Vitamin K is a family of structurally similar, fat-soluble 2-methyl-1,4-naphthoquinones. Originally identified by German researchers as the fat-soluble nutrient required for normal blood coagulation, recent research reveals that these compounds are also necessary for integrating calcium into bone and preventing its deposition within blood vessels. Research also suggests that vitamin K may possess significant antioxidant, anti-cancer, anti-inflammatory, and insulin-sensitizing actions.

In nature, vitamin K is primarily found in 2 forms: K$_1$ (phylloquinone) and K$_2$ (menaquinone). A third, much simpler form of the vitamin is K$_3$ (menadione). For the most part K$_3$ is synthetically created, although intestinal bacteria can produce small amounts of K$_3$ from K$_1$. Although K$_3$ cannot perform all the functions of K$_1$ or K$_2$, it has been the form most used in research demonstrating vitamin K’s anti-cancer effects. This is because K$_3$ potentiates the cytotoxic activity of chemotherapeutic agents and of vitamin C. K$_1$ is described as an alkylating and thiol-depleting agent; i.e., an agent that increases production of reactive oxygen species (ROS) and depletes glutathione (GSH). When metabolized in the mitochondria, K$_1$ results in the production of superoxide anion (O$_2^-$, a highly reactive and destructive ROS) and, due to K$_1$’s concomitant regeneration, the cycle recurs until apoptosis is initiated. Because of its toxicity, the use of K$_1$ has been banned by the Food and Drug Administration (FDA) in human (but not pet) nutritional supplements.

K$_1$, which is involved in plant photosynthesis, is produced by plants and algae; it is found in highest concentrations in green leafy vegetables. Primary dietary sources of K$_1$ are vegetables such as broccoli, kale, and Swiss chard, and plant oils, such as canola and soybean oils.

K$_2$ is produced by bacteria and also via the conversion of K$_1$ to K$_2$ by beneficial bacteria in the intestines of animals, including humans. Natto (fermented soybean) is the richest dietary source of vitamin K$_2$. Dairy products (milk, butter, cottage cheese, cheese) and egg yolk also provide small amounts.

K$_2$ is more potent than K$_1$ and has a wider range of activity, including being far more active than K$_1$ in promoting bone formation and reducing bone loss. K$_2$ is also the form that has been found to protect against arterial calcification and oxidation of LDL cholesterol.

In addition, K$_2$ is a more powerful antioxidant than K$_1$ by 15-fold and is the predominant form of vitamin K in the brain and all other tissues, except the liver. K$_2$ also protectively modulates estrogen metabolism, has more powerful anti-tumor actions in various cancer cells than K$_1$, and exerts additional anti-cancer mechanisms as compared with K$_3$.

Finally, K$_2$ is better absorbed than K$_1$ and remains biologically active far longer; K$_1$ is cleared by the liver within 8 hours, but measurable levels of K$_2$ have been detected 72 hours after ingestion.

**Physiological and Clinical Effects**

Vitamin K is a known cofactor for a single enzyme, y-glutamylcarboxylase, which catalyzes the posttranslational conversion of glutamic acid to y-carboxyglutamic acid (Gla) in vitamin-K-dependent proteins. Carboxylation activates the Gla-proteins, which perform a number of essential activities throughout the body, including regulation of both blood clotting and calcium. Currently, 15 Gla-proteins have been identified. Researchers think as many as 100 may eventually be discovered.

K$_1$ is preferentially utilized by the liver in the carboxylation of clotting factors, while K$_2$ is preferentially used in the rest of the body to carboxylate the other vitamin K-dependent Gla-proteins, including osteocalcin, which is essential for bone health, and matrix-Gla protein (MGP), which prevents calcification of soft tissue (e.g., the vasculature, breasts, and kidneys).

Independent of its carboxylation activities, vitamin K$_2$ is found in high concentrations in the brain, where it contributes to the production of myelin and sphingolipids, protects brain cells against oxidative injury, and is thought to play a role in development of the central nervous system as the vitamin-K-dependent growth-arrest-specific gene-6 (Gas6).

**Effects on Blood Coagulation**

Vitamin-K-dependent Gla-proteins are responsible for maintaining the delicate balance between coagulation and anti-coagulation. In a system called the “coagulation cascade,” pro-coagulant vitamin K-dependent proteins (including prothrombin and coagulation factors II, VII, IX, and X) create a dense mesh of fibrin that traps platelets and stops the loss of blood. At the same time, their anti-coagulant K-dependent partners—proteins C, S, and Z—inhibit the process, preventing excessive clotting and promoting rapid clearance once clots are no longer necessary.

The vitamin K-dependent protein C anticoagulant pathway is highly anti-inflammatory, with activity so potent it has been used to prevent fatal inflammatory effects of bacterial sepsis in animal studies and to significantly improve the outcome of human patients with severe sepsis.

**Controlling Calcium: Mineralizing Bone, Not Blood Vessels**

Osteocalcin, the major non-collagenous protein responsible for inducing bone mineralization in human osteoblasts, is a vitamin K-dependent Gla-protein. Only after its carboxylation by vitamin K is osteocalcin able to attract calcium ions and incorporate them into the hydroxyapatite crystals that form the bone matrix. Without adequate vitamin K, osteocalcin remains uncarboxylated, impairing bone mineralization. K$_2$ is the most important inducer...
of bone mineralization in human osteoblasts, and, in combination with vitamin D$_3$, increases osteocalcin production.

Vitamin K aids bone health in a number of other ways as well. Vitamin K completes the bone-building effects of vitamin D$_3$’s upregulation of osteoblasts’ expression of osteocalcin, while also inhibiting the differentiation of osteoclasts.$^{4,19-22}$

A deficiency of vitamin K results in high levels of uncarboxylated osteocalcin (ucOC) in the bloodstream. Not only is calcium not delivered to the bones, which become porous, but it is then deposited in the arteries, which become calcified.$^{5,23-29}$ In animal studies, vitamin K has been shown to prevent bone loss associated with the following: use of corticosteroids and the anti-epileptic drug phenytoin, immobilization (such as would occur during extended illness or hospitalization), testosterone deficiency (as might occur with treatment for prostate cancer or aging), menopause (estrogen deficiency), and weightlessness (as occurs during space flight). Each of these is known to reduce bone formation while increasing bone turnover, leading to bone loss and increased fracture risk. Vitamin K greatly lessens or completely reverses this trend.$^4$

Vitamin K has even been shown to help prevent skeletal unloading in astronauts living in zero-gravity conditions. An astronaut on the EUROMIR-95 mission experienced increased bone loss during the first part of a 6-month space flight. After administration of K$_2$ (10 mg/day for 6 weeks), his carboxylated osteocalcin levels rose 14%,$^{30}$ thus increasing calcium deposition in bone.

Even calcium-deficient animals are protected from bone loss by vitamin K$_2$ in rat models of postmenopausal osteoporosis (50 mg/kg) and testosterone deficiency (30 mg/kg).$^4$

A meta-analysis of all randomized controlled human trials of at least 6 months’ duration that assessed the use of vitamin K$_1$ or K$_2$ to lessen fracture risk identified 13 trials. All but one showed vitamin K reduced bone loss, with K$_2$ being most effective—resulting in a reduced risk of vertebral fracture by 60%, hip fracture by 77%, and all non-vertebral fractures by 81%.$^{31}$

**Prevention and Treatment of Osteoporosis**

For more than 20 years, research in humans has linked osteoporotic fracture with vitamin K insufficiency. A study published in 1984 found that patients who suffered fractures caused by osteoporosis had vitamin K levels 70% lower than age-matched controls. This association has been confirmed with 1 recent trial involving almost 900 men and women. The study found that those with the lowest blood levels of vitamin K had a 65% greater risk of hip fracture compared to those with the highest levels of the nutrient.$^{24,32-34}$

In other human research, vitamin K$_2$ has been shown to be an effective treatment for osteoporosis. A 2-year group-comparison study of patients with osteoporosis due to corticosteroid use found that K$_2$ greatly reduced vertebral fractures. Incidence of vertebral fractures was 13.3% in those taking K$_2$ compared to 41% in the control group.$^{35}$ Additionally, in a 24-week study, 80 patients with osteoporosis were given either 90 mg/day vitamin K$_2$ or placebo. In those taking K$_2$, bone mineral density (BMD) increased in the second metacarpal an average of 2.2%. In those who took placebo, BMD decreased an average of 7.31%.$^4$

In a 2-year study of 241 women with osteoporosis, subjects were given either 45 mg/day of K$_2$ plus 150 mg calcium or calcium alone. At the end of the study, women receiving only calcium had lost an average of 3.3% of their lumbar BMD, while those receiving vitamin K$_2$ lost just 0.5%. Women taking K$_2$ plus calcium had one-third the fracture risk of those receiving calcium only.$^{36}$

**Bone Loss Effects in Combination With Vitamin D**

*K2 partners with vitamin D to prevent bone loss.*

Vitamin D increases production of Gla-proteins, the activation of which depends on vitamin K-mediated carboxylation. Vitamin D thus increases both demand for vitamin K and potential for benefit from K-dependent proteins, including osteocalcin in bone and MGP in blood vessels.$^{20}$

A number of trials have shown that the combination of K$_2$ and vitamin D$_3$ is more effective in preventing bone loss than either nutrient alone.$^{37}$ In a study of 173 osteoporotic/osteopenic women, those given both K$_2$ and D$_3$ experienced an average 4.92% increase in BMD, while K$_2$ alone resulted in an average BMD increase of just 0.13%.$^{38}$

In another study performed over 2 years, 92 postmenopausal women were assigned to 1 of 4 groups: K$_2$ (45 mg/day), D$_3$ (0.75 µg/day), a combination of these dosages of K$_2$ and D$_3$, or calcium lactate (2 g/day). In the women receiving only calcium, lumbar BMD decreased. Those given either D$_3$ or K$_2$ experienced a slight increase in BMD, while those taking both K$_2$ and D$_3$ group fared much better, increasing their lumbar BMD by 1.35%.$^{37}$

K$_2$ has also been shown to work with D$_3$ to lessen the risk of osteoporosis in Parkinson’s disease, which is thought to be related in part to immobilization as well as a deficiency of vitamin D—caused not by a lack of vitamin D but rather by suppression of D$_3$ by the high blood levels of calcium seen in Parkinson’s disease. When K$_2$ (45 mg/day for 12 months) was given to 54 female Parkinson’s patients with osteoporosis, only 1 hip fracture occurred, compared to 10 fractures in a control group of 54 women with Parkinson’s not treated with K$_2$. Average bone loss in the untreated group was 4.3% compared to 1.3% in those given K$_2$.$^4$

As a last note, K$_2$ also balances vitamin D, preventing soft tissue calcification.$^{39}$ Women taking D along with their calcium are absorbing more of the latter, and if they are vitamin K insufficient, they are at significantly increased risk of calcium deposition in the vasculature. Research published in the February 2, 2008, issue of *BMJ (British Medical Journal)* found that women taking calcium decreased their risk of fracture by 12% while simultaneously increasing their risk of death from cardiovascular-related disease by 212%.$^{40,41}$

**Preventing Arterial Calcification**

Vitamin K-dependent Gla-proteins have been shown to inhibit calcification in the heart and arteries. As mentioned above, MGP, one of the vitamin K-dependent proteins, is a strong inhibitor of vascular calcification. This was first demonstrated in rats bred to be MGP-deficient, all of which died of massive arterial calcification within 6 to 8 weeks after birth.$^{39}$

MGP is produced by small muscle cells in the vasculature where—once carboxylated by vitamin K—it binds to and inhibits
bone morphological protein-2 (BMP-2)—a protein that causes calcium deposition in blood vessels.\textsuperscript{13,25}

$K_2$ also helps promote blood vessel elasticity by safeguarding elastin, the core protein in the muscle fibers primarily responsible for the elasticity of the arterial wall. Existing elastin is damaged and new production is inhibited by calcium deposition.\textsuperscript{42}

In the Rotterdam study—a massive European clinical trial following 4807 subjects, aged at least 55, for a 7- to 10-year period—researchers found that $K_2$ significantly reduced risk of cardiovascular disease by 57%, death from all causes by 26%, and severe aortic calcification by 52%. $K_1$ had no beneficial effects.\textsuperscript{43}

Stopping calcification of the arteries is important because cardiovascular disease is not just about cholesterol’s contribution to endothelial plaque formation in atherosclerosis. Just as lethal is arteriosclerosis, calcification of the arterial intima. The elasticity characteristic of a healthy artery is what enables it to accommodate increases in blood flow. Add enough calcium and that pliability is lost; blood pressure rises.

In fact, sudden death from heart attack is even more highly correlated with calcification of the aorta than with cholesterol. In the Framingham study research, aortic calcification was associated with double the risk of death from cardiovascular disease in men and women younger than 65, even after other risk factors (eg, cholesterol) were taken into account. In men younger than 35, aortic calcification increased risk of sudden coronary death 7-fold.\textsuperscript{44,45}

In other research involving more than 100 000 men and women in California, aortic calcification increased risk of coronary heart disease by 127% in men and 122% in women. Among women, risk of stroke increased concurrently by 146%.\textsuperscript{46} A high coronary artery calcium score on electron beam tomography has been found to be a better predictor of mortality than age. A calcium score of less than 10 confers a reduction in functional age by 10 years in subjects older than 70, while a calcium score of >400 adds as much as 30 years of functional aging to younger patients.\textsuperscript{47-49}

**Prevention of Varicose Veins**

Uncarboxylated MGP was identified as a key player in the increased calcification seen in the development of varicosis, as observed in other vascular diseases. Researchers compared healthy veins from 36 male patients aged 30 to 83 and varicose veins from 50 male patients aged 40 to 81. MGP levels, specifically uncarboxylated MGP, were high, indicating the local vascular vitamin K status in varicose veins is insufficient to mediate full carboxylation of all newly formed MGP. Vitamin K supplementation inhibited the mineralization process in varicose small muscle cell cultures, suggesting that, in vitro, carboxylation of MGP could be partly induced and that its inhibitory effect on varicosis could be restored.\textsuperscript{50}

**Prevention of Tissue Calcification**

Vitamin-K-dependent Gla-proteins have been shown to inhibit calcification in the kidneys, where $K_2$ prevents the calcification that typically accompanies dialysis and diabetes.\textsuperscript{42}

In women, those whose diets provide the most vitamin $K_2$ have significantly less breast calcification compared to those whose diets provide the least. Calcification of a woman’s breast tissue is associated with a 132% increased risk of cardiovascular disease, a 141% increased risk of stroke, and a 152% increased risk of heart failure.\textsuperscript{51,52}

**Special Benefits for Postmenopausal Women: Combating the Calcification Paradox**

As women enter menopause, they simultaneously lose calcium from bone and experience an increase in its deposition in arteries—a negative double whammy called the “calcification paradox” that greatly increases risk of both osteoporosis and cardiovascular disease.\textsuperscript{28} Both problems are related to a drop in estrogen levels; vitamin K can help rectify them.

Estrogen affects bone metabolism through a number of pathways. Estrogen helps convert vitamin D to its active bone-building form ($D_3$). When estrogen levels drop, osteoclasts become more sensitive to parathyroid hormone, which signals them to increase their activity. Plus, the decline in estrogen allows production of the inflammatory cytokine, interleukin-6, to increase, and IL-6 stimulates the production of even more osteoclasts.\textsuperscript{52,53}

Among postmenopausal women not using estrogen replacement, low levels of vitamin K or high levels of ucOC are associated with low spine BMD.\textsuperscript{54} A 3-year study of 325 postmenopausal women receiving either $K_2$ (45 mg/day) or placebo shows that supplementation with $K_2$ can prevent bone loss associated with estrogen decline. In the women given $K_2$, bone mineral content increased, and hip and bone strength remained unchanged, whereas in the placebo group, bone mineral content and bone strength decreased significantly.\textsuperscript{55}

In terms of cardiovascular disease, estrogen protects premenopausal women by increasing endothelial production of prostacyclin, PG1$_2$, which inhibits platelet aggregation and promotes vasodilation. When estrogen levels drop in menopause, these protective effects are lost.\textsuperscript{56}

However, the vitamin-K-dependent MGP that inhibits vascular calcification also helps maintain the elasticity of blood vessels in postmenopausal women. In a 3-year study of 181 postmenopausal women, one-third were given a supplement containing vitamin D; one-third got a supplement providing both vitamin $K_2$ and $D$, and one-third received a placebo. In both the vitamin D and placebo groups, elasticity of the common carotid artery decreased, while in those given $K$ along with $D$, elasticity was maintained.\textsuperscript{27}

**Effects on Liver Cancer**

Researchers are just beginning to identify K-dependent proteins that are important in a number of cell signaling processes. $K_2$ binds to and activates a subfamily of receptor tyrosine kinases that inhibit cancer cell growth via regulation of cell signaling processes, including cellular survival, transformation, replication, and tumorogenesis.\textsuperscript{57}

One example is 17β-HSD4, a key enzyme in the conversion of estradiol to estrone. Estradiol is a much-more potent form of estrogen than estrone, and is often elevated in cancerous liver tissue. By promoting the conversion of estradiol to less-active estrone, $K_2$ helps inhibit the development of liver cancer in vitro.\textsuperscript{58}
In animal studies, K\textsubscript{3} has been used to increase survival time in animals with leukemia and liver cancer, and, when used in combination with them, has significantly improved the effectiveness of certain chemotherapy drugs, including 5-fluorouracil, cisplatin, methotrexate, and doxorubicin.\textsuperscript{4}

In humans, studies suggest that K\textsubscript{3} helps prevent progression of cirrhosis to hepatocellular carcinoma and also inhibits disease recurrence in patients with hepatocarcinoma, a form of cancer for which the rate of recurrence is especially high.\textsuperscript{59-61}

In a study of 40 postmenopausal women with cirrhosis due to hepatitis, K\textsubscript{3} at 45 mg/day greatly lessened risk of progression to hepatocarcinoma. All but 1 of the women in the treatment and control groups had hepatitis C; the other 2 women had hepatitis B. After 8 years, the risk of having developed hepatoma was 80% lower in the women given K\textsubscript{3}.\textsuperscript{62}

In a trial of 121 patients with hepatocellular carcinoma, the addition of K\textsubscript{3} also at 45 mg/day, to conventional therapy significantly improved survival. After 12 months, cancer had progressed to the portal vein in only 2% of those receiving K\textsubscript{3} compared to in 23% of the control group. After 2 years, cancer had invaded the portal vein of 47% of controls but only of 23% of those taking K\textsubscript{3}.\textsuperscript{4}

In another study, a group of 61 patients who were diagnosed as free of hepatocellular carcinoma after surgery were randomly assigned to receive 45 mg/day of K\textsubscript{3} (32 patients) or placebo (29 patients). Cancer recurrence rates in the K\textsubscript{3} group were 12.5% at 1 year, 39.0% at 2 years, and 64.3% at 3 years. In those given placebo, corresponding cancer recurrence rates were 55.2%, 83.2%, and 91.6%, respectively. Survival rates for those who took K\textsubscript{3} were 100% at 1 year, 96.6% at 2 years, and 87.0% at 3 years. Corresponding survival rates for patients in the control group were 96.4%, 80.9%, and 64.0%, respectively.\textsuperscript{63}

In a similar study of 60 hepatocellular carcinoma patients who had had surgery, 30 of whom received K\textsubscript{3} and 30 a placebo, cancer-free rates in the vitamin K\textsubscript{3} group were 92.3% at 1 year, 48.6% at 2 years, and 38.8% at 3 years, while those in the control group were 71.7%, 35.9%, and 9.9%, respectively ($P=0.045$). Survival rates in the vitamin K\textsubscript{3} group were 100% at 1 year, 95.0% at 2 years, and 77.5% at 3 years, while those in the control group were 95.8%, 90.2%, and 66.4%, respectively.\textsuperscript{64}

**Brain Cell Protection and Antioxidant Effects**

In the vitamin K cycle, vitamin K-hydroquinone (the active cofactor for \(\gamma\)-glutamylcarboxylase) is continuously regenerated. The successive pathways contain oxidation of the hydroquinone to the epoxide, followed by reduction to the quinone and reduction to the hydroquinone. Vitamin K-hydroquinone is a potent radical-scavenging species, inactivating reactive oxygen species (ROS) that would otherwise damage lipids, including cholesterol and the delicate essential fatty acids that are primary constituents of the brain, central nervous system, and cellular membranes.\textsuperscript{65}

In addition, intriguing lab research has shown that vitamin K specifically protects neurons against free radical damage by some mechanism not yet understood. Oxidative stress is a central factor in the damage caused by many brain disorders, including Alzheimer’s disease, stroke, and neuronal cell death in developing oligodendrocytes (the predominant cell form in the cerebral matter of premature infants). Reduced GSH is a major intracellular antioxidant and plays a pivotal role in maintaining cellular redox homeostasis. GSH depletion results in accumulation of endogenous ROS and oxidative stress and is the underlying mechanism by which glutamate induces receptor-independent cell death in neurons and oligodendrocytes. Studies of both the K\textsubscript{1} and K\textsubscript{2} forms show prevention of GSH depletion, ROS accumulation, oxidative stress, and cell death in neurons and oligodendrocytes.\textsuperscript{11,16}

Under oxidative stress, growth-arrest-specific gene-6 (Gas6) increases in growth-arrested cells and in neurons, improving their survival, in part by acting as an anti-inflammatory. Gas6 also prevents neuronal apoptosis caused by amyloid beta protein, whose accumulation in the brain is a characteristic feature of Alzheimer’s disease.\textsuperscript{30,66,67}

**Insulin-sensitizing effects**

Intriguing new animal research indicates that vitamin K-activated osteocalcin is also directly involved in pancreatic \(\beta\)-cell proliferation, glucose tolerance, and insulin sensitivity. Mice that have been genetically engineered to lack the genes expressed in osteoblasts that enable osteocalcin secretion are unable to produce normal levels of pancreatic \(\beta\)-cells, and become glucose intolerant and insulin resistant. In addition to stimulating production of insulin by \(\beta\)-cells, carboxylated osteocalcin also increases production of adiponectin, an insulin-sensitizing hormone produced by fat cells (adipocytes), further improving glucose tolerance.\textsuperscript{68}

**Dosage**

K\textsubscript{3} is preferentially concentrated in the liver, where it is used to carboxylate clotting factors and is typically cleared within 8 hours from the body, although a small amount of K\textsubscript{4} is converted to K\textsubscript{3} in the intestines. K\textsubscript{3} is the predominant form found in bone and blood vessels, where it carboxylates osteocalcin and MGP.\textsuperscript{69}

**Dietary Reference Intakes.** In 2000, the National Academy of Sciences established revised adequate intake (AI) levels for vitamin K (see Table 1).

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<th>Table 1. Adequate Intake (AI) Levels for Vitamin K</th>
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<td>Pregnant or lactating females, 19 years and older</td>
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From: National Academy of Sciences\textsuperscript{60}
Therapeutic dosage. The vast majority of studies evaluating the effectiveness of vitamin K for prevention of both osteoporosis and arterial calcification have used K\textsubscript{2} (menaquinone) at a dosage of 45 mg/day.

Vitamin K Deficiency

Beneficial bacteria in the intestines produce about 75% of the vitamin K that the body absorbs each day. However, even a diet rich in leafy greens (thus rich in K\textsubscript{1}, from which the body produces K\textsubscript{2}) supplies less vitamin K than is needed for calcium-regulating activities. In other words, the level of vitamin K produced and absorbed by the body each day is generally not enough. Thus, most people are likely to benefit from supplemental vitamin K.

In addition, unlike the other fat-soluble nutrients (vitamins A, D, and E), vitamin K is not stored in the body, so it must be provided daily. Despite the production of vitamin K\textsubscript{2} by healthy intestinal bacteria, humans can develop a deficiency of the vitamin in as few as 7 days on a vitamin K-deficient diet.\textsuperscript{70}

People who eat processed or fast foods that contain hydrogenated oils are at increased risk of functional vitamin K deficiency.\textsuperscript{71} Canola and soybean oils are a primary source of vitamin K in the American diet, but hydrogenation changes the vitamin K\textsubscript{1} (phyllloquinone) in these oils into dihydrophylloquinone, a form that does not carboxylate osteocalcin and other vitamin-K dependent proteins. In 2544 men and women (average years of age 58.5) who participated in the Framingham Offspring Study, those with the highest intake of vitamin K from hydrogenated oils had the lowest BMD at the neck, hip, and spine.\textsuperscript{72}

Absorption of vitamin K—like that of other fat-soluble nutrients—depends on healthy liver and gallbladder function. Digestive health is also a factor. Deficiency is more likely in people with digestive problems such as celiac disease or irritable bowel disease or in those who have had intestinal bypass surgery, as all of these conditions increase likelihood of fat malabsorption.

Bile acid sequestrants (eg, the drugs cholestyramine and colestipol), which bind to bile acids and form large compounds that are poorly reabsorbed from the gut and eliminated in the feces, also bind and remove fat-soluble vitamins, including vitamin K, thus contributing to deficiency.

While vitamin K levels are rarely insufficient enough that they won’t meet clotting needs, levels of vitamin K necessary for clotting are much lower than those needed for bone and arterial protection. Studies on healthy adults have found high levels of both uncarboxylated osteocalcin and MGP in all subjects tested.\textsuperscript{28}

Vitamin K needs increase with age. Older individuals (>70) require higher levels of vitamin K\textsubscript{1} or K\textsubscript{2} to maintain low levels of uncarboxylated vitamin-K dependent proteins.\textsuperscript{73}

Laboratory Assessment of Vitamin K Status

Even a normal prothrombin time, the standard way of checking vitamin K status, is not an indication that sufficient vitamin K is present to maintain carboxylation of osteocalcin or MGP.\textsuperscript{19,26}

To check vitamin K levels, a physician should request an osteocalcin test that measures how much ucOC is present in the blood. High levels of ucOC indicate insufficient vitamin K for bone health. Similarly, high levels of undercarboxylated MGP indicate insufficient vitamin K is present to prevent vascular calcification.\textsuperscript{29}

Safety

It is generally accepted that, even in high doses, supplementation with K\textsubscript{1} or K\textsubscript{2} has not produced adverse effects. For this reason, the Institute of Medicine at the National Academy of Sciences chose not to set a Tolerable Upper Limit (UL) for vitamin K in 2000 when it revised its public health recommendations for this vitamin.

The synthetic form of vitamin K\textsubscript{3} (the form used as a chemo drug) promotes production of ROS and depletes GSH. High doses of K\textsubscript{3} have been used in cancer research precisely for their ability to promote oxidative stress and cell death. Even in lower doses, K\textsubscript{3} has produced jaundice and hemolytic anemia in human infants. For these reasons, the FDA banned the use of K\textsubscript{3} in human nutritional supplements.

Drug Interactions

While most clinicians are well aware of vitamin K’s potential adverse interaction with anti-coagulant medications, the beneficial synergy between K\textsubscript{3} and bisphosphonates is less well known.

Bisphosphonates. K\textsubscript{3} appears to improve the effectiveness of bisphosphonate drugs (eg, etidronate, alendronate, risdonate), which lessen bone loss by inducing apoptosis of osteoclasts. In a study of 98 postmenopausal women with osteoporosis, fractures were experienced by 2 out of 25 women taking etidronate, 2 of 23 women taking K\textsubscript{3} (45 mg/day), 6 of 24 women taking calcium lactate, and only 1 of 26 women taking vitamin K and etidronate.\textsuperscript{74}

Anticoagulant medications. In patients on warfarin, vitamin K in amounts as small as 1 mg/day can interfere with its anti-clotting activity.

Oral anticoagulant medications such as warfarin promote arterial calcification by preventing vitamin K from activating matrix Gla-protein.\textsuperscript{10,75} A case report recommended physicians prescribing warfarin consider arterial calcification as a potential consequence after routine examination of a healthy man on long-term warfarin treatment found his coronary arteries were highly calcified.\textsuperscript{76}

Two recent studies involving more than 100 subjects have shown that patients treated with oral anticoagulants have double the calcification of patients not on these vitamin K-blocking drugs.\textsuperscript{76} Anticoagulant medications such as Coumadin (warfarin) decrease clotting by interfering with vitamin K, thus greatly increasing risk of vitamin K deficiency. When improving vitamin K status, however, patients on these medications must be closely monitored. A dose of just 1 to 2.5 mg of oral vitamin K\textsubscript{1} will, within 24 to 48 hours, reduce the range of the international normalized ratio from 5.0 to 9.0 to 2.0 to 5.0. In fact, even eating a vitamin K-rich diet can make anticoagulant medications less effective.\textsuperscript{77}

Conclusion

If your patients are supplementing with calcium to prevent
osteoarthritis — especially if they are also supplementing with vitamin D, which will, among its numerous other benefits, increase calcium absorption — then monitoring vitamin K status is essential. In addition to regular consumption of vitamin K-rich leafy greens, supplemental vitamin K₂ may be necessary to ensure that calcium is deposited in bone rather than in the vasculature. Calcium, vitamin D, and vitamin K interact, and we ignore this fact at our peril.

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