perhaps leading to better anti-coagulants by targeting this enzyme.

### The Structures of Vitamins K1 and K2.

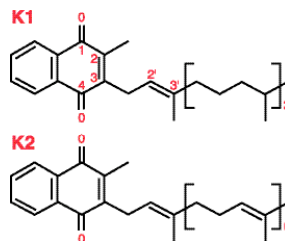


Figure 1.

### The Calcium Connection

Clotting factors are not the only proteins activated by the vitamin K cycle. For example, osteocalcin (OC), which helps to build the structural framework of bone by attracting and holding calcium, must be carboxylated to become active. In fact, vitamin K status can be assessed by measuring the percent of undercarboxylated OC in blood (%ucOC).

Although one might think that bone mineral density (BMD) should increase with greater consumption of vitamin K, the story is not so simple. Generally, studies find that bone quality improves with increased vitamin K intake (reducing risk of hip fracture by 65%), but that BMD, paradoxically, does not increase significantly. Nonetheless, oral vitamin K is an approved treatment for osteoporosis in Japan. Another potential reason for oral vitamin K to treat/prevent post-menopausal bone loss relates to vitamin D: too much vitamin D produces symptoms remarkably similar to a lack of vitamin K. It appears that vitamin D increases the synthesis of vitamin K-dependent proteins (including OC), leading to a greater demand for vitamin K and then to its subsequent deficiency. Since many persons take extra vitamin D (although generally not in toxic amounts) to prevent bone loss, it is not unreasonable to suggest increased vitamin K consumption to maintain adequate levels of active OC.

On the other side of the coin, if calcium fails to be properly incorporated into bone, it can be deposited in arterial walls, leading to vascular calcification in liver, lung, kidney, and heart tissues, thereby contributing to cardiovascular disease and other complications. Compounding the problem, matrix Gla protein (MGP), a potent inhibitor of soft-tissue calcification when adequately carboxylated by the vitamin K cycle, is vulnerable to low levels of vitamin K.

Depletion of vitamin K by Coumadin® therapy increases risk of arterial and heart valve calcification. However,

physicians usually strongly advise patients on Coumadin® against taking vitamin K supplements and to limit their dietary intake. Yet recent reports show that a small, daily supplemental dose of 50 to 150µg/day vitamin K leads to a more stable blood K level (which fluctuates sharply with foods consumed) and to a more predictable and controllable International Normalized Ratio (INR), a common measure of blood clotting time. Physicians must assess Vitamin K supplementation for those on anti-coagulants (no self treatment, please!), but supplementation is worth investigating if your INR proves difficult to stabilize. If a vitamin K supplement is ruled out, bisphosphonates such as Fosamax® (osteoporosis treatment) can help to avert the arterial calcification associated with poor vitamin K status from Coumadin® therapy. Surprisingly, poor vitamin K status raises the risk of heart attack to the same degree as smoking does.

## Vitamin K Status

This is assessed by measuring the INR, the traditional but fairly insensitive measure of vitamin K status used primarily for patients on anti-coagulant therapy, or by measuring uncarboxylated prothrombin (this test is typically called PIVKA-II). Because neither test tells you about the carboxylation of proteins important to bone metabolism, other tests are required. These include blood levels of phyloquinone (fairly insensitive), % ucOC, and/or urinary excretion of Gla residues (reflecting the turnover of all vitamin K-dependent proteins).

## Adequate Intake

The recommended adequate intake (AI) of vitamin K to maintain normal blood coagulation is 90µg/day for women and 120µg/day for men (about 1µg/kg of body weight per day). Most persons get the AI from foods each day, so blood coagulation problems from vitamin K deficiency are rare. Yet, at this level of vitamin K intake, a large percentage of OC is undercarboxylated—up to 50% or more. Thus, the typical diet falls far short of the optimal Vitamin K level that ensures maximal activation of other vitamin K-dependent proteins such as OC, which might require up to 1000µg/d (1mg/d) of vitamin K1. This is because the body uses a

triage system of sorts; that is, the clotting factors get preferentially carboxylated when vitamin K is limited. Intake of K1 up to 4500µg/d (45mg/d)—450 times the AI—causes no apparent problems in healthy adults. Supplements are available that contain both K1 (as phytonadione) and K2 (usually MK-4 or MK-7), which is probably a good idea, since K1 and K2 might have unique roles.

If everyone took all the touted vitamin and nutrient supplements, we would live on a diet consisting mostly of pills. For vitamin K, the good news is that most persons can get enough K1 by increasing their dietary intake of dark, leafy greens: a half-cup of cooked kale contains 530ug and spinach 440ug. Soybean, cottenseed, canola, and olive oils contain high amounts as well ([www.ars.usda.gov/is/pr/2007/070801.htm](http://www.ars.usda.gov/is/pr/2007/070801.htm)). Be advised, though, that vitamin K is poorly absorbed from food—only about 30%—and this must be factored in when calculating your daily intake; oil added to dark, leafy greens aids in the extraction and absorption of vitamin K. Cow liver, egg yolks, butter, and fermented soybeans are good sources of K2. Vitamin K in supplement form is actually better absorbed than from food and can be targeted to individuals

with specific needs upon physician advice: those concerned about osteoporosis and individuals taking Coumadin® or with the following conditions that lead to low blood levels of vitamin K:

- Liver disease (impairs vitamin K storage)
- Gastrointestinal disorders *e.g.*, Crohn's disease (reduces absorption)
- Broad-spectrum antibiotic use (destroys vitamin K2-synthesizing gut bacteria)
- Use of cholesterol-lowering

drugs (vitamin K is carried by cholesterol and triglyceride lipoprotein particles in the blood; the lower the level of these particles, the lower the level of vitamin K.)

## On the Horizon

There is much to learn about vitamin K. New studies suggest potential therapeutic uses for vitamin K: combating Alzheimer's disease and diabetes; treating certain cancers, including pancreatic, ovarian, and leukemia; and preserving skin health.

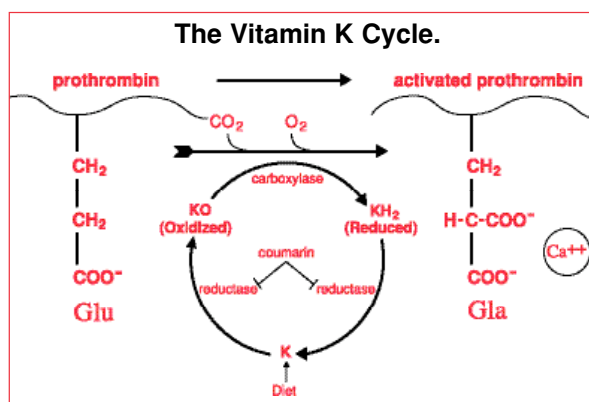


Figure 2.

## Information for Donors

**The Orentreich Foundation for the Advancement of Science, Inc., was founded in 1961. OFAS is a non-profit institution dedicated to biomedical research to prevent, halt, or reverse those disorders that decrease the quality or length of life. It is duly registered with the US Internal Revenue Service as an Operating Private Foundation under Section 4942(j)(3).**

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