Vitamin K in the treatment and prevention of osteoporosis and arterial calcification

JAMIE ADAMS AND JOSEPH PEPPING

Purpose. The role of vitamin K in the prevention and treatment of osteoporosis and arterial calcification is examined.

Summary. Vitamin K is essential for the activation of vitamin K-dependent proteins, which are involved not only in blood coagulation but in bone metabolism and the inhibition of arterial calcification. In humans, vitamin K is primarily a cofactor in the enzymatic reaction that converts glutamate residues into \( \gamma \)-carboxyglutamate residues in vitamin K-dependent proteins. Numerous studies have demonstrated the importance of vitamin K in bone health. The results of recent studies have suggested that concurrent use of menaquinone and vitamin D may substantially reduce bone loss. Menaquinone was also found to have a synergistic effect when administered with hormone therapy. Several epidemiologic and intervention studies have found that vitamin K deficiency causes reductions in bone mineral density and increases the risk of fractures. Arterial calcification is an active, cell-controlled process that shares many similarities with bone metabolism. Concurrent arterial calcification and osteoporosis have been called the "calcification paradox" and occur frequently in postmenopausal women. The results of two dose–response studies have indicated that the amount of vitamin K needed for optimal \( \gamma \)-carboxylation of osteocalcin is significantly higher than what is provided through diet alone and that current dosage recommendations should be increased to optimize bone mineralization. Few adverse effects have been reported from oral vitamin K.

Conclusion. Phytonadione and menaquinone may be effective for the prevention and treatment of osteoporosis and arterial calcification.

Index terms: Calcinosis; Combined therapy; Dosage; Drug interactions; Estrogens; Mechanism of action; Menaquinone; Osteoporosis; Phytonadione; Toxicity; Vitamin D; Vitamins

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Osteoporosis and arterial calcification are major health concerns in modern societies. It is estimated that 30% of postmenopausal Caucasian women in the United States have osteoporosis and 54% have osteopenia and 75–95% of men and women have some degree of coronary artery calcification on autopsy. Although osteoporosis and arterial calcification were once thought to be unrelated conditions, recent studies suggest there may be a connection. It appears that a common factor in the development of these two disorders may be vitamin K deficiency.

Over the past 20 years, several vitamin K-dependent (VKD) proteins have been discovered. Recent studies have shown that, in addition to their role in carboxylating coagulation factors, VKD proteins are involved in bone metabolism and the inhibition of arterial calcification. The two VKD proteins examined in this review are osteocalcin and matrix Gla protein (MGP). Osteocalcin appears to play a key role in bone metabolism but its mechanism of action has not been fully elucidated. Osteocalcin is synthesized mainly by osteoblasts and, when carboxylated, has molecular properties that allow it to tightly bind hydroxyapatite in bone, thereby promoting mineralization. Vitamin K is thought to promote bone mineralization by enhancing the carboxylation of osteocalcin. MGP is synthesized primarily by chondrocytes and vascular smooth muscle cells. Recent animal studies have shown that MGP plays a key role in the inhibition of tissue calcification. As with all VKD proteins, MGP must be carboxylated to function properly.

Vitamin K

Vitamin K refers to a group of re-

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lated compounds. There are two natural forms: phylloquinone (vitamin K\textsubscript{1}) and menaquinone (vitamin K\textsubscript{2}). Phylloquinone is the most common form of vitamin K and is found in leafy green vegetables (e.g., lettuce, broccoli, spinach, cabbage) and vegetable oils (e.g., soybean and canola oils). Commercially prepared vitamin K\textsubscript{1} (phytonadione) is chemically identical to naturally occurring vitamin K\textsubscript{1} (phylloquinone).

Menaquinone includes a range of related forms generally designated as menaquinone-\textit{n} (MK-\textit{n}), where \textit{n} is the number of isoprenyl groups. Menaquinone is found in meat, fermented products, and cheese. The menaquinones most commonly found in food are MK-4, which is a short-chain menaquinone, and the long-chain menaquinones MK-7, MK-8, and MK-9.\textsuperscript{20} Intestinal bacteria also produce the longer-chain menaquinones (MK-7–MK-10)\textsuperscript{21}; however, bacteria-derived menaquinone appears to contribute minimally to overall vitamin K status.\textsuperscript{1,22,23} Menaquinone, in the form of MK-4 (also known as menatetrenone), has been used in Japan for the treatment of osteoporosis since 1995. Dietary supplements containing up to 15 mg of menaquinone (MK-4) per capsule have recently become available in the United States.

In humans, vitamin K is primarily a cofactor in the enzymatic reaction that converts glutamate residues into \(\gamma\)-carboxyglutamate residues in VKD proteins.\textsuperscript{21,24-28} Vitamin K deficiency can lead to suboptimal \(\gamma\)-carboxylation of these proteins and impairment of their function.\textsuperscript{29-32} These VKD proteins are involved in such functions as coagulation-factor activation (factors V, VII, and X; prothrombin; and fibrinogen), bone metabolism, and inhibition of vascular calcification. The vitamin K requirement for carboxylation of bone and arterial wall VKD proteins is higher than that for the carboxylation of coagulation factors in the liver.\textsuperscript{33} Daily vitamin K requirements for maximal \(\gamma\)-carboxylation of the extrahepatic VKD proteins may be significantly higher than recommended by current dietary guidelines.\textsuperscript{33} Vitamin K deficiency, resulting in the undercarboxylation of specific VKD proteins, may be an independent risk factor for osteoporosis and arterial calcification.

### Vitamin K for osteoporosis: Rationale

A number of human-cell studies have helped define the role of vitamin K and osteocalcin in bone health. Both phylloquinone and menaquinone promote bone mineralization; however, menaquinone has been shown to be more potent,\textsuperscript{34} likely because of the enhanced carboxylation of osteocalcin by menaquinone. Menaquinone has been shown to increase osteocalcin accumulation on the cell layer.\textsuperscript{35} In vitro, phylloquinone and menaquinone (MK-4) inhibit osteoclast formation and induce the differentiation of osteoprogenitor cells into osteoblasts.\textsuperscript{35}

The results of recent human and animal studies have suggested that concurrent use of menaquinone and vitamin D may substantially reduce bone loss.\textsuperscript{9,36,37} In rats with ovariectomy-induced bone loss, menaquinone and vitamin D had a synergistic effect on bone-loss reduction.\textsuperscript{9} Hirano and Ishii\textsuperscript{37} found that the coadministration of calcium, menaquinone, and vitamin D in rats increased the peak bone mass and reduced the loss of bone mineral density (BMD).

### Vitamin K for osteoporosis: Clinical studies

The relationship between dietary vitamin K intake and bone status has been investigated in several epidemiologic (Table 1) and intervention studies (Table 2). These studies suggest that vitamin K deficiency causes reductions in BMD and increases the risk of fractures, resulting from the undercarboxylation of osteocalcin. Low intakes of vitamin K have been associated with an increased risk of hip fractures. In a study of 72,327 women and 212 men

### Table 1. Epidemiologic Studies of Vitamin K and Bone Health\textsuperscript{a}

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Subjects</th>
<th>Variables Studied</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>113 postmenopausal women</td>
<td>UcOC, BMD</td>
<td>UcOC and BMD inversely related</td>
</tr>
<tr>
<td>38</td>
<td>72,327 women</td>
<td>Vitamin K intake, hip fracture rate, BMD</td>
<td>Vitamin K intake of &gt;109 (\mu)g/day reduced risk of hip fracture by 30%; no correlation between vitamin K and BMD</td>
</tr>
<tr>
<td>39</td>
<td>888 men and women</td>
<td>Vitamin K intake, hip fracture rate, BMD</td>
<td>65% reduced risk of fractures in highest quartile of vitamin K intake compared with lowest quartile</td>
</tr>
<tr>
<td>40</td>
<td>104 elderly women with hip fractures; 255 controls</td>
<td>UcOC, hip fracture rate, BMD</td>
<td>UcOC (not total OC) predicted fracture risk independently of femoral BMD</td>
</tr>
<tr>
<td>41</td>
<td>195 elderly women\textsuperscript{a}</td>
<td>UcOC, hip fracture rate</td>
<td>Fracture risk 5.9 times higher in women with elevated UcOC at start of study</td>
</tr>
<tr>
<td>42</td>
<td>183 elderly women\textsuperscript{a}</td>
<td>UcOC, hip fracture rate</td>
<td>Fracture risk 3.1 times higher in women with elevated UcOC at start of study</td>
</tr>
<tr>
<td>43</td>
<td>212 women</td>
<td>UcOC, BMD</td>
<td>UcOC was independent marker for BMD in women 1–10 yr postmenopause</td>
</tr>
</tbody>
</table>

\(\text{UcOC} = \text{undercarboxylated osteocalcin level, BMD = bone mineral density, OC = osteocalcin level.} \\
\text{\textsuperscript{a}18-month prospective study.} \\
\text{\textsuperscript{a}Three-year follow-up study.} \\

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*A myriad of osteoporosis studies have shown that dietary vitamin K intake is inversely related to fracture risk.*

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women, vitamin K intakes (assessed through the use of a food-frequency questionnaire) were inversely related to the risk of hip fracture.44 The adjusted relative risk (RR = 0.70; 95% confidence interval [CI], 0.53–0.93) of hip fracture was 30% less in the women from the top four quintiles of vitamin K intake (>109 μg daily) compared with women from the lowest quintile (<109 μg daily). This finding is supported by a study of 888 men and women from the Framingham Heart Study.39 Patients with the highest quartile of vitamin K intake (median, 254 μg daily) had a 65% lower adjusted RR (RR = 0.35; 95% CI, 0.13–0.94) of hip fracture than did those in the lowest quartile of intake (median, 56 μg daily).

**Undercarboxylated osteocalcin and bone health.** Numerous studies have shown that an association exists among undercarboxylated serum osteocalcin, BMD, and fracture rate.40-44 In a study of 359 independently-living women, increased levels of undercarboxylated osteocalcin were associated with increased risk of hip fracture, with an odds ratio of 1.9 (95% CI, 1.2–3.0).44 In a series of reports involving institutionalized elderly women, a strong correlation was found between undercarboxylated serum osteocalcin levels and the subsequent risk of hip fracture.41 Women with abnormally high undercarboxylated osteocalcin concentrations (≥1.65 ng/mL) had a RR between 3.1 (99.9% CI, 1.7–6.0; p < 0.001)42 and 5.9 (99.9% CI, 1.5–22.7; p < 0.001) times higher than those with normal undercarboxylated osteocalcin levels (<1.65 ng/mL). Knapen et al.43 conducted a cross-sectional study of 212 women and found a strong inverse correlation (adjusted RR = 0.5–0.7) between serum undercarboxylated osteocalcin levels and BMD in postmenopausal women. In a trial of 141 postmenopausal women, the percentage of carboxylated osteocalcin to total osteocalcin was measured.44 The value of that variable was positively correlated with BMD of the lumbar spine (r = 0.32, p < 0.005) and femoral neck (r = 0.25, p < 0.005).

**Vitamin K, osteocalcin carboxylation, and bone health.** A number of clinical studies have been conducted investigating the effect of vitamin K administration on the carboxylation of osteocalcin, BMD, and fracture rates.29,36,46,47 Various dosages of both phylloquinone and menaquinone have been used in clinical trials; however, in all studies, undercarboxylated osteocalcin levels declined significantly with vitamin K intake.

### Table 2.
**Intervention Studies of Vitamin K’s Effect on Bone Variables**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Subjects</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>92 postmenopausal women with osteoporosis</td>
<td>Group D: Vitamin D, 0.75 μg/day Group K: Menaquinone 45 mg/day Group DK: D and K treatment Group C: Calcium 2 g/day All treatments for 2 yr</td>
<td>BMD improved more in group DK than in group D or group K; increase in lumbar spine BMD significantly greater in group DK than group C</td>
</tr>
<tr>
<td>29</td>
<td>219 healthy men and women</td>
<td>Phytonadione 1 mg/day for 2 wk</td>
<td>In all treated groups, mean UcOC decreased from 7.6% to 3.4%; age and sex did not affect the decrease</td>
</tr>
<tr>
<td>32</td>
<td>100 healthy adults</td>
<td>Phytonadione 250, 375, 500, or 1000 μg/day or placebo for 2 wk</td>
<td>Phytonadione 1000 μg/day produced greatest carboxylation of OC</td>
</tr>
<tr>
<td>33</td>
<td>21 healthy older women</td>
<td>Phytonadione 18 μg/day for 4 wk, then 86, 200, and 450 μg/day, each for 2 wk</td>
<td>Carboxylation of OC not restored by phytonadione 450 μg/day</td>
</tr>
<tr>
<td>44</td>
<td>23 postmenopausal women</td>
<td>Phytonadione 80 μg/day, vitamin D3 350–400 units/day, both, or placebo for 1 yr</td>
<td>Phytonadione at study dosage needed to attain premenopausal %carbOC</td>
</tr>
<tr>
<td>46</td>
<td>46 women with osteoporosis</td>
<td>Menaquinone 45 mg/day for 2 yr</td>
<td>Treated group had fewer new vertebral fractures (13) than placebo group (30)</td>
</tr>
<tr>
<td>47</td>
<td>20 elderly women with osteoporosis</td>
<td>Calcium 200 mg/day for 2 wk with or without menaquinone 45 mg/day</td>
<td>Menaquinone group had reduction in UcOC without change in OC</td>
</tr>
<tr>
<td>48</td>
<td>20 postmenopausal women</td>
<td>Phytonadione 1 mg/day for 2 wk with or without vitamin D3 400 units/day</td>
<td>Carboxylation of OC improved in both groups; vitamin D3 had no effect</td>
</tr>
<tr>
<td>49</td>
<td>113 women with fractures and 91 women without fractures</td>
<td>Menaquinone 45 mg/day, vitamin D3 1 μg/day, or both for 4 wk</td>
<td>UcOC decreased in menaquinone groups but not group receiving vitamin D3 only</td>
</tr>
<tr>
<td>54</td>
<td>94 postmenopausal women with osteoporosis (84 controls, 10 treated)</td>
<td>Menaquinone 45 mg/day with either conjugated estrogens 0.625 mg/day or medroxyprogesterone acetate 2.5 mg/day for 1 yr</td>
<td>Menaquinone–hormonal treatment improved BMD that had been decreasing during hormonal treatment alone</td>
</tr>
</tbody>
</table>

*BMD = bone mineral density, UcOC = undercarboxylated osteocalcin level, OC = osteocalcin level, %carbOC = percentage of total osteocalcin that is carboxylated.*
supplementation. In a study to determine the prevalence of suboptimal carboxylation of osteocalcin in healthy North American adults, Binkley et al. conducted a single-blind, placebo-controlled trial with 219 healthy young and elderly adults. The treatment group received 1 mg of phytonadione daily for two weeks. At the end of the study, patients receiving phytonadione had a significant decrease in the mean percentage of undercarboxylated osteocalcin, from 7.6% to 3.4% (p < 0.001), without significant differences when stratified by age or sex. In a randomized, open-label, controlled trial of 241 Japanese postmenopausal osteoporotic women, the treatment group received 45 mg of menaquinone daily for two years. At the end of the study, the undercarboxylated serum osteocalcin concentrations in the treatment group were significantly lower than in the control group (1.7 ± 0.5 ng/mL and 3.0 ± ng/mL, respectively) (p < 0.0001). In addition, the occurrence of fracture in the treatment group was significantly lower than in the control group (χ² = 10.935, p = 0.00273). In a smaller, randomized, open-label study of Japanese osteoporotic women, Miki et al. found that undercarboxylated serum osteocalcin levels could be reduced in as little as two weeks. The treatment group received 45 mg of menaquinone (specifically MK-4) plus 200 mg of calcium daily. The control group received only 200 mg of calcium daily. After two weeks, the mean ± S.D. serum undercarboxylated osteocalcin concentrations in the treatment group declined from a baseline value of 2.8 ± 0.9 ng/mL to 1.7 ± 0.5 ng/mL (p < 0.05). No significant changes occurred in the control group over the same period.

**Involvement of vitamin D.** It appears that adequate levels of both vitamins D and K may have additive effects in improving bone health. Many studies have investigated the combined effects of vitamins D and K, An excellent review on the additive effects of vitamin D₃ and menaquinone was recently published by Iwamoto and colleagues. In a three-year, randomized, open-label trial of 241 Japanese postmenopausal osteoporotic women, Braam et al. found that vitamin D₃ and phytonadione had a complementary effect on the attenuation of bone loss. Participants were divided into three groups: (1) placebo, (2) vitamin D and mineral (8 μg of vitamin D₃, 500 mg of milk-derived calcium, 150 mg of magnesium, and 10 mg of zinc daily), and (3) vitamin D, mineral, and phytonadione (same as vitamin D and mineral group plus 1 mg of phytonadione daily). After three years, patients who received vitamin D, minerals, and phytonadione demonstrated a 1.7% reduction (95% CI, 0.35–3.44%) in bone loss from the femoral neck (absolute bone loss of 3.3%) compared with the placebo group (absolute bone loss of 5.0%) and a 1.3% reduction (95% CI, 0.10–3.41%) compared with those receiving only vitamin D and mineral supplements (absolute bone loss of 4.6%). No significant differences were observed among the three groups with respect to changes in BMD of the lumbar spine.

In a two-week, single-blind study, 20 postmenopausal, osteoporotic women were given either 1 mg of phytonadione daily or 1 mg of phytonadione plus 400 IU of vitamin D₃ daily. The mean carboxylation level of osteocalcin was corrected to premenopausal levels (~72%) in both groups, but the addition of vitamin D₃ had no effect on study results. The percentage of carboxylated osteocalcin increased from 57% before treatment to 73% after treatment (p < 0.001). A similar finding was reported in a study conducted by Takahashi et al. In that open-label trial of 113 osteoporotic women with femoral hip or vertebral fractures and 91 premenopausal and postmenopausal women without fractures or osteoporosis, participants were randomized to receive menaquinone (45 mg daily), vitamin D₃ (1 μg daily), or menaquinone (45 mg daily) plus vitamin D₃ (1 μg daily) for four weeks. Significant decreases occurred in undercarboxylated serum osteocalcin levels in the menaquinone only (p = 0.0001) and the menaquinone plus vitamin D₃ (p = 0.0018) groups but not in women treated with vitamin D₃ only.

In a randomized, double-blind study investigating the effects of vitamin D₃ and phytonadione in postmenopausal women, Schaafsma et al. found that a daily intake of 80 μg of phytonadione was necessary to reach premenopausal percentages of carboxylated osteocalcin. At the end of the study, improvements in the percentage of carboxylated osteocalcin were seen in both the phytonadione-treated group with normal BMD (p = 0.001) and the phytonadione-treated group with low BMD (p ≤ 0.0001), compared with the control group, who received no phytonadione. Surprisingly, the percentage of carboxylated osteocalcin also increased in those receiving vitamin D₃ only (p ≤ 0.006). Another randomized, open-label study supporting the combined effects of vitamin D₃ and menaquinone on BMD in osteoporotic women was conducted by Iwamoto et al. Ninety-two postmenopausal women with osteoporosis were given vitamin D₃ (0.75 μg), menaquinone (45 mg daily), vitamins D₃ (0.75 μg daily) plus menaquinone (45 mg daily), or calcium (2 g daily). After two years, BMD increased significantly in the vitamin D₃- and menaquinone-treated groups, compared with the calcium-treated group (p < 0.05 and p < 0.001, respectively). However, the most significant increase in BMD.
was seen in the vitamin D₃ plus menaquinone group (p < 0.0001).

Menaquinone was also found to have a synergistic effect when administered with postmenopausal hormone therapy.54 Hormone therapy is known to increase BMD for two to three years after menopause and maintain it thereafter. For some women taking hormone therapy, the increase in BMD reaches a plateau and then declines. A combined administration of menaquinone (45 mg of MK-4 daily) and hormone therapy was investigated in 10 women who had declining BMD levels. The mean ± S.D. rate of change in their BMD increased significantly, from −2.4% ± 2.5% to 6.7% ± 2.9% (p < 0.03) after 12 months of combination therapy.

Two recent studies have provided dose–response data on phytonadione that indicate that current dietary intake recommendations may be inadequate. Binkley et al.32 conducted a single-blind, placebo-controlled trial to identify the lowest dosage of phytonadione needed to maximally carboxylate osteocalcin. One-hundred healthy adults age 19–36 years were randomly assigned to receive placebo or 250, 375, 500, or 1000 µg of phytonadione daily for two weeks. The percentage of undercarboxylated serum osteocalcin decreased with increasing dosages (p < 0.0001), with the greatest reduction occurring in those who received 1000 µg daily. In an 84-day depletion and repletion study, 21 older women received a phylloquinone-restricted diet (18 µg daily), followed by a stepwise repletion of 86, 200, and 450 µg of phytonadione.33 Various markers of vitamin K status were evaluated to measure participants' response. The carboxylation of prothrombin was restored to prestudy levels with an intake of 200 µg daily. However, carboxylated osteocalcin remained below normal levels after supplementation of up to 450 µg of phytonadione daily. The efficacy of phytonadione and menaquinone supplementation in the treatment of osteoporosis is currently under study in the United States.55

Arterial calcification

Similarity to bone metabolism. Arterial calcification was once thought to be a passive process that occurred in response to tissue injury. Evidence now suggests that it is an active, cell-controlled process that shares many similarities with bone metabolism.5,21,36,57 Arterial calcification occurs at two sites in the vessel wall: the media and the intima. Medial calcification is known as Mönckeberg’s arteriosclerosis. Unlike intimal calcification, Mönckeberg’s arteriosclerosis occurs independently of atherosclerosis.21,58,59 Although the cells involved differ depending on the site of calcification, MGP is expressed at both sites.3 The connection between MGP and vascular calcification has been documented by both cell culture and animal studies. Human cell studies have shown that normal vascular smooth muscle cells express MGP and, at sites of calcification, it is substantially upregulated.56,58,60 This may be a physiological attempt to minimize calcification and tissue damage.21,61 In an animal cell study, it was found that endochondral calcification triggered by warfarin could be inhibited by an overexpression of MGP.35 Animal studies of MGP-deficient mice and warfarin-treated rats provide strong evidence that MGP is a potent inhibitor of vascular calcification.14,18 Extensive arterial calcification was found in animals that do not express MGP and those that could not carboxylate it. Assuming that the VKD paradox9 and sudden cardiovascular death.62
The most convincing data to date were recently reported by Braam et al.63 In this three-year, random-ized, placebo-controlled trial of 181 healthy, Caucasian postmeno-pausal women, daily supplementation with 1 mg of phytonadione (plus 8 μg of vitamin D3 and minerals [500 mg of calcium, 150 mg of magne-sium, and 10 mg of zinc per day]) inhibited the loss of carotid artery elasticity, compared with those re-ceiving placebo and those in the vita-min D3 plus minerals group (–13.2 kPa; 95% CI, –35.8 to –5.3) (p < 0.01). No significant differences in arterial elasticity were noted between the placebo group and the vitamin D3 plus minerals group. In this study, no significant differences were observed in carotid artery intima–media thick-ness between the three study groups.

Interestingly, no prospective in-terventional studies have been pub-lished investigating menaquinone deficiency as a risk factor for arterial calcification or whether supplemen-tation with menaquinone affects ar-terial elasticity, arterial calcification, or intima–media thickness.

Adverse effects and dosage of vitamin K

Few adverse effects have been re-port ed from oral vitamin K.64-66 In the articles reviewed, there was no evidence of toxicity associated with the intake of phytonadione or mena-quinone even at a daily dose of the latter of 45 mg.

Adequate intake of phylloquinone for the carboxylation of blood coagulation factors was recently set at 90 μg per day for adult women and 120 μg daily for adult men, based on me-dian dietary intake data from the Third National Health and Nutrition Examination Survey.

In the treatment of osteoporosis, Schurgers and Vermeer20 suggested a phytonadione dosage of 1000 μg dai-ly. Braam et al.63 used the same daily dose to inhibit the loss of carotid ar-tery elasticity. However, several trials of osteoporotic, postmenopausal women have used menaquinone dos-ages as high as 45 mg per day.12,46,47,48

Because of the very low toxicity of phytonadione and menaquinone, a 1000-μg daily dose of each is warrant-ed. Doses of menaquinone exceeding 1 mg are not readily available in the United States at this time, but it is being produced in 15-mg capsules by a Canadian nutraceutical company.

Discussion

Over the past decade it has become evident that vitamin K plays a far greater role in human health than previously thought. Vitamin K is essential for the activation, via γ-carboxylation, of VKD proteins. These proteins have various functions and are found throughout the body. Some of these proteins, such as those involved in blood coagulation, have been thor-oughly researched. Others, notably those involved in bone metabolism and the inhibition of arterial calcifi-cation, have drawn new attention to vitamin K.

Numerous studies have demon-strated the importance of vitamin K in bone health. Cell studies have helped delineate the mechanism by which menaquinone promotes bone mineralization and inhibits resorp-tion.85 Human and animal studies have clearly demonstrated that vita-min K can improve bone health by increasing bone mass and reducing bone loss.12,37,46,54

The results of two dose–response studies have indicated that (1) the amount of vitamin K needed for opt-imal γ-carboxylation of osteocalcin is significantly higher than what is provided by diet alone and (2) there is a need to increase current dosage recommendations to optimize bone mineralization.22,23

The combination of menaquin-one and vitamin D3 has additive ben-eificial effects on sustaining lumbar BMD and preventing osteoporotic vertebral fractures in postmenopaus-al women with osteoporosis.12,50

The role of vitamin K in the preven-tion of arterial calcification is not as well researched. Several epidemi-o logic studies,5,9 as well as a recent clinical trial of postmenopausal women,63 have implicated phyllo-quinone deficiency as a risk factor for arterial calcification and have alluded to a connection between the defi-ciency and osteoporosis.

Additional research is needed to address several important questions: What is the optimal intake of phy-tonadione, menaquinone, and vita-min D3 to support bone mineraliza-tion and reduce fracture risk? What is the optimal dosage of phytonadi-one and menaquinone to preserve the elasticity of arterial endothelial tissue by decreasing the calcification of the intima and media? Do phy-tonadione, menaquinone, and vita-min D3 have additive bone mineraliza-tion effects with bisphosphonates, selective estrogen-receptor modula-tors, or hormone therapies (e.g., es-trogen for women and testosterone for men)? Is menaquinone more effi-cacious in reducing fracture risk than phytonadione? Does vitamin K play a role in immune modulation with re-spect to cytokine expression? Is there a potential relationship between chronic inflammation (as seen in both vascular calcification and os-teoporosis) and vitamin K deficien-cy? For example, is synthesis or the activities of inflammatory cytokines, such as tumor necrosis factor, pros-taglandin E2, and interleukin-1, af-fected by vitamin K levels?

Because of their very low toxicity and potentially beneficial effects on both bone mineralization and atten-uation of arterial calcification, phy-tonadione and menaquinone should be strongly considered as nutritional adjuncts in patients most susceptible to these disorders, such as post-menopausal women, diabetics, and hemodialysis patients.

Conclusion

Phytonadione and menaquinone
may be effective for the prevention and treatment of osteoporosis and arterial calcification.

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