

The Role of Vitamin K₂ in Bone and Cardiovascular Health

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ABSTRACT

Vitamin K is an essential nutrient present in plants, animals, and fermented products that plays an important role in a number of biological systems. Recent evidence suggests that vitamin K has potential health benefits far beyond its role in activating coagulation factors. It appears that vitamin K₂ (menaquinones) play an important role in optimal bone and cardiovascular health. The central role of vitamin K is the synthesis of γ -carboxyglutamate, which occurs during the vitamin K cycle. The vitamin K cycle allows important proteins, namely osteocalcin and matrix Gla protein, to become activated. These vitamin K-dependent proteins are of particular importance to bone and cardiovascular health. It has been noted that activated matrix GLA protein may inhibit the formation of vascular calcifications, while activated osteocalcin is implicated in proper bone mineralization and overall calcium homeostasis. Evidence has also shown that a significant number of otherwise healthy persons may be consuming inadequate amounts of menaquinones and are at greater risk for bone and cardiovascular illness. Although more research is needed to elucidate appropriate therapeutic dosage ranges, it would seem that ensuring adequate intake of menaquinone may be of great importance for bone and cardiovascular disease prevention.

Keywords: Vitamin K; Menaquinone; Osteoporosis; Cardiovascular disease; Bone mineral density; Calcification

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INTRODUCTION

The term *vitamin K* is a generic term that refers to a number of related compounds that are characterized by a methylated naphthoquinone ring as well as an aliphatic side chain. Phylloquinone (vitamin K₁), menadione (vitamin K₃), and all the menaquinone (vitamin K₂) structures are known as vitamers of vitamin K.¹ All of the differences between the various forms of vitamin K originate in the length and saturation of the isoprenoid residue side chains.² Phylloquinone has a saturated side chain, while menaquinones have unsaturated side chains.² Phylloquinone is a single compound with a side chain of four isoprenoid residues.² *Menaquinones* are a group of structures that vary in side chain length (MK-4–MK-13).² Menaquinones have been found with up to 13 isoprene groups. Menadione, the core ring structure, lacks a side chain entirely² (Figure 1).

All of the vitamin K vitamers are known to be lipophilic. As the chain length increases into the MK-7 range and above, lipophilicity further increases relative to the shorter-chain menaquinones.³

SOURCES

The main dietary form of vitamin K is K₁.⁴ The main dietary sources of phylloquinone come predominantly from dark green vegetables, along with fats, such as cooking oils, as a lesser source.⁵ Menaquinones (K₂) are either synthesized in animals (shorter-chain menaquinones) or synthesized by bacteria (longer-chain menaquinones).⁶ Significant dietary sources of menaquinones include cheese, curd, and natto (Japanese food composed of fermented soya beans).³

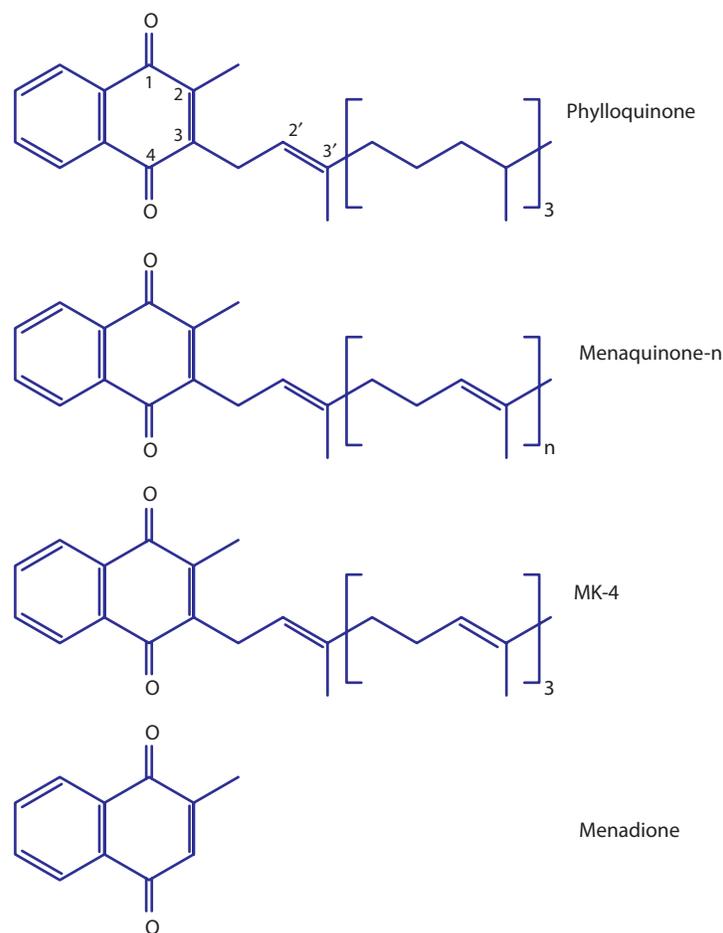


Figure 1: Chemical structure of phylloquinone, menaquinone, MK-4, and menadione.¹

On the basis of the menaquinone content of specific foods, regional differences exist for both the form and the amount consumed.³ For example, in Japan, MK-7 intake in the diet has been documented mostly in the consumption of natto. In comparison, high dairy intake in European countries supplies the majority of long-chain menaquinones (MK-7–MK-10).³

VITAMIN K CYCLE

The synthesis of γ -carboxyglutamate is said to be the main mechanism of action for the biological effects of all vitamin K vitamers. This synthesis is achieved through a process known as the *vitamin K cycle*.⁷ Vitamin K hydroquinone (KH₂) is oxidized to vitamin K epoxide (KO). This reaction enables γ -glutamylcarboxylase to carboxylate-selective glutamic acid residues on vitamin K–dependent proteins (VKDPs).^{7,8} The recycling of KO to KH₂ is carried out by two reactions that reduce KO to vitamin K quinone and then to KH₂. The enzyme vitamin K oxidoreductase catalyzes the reduction of KO to vitamin K quinone and may be involved in the production of KH₂ from vitamin K quinone.^{7,8} The reduction of KO is achieved by only a single enzyme that is sensitive to vitamin K antagonists (VKAs; e.g. warfarin), while the reduction to KH₂ can be accomplished by two enzymes, only one of which is sensitive to VKAs⁸ (Figure 2). γ -Carboxyglutamate is important because it can bind to calcium ions, which alters the

biological activity of the protein that has become carboxylated.⁹

VITAMIN K–DEPENDENT PROTEINS

VKDPs are involved in a number of biological systems (Table 1). The proteins involved in the coagulation cascade and those involved in bone metabolism are some of the most well-known. Although the actions of vitamin K are not exclusive to these areas, coagulation and bone metabolism are seen as the main areas of action.

OSTEOCALCIN AND BONE METABOLISM

OSTEOCALCIN

Osteocalcin is the most abundant VKDP found in bone and the only VKDP produced exclusively in bone tissue.¹¹ Osteocalcin is produced in osteoblasts under the regulation of vitamin D. Once carboxylated, osteocalcin can bind to hydroxyapatite in bone tissue.^{23,24}

The activity of osteocalcin activity appears to be suppressive of excessive bone growth in youth, as *in vitro* it can reduce bone mineral deposition.²⁵ This effect is seen in younger, osteocalcin-deficient rats, as they develop excessive bone growth in the absence of osteocalcin.²⁶

Reduced osteocalcin activity in mature bone is associated with reduced remodeling, which would

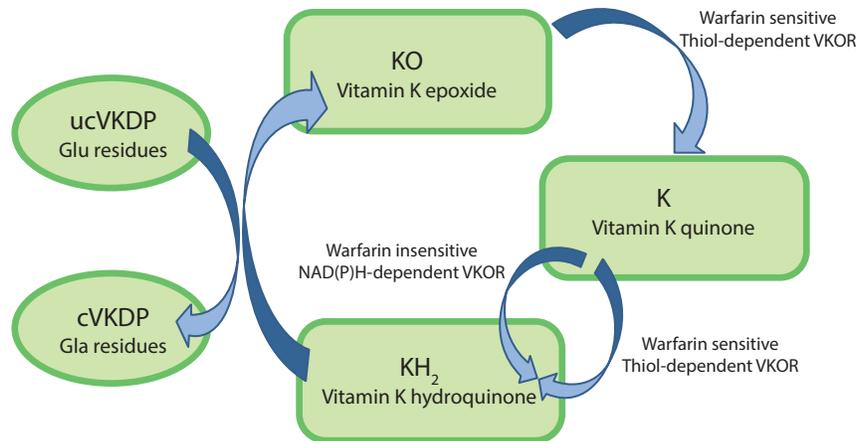


Figure 2: The vitamin K cycle.¹⁰

Table 1: Significant vitamin K–dependent proteins.

Name	Function	References
Osteocalcin	Negative regulator of bone growth	11
	Negative regulator of soft tissue calcification	12
	Positive regulator of bone maturation	11
	Positive regulator of angiogenesis	13
Prothrombin (factor II)	Clotting factor	14
Factors VII, IX, and X	Clotting factor	15,16
Matrix Gla protein	Bone metabolism	11
	Negative regulator of soft tissue calcification	12
Gla rich protein	Negative regulator of soft tissue calcification	12
Growth Arrest Specific Gene-6 protein (Gas6)	Cell-cycle regulation	17,18
	Proliferation of vascular smooth muscle cells	17
	Myelination	18
Periostin	Collagen and bone tissue (wound repair)	19
	Allergies/inflammation	20,21
	Dental tissue maintenance	22

suggest that osteocalcin may support bone remodeling.²⁷ This has also been seen in rats, as osteocalcin deficiency in menopausal rats is associated with less bone remodeling.²⁸

The percentage of overall osteocalcin that remains uncarboxylated appears to be the most sensitive marker for vitamin K status in humans.^{14,29} Osteocalcin is also thought to be the best marker to reflect bone health, as osteocalcin can be carboxylated only from within bone cells.¹¹ Osteocalcin continually gets carboxylated up to a daily intake of approximately 1 mg of phylloquinone.³⁰ MK-7 is superior to an equal dose of MK-4 at carboxylating osteocalcin, although the exact oral dose for maximal carboxylation for K₂ is not yet determined.³¹

OSTEOBLASTS

With respect to osteoblast activity, vitamin K appears to stimulate stromal cell and consequent osteoblast formation in a concentration-dependent manner. Similar efficacy between phylloquinone and menaquinone has been seen in this regard.³²

MK-4 has been found to accumulate carboxylated osteocalcin in the extracellular matrix of bone cells, where it aids in mineral accumulation.³³ No effect has been seen on the total protein content of osteocalcin, but it was able to augment the increase in mRNA seen with vitamin D.³³ Additionally, MK-4 promotes vitamin D–induced bone cell

mineralization.³⁴ These mechanisms are dependent on osteocalcin and the vitamin K cycle, which is inhibited by warfarin, a VKA.³⁵ This may explain why some researchers have noted that warfarin prevents bone mineralization induced by vitamin K in osteoblasts.³⁶

OSTEOCLASTS

With respect to osteoclast activity, MK-4 has been noted to inhibit osteoclast-like multinucleated cell formation in a concentration-dependent manner.^{24,37} K₁ appears not to have any function on osteoclast activity.^{24,38–40} The side chain of MK-4 seems to be of importance in this regard, as MK-4 appears to be the only menaquinone with this effect.³⁸

HUMAN STUDIES

There have been noted associations between vitamin K and bone mineral density (BMD) in observational research, with the lowest quartiles of vitamin K dietary intake having lower bone mass than the highest quartile.^{41,42}

In a randomized, open-label study, 241 osteoporotic women were given either 45 mg/day vitamin MK-4 and 150 mg of elemental calcium ($n=120$) or 150 mg of elemental calcium as a control ($n=121$).⁴³ The trial lasted 24 months. At the end of the trial, analysis of new clinical fractures was performed

in 190 subjects. (Radiographs were not obtained for some subjects.) Thirty new vertebral fractures, two forearm fractures, two femoral neck fractures, and one metacarpal bone fracture in the foot were observed in the control group. In the MK-4 treated group, 13 new vertebral fractures and 1 forearm fracture occurred.⁴³ The fracture incidence in the vitamin K–treated group was significantly lower than in the treated group ($P<0.0273$).⁴³ There was also a significant difference between the two groups at each of the observed times with regard to lumbar spine BMD ($P<0.0010$ at 6 months, $P<0.0153$ at 12 months, and $P<0.0339$ at 24 months).⁴³ MK-4 was able to better preserve BMD.

In a randomized, double-blind clinical trial, 172 osteoporotic and/or osteopenic women (confirmed by dual-energy X-ray absorptiometry) were randomly assigned to receive MK-4 (45 mg/day), 1 α -hydroxycholecalciferol vitamin D₃ (1 μ g/day), both, or dietary interventions alone for 24 months.⁴⁴ One hundred twenty-six subjects had completed the study by the end of the 24 months. A dose of 45 mg/day of MK-4 for 24 months was noted to slightly increase BMD, which was significant relative to the control condition.⁴⁴ The percentage change in BMD was significantly higher than in the control group at 18 months ($0.278\pm 6.55\%$, $P<0.05$) and 24 months ($0.135\pm 5.44\%$, $P<0.05$).⁴⁴ Combination therapy of MK-4 and vitamin D outperformed vitamin K alone.⁴⁴ The percentage changes in the combined therapy group were significantly higher ($4.10\pm 5.88\%$ at 6 months, $P<0.001$; $5.86\pm 6.85\%$ at 12 months, $P<0.001$; $5.01\pm 8.11\%$ at 18 months, $P<0.001$; and $4.92\pm 7.89\%$ at 24 months, $P<0.001$) than those in the control group.⁴⁴ The control group lost BMD during the course of the trial.⁴⁴

In another study comparing and combining MK-4 and vitamin D, 92 postmenopausal women ages 55–81 years were randomly assigned to one of four groups: MK-4 (45 mg/day), 1 α -hydroxyvitamin D₃ (0.75 μ g/day), a combination of MK-4 and vitamin D, or calcium lactate (2 g/day).⁴⁵ The MK-4 and MK-4 combined with vitamin D groups both experienced significant increases in BMD compared with the calcium group at the 12- and 24-month time points.⁴⁵ Corresponding changes were -0.44% and $+0.38\%$ in the MK-4 combined with vitamin D group and -0.20% and $+0.90\%$ in the MK-4 group.⁴⁵ The changes at 2 years in both these groups

were significant compared with those in the calcium group (both $P<0.05$).⁴⁵ The combined vitamin D and MK-4 treatment was synergistic, showing greater improvements than any group at the 12- and 24-month time points. The corresponding changes were $+1.49\%$ and $+1.35\%$. The changes at 2 years in the combined group were significant over the calcium group ($P<0.01$).⁴⁵

Researchers in another study aimed to determine the effects of effects of the combination of vitamin K₂ and bisphosphonates on osteoporosis in postmenopausal women. They randomized 98 postmenopausal, osteoporotic women to receive MK-4 (45 mg/day), etidronate (200 mg/day for 2 weeks every 3 months), calcium lactate (2 g/day), or MK-4 and etidronate at the doses previously mentioned.⁴⁶ The forearm (distal radius) BMD was decreased from baseline over 24 months with calcium treatment, sustained with vitamin K₂ treatment, and increased similarly by treatment with vitamin MK-4 plus etidronate or etidronate alone.⁴⁶ After 24 months of treatment, the incidence of vertebral fracture was similarly reduced by treatment with vitamin K₂ or etidronate compared with that by treatment with calcium, and markedly reduced by treatment with MK-4 plus etidronate.⁴⁶

A moderate reduction in BMD is one of the frequent side effects of leuprolide.⁴⁷ In a study designed to gauge the efficacy of MK-4 (45 mg/day), 1,25-dihydroxyvitamin D₃ (0.5 μ g/day), the combination of MK-4 and D₃ in conjunction with leuprolide, or leuprolide alone (1.88 mg/mo),⁴⁸ researchers found that bone loss after 6 months, as measured by lumbar spine BMD, was $-5.25\pm 0.52\%$ in the leuprolide-only group, $-4.13\pm 0.70\%$ in the vitamin D group, $-3.72\pm 0.61\%$ in the vitamin K group, and $-3.59\pm 0.35\%$ in the group taking vitamins MK-4 and D ($P<0.01$).⁴⁸ Both the MK-4 group and the MK-4 and vitamin D₃ combination group had significantly reduced BMD loss compared with the leuprolide-only group ($P<0.05$ and $P<0.01$, respectively).⁴⁸

Researchers in another recent study investigated the use of MK-4 at a much lower dose than used in the previous studies. The study was performed as a randomized, double-blind, placebo-controlled trial.⁴⁹ The participants (50–65 years of age) were randomly assigned to receive placebo ($n=24$) or

1.5 mg of MK-4 ($n=24$).⁴⁹ There was no significant difference in hip BMD between the two groups at baseline and at 6 and 12 months.⁴⁹ The percentage change in total-body BMD at 6 months was significantly different between the two groups, but at the 12-month evaluation this difference was smaller and was no longer significant.⁴⁹ The forearm BMD in the control group had significantly decreased after 12 months ($P<0.001$).⁴⁹ However, there was no significant decrease in forearm BMD in the MK-4 group during the study period.⁴⁹

Use of glucocorticoids is the most common cause of drug-induced secondary osteoporosis.⁵⁰ A number of studies have shown vitamin K to be beneficial in the prevention of glucocorticoid-mediated bone loss.

In a prospective study, researchers enrolled 20 patients (12 men and 8 women) with chronic glomerulonephritis who were scheduled for glucocorticoid treatment.⁵¹ The patients were randomized to receive either glucocorticoids alone or glucocorticoids with 45 mg of MK-4. After 12 months of treatment, the BMD of the lumbar spine was significantly reduced in the glucocorticoid only group ($P<0.001$).⁵¹ Additionally, one patient in the glucocorticoid only group had a lumbar vertebral fracture.⁵¹ No fractures and no significant reduction in BMD were seen in the MK-4 group.⁵¹

Researchers in another study examined the effects of MK-4 on BMD loss with glucocorticoid use. In that study, 20 children (ages 4–14 years) who were already being treated with oral prednisone (glucocorticoid) for over 1 year and with alfacalcidol (a vitamin D analogue) for 24 weeks.⁵² They were randomized to continue on alfacalcidol (0.03 µg/kg/day) or alfacalcidol (0.03 µg/kg/day) plus MK-4 (approximately 2 mg/kg/day).⁵² After 12 weeks, the group receiving alfacalcidol plus MK-4 showed significantly increased lumbar BMD ($P=0.0029$) compared with the group receiving alfacalcidol alone.⁵²

Loss of BMD is a major concern after organ transplant.⁵³ A trial was conducted to investigate the effects of MK-7 on BMD following solid organ transplant. In that trial, 35 lung and 59 heart transplant recipients were postoperatively randomized to be given MK-7 (180 µg/day) or placebo and followed for 1 year.⁵³ The difference in BMD

for the lumbar spine (L2–L4) between MK-7 and placebo was significant ($P=0.055$).⁵³ Insufficient vitamin D status was common among all subjects, and parathyroid hormone was highest in the MK-7 group, indicating a potential increased need for vitamin D.⁵³

MATRIX Gla PROTEIN AND VASCULAR CALCIFICATION

VASCULAR CALCIFICATION

Calcification of arteries is a process known to contribute to atherosclerosis, and particularly to arterial stiffness.^{54,55} Arteries that are heavily calcified are often deemed to be histomorphologically indistinguishable from bone tissue.^{56,57} Additionally, levels of calcium found in coronary arteries appears to be an independent predictor of all-cause mortality and cardiovascular disease mortality.^{58–60} This marker seems to apply to both individuals with disease and those without an apparent disease state.⁵⁸ This marker also holds true for both younger (under 45 years of age) and aged persons.⁵⁸

MATRIX Gla PROTEIN

Matrix Gla protein (MGP) is a VKDP that plays a major role in the process of vascular calcification. Like most vitamin VKDPs, it can be carboxylated or uncarboxylated (MGP or ucMGP, respectively), but it can also be phosphorylated or non-phosphorylated.^{61,62} As MGP is a peripheral protein and vitamin K₂ is the most abundant form found in nonhepatic tissue, K₂ is the vitamer most readily available to carboxylate MGP.¹⁰ Gla-containing proteins were detected in human and porcine calcified aortic valves, while no Gla-containing proteins were found in normal and stenotic tissues.⁶³

MGP is a negative regulator of calcification because it sequesters calcium ions when it is carboxylated and active.⁶⁴ Spontaneous calcification of arteries has been evidenced in mice with the gene coding for MGP knockout.⁶⁵ Uncarboxylated MGP has been shown to be a biomarker for cardiovascular disease.⁶⁶ ucMGP has also been shown to accumulate at sites of calcification, which indicates its inactivity, and MGP at these sites has been shown

to be related to the availability of vitamin K.^{61,64,66} MGP is not the only negative regulator of calcification, but it is the most potent VKDP for removing calcium from arterial walls.^{65,67,68}

Researchers in one study initially found that while ucMGP was absent from the innermost lining of the carotid arteries, in healthy subjects the majority of MGP in the carotid arterial lining of patients with atherosclerosis was uncarboxylated.⁶⁶ The results of another study suggested that circulating dephosphorylated ucMGP may be predictive of mortality risk in subjects with overt vascular disease.⁶⁹ What the authors found was that the risk of cardiovascular disease–related and all-cause mortality were nearly doubled in subjects with coronary artery disease or stroke in the highest vs. lowest quartile of dephosphorylated ucMGP concentrations.⁶⁹

VITAMIN K AGONISTS

VKAs (such as warfarin) and their derivatives are administered as anticoagulants to many patients. They inhibit the recycling of vitamin K in the vitamin K cycle, which in turn reduces the activation of VKDPs. In particular, VKAs such as warfarin have been shown to inactivate MGP and cause rapid calcification of the arteries.⁷⁰ Coronary calcification was also observed in patients with arterial fibrillation with low cardiovascular risk as a cause of VKA treatment.⁷¹

Researchers in another study examined the effect of VKAs on extracoronary calcification. The subjects in that study were younger than 55 years of age and had been using VKAs for over 10 years.⁷² The data analysis showed a correlation between femoral artery calcification and VKA use ($P<0.001$) and dephosphorylated ucMGP levels ($P<0.001$).⁷² It was also noted that calcification was visible in 14 of 19 VKA users compared with 4 of 18 controls ($P=0.002$).⁷²

HUMAN STUDIES

Observational research appears to show an inverse association between dietary K₂ and cardiovascular disease.^{39,40,73} In the Rotterdam study, high vitamin K₂ intake was linked to a lower risk of fatal heart attack, aortic calcification, and all-cause mortality.³⁹ In reviewing data from 4807 Dutch men and

women, the relative risk (RR) of coronary heart disease mortality was reduced in the middle and upper tertiles of dietary menaquinone compared with the lower tertile (RR=0.73 and RR=0.43, respectively).³⁹ Intake of K₂ was also inversely related to all-cause mortality (RR=0.91 and RR=0.74, respectively) and severe aortic calcification (odds ratios of 0.71 and 0.48, respectively).³⁹ Phylloquinone intake was not related to any of the outcomes.³⁹ Researchers in other observational studies have also found no relationship between phylloquinone intake and coronary heart disease.^{40,73,74}

In an observational study that included 16,057 women ages 49–70 who were followed for an average of 8.1 years, researchers found that each 10- μ g increase in daily vitamin K₂ consumption was associated with a 9% lower incidence of heart attack.⁴⁰ Subjects in the study consumed an average of 29 μ g/day of K₂, with a range of 0.9–128 μ g.⁴⁰ The authors of that study analyzed the K₂ subtypes and found that MK-7–MK-9 ($P=0.05$, $P=0.03$, and $P=0.02$, respectively) had the strongest association with reduced heart attack risk per microgram consumed, while MK-4 had no significant relationship ($P=0.11$).⁴⁰

Another observational study conducted on 564 postmenopausal women showed results similar to those of the previous studies.⁷³ Intake of phylloquinone was not associated with coronary calcification ($P=0.11$), while increased intake of menaquinone was significantly associated with decreased coronary calcification of 20% ($P=0.03$).⁷³ The authors concluded that “high intake of menaquinone, but probably not phylloquinone, is associated with reduced coronary calcification.”⁷³

In a 3-year, double-blind, controlled trial, researchers investigated the potential effect of vitamin K on the progression of coronary calcification in 401 older (60–80 years of age), community-dwelling adults who were free of cardiovascular disease.⁷⁵ The participants were randomized to receive a daily effervescent multivitamin with or without 500 μ g of phylloquinone.⁷⁵ On the basis of coronary artery calcification measurements at baseline and in follow-up, the researchers found that phylloquinone supplementation was able to limit the progression of vascular calcification in those with preexisting

coronary artery calcification.⁷⁵ In contrast, phylloquinone supplementation did not reduce the development of new coronary artery calcification, of which there was an annual increase of 5% in both groups.⁷⁵

Dialysis patients are at an increased cardiovascular disease risk due to premature vascular calcification.⁷⁶ Elevated levels of ucMGP are frequently present in this population, and they can indicate insufficient intake of vitamin K.⁷⁷

In an observational study, 3401 participants with chronic kidney disease from the Third National Health and Nutrition Examination Survey were assessed for vitamin K intake and cardiovascular disease.⁷⁶ Of these, 1815 and 876 participants died as a result of all causes and cardiovascular disease, respectively.⁷⁶ Seventy-two percent of the participants had vitamin K consumption less than the recommended dietary intake.⁷⁶ Study participants with vitamin K intake higher than adequate levels had a 15% lower risk of all-cause mortality and 22% lower risk of cardiovascular disease mortality.⁷⁶

As stated previously, ucMGP is a biomarker for cardiovascular disease.⁶⁴ In a recent placebo-controlled study, daily supplementation with 180 µg or 360 µg of MK-7 led to significant reductions in ucMGP of 31% and 46%, respectively, compared with placebo.⁶² Researchers in another study examined 200 dialysis patients who were administered supplementation with 360 µg, 720 µg, or 1080 µg of MK-7 three times weekly over an 8-week period. In these patients, the proportions of ucMGP were significantly reduced by 17%, 33%, and 46%, respectively ($P < 0.001$ for all doses).⁷⁷ The authors concluded that menaquinone supplementation may be a novel approach to preventing vascular calcification in chronic hemodialysis patients.⁷⁷

A long-term trial in which researchers studied the effects of MK-7 effects on arterial stiffness also demonstrated encouraging results. A total of 244 healthy postmenopausal women aged between 55 and 65 years were randomized to receive either 180 µg of MK-7 or placebo daily for 3 years. After 3 years of treatment, overall arterial stiffness in the MK-7 group had decreased significantly, as

compared with a slight increase seen in the placebo group ($P = 0.018$).⁷⁸ It is interesting to note that the authors found that women with more carotid arterial stiffness at the trial's start saw greater benefit than those with less carotid arterial stiffness ($P = 0.009$).⁷⁸ The authors also noted a significant decrease in circulating ucMGP in the MK-7 group compared with the placebo group ($P < 0.0001$).⁷⁸

NUTRIENT INTERACTIONS

Vitamins A, D, and K have been noted to be highly synergistic as they interact with proteins involved in bone and tissue calcification. Osteocalcin and MGP are the most notable of these proteins, as vitamins A and D regulate the expression and creation of the proteins and vitamin K is needed for carboxylation of both osteocalcin and MGP.⁷⁹⁻⁸¹ They appear to be synergistic in osteoblasts, where the addition of MK-4 to bone cells is able to augment osteocalcin production induced by vitamins A and D.^{33,82} MK-4 localizes osteocalcin to the extracellular matrix to promote bone mineralization.^{33,34,83} In osteoclasts, MK-4 suppresses the proliferative effects of vitamin D.³⁷ This is also supportive of bone mass, and this particular effect is independent of the vitamin K cycle.

Vitamin D toxicity is hypothesized to be related to an imbalance with vitamin K, or rather a relative deficiency of vitamin K.⁷⁹ Vitamin D causes increases in MGP, while vitamin K activates MGP via carboxylation. If MGP is not carboxylated, it can independently promote arterial calcification.⁷⁹ The phenotypic similarities of vitamin D toxicity and vitamin K deficiency help to support this hypothesis. It is also supported by examining how vitamin D can enhance the toxicity of VKAs such as warfarin.⁸⁴

DOSING STRATEGIES AND SAFETY

SAFETY

There are no documented cases of toxicity for phylloquinone or menaquinones.⁸⁵ In its safety

assessment of menaquinones as a source of vitamin K, the European Food Safety Authority concluded that low doses of menaquinones present no safety concerns.⁸⁵

The major concerns surrounding vitamin K₂ in treatment are focused on the possibility of achieving a hypercoagulable state. A study on hypercholesterolemic rabbits showed that such a state was not reached at high doses (up to 100 mg/kg/day) administered for a 10-week period.⁸⁶ Researchers in a rat study also found that thrombosis risk is not increased at doses up to 250 mg/kg of MK-4.⁸⁷

In human subjects not receiving oral anticoagulation treatment, no effects of the use of such doses on coagulation was found with a highly sensitive chloramphenicol acetyltransferase assay.⁸⁸ It has also been noted that endogenous thrombin potential was not affected by MK-7 intake as high as 360 µg/day for 6 weeks.⁸⁹ Furthermore, it has been observed that long-term treatment with 180 µg of MK-7 in healthy postmenopausal women had no effect on fasting glucose, high-sensitivity C-reactive protein, interleukin 6, tumor necrosis factor α, or markers of endothelial dysfunction.⁷⁸

With this being said, the administration of vitamin K, particularly MK-7, should be closely monitored in patients receiving VKA treatment because MK-7 is a three to four times more potent inhibitor of VKA than phylloquinone, with the potential to interfere at doses greater than 50 µg.^{70,90} It is also important to note that phase I clinical trials have not yet been designed to test the safety of menaquinones, nor has any form of vitamin K been adequately tested for mutagenicity.⁸⁵

DOSAGE CONSIDERATIONS

On one hand, it must be restated that, in persons receiving oral anticoagulants (VKAs), excess vitamin K intake will interfere with this medication and caution must be observed. On the other hand, it is becoming increasingly clear that the long-term use of these agents is associated with accelerated bone

loss, low bone mass, and vascular and/or arterial calcifications.

In the general population, it has been shown that increased vitamin K intake is associated with a number of health benefits. However, in a study done at the University of Maastricht in which 896 blood samples of healthy subjects were analyzed, it was shown that, although all coagulated proteins were completely carboxylated by vitamin K, high concentrations of osteocalcin and MGP were present in the majority of the samples investigated.⁹¹ It can be said that a large number of otherwise healthy persons may be consuming inadequate amounts of menaquinones and are at a greater risk for bone and cardiovascular disease.⁹¹

A typical therapeutic oral dosage of MK-4 is 45 mg/day.^{45,46,48,51} One study, however, suggested that a dosage as low as 1.5 mg/day may provide bone health benefits in already healthy postmenopausal women.⁵¹ The dosages of MK-7 used are much lower, typically between 180 and 360 µg/day, although dosages up to 1080 µg three times per week have been used.^{53,62,77}

CONCLUSIONS

Vitamin K, specifically K₂, has a range of potential treatment and prevention implications, including coronary heart disease, arterial and vascular calcification, BMD, and reduced fracture risk. Additionally, it is important to note the synergy that vitamin K has with vitamin D. The benefits are increased when the two are used together, and vitamin K may ameliorate the potential for vitamin D toxicities. Further research is needed to elucidate the optimal dosage ranges for the various types of menaquinones and to assess their safety, but seems as though menaquinones have been therapeutically underused.

DISCLOSURE OF INTERESTS

The author has nothing to disclose.

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