



## VITAMIN K – MUCH MORE THAN A COAGULATION VITAMIN

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Most of us were only taught about the Coagulation Vitamin discovered in 1930's Denmark (abbreviated to Vitamin K), as a requirement for a normal hemostasis. Research suggests, however, that vitamin K possesses significant antioxidant, anti-cancer, anti-inflammatory, and insulin-sensitizing actions. Perhaps even more importantly, vitamin K is necessary for integrating calcium into bone and preventing deposition of calcium into blood vessel walls and other tissues.

Vitamin K is a fat-soluble vitamin that the body recycles but does not store. There are three types of vitamin K. Phylloquinone (vitamin K<sub>1</sub>) is found mainly in green leafy vegetables and canola and soybean oils, which are its most important dietary sources for humans. Vitamin K<sub>2</sub> (menaquinone) is mainly of microbial origin in the gut, and it is also formed from vitamin K<sub>1</sub> in the body. Relevant dietary menaquinones range from menaquinone-4 (MK-4) with a half life of about one hour, through menaquinone-10 (MK-10), all named according to the number of isoprenoid residues in their side chains. The main dietary sources of menaquinones are cheese, curd, and the Japanese food natto. Only MK-4 can be produced in mammalian tissues, where it is formed by conversion of K<sub>1</sub> to K<sub>2</sub> (MK-4). Vitamin K<sub>3</sub> (menadione) is primarily created synthetically, and is a toxic alkylating agent banned by the FDA from human supplements.

K<sub>2</sub> is more potent than K<sub>1</sub> and more active in promoting bone formation and reducing bone loss, and provides more protection against arterial calcification and oxidation of LDL cholesterol (Jono et al. *Thromb Haemost* 2004; 91(4):790-794.) These beneficial actions are based on K<sub>2</sub>'s preferential use by the body to carboxylate the vitamin K-dependent Gla proteins, which include osteocalcin (essential for bone health), and matrix-Gla protein (MGP), which prevents calcification of soft tissues such as blood vessels, breast, and kidney.

Despite its action in patients receiving warfarin, too much vitamin K does not enhance coagulation abnor-

mally because it has K-dependent partners, the proteins C, S, and Z, which inhibit excess clotting. The vitamin K-dependent protein C anti-coagulant path is also highly anti-inflammatory.

Osteocalcin is able to attract calcium ions and incorporate them into the hydroxyapatite crystals that form bone matrix only after it has been carboxylated by vitamin K. Thus, low levels of vitamin K cause uncarboxylated osteocalcin (ucOC) to accumulate in the blood. This not only prevents calcium delivery to bones, which become porous, but the calcium is then more easily deposited in arterial walls. Parenthetically, those taking supplemental calcium have recently been shown to have more coronary disease (BMJ on-line 1/15/2008.)

Measurements of ucOC and MGP are primarily research oriented. The only non-research lab test available at LGH for osteocalcin is carried out by Quest diagnostics (\$65, lab number 5586X), and does not differentiate between the carboxylated and uncarboxylated forms. Research surprisingly has shown in apparently **healthy** subjects that a substantial fraction of both proteins occurs in the uncarboxylated forms, which have no biologic function. Does this mean that most healthy adults are subclinically vitamin K deficient? This question is reminiscent of the unfolding story of vitamin D, as told in a previous issue of JLGH (Vol. 1, No. 3, Winter 2006-7). Increased levels of ucOC were found in post-menopausal women with increased bone loss and osteoporosis (Szule et al. *Bone* 1996;18:487-488). Also, ucMGP has been associated with arterial calcification (Braam et al. *Arterioscler Thromb Vasc Biol* 2000;20:1257-1261).

These studies suggest that although dietary vitamin K intake is adequate for normal blood clotting, it may be insufficient for these extrahepatic tissues and processes. (The present dietary reference values for vitamin K are based on proper functioning of blood coagulation only. The National Academy of Sciences guidelines for daily Adequate Intake (AI) of vitamin K are 90 mcg for

adult females and 120 mcg for adult males. There is no maximum dose noted. An AI is established when an RDI (Recommended Daily Intake) can't be determined.)

Poor vitamin K status should be regarded as an increased risk factor for osteoporosis (as is inadequate vitamin D, again as referenced by previous JLGH articles), and also for arterial calcification, especially for those with diabetes, end stage renal disease, other aging processes, and perhaps even those on just added calcium supplementation. Concurrent arterial calcification and osteoporosis have been called the “calcification paradox” and occur frequently in post-menopausal women (Med Res Rev. 2001;21:274-301.)

Other positive effects of vitamin K are decreasing progression of cirrhosis to hepatocellular carcinoma (and decreased mortality in those with hepatocellular carcinoma), brain cell protection and antioxidant effects, insulin-sensitizing effects, prevention of varicose veins, and various anti-inflammatory effects [decreasing CD40 ligand, osteoprotegerin, and interleukin-6 (IL-6)]. A potential recent application may be for patients on warfarin to protect against vascular calcification and reduce diet-influenced fluctuations in INR. (Blood. 2004;104(9):2682-2689.)

“Concerning insulin resistance in older men (but not women), use of vitamin K<sub>1</sub> supplements for three years (500 mcg/day of phylloquinone, an amount achievable through dietary intake) was associated with reduced insulin resistance and insulin levels, and no change in fasting glucose.” (Diabetes Care, published online 8/12/08).

Although vitamin K has been known since the 1930's, we are still in the early stages of elucidating all of its bodily uses. Where does this leave us today? The data are still being accumulated for many of its extrahepatic effects. However, the results of two dose-response studies indicate that (1) the vitamin K amount needed for optimal carboxylation of osteocalcin is significantly higher than

what is provided by diet alone and (2) there is a need to increase current dose recommendations to optimize bone mineralization (Am J Clin Nutr. 2002;76:1055-1060, and J Nutr. 2003;133:2565-2569). Since the mid 1990's in Japan, multiple studies have shown no side effects of added vitamin K even up to 45 mg (milligrams) daily, unless one is taking warfarin. It obviously can decrease warfarin's effect, especially over doses of 150 mcg daily of vitamin K. (By the way, warfarin use has been shown to increase calcium deposition in arteries by inactivating MGP. (Clin Invest Med. 2004;27(2):107-109 and Blood. 2004;104(10):3231-3232).

For the rest of us, a bit more than a half cup, for example, of chopped broccoli or a large mixed green salad provides about 250 mcg daily of vitamin K<sub>1</sub>. The more greens one eats, the more one gets. Some multivitamins provide a small amount of vitamin K. But large doses of vitamin A and vitamin E antagonize vitamin K. Those of us that have some of the other medical conditions discussed might want to consider more vitamin K<sub>2</sub> (MK-4). Studies of doses range between 1 mcg and 45 mg daily, as long as warfarin is not being taken. (1 mg = 1000 mcg). It has not been found to be toxic even at 45 mg/day. Vitamin K<sub>2</sub> (MK-4) is commercially available on line and seems to be more active in the decrease of vascular calcification than vitamin K<sub>1</sub>. It is also the form that many Japanese have been using for years in osteoporosis treatment. Vitamin K<sub>7</sub> (MK-7) as found in the Japanese fermented food natto and also commercially available on line in a capsule, has a longer half life (about 3 days) compared to about 1 hour for MK-4. Perhaps lower doses will be the way of the future using vitamin K<sub>7</sub> (MK-7). Remember that these “supplements” are not regulated by the FDA. They are only as pure as the company making them.

As we have more patients with osteopenia and osteoporosis, and as we learn more about vascular and other tissue calcifications, this will become a “hotter” topic. Will the future be filled more vitamin K and/or less use of statins and bisphosphonates? Stay tuned.

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