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# Influence of Vitamin K on Anticoagulant Therapy Depends on Vitamin K Status and the Source and Chemical Forms of Vitamin K

Mary Ann Johnson, PhD

*Warfarin therapy requires close monitoring to avoid excessive bleeding and to maintain the effective therapeutic concentration assessed with the internationalized ratio (INR). High vitamin K intake can decrease the therapeutic effectiveness of warfarin, while poor vitamin K status appears to increase the sensitivity to small changes in vitamin K intake, especially from supplements. Very large amounts of vitamin K from a single meal with vegetables (400 g of vegetables with 700 to 1500 μg of vitamin $K_1$) can measurably change INR, but occasional typical servings (<100 g) would probably have little lasting impact on INR. Warfarin requirements may change in those altering their intake of dark-green vegetables. The 2005 Dietary Guidelines for Americans recommends 3 cups/week of dark-green vegetables, which contain about 100 to 570 μg/serving of vitamin $K_1$. Less well-known sources and chemical forms of vitamin K, such as MK-7 in natto (a fermented Japanese product), also measurably influence INR. Additional research is needed in warfarin-treated patients to fully quantify the interactions among various sources and chemical forms of vitamin K, age, genotype, and other factors.*

Key words: vitamin K, anticoagulant, warfarin



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## Vitamin K Functions, Recommendations, Intakes, and Food and Supplement Sources

Vitamin K is essential for the posttranslational carboxylation of glutamyl residues to γ-carboxyglutamyl residues in a limited number of proteins.[1] These proteins are needed for blood coagulation, bone metabolism, and possibly vascular health.[1,2] The adequate intake (AI) of vitamin K for ages 19 to 70+ for women is 90 μg/d and for men is 120 μg/d.[1] This is an increase from the previous recommended dietary allowance of 65 to 80 μg/d for adults. The daily value used for labeling of foods and dietary supplements is 80 μg.[3] Median intake of vitamin K assessed in the National Health and Nutrition Examination Survey III varied between 74 and 117 μg/d in adults.[1] Phylloquinone ($K_1$) is the main food source and is used in dietary supplements.[1] Vitamin $K_1$ from supplements is 3 to 20 times more bioavailable than that from food sources.[1] Fat promotes vitamin K absorption.[1]

The vitamin K content of about 900 foods and beverages is available online.[4] The primary food sources in the US diet are green vegetables and vegetable oils.[1] These foods vary widely in their vitamin K content (Table 1)[4]; for example, kale has over 20 times more vitamin K than green peas, and vegetable oils vary by 170-fold in their vitamin K content. The 2005 Dietary Guidelines for Americans suggests consuming 3 cups/week of dark-green vegetables such as broccoli, spinach, romaine, and collard, turnip, and mustard greens.[5] This is substantially more dark-green vegetables than Americans are currently consuming.[5] Green vegetables are a rich source of several of the "shortfall" nutrients: vitamin A, vitamin C, vitamin E, calcium, magnesium, potassium, and fiber,[5] and they are the primary dietary source of lutein,[5,6] which may protect against age-related macular degeneration, cataracts, and other disorders.[6] Multivitamins and some calcium supplements contain vitamin K in amounts ranging from 10 to 80 μg (Table 2).

Warfarin and other coumarin derivatives act as anticoagulants by interfering with the conversion of vitamin K to its reduced form, which is needed for the γ-carboxylation of several vitamin K-dependent proteins that regulate blood coagulation.[7] The effectiveness of warfarin has been established for primary and secondary prevention of venous thromboembolism, for prevention of systemic embolism in patients with prosthetic heart valves or atrial fibrillation, for prevention of acute myo-

Dr. Johnson is Professor of Foods and Nutrition at the Department of Foods and Nutrition and Faculty of Gerontology, The University of Georgia, Athens, Georgia.

Address for correspondence: Dr. Mary Ann Johnson, Department of Foods and Nutrition, The University of Georgia, Dawson Hall, Athens, GA 30602; Phone: 706-542-2292; Fax: 706-542-5059; E-mail: mjohnson@fcs.uga.edu.

**Table 1.** Vitamin K in Green Vegetables and Vegetable Oils[4]

| Source | Vitamin K (μg)* |
|---|---|
| Kale, frozen, cooked, boiled, drained, ½ C (65 g) | 573 |
| Collards, frozen, chopped, cooked, boiled, drained, ½ C (85 g) | 530 |
| Spinach, frozen, chopped or leaf, cooked, boiled, drained, ½ C (95 g) | 514 |
| Turnip greens, frozen, cooked, boiled, drained, ½ C (82 g) | 425 |
| Beet greens, cooked, boiled, drained, ½ C (72 g) | 348 |
| Mustard greens, cooked, boiled, drained, ½ C (70 g) | 210 |
| Brussels sprouts, frozen, cooked, boiled, drained, ½ C (78 g) | 150 |
| Broccoli, cooked, boiled, drained, ½ C (78 g) | 110 |
| Asparagus, frozen, cooked, boiled, drained, ½ C (90 g) | 72 |
| Sauerkraut, canned, solids and liquids, ½ C (71 g) | 41 |
| Okra, frozen, cooked, boiled, drained, ½ C (92 g) | 44 |
| Cabbage, cooked, boiled, drained, ½ C (75 g) | 37 |
| Peas, edible-podded, frozen, cooked, boiled, drained, ½ C (80 g) | 24 |
| Beans, snap, green, cooked, boiled, drained, ½ C (62 g) | 10 |
| Carrots, frozen, cooked, boiled, drained, ½ C (73 g) | 10 |
| Spinach, 1 C (30 g) | 145 |
| Endive, 1 C (50 g) | 116 |
| Lettuce, green leaf, 1 C (36 g) | 63 |
| Lettuce, butterhead (includes Boston and bibb types), 1 C (55 g) | 56 |
| Lettuce, cos or romaine, 1 C (47 g) | 48 |
| Lettuce, iceberg (includes crisphead types), 1 C (72 g) | 17 |
| Tea, brewed, prepared with tap water, ¾ C (178 g) | 0 |
| Canola oil, 1 TBS (14 g) | 17.1 |
| Olive oil, 1 TBS (13.5 g) | 8.1 |
| Peanut oil, 1 TBS (13.5 g) | 0.1 |
| Sesame oil, 1 TBS (13.6 g) | 1.8 |
| Soybean oil, 1 TBS (13.6 g) | 3.4 |
| Safflower oil, 1 TBS (13.6 g) | 1.0 |
| Corn oil, 1 TBS (13.6 g) | 0.3 |
| Sunflower oil, 1 TBS (13.6 g) | 0.7 |

*Adequate intake for men is 120 μg/d and for women is 90 μg/d.

cardial infarction in patients with peripheral arterial disease, and for prevention of stroke, recurrent infarction, or death in patients with acute myocardial infarction.[7] Warfarin is a racemic mixture of equal amounts of (R)- and (S)-enantiomers, with (S)-warfarin being several times more potent than (R)-warfarin. Warfarin has a narrow therapeutic window, which is assessed with prothrombin time expressed as the internationalized ratio (INR). The therapeutic INR is 2.0 to 3.0 for most conditions.[7] The risk of bleeding increases when INR exceeds 4.0 and rises sharply when INR exceeds 5.0.[7] Depending on the elevation in INR, patients who need their INR lowered may skip a dose of warfarin, have their warfarin dose decreased, be given high doses of oral vitamin K (1 to 10 mg), and/or receive a transfusion of fresh plasma or prothrombin, according to the urgency of the situation.[7]

Vitamin K intake has an inverse association with INR, such that increased vitamin K decreases INR and decreased vitamin K increases INR. However, the quantitative dose-response relationship of vitamin K and INR in patients receiving anticoagulant therapy is not well defined. Patients receiving warfarin therapy are advised to limit and/or keep their intake of vitamin K from foods and supplements constant.[1,8-10] It might be challenging for patients to distinguish between "limit" and "eliminate," to discern the meaning of "constant intake" (day to day or over a week), and to know the vitamin K content of various foods and dietary supplements. Some sources suggest avoiding and/or limiting foods high in vitamin K, as well as inappropriately targeting foods without appreciable vitamin K, such as milk.[10] The National Institutes of Health recommends keeping vitamin K intake constant from day to day, limiting intake of foods considered high in vitamin K to no more than 1 serving each day (e.g., dark-green leafy vegetables), and limiting intake of foods moderately high in vitamin K to no more than 3 servings each day (e.g., foods with about 50 to 160 μg vitamin K/serving).[8] The Institute of Medicine recommends that after the dose of warfarin has been established, patients can avoid complications from variable vitamin K intake by continuing to follow their normal dietary patterns.[1]

Because vitamin K is an essential nutrient, and evidence is emerging for its important roles in cardiovascular and bone health,[1,2] it is important to help patients consume an appropriate amount of vitamin K and to identify foods and supplements that may interfere with successful anticoagulation therapy.[9] To address these type of issues, Schurgers et al.[11] conducted a dose-response trial to compare the influence of vitamin K from supplements, green vegetables, and fermented foods on INR during anticoagulant therapy. This study and related studies are discussed below.

**Table 2.** Vitamin K in Selected Nutrient Supplements

| Product | Vitamin K ($\mu$g) |
|---|---|
| Centrum Silver Adults 50+® (Wyeth Consumer Healthcare, Madison, NJ) | 10 |
| Geritol Complete® (GlaxoSmithKline Consumer Healthcare, Moon Township, PA) | 24 |
| GNC Women's Ultra Mega® (General Nutrition Centers, Pittsburgh, PA) | 80 |
| Nature Made Essential Man 50+ Complete® (Nature Made Nutritional Products, Mission Hills, CA) | 10 |
| Nature Made Essential Women 50+ Complete® | 50 |
| Olay Vitamins Women 50+® (Pharmaville LLC, Mission Hills, CA) | — |
| One-A-Day 50+® (Bayer Healthcare, Morristown, NJ) | 20 |
| Theragran-M® (Bristol-Myers Squibb, New York, NY) | 28 |
| Viactiv 500+D+K® (McNeil Nutritionals, Ft. Washington, PA) | 40 |

## Influence of Changes in Vitamin K Intake on INR During Anticoagulant Therapy

Schurgers et al.[11] conducted a vitamin K dose-response study in 12 young healthy adults (6 women, 6 men, ages 26 to 31) who did not require anticoagulant therapy, had no history of coagulation disorders, and had plasma vitamin $K_1$ in the normal range (1.27 $\pm$ 0.4 nmol/L). Throughout the study, participants were asked to refrain from consuming vitamin K-rich foods. In an initial 4-week dose-adjustment phase, participants were anticoagulated with acenocoumarol to a target INR of 2.0, which is in the lower range of anticoagulant therapy regimens. Acenocoumarol is similar to warfarin but has a shorter half-life.[12] Maintenance doses averaged 3.3 mg/d in men and 2.8 mg/d in women.

In phase I, participants were supplemented with increasing doses of synthetic vitamin $K_1$ in tablets to be taken daily before the evening meal for 7 weeks (week 1: 50 $\mu$g/d, followed by 100, 150, 200, 250, 300, and 500 $\mu$g/d in succeeding weeks; Table 3). Compliance was assessed with pill counts. The INR was measured 4 times per week, and other vitamin K-dependent proteins were assessed 2 times per week. Venous blood samples for all coagulation and biochemical assays were collected after an overnight fast.

In phase II, participants underwent a 2-week washout period in which they continued to take acenocoumarol and to avoid vitamin K-rich foods (daily vitamin K intake was 55 $\mu$g/d). For the following 4 weeks, they received one test meal each week of spinach, broccoli, curd (cottage) cheese, or the Japanese food natto, all of which had been analyzed for vitamin K content (Table 3). Natto is a traditional Japanese fermented soybean food, which is produced by growing the MK-7-generating *Bacillus natto* on the surface of cooked soybeans.[11] Spinach and broccoli were each cooked as a single meal, while the curd cheese and natto were ready-to-use products. Foods were purchased locally. To facilitate absorption, 30 g of corn oil with negligible vitamin K (2.7 $\mu$g/100 g) was used for cooking the spinach and broccoli and for mixing into the curd cheese and natto meals. The vitamin K-rich meals were prepared and consumed at the University of Maastricht in The Netherlands. Meals were consumed after an overnight fast and after a venous blood sample was drawn.

Baseline mean INRs were variable, as would be

**Table 3.** Internationalized Ratio (INR) Responses to Supplemental and Food Sources of Vitamin K[11]

| Treatment | Statistically Significant Decrease in INR | Clinically Significant Decrease in INR* |
|---|---|---|
| $K_1$ 50 $\mu$g/d for 7 d | No | No |
| $K_1$ 100 $\mu$g/d for 7 d | 1/12 participants | No |
| $K_1$ 150 $\mu$g/d for 7 d | Women only | No |
| $K_1$ 200 $\mu$g/d for 7 d | Yes (mean maximum = 0.5) | 3/12 participants |
| $K_1$ 250 $\mu$g/d for 7 d | Yes (mean maximum = 0.6) | Data not provided |
| $K_1$ 300 $\mu$g/d for 7 d | Yes (mean maximum = 0.6) | Data not provided |
| $K_1$ 500 $\mu$g/d for 7 d | Yes (mean maximum = 0.7) | Data not provided |
| $K_1$ 1500 $\mu$g from 400 g spinach in one meal | Yes (mean maximum = 0.3) | 1/12 |
| $K_1$ 700 $\mu$g from 400 g broccoli in one meal | Yes (mean maximum = 0.4) | 1/12 |
| MK-9 103 $\mu$g from 500 g cottage cheese in one meal | No | No |
| MK-7 1000 $\mu$g from 100 g natto in one meal | Yes (mean maximum = 0.6) | 6/12 |

*Defined as a deviation in INR exceeding 1 standard deviation plus 20% of the mean INR attained after dose stabilization (i.e., mean of 8 consecutive INR values over the final 2 weeks of the adjustment phase).

expected. The 10 baseline INR means ranged from 1.93 to 2.19 (maximum difference of 0.26) and averaged 2.04 ± 0.3 at the beginning of phase I and 1.97 ± 0.3 at the beginning of phase II. The minimum INR within each treatment period is shown in Figure 1. Comparing the minimum INR among the 4 mean INRs within each treatment period may somewhat exaggerate the effect of the various vitamin K treatments. With supplemental vitamin $K_1$, decreases in INR became statistically significant with 150 μg/d in women and 200 μg/d in men, and became clinically significant in 3 of 12 participants with 200 μg/d (Figure 1, Table 3). These data suggest that the 10 to 50 μg of vitamin $K_1$ in supplements marketed to older adults are probably compatible with anticoagulant therapy. Use of high-dose supplements and/or several supplements may approach the 150 to 200 μg/d of synthetic vitamin $K_1$ that was found to decrease the effectiveness of anticoagulant therapy.

Schurgers et al.[11] found that meals with a very large amount of vitamin K-rich spinach, broccoli, or natto, but not curd cheese, significantly decreased INR by an average of about 0.3 to 0.6 in the anticoagulated participants (Figure 1, Table 3). The foods were prepared with oil, which would have improved vitamin K absorption and would simulate the effects of adding oil to cooked foods or fat-containing dressings to salads. These acute high doses of green vegetables (400 g) exceed the expected daily intake of green vegetables, given that recommended serving sizes are ½ cup of cooked vegetables (60 to 120 g) and 1 cup of uncooked leafy salad greens (30 to 56 g) (Table 1).

Some limitations of the study by Schurgers et al.[11] are that the participants may not represent the typical patient who requires anticoagulant therapy and has multiple comorbidities. Also, the anticoagulant was acenocoumarol rather than warfarin, which is the anticoagulant used in the United States. However, the study does provide important quantitative dose-response information on vitamin K from varying food and supplemental sources. Schurgers et al.[11] also provide evidence that chemical forms of vitamin K other than $K_1$ (such as MK-7 found in natto) that have long half-lives may interfere with anticoagulant therapy.

In contrast to Schurgers et al.,[11] Kurnik et al.[15,16] reported that the amount of vitamin K in multivitamins is sufficient to alter the response to anticoagulant therapy, particularly in vitamin K-depleted individuals. Kurnik et al.[15] found these changes in INR in three anticoagulated patients in Israel who changed their intake of a vitamin K-containing multivitamin (25 μg/tablet): after a 43-year-old women stopped taking a multivitamin, her INR increased from 2.9 to 13.2; after a 77-year-old man started taking a multivitamin, his INR decreased from 2.8 to 1.7; and after an 80-year old man started taking a multivitamin, his INR decreased from 2.5 to 1.6. Kurnik et al.[15] suggested that the low vitamin K status typically seen in their clinic population may have increased the susceptibility of these patients to small changes in vitamin K intake, and that some of the other ingredients in the multivitamin may have potentiated the effects of vitamin K.

In a second study, Kurnik et al.[16] recruited 16 warfarin-treated patients (age 20 to 82 years), of whom 9 were in the

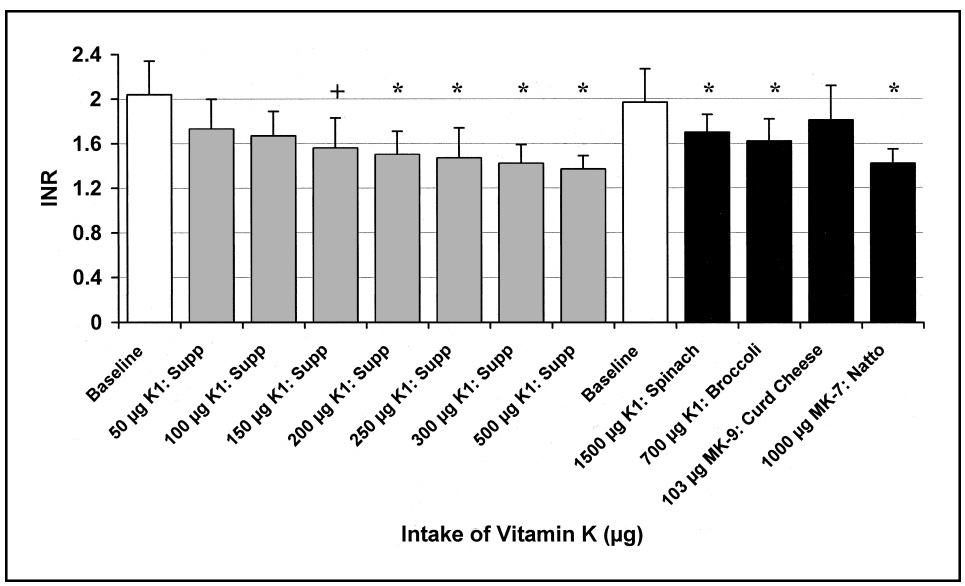


**Figure 1.** Data are from Schurgers et al.[11] in 12 healthy individuals anticoagulated with acenocoumarol to a target INR of 2.0 at baseline. INR values are mean ± SD. The first white bar and the seven gray bars describe the dose-response relationship of synthetic vitamin $K_1$. The addition of 150 μg/d vitamin K had a statistically significant effect in only women. The second white bar and the four black bars describe the effects of single meals of spinach, broccoli, curd cheese, and natto that naturally contain various chemical forms of vitamin K. *Significantly decreased from baseline ($P < 0.05$).

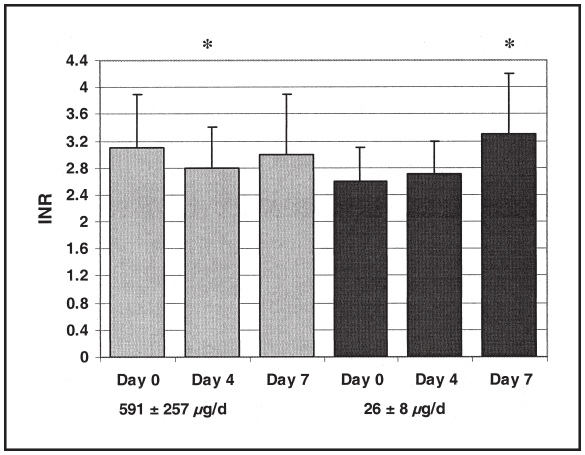


**Figure 2.** Data are from Franco et al.[17] in 12 patients anticoagulated with warfarin and phenprocoumon and assigned to 4 days of high dietary vitamin K intake (591 μg/d, range 88 to 1057 μg/d) and 4 days of low vitamin K intake (26 μg/d, range 16 to 42 μg/d) in a randomized crossover trial with a 1- to 2-week washout period between treatments. INR values are mean ± SD. On day 0, baseline intake of vitamin K was 118 μg/d (range 18 to 211 μg/d). During the high vitamin K intake period, there was a significant decrease in INR at day 4 that returned to baseline by day 7. During the low vitamin K intake period, there was no change in INR after 4 days, but there was a significant increase in INR 3 days after the low vitamin K diet had been stopped. *Significantly different from day 0 of that treatment period ($P < 0.05$).

lower range of vitamin K status (plasma vitamin $K_1$ averaged 0.9 nmol/L) and 7 had somewhat higher vitamin K status (plasma vitamin $K_1$ averaged 1.8 nmol/L) at baseline. Patients were given a multivitamin containing 25 μg of vitamin $K_1$ for 4 weeks. During this period, 9/9 patients with poor vitamin K status had subtherapeutic INRs, and the median decrease in INR was 0.5, while 1/7 with normal vitamin K status had subtherapeutic INRs with no change in the overall median INR.

Franco et al.[17] conducted a randomized crossover trial to examine the effects of changes in usual dietary intake of vitamin K on INR in 12 patients (age 59 ± 13 years) in Brazil anticoagulated with either warfarin or phenprocoumon. During the 4-day intervention, a registered nutritionist, taking into account individual food preferences, prepared all meals. Vegetables for each meal were weighed and vitamin K content was estimated from food composition tables from Europe and the United States. Patients were asked to avoid eating between meals and to keep a diary of any supplementary food consumed. Meals were served in the hospital and witnessed by one investigator to ensure compliance. Blood samples for INR testing were drawn on day 0 (before the first meal), day 4, and day 7 of the intervention. Baseline intake of vitamin K was 118 μg/d (range 18 to 211 μg/d). Changes in INR for the high vitamin K intake period (mean 591 μg/d, range 88 to 1057 μg/d) and the low vitamin K intake period (mean 26 μg/d, range 16 to 42 μg/d) are shown in Figure 2. During the high vitamin K period, INR was significantly decreased by 0.3 units by day 4 (the last day of food intervention), but INR had returned to initial values 3 days later (day 7). INR was not significantly increased after consuming the low vitamin K diet for 4 days, but was increased by about 0.7 INR units between day 0 and day 7. These data suggest that markedly decreasing vitamin K intake to less than 50 μg/d may have a greater effect on INR than markedly increasing vitamin K intake; however, these data are somewhat difficult to interpret because of the large variation of vitamin K during the high intake period.

## Other Factors that Alter the Response to Coumarins

Numerous medications, herbal supplements, and lifestyle- and diet-related factors may influence anticoagulant therapy, and older patients usually require less warfarin than younger patients.[7-9,13,14] Among the many herbal supplements that may influence anticoagulation therapy are garlic, *Ginkgo biloba*, ginseng, and St. John's wort,[13] as well as fish oil[18,19] and vitamin E.[20,21] Given that fish and fish oil may reduce mortality and improve some cardiovascular disease outcomes,[22] and because of concerns about the safety of vitamin E in patients with health problems,[23] it is possible that people may change their intake of these supplements.

Case reports suggest that fish oil and vitamin E increase INR in anticoagulated patients, but small randomized, controlled trials do not provide much support. For example, a patient receiving warfarin who increased their intake of fish oil from 1 g/d to 2 g/d had an increase in INR from 2.8 to 4.3.[18] However, a randomized, controlled trial of 11 patients receiving warfarin showed no statistically significant changes in INR during 4 weeks in those receiving placebo (n = 5), 3 g of fish oil (n = 3), or 6 g of fish oil (n = 3).[19] Similarly, a randomized, controlled trial of 12 patients receiving warfarin showed no statistically significant changes in INR in those receiving 800 IU vitamin E/d (n = 4) or 1200 IU vitamin E/d during the 25-day study; however, the INR of the placebo group (n = 4) was somewhat variable.[20] The European Commission[21] suggested that high intakes of vitamin E may primarily affect blood coagulation when vitamin K status is inadequate. Limitations of these randomized, controlled trials are that there may have been too few subjects to identify rare adverse responses to supplements such as vitamin E and fish oil.

Genetic variants associated with the metabolism of (S)-warfarin through the cytochrome P450 system, specifically *CYP2C9*, also influence the sensitivity to warfarin and the amount required to achieve therapeutic anticoagulation status.[24-27] Several single nucleotide polymorphisms in the coding and noncoding regions of

the *CYP2C9* gene have been identified. Among the most widely studied polymorphisms are *CYP2C9*1* (the most common allele and considered the wild type), *CYP2C9*2*, and *CYP2C9*3*, which combine to produce six genotypes: *CYP2C9*1/*1* (wild type), **1/*2, *1/*3, *2/*2, *2/*3*, and **3/*3*. The *CYP2C9*2* and **3* alleles are present in white populations (American, European, Scandinavian, Turkish, and possibly Hispanic) at frequencies of 10% to 15% and 5% to 10%, respectively, but occur at lower frequencies in black and Asian populations, who carry predominantly the *CYP2C9*1/*1* allele.[24] In a review of several reports, Lee[24] calculated that warfarin requirements for **1/*1*, **1/*2, *1/*3, *2/*2, *2/*3*, and **3/*3* were 5.52, 4.65, 3.56, 3.48, 3.03, and 1.50 mg/d, respectively. The **3* and **2* genotypes were also associated with more bleeding complications and elevated INR in some studies.[24,25] Genotype and age had somewhat more of an effect on the warfarin requirement than did vitamin K status in some studies.[26,27] Loebstein et al.[26] examined 156 patients with stable anticoagulation therapy. Among those 65 years of age or less, the warfarin requirements in genotype groups **1/*1*, **1/*2*, or **1/*3* plus **2/*3* were 7.9, 5.5, and 4.4 mg/d, respectively, while for those 66 or over, the warfarin requirements were 5.3, 4.8, and 2.2 mg/d, respectively. Thus, the combination of age and genotype may alter the warfarin requirement by as much as 4-fold. In comparison, Lubetsky et al.[28] reported that among 50 patients treated with warfarin, those consuming 505 ± 181 μg/d of vitamin K required 5.8 ± 1.8 mg/d of warfarin, while those consuming 133 ± 50 μg/d of vitamin K required 4.4 ± 1.3 mg/d of warfarin.

## Practical Advice about Vitamin K and Warfarin

Recent recommendations and reports may prompt some individuals to change their intake of dark-green vegetables,[5] fish, and fish oils,[22] and/or vitamin E supplements.[23] The information reviewed in this report confirms that those using warfarin should continue to keep their intake of vitamin K adequate and constant and to inform their physician of any changes in their dietary habits, supplements, and medications so that, if needed, adjustments to their warfarin dose can be made in a timely manner. Because of increasing evidence that poor vitamin K status increases the sensitivity to small changes in vitamin K intake, especially from supplements,[15,16] patients should consume sufficient vitamin K to meet the AI. The amount of vitamin K in multivitamins is typically less than 50 μg, but patients should read labels carefully and avoid taking several vitamin K-containing supplements. The vitamin K content found in foods is readily accessible to assist with achieving a constant intake.[4] Although very large amounts of vitamin K from a single meal with vegetables (400 g of vegetables containing 700 to 1500 μg of vitamin $K_1$) measurably changed INR, it is likely that occasional typical servings (<100 g) would have little measurable impact. Those attempting to meet the 2005 Dietary Guidelines for Americans recommendation of 3 cups/week of dark-green vegetables could consume at least 100 and possibly up to 600 μg/d of vitamin K from these sources alone, which may increase warfarin requirements.[11,17,28] Patients and physicians should be alert to less well-known sources and chemical forms of vitamin K, such as MK-7 in natto, that measurably influence INR.[11] Genotyping may also identify individuals with increased sensitivity to warfarin and its complications.[24,25] Additional research is needed in warfarin-treated patients to fully quantify the interactions and dose-response effects of various sources and chemical forms of vitamin K with age, genotype, and other factors.

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# Function of the Protein RPE65 in the Visual Cycle

George Wolf, DPhil

*A protein called RPE65 performs a key role in the trans-cis isomerization of retinol in the retinal pigment epithelium of the eye. The palmitoylation of RPE65 serves to switch off the visual cycle in darkness and to switch it on in the light.*

Key words: retina; retinal pigment epithelium; vitamin A; all-trans-retinyl palmitate; all-trans-retinol; 11-cis-retinol; isomerohydrolase; lethicin; lecithin retinol acyl transferase



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Dr. Wolf is with the Department of Nutritional Sciences and Toxicology, University of California, Berkeley.

Please address all correspondence to: Editorial Office, International Life Sciences Institute, One Thomas Circle NW, Ninth Floor, Washington, DC 20005; Phone: 202-659-0074; Fax: 202-659-3859; e-mail: nutritionreviews@ilsi.org.

Since 1993,[1] it has been known that the major protein of the microsomal membranes in the retinal pigment epithelium (RPE) is RPE65. Mutations in the RPE65 gene are responsible for a number of congenital eye diseases, such as Leber's congenital amaurosis,[2] a severe and relatively common recessive disease resulting in blindness at birth, as well as some forms of retinitis pigmentosa.[3] However, the biochemical function of RPE65 has been unknown until recently.

In the visual cycle (Figure 1), a photon triggers the transformation of rhodopsin in the retinal outer segment