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REPORT

Vitamin K's Delicate Balancing Act

By Julius G. Goepp, MD

Advances in health, nutrition, and the biology of aging are enabling growing numbers of adults to achieve extended life spans.[1] Some of the most surprising research findings of recent years revolve around vitamin K.[2,3]

Scientists have discovered that vitamin K regulates several biochemical processes that require exquisite balance to function normally, including blood coagulation, bone mineralization, and vascular health. Through these diverse actions, vitamin K holds promise in helping to prevent and manage some of the most crippling conditions associated with advancing age, including osteoporosis, coronary artery disease, and blood clots that can induce heart attack or stroke.

Observations of how vitamin K affects the health of domestic cattle led to fundamental discoveries about the vitamin and to breakthroughs in our ability to treat some of the most debilitating diseases associated with aging.[4] Warfarin (Coumadin®), the drug derived from these observations, has saved millions of lives by preventing or reducing blood clots.[5] Advanced surgical techniques such as the use of artificial heart valves and vascular shunts are made possible by the careful interplay between warfarin-like drugs and vitamin K itself.[6]

This article will focus on how vitamin K works to maintain tight control over three vital bodily processes: blood coagulation, bone mineralization, and vascular health and elasticity This article also describes breakthrough research indicating that the use of low-dose vitamin K supplements might reduce the side effects associated with long-term Coumadin® drug therapy.

Unique Among All Vitamins

Vitamin K is unique among the vitamins in several respects. It is the only vitamin that can be

produced within the human body, but not by the body (to be defined as a vitamin, a substance cannot be produced by human tissue).[7] Beneficial bacteria in the human intestine produce about 75% of the vitamin K the body absorbs each day, with the other 25% coming from dietary sources.[8] The amount of vitamin K absorbed each day from both sources usually is equal to the minimum amount required for normal bodily function.[9]

Like the body's absorption of other fat-soluble vitamins (A, D, and E), vitamin K absorption depends on healthy liver and gallbladder function.[10-13] Unlike the other fat-soluble vitamins, however, vitamin K is not stored in the body.[9] Taken together, these factors explain why the net daily balance of vitamin K is so delicate. As people live longer and vitamin K-dependent processes are discovered in more and more tissues, more scientists are suggesting that vitamin K is needed in larger quantities than what was once thought, particularly in aging adults.[14,15]

Vitamin K occurs in nature in two major forms—K1 and K2—with molecular structures that are similar to cholesterol. These structures make the molecules fat soluble, and seem to be what gives the vitamin its activity. The terminology about vitamin K can be confusing, partly because researchers are learning more about the vitamin each day. In general, K1 (phylloquinone) is the form of the vitamin chiefly derived from dietary sources such as leafy green vegetables and soybean oil, while K2 (menaquinone) is produced by bacteria in the intestine.[16] While K2 may be more important in bone mineralization than K1, the amount of K2 absorbed from the gut provides only a fraction of the total daily requirement.[17] Laboratory and some human data now suggest that K1 is in fact converted to K2 in tissues.[18,19] This means that supplementing with vitamin K1 produces reliable absorption and supports all the important functions discussed in this article.

Although vitamin K affects many vital processes, it has the same fundamental action in all tissues. Vitamin K acts as a cofactor in converting the amino acid glutamate into gamma-carboxyglutamate, or Gla.[20] Gla-containing proteins (Gla-proteins) regulate many of the myriad physiological processes controlled by calcium. Vitamin K thus participates in some of the body's most finely tuned systems. Vitamin K's action was first discovered, and is still most thoroughly understood, in the control of blood coagulation. It is now known to be fundamental as well in regulating the mineral content of bone and of blood vessel walls, with important implications for aging.

Regulating Blood Coagulation

The coagulation system is one of the body's most tightly regulated systems. Blood must flow smoothly as a liquid through miles of blood vessels each day, yet also be capable of starting a solid clot within seconds of encountering a breach in the vascular system, such as a laceration or other injury. If the blood fails to clot reliably, fatal hemorrhage can result; if the blood clots

just a little too readily, blood vessel blockage can occur, leading to rapid tissue and organ damage called ischemia. This delicate balance is maintained, with the help of vitamin K, by a system known as the coagulation cascade.[21]

Gamma-carboxylation by vitamin K activates many of the Gla-protein molecules that are essential to coagulation (pro-coagulants).[22] When triggered by a stimulus, these proteins work together to create the dense mesh of fibrin that traps platelets and stanches the flow of blood.

Vitamin K promotes the gamma-carboxylation of certain naturally occurring anticoagulant proteins as well. These proteins, known as proteins C and S, are intimately involved in the delicate balance between coagulation and anticoagulation.[23] Low levels of active forms of these proteins produce increased coagulation within blood vessel that can result in abnormal clotting, sometimes with devastating consequences.[24] Fortunately, because vitamin K seems to activate the pro-coagulation parts of the pathway simultaneously and proportionately to its activation of the anticoagulation branches, most people maintain fairly normal clotting levels across a wide range of vitamin K status.[25]

The protein C anticoagulant pathway has some natural anti-inflammatory effects, which are down-regulated during inflammation.[24,26] Protein C's anti-inflammatory activity is potent enough to prevent the inflammatory-mediated fatal effects of bacterial sepsis (blood poisoning) in laboratory animals, and to improve the outcome of human patients with severe sepsis. These effects have been shown to be mediated by reducing organ damage in animal models of sepsis, ischemic injury, and stroke.[23]

Effects on Bone Mineralization

Scientific attention remained focused on vitamin K's action in the clotting cascade for nearly two decades after it was discovered in the 1970s.[23] Only in last 10 years has vitamin K's importance in other major biological processes been recognized. The body's need for vitamin K to form critical Gla-proteins is the key to vitamin K's activity in systems other than the clotting cascade.[22] Scientists' growing awareness of how the vitamin helps form these proteins is providing insights into two crucial aspects of the science of aging: bone and vascular health.[27] Many different health and disease processes affect both areas. Bone and vascular health are also affected not only by vitamin K intake, absorption, and metabolism, but also by the use of vitamin K antagonists such as the drug warfarin (Coumadin®).

THE COAGULATION CASCADE: TO CLOT OR NOT TO CLOT?

Vitamin K-dependent Gla-proteins are critical in the “coagulation cascade” that controls whether blood clots, how much it clots, and when to reverse the process and destroy the clot.

The primary stimulus for normal clotting is triggered when platelets stick to damaged blood vessel walls with exposed collagen and other proteins. This process happens within seconds of an injury. Aggregated platelets and damaged vessel walls release tissue factor, which combines with circulating factor VII. This complex then activates other factors, which in turn trigger the conversion of pro-thrombin (factor II) to thrombin. This active enzyme in turn converts fibrinogen, a dissolved protein, to fibrin. Fibrin forms long strands to create a semisolid mesh that traps platelets, ultimately forming the firm clot that blocks further blood flow.

To prevent overactive clotting, tissue factor pathway inhibitor combined with antithrombin, protein S, and activated protein C acts to inhibit the pro-coagulation system at several points in the cascade. Under normal circumstances, this finely tuned system maintains a perfect balance, permitting clot formation where necessary, but beginning the process of taking down the clot almost as soon as it has begun to form. This minimizes the risk of blood clots forming within vessels, and allows for rapid “cleanup” of those clots that are necessary.[21]

Adequate intake or supplementation with vitamin D and calcium is required to prevent osteoporosis. Neither vitamin D nor calcium, however, can produce healthy bone mineralization without adequate supplies of vitamin K. Bone is a complex living structure comprising cells, mineral crystals, and thick matrix proteins that, like glue, hold the entire bone together. The chief bone matrix protein, osteocalcin, is a Gla-protein that is dependent on vitamin K for its production.[20] A deficiency of vitamin K causes impaired activation of osteocalcin and reduced activity of bone-forming cells, thereby resulting in decreased new bone formation.[28]

Low vitamin K nutritional status (as measured by circulating levels of vitamin K, as well as by products of its activity, such as the amount of Gla-proteins) is associated with increased risk of fracture. Standard measures of osteoporosis correlate poorly with vitamin K status.[29] This observation suggests that relying entirely on standard measures of osteoporosis risk such as bone mineral density may not prove to be reliable as measures of overall vitamin K sufficiency.

Several compelling lines of evidence support the use of vitamin K in preventing and treating osteoporosis.[30] In epidemiological studies, lower intake of vitamin K is associated with increased risk of osteoporosis.[31,32] Both animal and human studies suggest that vitamin K may have a role in preventing and treating osteoporosis.[33-35] In small studies, daily doses of vitamin K2 have prevented bone loss.[30]

GLA PROTEINS: SENSITIVE MEASURES OF TRUE VITAMIN K STATUS

Vitamin K's primary function is to aid in the carboxylation of Gla-proteins.[14] Once thought to be involved only in coagulation, Gla-proteins are now known to exist in many tissues. Without enough vitamin K, some Gla-proteins remain under-carboxylated and cannot function properly. Under-carboxylated osteocalcin, for example, has little activity in bone formation.[39]

While vitamin K deficiencies severe enough to cause defects in the blood coagulation system are rare, growing evidence suggests that less severe deficiencies affecting bone health may be quite common.[39] Improvements in technology for measuring under-carboxylated Gla-proteins have led to the observation that almost everyone exhibits evidence of insufficient vitamin K activity, as indicated by under-carboxylation of at least one Gla-protein.[14] This revelation was important in the recent movement to increase the recommended daily consumption of vitamin K.[14,27,37,40] It is important to remember that because foods provide only about a quarter of the daily requirement, increasing one's intake of this vitamin almost always entails supplementation.

According to a review of the recent literature published in 2004, reasonably strong evidence indicates that daily vitamin K intake of less than 100 mcg is not optimal for bone health.[36] The authors recommend that family physicians stress the importance of adequate vitamin K intake to their patients, particularly those at risk for bone loss and osteoporosis. In a critical review published in 2005, Dr. Jamie Adams of Castle Medical Center in Kailua, Hawaii, noted that "numerous studies have demonstrated the importance of vitamin K in bone health."[37] Dr. Adams pointed out that the combination of vitamins K2 and D may substantially reduce bone loss, and that vitamin K2 is synergistic when used together with hormone therapy. Vitamin K is now among the mix of micronutrients considered vital for maintaining good bone health.[38]

The primary medical treatment for osteoporosis is a class of drugs known as bisphosphonates. These drugs reduce the activity of osteoclasts, the cells responsible for resorption of bone minerals. The bisphosphonates do not, however, increase new bone formation, so they address only part of the problem.

By increasing the production of osteocalcin, vitamin K may provide additional bone-strengthening effects. Indeed, in a rat model of osteopenia (bone loss that precedes osteoporosis), a vitamin K2 derivative at low doses increased bone mineral gain and the overall bone formation rate.[33] Building on this observation, other researchers have established that the combination of the bisphosphonate etidronate and vitamin K2 is more effective than etidronate alone in preventing new fractures in patients with osteoporosis.[35]

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Critical Role in Vascular Health

Scientists are continuing to learn more about the process by which atherosclerotic arteries become calcified. Calcification is now recognized not merely as an accumulation of calcium similar to build-up inside a pipe, but as an active biological process virtually identical to bone mineralization.[40,41] Crucial to both processes, vitamin K produces opposite effects in bone and blood vessels: matrix Gla-proteins in bone increase mineralization when activated by vitamin K, while similar proteins in blood vessel walls decrease vascular calcification.[42] Both actions are healthy responses that maintain strong bone and supple blood vessels.

Inflammatory change in the blood vessel wall, and an increase in the size and number of smooth muscle cells, play a major role in atherosclerosis.[43,44] Vitamin K-dependent matrix Gla-proteins holding vascular cells and other components together have proven to be vital in preventing calcification following an initial inflammatory injury.[45]

The simultaneous loss of calcium from bone and deposition of calcium in arteries has been called the “calcification paradox.”[37] This double-jeopardy situation occurs frequently in postmenopausal women, apparently in part because of incomplete formation of the crucial Gla-proteins that normally both increase bone calcification and prevent arterial wall calcification.

Scientists are greatly interested in vitamin K’s role as a possible anti-atherosclerosis or anti-calcification agent.[30] In an observational study of dietary vitamin K in coronary heart disease, researchers in the Rotterdam Study found that subjects with above-average intake of vitamin K2 had reduced mortality from coronary heart disease, as well as lower all-cause mortality.[46] In addition, the likelihood of having severe aortic calcification was lower in subjects with higher K2 intake. The authors suggest that an adequate intake of vitamin K2 could be important in preventing coronary heart disease. Vitamin K intake earlier in life does not seem to be associated with premature coronary calcification, suggesting that vitamin K’s effects on blood vessels become more important with advancing age.[47]

Deficiencies in Intake and Production

Unlike the other fat-soluble vitamins A, D, and E, which can be stored in body fat, vitamin K has no significant storage pool in the body. Humans can therefore develop a vitamin K deficiency in as few as 7-10 days of a vitamin K-deficient diet, even with functioning intestinal bacteria.[9]

Despite the fact that older adults typically consume more dietary vitamin K than younger adults,[21] elderly people may suffer from low levels of vitamin K. In one study, 12% of patients at an older adult outpatient clinic had very low plasma levels of vitamin K.[48]

VITAMIN K AND VASCULAR CALCIFICATION

A recent study from the Netherlands provides strong laboratory and clinical support for vitamin K's role in preventing vascular calcification.[45]

After staining both healthy and diseased tissue for normal, carboxylated Gla-proteins and for under-carboxylated proteins, researchers found that carboxylated Gla-proteins were located in the healthy middle layer of arteries, while under-carboxylated proteins were present in the cells lining the arteries, where they were associated with microscopic bubbles in the lining. The same researchers then measured carboxylated Gla-protein levels in the blood of patients who had required coronary angioplasty, and found them to be lower than those of healthy people.

Newborn infants represent the largest population that regularly suffers from bleeding due to overt vitamin K deficiency. Because newborns do not have any bacteria in their intestines at birth, for several days they are vulnerable to bleeding until they develop a normal intestinal population. For these reasons, the American Academy of Pediatrics recommends that all newborns receive an intramuscular dose of vitamin K at birth.[49] Babies who are exclusively breast fed may require additional doses of vitamin K to support them until they develop healthy intestinal flora.[50]

A report of two cases of post-operative bleeding in non-infants (a 73-year-old and a 6-year-old) highlights the complex balance of vitamin K supply and demand.[51] While normal gut bacteria almost always ensure ample vitamin K to prevent clotting problems, these two patients had undergone long courses of antibiotics that may have destroyed those beneficial bacteria. This internal deficiency state, added to high utilization of vitamin K-dependent pro-coagulant proteins in the post-operative period, was thought to account for the bleeding. When the patients were given vitamin K, coagulation immediately returned to normal. Such cases are mercifully rare, but they serve as additional evidence of the narrow window between vitamin K sufficiency and deficiency states.

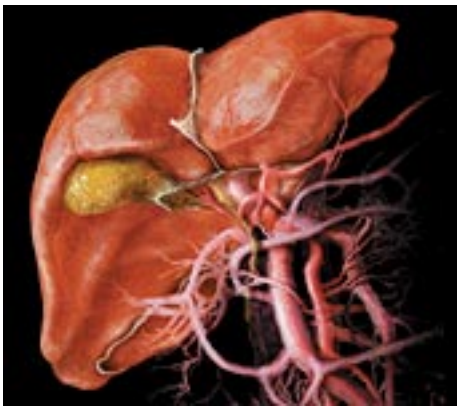
The use of broad-spectrum anti-biotics to treat serious infections is known to produce vitamin K deficiency that can be severe enough to cause bleeding.[52] Patients who undergo bone marrow transplants are often dependent on vitamin K supplementation, as their intestinal bacteria are intentionally obliterated in preparation for the destruction of their own bone marrow germ-fighting cells.[53]

Deficiencies in Absorption

Poor absorption of fats is generally a hallmark of liver and gall bladder diseases. Bile acids, produced in the liver and excreted by the gall bladder, function as "detergents" in the small intestine, aiding in the absorption of fats and the fat-soluble vitamins. For these reasons, people with obstructed bile ducts and decreased small intestinal bile acid concentrations

almost always develop deficiencies of the fat-soluble vitamins A, D, E, and K.[10,12] Fortunately, proper management of diet and vitamin supplementation usually prevents significant vitamin deficiencies in patients with chronic obstructive biliary diseases.[13]

Consumption of hydrogenated and saturated fats has well-known adverse effects on blood lipid profiles. The hydrogenation of fats produces a hydrogenated form of vitamin K called dihydrophylloquinone, which is not absorbed as well as unsaturated (normal) vitamin K and also appears to be ineffective in promoting bone production.[54] These data further support avoiding foods that contain saturated fat and supplementing with vitamin K when a diet high in saturated fat cannot be avoided.



Interior view of the liver, gallbladder, and associated vessels

Vitamin K Antagonist Drugs

The most important form of vitamin K "deficiency" in adults is not related to intake or absorption, but rather to the use of vitamin K antagonists such as warfarin (Coumadin®).[55,56] Vitamin K antagonists prevent vitamin K from activating Gla-proteins in the coagulation cascade. Warfarin is a commonly used drug among older patients, and has been approved for many conditions requiring short- and long-term anticoagulation.[57] Long-term anticoagulation, however, carries certain risks, such as bleeding complications. The likelihood of these complications is greater in patients with preexisting vitamin K deficiency.

It takes several days after beginning warfarin therapy to achieve the desired antithrombotic effect.[58] Almost all patients subsequently experience periods of fluctuation in their international normalized ratio (INR), a measure of the blood's ability to clot properly. This sometimes leads to bleeding or clotting complications. Older patients generally tend to be more sensitive to warfarin's effects, both near the beginning of treatment when coagulation status may fluctuate widely, and later during maintenance treatment.[58] Genetic differences in sensitivity to warfarin account for some of the fluctuations as well. For example, Asian-Americans tend to require much lower doses of warfarin to achieve anticoagulation than do African-Americans.[59,60]

For people using warfarin, maintaining normal INR values is usually adequate to prevent dangerous clots without posing the risk of serious bleeding. The risk of clinically significant bleeding rises with elevation of INR to levels above the normal range.[61]

When warfarin causes excessive INR elevation but no active bleeding is evident, doctors may sometimes recommend skipping one or more doses of warfarin, which will slowly restore the INR level back to normal. More rapid, safe reversal can be accomplished with small oral doses of vitamin K1.[57] Oral vitamin K at a dose of 1 mg (1000 mcg) daily is effective in treating patients whose INR has become too high, even up to levels that are three times higher than the upper limit of the normal range.[62] In a placebo-controlled trial among patients with elevated INR but no symptomatic bleeding, 1 mg of oral vitamin K restored INR to safe therapeutic levels faster than placebo (all patients had their warfarin doses stopped). Patients treated with vitamin

K also had fewer episodes of bleeding than control patients.[63] This study is one of several that demonstrate the safety and effectiveness of using low-dose vitamin K in patients still on warfarin.[64-66] A recent systematic review of the literature concluded that low-dose oral vitamin K is the preferred strategy for rapidly restoring INR levels in patients who were not actively bleeding.[61]

Fluctuating INRs can also go below the therapeutic range, putting patients at risk for clotting complications, especially when the warfarin dose is held constant.[67] In 2005, University of Texas researchers studied eight patients on warfarin treatment whose INRs had been fluctuating.[68] All patients were started on daily supplementation with oral vitamin K (100 mcg/day) while their INR responses were monitored. Nearly all patients experienced diminished fluctuations while taking the supplements, with more INRs in the therapeutic range than before treatment. The patients' total amount of time with INRs within the target range also increased. These results suggest that low-dose vitamin K may help to maintain a small reserve capacity of active coagulation factors that can smooth out the variability in INR caused by warfarin, without creating excessive coagulation.

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Other Effects of Vitamin K Antagonists

Supporting active vitamin K-dependent Gla-proteins in patients on warfarin is also a good idea in light of what we have learned about the importance of these proteins in tissues besides blood. Because warfarin inhibits activation of Gla-proteins, it has the potential to reverse vitamin K's effects, causing reduced calcification of bone and increased calcification of blood vessels. Both laboratory and clinical evidence support this suspicion.[42] Warfarin blocked vitamin D-induced production of the bone protein osteocalcin in a laboratory model;[69] subsequently, doses of warfarin comparable to those used in humans reduced bone strength and volume in laboratory rats.[70] Reduced bone mineral density has been observed in warfarin-treated patients,[71] and an association between the chronic use of warfarin and fracture risk has been reported in humans.[72,73] A recent study of children on long-term warfarin therapy found significantly lower bone mineral density in the lumbar spine of treated patients than in a group of randomly selected controls.[74]

TOPICAL VITAMIN K REDUCES BRUISING SEVERITY

Topical application of vitamin K may help speed the healing of bruises, according to a study from the University of Miami School of Medicine.[77] Cosmetic procedures such as pulsed dye laser treatment often result in significant bruising. The Miami team investigated whether topical vitamin K could help prevent or clear bruising induced by laser treatment.

Twenty-two patients were enrolled in this randomized, double-blind, placebo-controlled trial. Eleven participants applied vitamin K cream to half of the face and a similar cream containing no vitamin K to the other half of the face for two weeks prior to laser treatment. The other 11 subjects followed the same procedure each day for two weeks following the laser procedure.

The side of the face treated with topical vitamin K prior to laser treatment showed no significant difference in bruising compared to placebo. However, the side of the face treated with vitamin K after treatment demonstrated significantly lower scores of bruising compared to the placebo-treated side.[77]

While pre-treatment with vitamin K cream does not appear to prevent bruising, application of vitamin K cream following laser treatment may help reduce the severity of bruising, particularly in the initial days of application.[77]

Arterial calcification, which is prevented by vitamin K-dependent matrix proteins, might also be influenced by warfarin treatment.[14] Arterial calcification has been produced experimentally in

rats by treatment with warfarin.[40,41] In a 2005 study of older patients with known calcification of the aortic valve, those who had been on long-term oral anticoagulation therapy had markedly more calcium in their coronary arteries and aortic valves than did patients who had not been on such treatment.[75]

Conclusion

In addition to its effects on the coagulation cascade, vitamin K is now known to be involved in many of the body's most critical functions. Bone mineralization and vascular calcification, two bodily functions affected by aging, are fundamentally related to each other through the actions of vitamin K. It is becoming increasingly clear that vitamin K antagonists (like warfarin) may have the unintended effects of exacerbating osteoporosis and atherosclerosis. Fortunately, the very science that revealed this new threat probably holds the answer to preventing it.

In 2005, a Japanese study demonstrated that the Gla-proteins governing coagulation require higher doses of warfarin for inhibition than do those that control bone mineralization.[76] If confirmed, this exciting finding raises the possibility that careful, low-dose vitamin K supplementation could prevent warfarin's deleterious effects on bone and blood vessel calcification, while preserving its beneficial effect of anticoagulation. University of Texas researchers have already demonstrated the safety and benefit of low-dose vitamin K supplementation in patients taking warfarin.[68]

NEW APPLICATIONS FOR VITAMIN K

In the last two years, scientists have uncovered several potential applications for vitamin K. Here is a summary of the most recent research demonstrating vitamin K's wide applicability in human health beyond its well-known role in blood clotting.

- **Cancer-fighting effects.** The hepatitis C virus is a leading cause of liver cancer. An 85-year-old man with hepatitis C and advanced liver cancer recently underwent marked regression of his tumor while using vitamin K therapy.[78] Laboratory evidence in the last year provides an understanding of the mechanism of this anti-cancer effect.[79-82] In 2005, vitamin K was also shown to have anti-leukemia effects.[83] These anti-cancer capabilities seem to arise from vitamin K's power to selectively inhibit cell growth and induce apoptosis (programmed cell death).[84] This is an exciting and growing area of cancer therapy.
- **Improving cancer detection.** Blood levels of "proteins induced by vitamin K absence or antagonist" (PIVKA) are elevated in liver cancer patients.[85] PIVKA is a measure of insufficient vitamin K activity. In 2005, elevated PIVKA levels were correlated with a variety of other cancers.[86,87] PIVKA testing may one day serve as a useful and sensitive marker of tumor progression or treatment success. Elevated PIVKA levels also raise the intriguing possibility that vitamin K deficiency could be related to the cause and possibly the treatment of some cancers.
- **Modulating inflammation.** The vitamin K-dependent protein C has powerful anti-inflammatory capabilities. Activated protein C has been used in reducing the damage

caused by the immune system in advanced bacterial sepsis.[24,88]

- **Supporting healthy bones.** Earlier this year, researchers demonstrated that long-term use of anticoagulants is associated with increased risk of osteoporotic fractures.[89] This is an unsurprising finding in light of other work demonstrating a link between anticoagulant drugs and abnormalities in measures of bone calcification.71 In a 2005 study, vitamin K-rich compounds in sweet potato leaves not only stimulated bone formation through vitamin K activity, but also seemed to inhibit bone resorption through the actions of other components.[90]
- **Protecting vascular health**. Very recent work has shown that vitamin K antagonists such as warfarin may promote blood vessel calcification.[45,91] Postmenopausal women who supplemented with vitamins D and K had less calcification and superior arterial vessel wall elasticity than placebo-treated subjects.[92]

Patients taking warfarin (Coumadin®) or other vitamin K antagonists should talk with their doctors about this recent literature, to learn whether regular, low-dose supplements of vitamin K (100 mcg/day), taken under careful medical supervision, may be right for them. Because of the considerable evidence for increasing the daily recommended dose of vitamin K,[14,15,17,20] people who are not taking anticoagulant medication may want to consider beginning daily supplements of vitamin K to support the Gla-proteins that can slow osteoporosis and reduce arterial calcification.[36] For people in good health, doses of 10 mg to 40 mg have been used.[39]

References

1. Saltzman JR, Russell RM. The aging gut. Nutritional issues. Gastroenterol Clin North Am. 1998 Jun;27(2):309-24.

2. Moriuchi S, Hosoya N. Changes of vitamin status and calcium metabolism in aging. J Nutr Sci Vitaminol.(Tokyo). 1985 Dec;31 SupplS11-4.

3. Tsaioun KI. Vitamin K-dependent proteins in the developing and aging nervous system. Nutr Rev. 1999 Aug;57(8):231-40.

4. Saunders LZ. Frank Schofield (1889-1970) and anticoagulant therapy. Med Herit. 1986 Jul;2 (4):310-2.

5. Meier B. Blood thinning in heart patients. Ther Umsch. 1995 Oct;52(10):661-71.

6. Dorffler-Melly J, Schmidli J, Mahler F. Anticoagulation and antiaggregation in patients with peripheral arterial occlusive diseases. Ther Umsch. 2003 Jan;60(1):36-42.

7. Mueller RL, Scheidt S. History of drugs for thrombotic disease. Discovery, development, and directions for the future. Circulation. 1994 Jan;89(1):432-49.

8. Miggiano GA, Robilotta L. Vitamin K and diet: problems and prospects. Clin Ter. 2005 Jan;156(1-2):41-6.

9. Israels LG, Israels ED, Saxena SP. The riddle of vitamin K1 deficit in the newborn. Semin Perinatol. 1997 Feb;21(1):90-6.

10. Kowdley KV. Lipids and lipid-activated vitamins in chronic cholestatic diseases. Clin Liver Dis. 1998 May;2(2):373-89.

11. Krahenbuhl S. Consequences of cholestasis from the hepatologist's viewpoint. Schweiz Med Wochenschr. 1997 May 10;127(19):821-8.

12. Mager DR, McGee PL, Furuya KN, Roberts EA. Prevalence of vitamin K deficiency in children with mild to moderate chronic liver disease. J Pediatr Gastroenterol Nutr. 2006 Jan;42 (1):71-6.

13. Sokol RJ. Fat-soluble vitamins and their importance in patients with cholestatic liver diseases. Gastroenterol Clin North Am. 1994 Dec;23(4):673-705.

14. Berkner KL, Runge KW. The physiology of vitamin K nutriture and vitamin K-dependent protein function in atherosclerosis. J Thromb Haemost. 2004 Dec;2(12):2118-32.

15. Shoji S. Vitamin K and vascular calcification. Clin Calcium. 2002 Aug;12(8):1123-8.

16. Plaza SM, Lamson DW. Vitamin K2 in bone metabolism and osteoporosis. Altern Med Rev. 2005 Mar;10(1):24-35.

17. Booth SL, Suttie JW. Dietary intake and adequacy of vitamin K. J Nutr. 1998 May;128 (5):785-8.

18. Davidson RT, Foley AL, Engelke JA, Suttie JW. Conversion of dietary phylloquinone to tissue menaquinone-4 in rats is not dependent on gut bacteria. J Nutr. 1998 Feb;128(2):220-3.

19. Thijssen HH, Drittij-Reijnders MJ. Vitamin K status in human tissues: tissue-specific accumulation of phylloquinone and menaquinone-4. Br J Nutr. 1996 Jan;75(1):121-7.

20. Askim M. Vitamin K in the Norwegian diet and osteoporosis. Tidsskr Nor Laegeforen. 2001 Sep 20;121(22):2614-6.

21. Jesty J, Beltrami E. Positive feedbacks of coagulation: their role in threshold regulation. Arterioscler Thromb Vasc Biol. 2005 Dec;25(12):2463-9.

22. Bern M. Observations on possible effects of daily vitamin K replacement, especially upon warfarin therapy. JPEN J Parenter Enteral Nutr. 2004 Nov;28(6):388-98.

23. Espana F, Medina P, Navarro S, et al. The multifunctional protein C system. Curr Med Chem Cardiovasc Hematol Agents. 2005 Apr;3(2):119-31.

24. Dahlback B, Villoutreix BO. The anticoagulant protein C pathway. FEBS Lett. 2005 Jun 13;579(15):3310-6.

25. Matsuzaka T, Tanaka H, Fukuda M, et al. Relationship between vitamin K dependent coagulation factors and anticoagulants (protein C and protein S) in neonatal vitamin K deficiency. Arch Dis Child. 1993 Mar;68(3 Spec No):297-302.

26. Esmon CT. Coagulation inhibitors in inflammation. Biochem Soc Trans. 2005 Apr;33(Pt 2):401-5.

27. Vermeer C, Shearer MJ, Zittermann A, et al. Beyond deficiency: potential benefits of increased intakes of vitamin K for bone and vascular health. Eur J Nutr. 2004 Dec;43(6):325-35.

28. Okano T. Vitamin D, K and bone mineral density. Clin Calcium. 2005 Sep;15(9):1489-94.

29. McLean RR, Booth SL, Kiel DP, et al. Association of dietary and biochemical measures of vitamin K with quantitative ultrasound of the heel in men and women. Osteoporos Int. 2006 Jan 6;1-8.

30. Kaneki M. Vitamin K2 as a protector of bone health and beyond. Clin Calcium. 2005 Apr;15 (4):605-10.

31. Bonjour JP, Schurch MA, Rizzoli R. Nutritional aspects of hip fractures. Bone. 1996 Mar;18 (3 Suppl):139S-44S.

32. Weber P. The role of vitamins in the prevention of osteoporosis—a brief status report. Int J Vitam Nutr Res. 1999 May;69(3):194-7.

33. Iwasaki Y, Yamato H, Murayama H, et al. Menatetrenone prevents osteoblast dysfunction in unilateral sciatic neurectomized rats. Jpn J Pharmacol. 2002 Sep;90(1):88-93.

34. Kishimoto H. Vitamin K and bone quality. Clin Calcium. 2004 Apr;14(4):621-6.

35. Iwamoto J, Takeda T, Ichimura S. Combined treatment with vitamin k2 and bisphosphonate in postmenopausal women with osteoporosis. Yonsei Med J. 2003 Oct 30;44(5):751-6.

36. Ryan-Harshman M, Aldoori W. Bone health. New role for vitamin K? Can Fam Physician. 2004 Jul;50:993-7.

37. Adams J, Pepping J. Vitamin K in the treatment and prevention of osteoporosis and arterial

calcification. Am J Health Syst Pharm. 2005 Aug 1;62(15):1574-81.

38. Nieves JW. Osteoporosis: the role of micronutrients. Am J Clin Nutr. 2005 May;81 (5):1232S-39S.

39. Available at: http://www.pdrhealth.com/drug_info/nmdrugprofiles/nutsupdrugs/vit_0267. shtml. Accessed February 8, 2006.

40. Bostrom K, Demer LL. Regulatory mechanisms in vascular calcification. Crit Rev Eukaryot Gene Expr. 2000;10(2):151-8.

41. Price PA, Faus SA, Williamson MK. Bisphosphonates alendronate and ibandronate inhibit artery calcification at doses comparable to those that inhibit bone resorption. Arterioscler Thromb Vasc Biol. 2001 May;21(5):817-24.

42. Demer LL, Tintut Y, Parhami F. Novel mechanisms in accelerated vascular calcification in renal disease patients. Curr Opin Nephrol Hypertens. 2002 Jul;11(4):437-43.

43. Devaraj S, Rosenson RS, Jialal I. Metabolic syndrome: an appraisal of the pro-inflammatory and procoagulant status. Endocrinol Metab Clin North Am. 2004 Jun;33(2):431-53.

44. Seyama Y, Wachi H. Atherosclerosis and matrix dystrophy. J Atheroscler Thromb. 2004;11 (5):236-45.

45. Schurgers LJ, Teunissen KJ, Knapen MH, et al. Novel conformation-specific antibodies against matrix gamma-carboxyglutamic acid (Gla) protein: undercarboxylated matrix Gla protein as marker for vascular calcification. Arterioscler Thromb Vasc Biol. 2005 Aug;25 (8):1629-33.

46. Geleijnse JM, Vermeer C, Grobbee DE, et al. Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. J Nutr. 2004 Nov;134 (11):3100-5.

47. Villines TC, Hatzigeorgiou C, Feuerstein IM, O'Malley PG, Taylor AJ. Vitamin K1 intake and coronary calcification. Coron Artery Dis. 2005 May;16(3):199-203.

48. Kurnik D, Lubetsky A, Loebstein R, Almog S, Halkin H. Multivitamin supplements may affect warfarin anticoagulation in susceptible patients. Ann Pharmacother. 2003 Nov;37 (11):1603-6.

49. Collier S, Fulhan J, Duggan C. Nutrition for the pediatric office: update on vitamins, infant feeding and food allergies. Curr Opin Pediatr. 2004 Jun;16(3):314-20.

50. Cornelissen M, von KR, Loughnan P, Schubiger G. Prevention of vitamin K deficiency bleeding: efficacy of different multiple oral dose schedules of vitamin K. Eur J Pediatr. 1997 Feb;156(2):126-30.

51. Eguchi T, Nakase H, Morimoto T, et al. Postoperative intracranial hemorrhage due to vitamin K deficiency: report of two cases. No Shinkei Geka. 1992 Jan;20(1):73-7.

52. Huilgol VR, Markus SL, Vakil NB. Antibiotic-induced iatrogenic hemobilia. Am J Gastroenterol. 1997 Apr;92(4):706-7.

53. Gordon BG, Haire WD, Stephens LC, Kotulak GD, Kessinger A. Protein C deficiency following hematopoietic stem cell transplantation: optimization of intravenous vitamin K dose. Bone Marrow Transplant. 1993 Jul;12(1):73-6.

54. Booth SL, Lichtenstein AH, O'Brien-Morse M, et al. Effects of a hydrogenated form of vitamin K on bone formation and resorption. Am J Clin Nutr. 2001 Dec;74(6):783-90.

55. Shetty HG, Woods F, Routledge PA. The pharmacology of oral anticoagulants: implications for therapy. J Heart Valve Dis. 1993 Jan;2(1):53-62.

56. Hathcock JN. Metabolic mechanisms of drug-nutrient interactions. Fed Proc. 1985 Jan;44(1 Pt 1):124-9.

57. Sebastian JL, Tresch DD. Use of oral anticoagulants in older patients. Drugs Aging. 2000 Jun;16(6):409-35.

58. Weiss P, Soff GA, Halkin H, Seligsohn U. Decline of proteins C and S and factors II, VII, IX and X during the initiation of warfarin therapy. Thromb Res. 1987 Mar 15;45(6):783-90.

59. Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med. 2005 Jun 2;352(22):2285-93.

60. Veenstra DL, You JH, Rieder MJ, et al. Association of Vitamin K epoxide reductase complex 1 (VKORC1) variants with warfarin dose in a Hong Kong Chinese patient population. Pharmacogenet Genomics. 2005 Oct;15(10):687-91.

61. Dentali F, Ageno W. Management of coumarin-associated coagulopathy in the non-bleeding patient: a systematic review. Haematologica. 2004 Jul;89(7):857-62.

62. Crowther MA, Donovan D, Harrison L, McGinnis J, Ginsberg J. Low-dose oral vitamin K reliably reverses over-anticoagulation due to warfarin. Thromb Haemost. 1998 Jun;79(6):1116-8.

63. Crowther MA, Julian J, McCarty D, et al. Treatment of warfarin-associated coagulopathy

with oral vitamin K: a randomized controlled trial. Lancet. 2000 Nov 4;356(9241):1551-3.

64. Duong TM, Plowman BK, Morreale AP, Janetzky K. Retrospective and prospective analyses of the treatment of overanticoagulated patients. Pharmacotherapy. 1998 Nov;18 (6):1264-70.

65. Gunther KE, Conway G, Leibach L, Crowther MA. Low-dose oral vitamin K is safe and effective for outpatient management of patients with an INR>10. Thromb Res. 2004;113(3-4):205-9.

66. Poli D, Antonucci E, Lombardi A, et al. Safety and effectiveness of low dose oral vitamin K1 administration in asymptomatic out-patients on warfarin or acenocoumarol with excessive anticoagulation. Haematologica. 2003 Feb;88(2):237-8.

67. Shetty HG, Backhouse G, Bentley DP, Routledge PA. Effective reversal of warfarin-induced excessive anticoagulation with low dose vitamin K1. Thromb Haemost. 1992 Jan 23;67(1):13-5.

68. Reese AM, Farnett LE, Lyons RM, et al. Low-dose vitamin k to augment anticoagulation control. Pharmacotherapy. 2005;25(12):1746-51.

69. Koshihara Y, Hoshi K, Ishibashi H, Shiraki M. Vitamin K2 promotes 1alpha,25(OH)2 vitamin D3-induced mineralization in human periosteal osteoblasts. Calcif Tissue Int. 1996 Dec;59 (6):466-73.

70. Simon RR, Beaudin SM, Johnston M, Walton KJ, Shaughnessy SG. Long-term treatment with sodium warfarin results in decreased femoral bone strength and cancellous bone volume in rats. Thromb Res. 2002 Feb 15;105(4):353-8.

71. Philip WJ, Martin JC, Richardson JM, et al. Decreased axial and peripheral bone density in patients taking long-term warfarin. QJM. 1995 Sep;88(9):635-40.

72. Booth SL, Mayer J. Warfarin use and fracture risk. Nutr Rev. 2000 Jan;58(1):20-2.

73. Hansen LB, Vondracek SF. Prevention and treatment of nonpostmenopausal osteoporosis. Am J Health Syst Pharm. 2004 Dec 15;61(24):2637-54.

74. Barnes C, Newall F, Ignjatovic V, et al. Reduced bone density in children on long-term warfarin. Pediatr Res. 2005 Apr;57(4):578-81.

75. Koos R, Mahnken AH, Muhlenbruch G, et al. Relation of oral anticoagulation to cardiac valvular and coronary calcium assessed by multislice spiral computed tomography. Am J Cardiol. 2005 Sep 15;96(6):747-9.

76. Hara K, Kobayashi M, Akiyama Y. Comparison of inhibitory effects of warfarin on gamma-

carboxylation between bone and liver in rats. J Bone Miner Metab. 2005;23(5):366-72.

77. Shah NS, Lazarus MC, Bugdodel R, et al. The effects of topical vitamin K on bruising after laser treatment. J Am Acad Dermatol. 2002 Aug;47(2):241-4.

78. Nouso K, Uematsu S, Shiraga K, et al. Regression of hepatocellular carcinoma during vitamin K administration. World J Gastroenterol. 2005 Nov 14;11(42):6722-4.

79. Yoshiji H, Kuriyama S, Noguchi R, et al. Amelioration of carcinogenesis and tumor growth in the rat liver by combination of vitamin K2 and angiotensin-converting enzyme inhibitor via anti-angiogenic activities. Oncol Rep. 2006 Jan;15(1):155-9.

80. Kuriyama S, Hitomi M, Yoshiji H, et al. Vitamins K2, K3 and K5 exert in vivo antitumor effects on hepatocellular carcinoma by regulating the expression of G1 phase-related cell cycle molecules. Int J Oncol. 2005 Aug;27(2):505-11.

81. Enokimura N, Shiraki K, Kawakita T, et al. Vitamin K analog (compound 5) induces apoptosis in human hepatocellular carcinoma independent of the caspase pathway. Anticancer Drugs. 2005 Sep;16(8):837-44.

82. Hitomi M, Yokoyama F, Kita Y, et al. Antitumor effects of vitamins K1, K2 and K3 on hepatocellular carcinoma in vitro and in vivo. Int J Oncol. 2005 Mar;26(3):713-20.

83. Lin C, Kang J, Zheng R. Vitamin K3 triggers human leukemia cell death through hydrogen peroxide generation and histone hyperacetylation. Pharmazie. 2005 Oct;60(10):765-71.

84. Yokoyama T, Miyazawa K, Yoshida T, Ohyashiki K. Combination of vitamin K2 plus imatinib mesylate enhances induction of apoptosis in small cell lung cancer cell lines. Int J Oncol. 2005 Jan;26(1):33-40.

85. Gad A, Tanaka E, Matsumoto A, et al. Assessment of KL-6 as a tumor marker in patients with hepatocellular carcinoma. World J Gastroenterol. 2005 Nov 14;11(42):6607-12.

86. Iso Y, Sawada T, Shimoda M, et al. Solitary AFP- and PIVKA-II-producing hepatoid gastric cancer with giant lymph node metastasis. Hepatogastroenterology. 2005 Nov;52(66):1930-2.

87. Hasegawa Y, Tomita K, Hashimoto K, et al. Des-gamma-carboxy prothrombin (PIVKA-II)-producing mediastinal embryonal carcinoma with features of hepatoid differentiation. Anticancer Res. 2005 Nov;25(6C):4569-71.

88. Dahlback B, Villoutreix BO. Regulation of blood coagulation by the protein C anticoagulant pathway: novel insights into structure-function relationships and molecular recognition. Arterioscler Thromb Vasc Biol. 2005 Jul;25(7):1311-20.

89. Gage BF, Birman-Deych E, Radford MJ, Nilasena DS, Binder EF. Risk of osteoporotic fracture in elderly patients taking warfarin: results from the National Registry of Atrial Fibrillation 2. Arch Intern Med. 2006 Jan 23;166(2):241-6.

90. Tang QY, Kukita T, Ushijima Y, et al. Regulation of osteoclastogenesis by Simon extracts composed of caffeic acid and related compounds: successful suppression of bone destruction accompanied with adjuvant-induced arthritis in rats. Histochem Cell Biol. 2005 Oct 5;1-11.

91. Schurgers LJ, Aebert H, Vermeer C, Bultmann B, Janzen J. Oral anticoagulant treatment: friend or foe in cardiovascular disease? Blood. 2004 Nov 15;104(10):3231-2.

92. Braam LA, Hoeks AP, Brouns F, et al. Beneficial effects of vitamins D and K on the elastic properties of the vessel wall in postmenopausal women: a follow-up study. Thromb Haemost. 2004 Feb;91(2):373-80.