Roles for Vitamin K Beyond Coagulation

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vitamin K, phylloquinone, menaquinones, osteoporosis, calcification

Abstract

Recent interest in vitamin K has been motivated by evidence of physiological roles beyond that of coagulation. Vitamin K and vitamin K–dependent (VKD) proteins may be involved in regulation of calcification, energy metabolism, and inflammation. However, the evidence for many of these proposed roles in the maintenance of health is equivocal. There is also an emerging viewpoint that the biochemical function of vitamin K may extend beyond that of a cofactor for the VKD carboxylation of glutamyl residues (Glus) to carboxylated Glus in VKD proteins.

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INTRODUCTION

Vitamin K exists naturally in multiple dietary forms. Phylloquinone (vitamin K_1) is a 2-methyl-1,4-napthoquinone ring with a phytyl group at the 3-position (**Figure 1**). Menaquinones (vitamin K_2) are endogenously synthesized and differ in structure from phylloquinone in their 3′-substituted unsaturated multiprenyl group. The primary menaquinones, menaquinone-4 (MK-4) through menaquinone-10 (MK-10), contain 4–10 repeating isoprenoid units on their side chain, respectively. Menadione (vitamin K_3), which is the 2-methyl-1,4-napthoquinone ring common to all forms of vitamin K, can function as an enzyme cofactor in the prevention of subclinical vitamin K deficiency (31) and has been identified as a metabolite of vitamin K formed during absorption (91, 123). The use of a simplified nomenclature to describe the multiple forms of vitamin K (i.e., vitamins K_1, K_2, and K_3), which still persists in the literature today, undermines the complexity of biological differences among the various forms, particularly among the menaquinones. Beyond the scope of this review, the reader is referred to the work of others for an in-depth discussion of the differences in absorption, transport, and tissue distribution among different forms of vitamin K (113, 116).

In terms of dietary sources, phylloquinone is the principal form of vitamin K found in green leafy vegetables and vegetable oils (11, 18, 64, 121). MK-4 is unique to the menaquinones in that it is alkylated from menadione present in

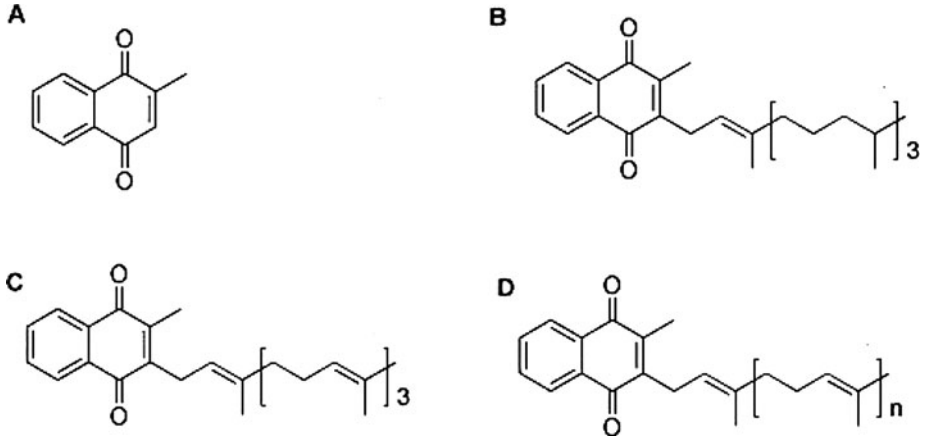

Figure 1

Forms of vitamin K. (*A*) Menadione (formerly referred to as vitamin K_3). (*B*) Phylloquinone (formerly referred to as vitamin K_1). (*C*) Menaquinone-4 (MK-4). (*D*) Menaquinone n + 1 (MKn + 1) (formerly referred to collectively as vitamin K_2).

animal feed and is also the product of tissue-specific conversion directly from dietary phylloquinone (91). Menaquinones 4 through 9 are found in low concentrations in animal-based foods, such as chicken meat and certain types of cheese (42, 108). Menaquinone-7 is found in large amounts in legumes, specifically fermented soybeans (commonly called *natto*), which is a traditional food in eastern Japan (64).

The adequate intake (AI) for vitamin K is established at 90 μg/d for women and 120 μg/d for men, based on median intakes from food, as estimated from NHANES III (1988–1994) (1). There are wide ranges of vitamin K intakes across geographic regions and age groups (13). Certain subgroups appear to be at risk for low phylloquinone intakes, including children (96) and the elderly (1), especially those with Alzheimer's disease (93), and it is not known what the long-term implications of these chronic low vitamin K intakes are with respect to health. There is also speculation that the AI may not be sufficient to attain complete carboxylation of all vitamin K-dependent proteins (VKDPs) (9, 16). However, limited understanding of the physiological implications of changes in vitamin K biomarkers precludes determination of more precise dietary recommendations at this time.

No single biomarker of vitamin K status is a robust measure of vitamin K sufficiency and deficiency (13). Instead, the current practice is to use multiple biomarkers where possible, each of which reflects a different aspect of vitamin K intake, absorption, and transport, or functions as a cofactor for the γ-carboxylation of VKDPs. Of the more common ones, plasma phylloquinone fluctuates in accordance with recent dietary phylloquinone intakes, and it is closely correlated with triglyceride concentrations (17, 18, 110). Percent uncarboxylated osteocalcin (%ucOC) is a measure of carboxylation of OC, a vitamin K-dependent protein found in bone. The %ucOC varies according to vitamin K intake and supplementation (13, 60), and a high %ucOC is considered to be a sensitive indicator of poor vitamin K status in bone (51). Urinary measures of phylloquinone metabolites show promise as an overall biomarker of vitamin K status. Phylloquinone is catabolized in the liver where the side chain undergoes ω- and β-oxidation to form five- and seven-carbon metabolites (**Figure 2**). These metabolites correspond to approximately 20% excretion of a daily physiological dose of phylloquinone and respond to dietary manipulation of phylloquinone (54). It is not known if similar excretion pathways exist for the menaquinones (113).

ROLE OF VITAMIN K IN BONE

In a review written more than a decade ago in this journal, the authors presented a biological argument for a role of vitamin K in the prevention of osteoporotic fractures based on its role as an enzyme cofactor for several VKDPs present in bone, most notably osteocalcin (OC) (129). These authors concluded, "Whether vitamin K supplementation will reduce the rate of bone loss in postmenopausal women remains a matter of debate" (129). The debate is still ongoing in recent reviews of the evidence (29, 60, 111), and a divergence of conclusions is emerging regarding the efficacy of vitamin K supplementation in reducing age-related bone loss.

OC is a VKDP produced by osteoblasts during bone formation and is the primary noncollageneous protein in bone. Although the exact role of OC is not clear, it most likely functions as a regulator of bone mineral maturation (21, 41). The transcription and translation of OC is regulated by 1,25-dihydroxyvitamin (2), and its ability to bind calcium is dependent on the VKD γ-carboxylation of 3 glutamic acid residues (Glus) (27, 87). The γ-carboxylation of OC is the primary mechanism underlying the hypothesized protective influence of vitamin K on bone. However, two new VKDPs have recently been identified that may shed further light on the putative role of vitamin K in bone. The γ-carboxyglutamic acid residue (Gla)-rich protein (GRP) is a 10.2 kDa protein that contains 16 Glas in its 72 amino acids sequence, which is the highest proportion of

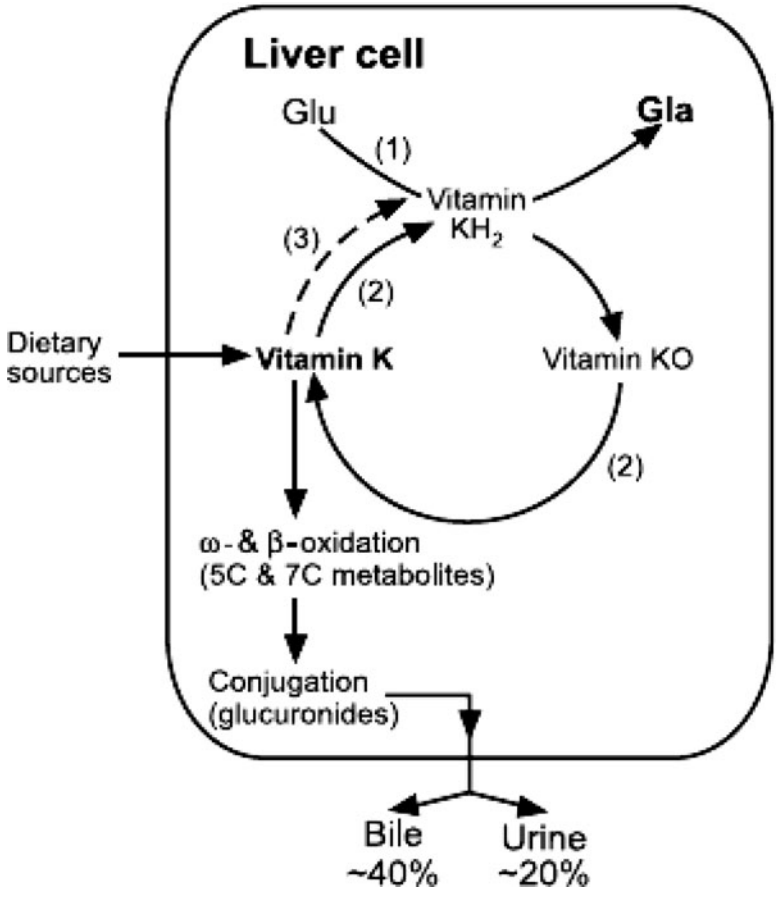

Figure 2

Scheme showing the hepatic metabolism of vitamin K (adapted with permission from Reference 113). The conversion of Glu to Gla in vitamin K-dependent proteins is linked to an enzymic cycle called the vitamin K–epoxide cycle, which carries out both γ-glutamyl carboxylation and serves as a salvage pathway to recover vitamin K from its epoxide (KO) for reuse in carboxylation. Enzyme activities shown are (*1*) γ-glutamyl carboxylase, (*2*) vitamin K epoxide reductase (VKOR), and (*3*) NAD(P)H-dependent quinone reductase(s). The active form of vitamin K needed by the γ-glutamyl carboxylase is the reduced-form vitamin K quinol (KH_2). An obligatory metabolic consequence of γ-carboxylation is that KH_2 is oxidized to KO, which in turn undergoes reductive recycling, first to the quinone and then to KH_2. Under usual physiological conditions, vitamin K is probably mainly recycled by VKOR. The liver is also the site of a catabolic pathway, common to phylloquinone and menaquinones, whereby their respective side chains undergo ω-oxidation followed by β-oxidation, leading to two major aglycone metabolites with side chain lengths of five and seven carbon atoms, respectively (%C and 7C metabolited). After conjugation (mainly with glucuronic acid) these metabolites are excreted in the bile and urine. Phylloquinone, the major dietary form, is rapidly and extensively catabolized in humans, with about 40% of the daily physiological dose being excreted via the bile and 20% via the urine. There are no equivalent excretion data for the menaquinones.

Glas reported among the VKDPs (130). GRP is expressed in most tissues of species studied and, in particular, those containing cartilage and bone cells. GRP appears to regulate extracellular calcium. Periostin is a matricellular protein that is expressed in collagen-rich connective tissues, including bone (52). Although periostin (previously called osteoblast

specific factor-2) has been studied for 15 years, it has only just been identified as a VKDP, with a possible role in extracellular matrix mineralization (36).

Alternative mechanisms by which vitamin K reduces age-related bone loss have also been suggested. In vitro studies indicate MK-4 can enhance bone mineralization and decrease bone resorption more effectively than phylloquinone (53, 65, 75). MK-4 differs structurally from phylloquinone in the configuration of its side chain, but shares the same napthoquinone ring, which is the active site for the γ-carboxylation reaction. This suggests that MK-4 may influence bone turnover through a mechanism other than the γ-carboxylation reaction (53). Vitamin K can modulate certain cytokines involved in bone turnover, such as osteoprotegerin and interleukin-6 (67, 98, 112), which may be an additional mechanism by which vitamin K influences bone turnover. There is also speculation that a receptor specific to MK-4 exists (113).

Observational Studies

Although there is still debate regarding the actual mechanism underlying the putative role of vitamin K in the prevention of bone loss, phylloquinone intake is associated with a lower risk of hip fracture in the majority of studies, as summarized in **Table 1**. However, the associations between phylloquinone intake and bone mineral density (BMD) are less consistent. For example, in the same original cohort of elderly men and women (mean age 75 years) participating in the Framingham Heart Study, there were no significant associations between phylloquinone intake and BMD, but there was an increased risk for hip fracture associated with lower phylloquinone intake (19). In the younger Framingham offspring cohort, phylloquinone intake was positively associated with BMD cross-sectionally in women but not in men (mean age 59 years), whereas in prospective analyses of the same cohort, there was no association between phylloquinone intake and change in BMD over five years (12). Similar findings were reported in a recent population-based study of Scottish women (45–54 years) (85). Surprisingly, although most clinical trials investigating the role of vitamin K in fracture prevention are focused on the role of MK-4, there are very few reports of associations between dietary MK-4 intake and skeletal health. This in part reflects the limited number of dietary sources that are rich in MK-4. It is also assumed that phylloquinone obtained from the diet is converted to MK-4 in various tissues, including bone, albeit by an unknown mechanism. Reports from Japan suggest that consumption of *natto*, fermented soybeans rich in MK-7, is also associated with higher BMD (59, 66) and lower incidence of hip fracture (136). It is currently not known if MK-7 intake confers an additional benefit to phylloquinone intake or has an independent protective effect on reduction of fracture risk.

Associations between biochemical measures of vitamin K status and bone health are equivocal, as also summarized in **Table 1**. In cross-sectional and prospective analyses, elevated %ucOC, which occurs when vitamin K status is low, is a marker of increased risk for hip fracture in the elderly (83, 117, 128). However, when multiple indices of vitamin K status are used, conflicting results often emerge. For example, plasma phylloquinone concentrations were inversely associated with incidence of vertebral fracture in Japanese women (30–88 years), whereas %ucOC, MK-4, and MK-7 concentrations were not (125). Therefore, it seems premature to use any single measure of vitamin K status as a biochemical marker for osteoporosis diagnosis, as proposed by some (55).

One of the challenges in many of these observational studies is the inability to isolate the physiological effects of vitamin K deficiency from those of overall poor nutrition. Since the primary dietary source of phylloquinone is green leafy vegetables, any positive associations between vitamin K intake and skeletal outcomes are reflective of generally healthier diets, which are also positively associated with bone health in population-based studies (4). In one study (102), older women with severe Alzheimer's

Table 1 Observational studies assessing associations between vitamin K and bone mass or fracture risk (reproduced with permission from Reference 111)[a]

Subjects	Measure of vitamin K status	Primary outcome measure	Association	Reference
Women, 38–63 years	Phylloquinone intake	Hip fracture	Inverse	(48)
Men and women, mean age 75 years	Phylloquinone intake	Hip fracture	Inverse	(19)
		BMD	No association	
Men and women, 59 ± 9 years	Phylloquinone intake	BMD	Positive (women only)	(12)
Women, 45–54 years	Phylloquinone intake	BMD	Positive	(85)
Men and women, national survey	Phylloquinone intake	Hip fracture	Inverse	(136)
	MK-7 intake	Hip fracture	Inverse	
Women, 20–79 years	MK-7 intake	BMD	Positive	(59)
Women, 70–97 years	Serum ucOC	Hip fracture	Positive	(118)
Women, mean age 82 years	Serum ucOC	Hip fracture	Positive	(128)
Women, 20–90 years	Serum ucOC	BMD	Inverse (only within 10 years of menopause)	(70)
Women, mean age 61 years	Serum ucOC	BMD	Inverse	(104)
Men and women, 32–86 years	Serum ucOC	BMD	Inverse (men only)	(14)
	Plasma phylloquinone	BMD	Positive (men and postmenopausal women not taking HRT)	
Women, 30–88 years	Serum ucOC	Vertebral fracture	No association	(125)
	Plasma MK-4	Vertebral fracture	No association	
	Plasma MK-7	Vertebral fracture	No association	
	Plasma phylloquinone	Vertebral fracture	Inverse	
Women, 52–93 years	Plasma MK-4	Hip fracture	No association	(68)
	Plasma MK-7	Hip fracture	No association	
Boys and girls, 8–14 years	Serum ucOC	BMC	Inverse	(127)
Girls, 11–12 years	Serum ucOC	BMC	Inverse	(88)
Boys and girls with cystic fibrosis, 8–12 years	Serum ucOC	BMC	Inverse	(49)
Boys and girls with cystic fibrosis, median age 11 years	Serum ucOC	BMC, BMD	No association	(34)
	Plasma phylloquinone	BMC, BMD	No association	

[a]Abbreviations: BMC, bone mineral content; BMD, bone mineral density; HRT, hormone replacement therapy; ucOC, uncarboxylated osteocalcin.

disease were reported to have lower plasma phylloquinone concentrations, higher %ucOC, and lower metacarpal BMD compared to women with either mild or no Alzheimer's disease. However, the group with severe Alzheimer's disease also had a lower body mass index, suggestive of overall poor nutrition. Likewise, intakes of menaquinones obtained from soybean products may simply be dietary markers for isoflavones, which are also associated with protective effects against bone loss (3).

Outcomes of pediatric studies are also discrepant, as some report an inverse association

between vitamin K status, including ucOC, and bone mineral content in children (ages 8–14) (49, 88, 127), whereas others indicate no associations between vitamin K status and skeletal outcomes (34, 63). When using biomarkers of vitamin K status, it is important to consider that ucOC is also associated with sex hormone levels in children (127), and menopausal status (81, 138) and use of hormone replacement therapy (138, 139) in postmenopausal women, independent of any effect of vitamin K.

If vitamin K deficiency causes bone loss and increased fracture risk through the inadequate γ-carboxylation of OC or other VKDPs, one would predict that individuals with long-term exposure to the vitamin K antagonist, warfarin, would have a greater prevalence of osteoporosis compared to individuals not exposed to warfarin. However, the current evidence does not consistently support this hypothesis. In a meta-analysis of 11 published studies, oral anticoagulation was associated with a modest reduction in BMD at the radius but not at any other skeletal site (28). More recently, it was reported that warfarin use was not associated with either lower BMD or nonspine fracture risk among elderly men (135). Comparison of the baseline characteristics of warfarin users with nonwarfarin users in this study highlights the limitations of this approach to studying the effects of vitamin K inadequacy on bone. The warfarin users were older, in poorer self-reported health, and had more cardiovascular disease, more hypertension, and greater diuretic and β-blocker use (135). Although controlled for in the statistical analysis of this study, overall poorer health status is a consistent characteristic of these patients and may account for the findings by some that warfarin use, hence less available vitamin K in bone, is associated with reduced BMD (92, 103). Long-term exposure to warfarin has been reported to be associated with greater prevalence of osteopenia among children (5). However, the concomitant lower vitamin D status of these children limits one's ability to isolate the effects of vitamin K antagonism from that of overall poor nutrition.

Randomized Controlled Trials

Phylloquinone supplementation. Multiple randomized controlled trials have assessed the influence of phylloquinone supplementation on bone loss (8, 10, 15, 24, 32) (**Table 2**). Daily doses ranged from 200 μg to 10 mg of phylloquinone for durations of 12 to 48 months. Of these trials, only one study in postmenopausal women demonstrated a reduction in bone loss at the femoral neck in response to 1 mg of phylloquinone in combination with calcium and vitamin D for 36 months (24). The group treated with calcium and vitamin D experienced bone loss equivalent to that of the placebo group, which is in contrast to the findings of the majority of other studies (40) and may be indicative of a study group that has unique characteristics because no other studies have demonstrated an effect of phylloquinone on progression of bone loss at the hip. In a separate study of female endurance athletes, this same group of investigators reported no beneficial effect of 24 months of phylloquinone supplementation in doses of 10 mg/d on bone loss compared to a placebo arm (25). The authors suggested that phylloquinone supplementation may have a beneficial effect in prevention of bone loss only when coadministered with vitamin D. In a separate study, two years of supplementation with 200 μg/d phylloquinone, also with calcium and vitamin D, increased BMD at the ultradistal radius in postmenopausal women. However, there was no influence of supplementation on bone loss at the femoral neck and mid-radius (10). Likewise, in a study that examined phylloquinone supplementation in men and postmenopausal women, there were no differences in three-year change in BMD at the femoral neck, spine, or total body between those who received 500 μg/d phylloquinone with calcium and vitamin D compared to those who received calcium and vitamin D alone (15). There was also no effect of phylloquinone supplementation on change in biomarkers of bone turnover in any of the aforementioned studies (8, 10, 15, 24, 32). To date, there have been no randomized

Table 2 RCTs assessing the effect of phylloquinone on hip BMD and fracture risk[a]

Subject characteristics at baseline	Duration (months)	Intervention	Outcome[b]			Reference
			Hip BMD	BMD at other anatomical site	Fracture risk	
Women not taking HRT, ≥60 years; n = 244	24 m	200 μg/d phylloquinone	No effect	Increased BMD ultra distal radius	Not reported	(10)
Men and women not taking HRT, 60–80 years; n = 452	36 m	500 μg/d phylloquinone	No effect	No effect	No effect	(15)
Women not taking HRT, mean age 62 years; n = 381	12 m	1 mg/d phylloquinone	No effect	No effect	Not reported	(8)
Women not taking HRT, 50–60 years; n = 181	36 m	1 mg/d phylloquinone	Less bone loss	No effect	Not reported	(24)
Women not taking HRT, 40–82 years; n = 440	24 m (extension study to 48 m)	5 mg/d phylloquinone	No effect	No effect	Less total fx; no effect on vertebral fx	(32)

[a]Abbreviations: BMD, bone mineral density; fx, fractures; HRT, hormone replacement therapy; RCT, randomized controlled trial.
[b]Outcomes in the intervention group relative to the control group, both of which also received a calcium and vitamin D supplement. Some studies also included a placebo arm, but these were not taken into account in this table.

controlled trials using phylloquinone in populations at risk of vitamin K deficiency, such as children with cystic fibrosis.

Although hip fracture risk was not a primary study outcome, Cheung et al. (32) did report a significant reduction in total fractures in response to a daily dose of 5 mg phylloquinone for up to 48 months. However, as the authors cautioned, the study was not statistically powered to test this hypothesis, and by a priori definition, fractures included both fragility and nonfragility fractures. There were no statistically significant differences in incidence of vertebral fractures between the treatment and control group. No other studies of phylloquinone supplementation in the elderly have reported fracture risk as a study outcome, most likely because they lacked the statistical power and/or the study duration was too short for assessment of fracture outcome measures. Curiously, there were no reported differences in either BMD or bone turnover in response to phylloquinone in the study by Cheung et al. (32); hence, the mechanism underlying the reported protective effect against fracture is not known. Although it has been suggested that vitamin K confers protective effects against bone loss through alterations in femur geometry (71), others have not been able to replicate these findings (32, 126).

MK-4 supplementation. MK-4 in doses of 45 mg/d is used as a pharmacological treatment for osteoporosis in Japan, so numerous randomized controlled studies have assessed the efficacy of MK-4 supplementation on skeletal health. Such doses cannot be attained from the diet, regardless of the form of vitamin K consumed. As was reviewed elsewhere (60), studies indicate a beneficial effect of a therapeutic dose (45 mg/d) of MK-4 on spine or metacarpal BMD and fracture. There is also improvement of bone turnover, as measured by circulating markers of bone formation and bone resorption, in response to MK-4 supplementation studies. In a separate systematic review and

analysis of randomized clinical trials assessing the influence of vitamin K supplementation on hip fracture, Cockayne et al. (33) concluded that supplementation with MK-4 for longer than six months reduces risk for hip and vertebral fracture. Included in that analysis were 12 studies that used doses of 45 mg/d of MK-4. However, as discussed by these authors, several of the studies used for the meta-analysis lacked sufficient sample size, were non-placebo-controlled intervention trials, and/or used concurrent treatment with calcium and/or vitamin D. It was subsequently disclosed that a large unpublished surveillance study conducted in Japan ($n > 3000$) did not find a protective effect of 45 mg/d of MK-4 supplementation on bone loss and fracture in Japanese elderly and that inclusion of this study may have altered the results of the meta-analysis (119). More recently, two placebo-controlled studies with large sample sizes reported no protective effect of 45 mg/d of MK-4 on hip BMD (8, 71). Prior to these two publications, the majority of MK-4 supplementation studies did not report hip BMD as an outcome. Given the heterogeneity in quality of the studies used and considering the null findings of more recent larger placebo-controlled trials and unpublished surveillance data, prior systematic reviews and meta-analyses may need to be revisited.

In a recent review, the authors concluded that although bisphosphonates should be the first line of treatment of postmenopausal osteoporosis, there is a potential synergy between MK-4 and bisphosphonates in prevention of hip fracture risk among women with osteoporosis (60). This conclusion highlights one of the challenges in reviewing the literature on this topic. The role of vitamin K in fracture prevention has not been well defined in terms of the natural history of osteoporosis. Treatment with very high doses (45 mg/d) of MK-4 has been studied as a pharmacological treatment of a preexisting condition or disease, i.e., osteoporosis. The primary intent of studies using doses attainable within the diet (i.e., up to 1 mg/d) has been the measurement of the extent to which age-related bone loss is delayed among individuals at risk for developing osteoporosis. This presents a dilemma, not uncommon in nutrition, in which the clinical trials report efficacy at doses well above that which can be attained in the diet. More studies need to be completed, though, that substantiate the findings of Cheung et al. (32) in terms of fracture prevention in response to daily doses of 5 mg of phylloquinone before advocacy for widespread vitamin K supplementation. Furthermore, little is known regarding stages in the life cycle, if any, during which vitamin K supplementation is most effective in prevention of bone loss in later life. Interestingly, even though Iwamoto et al. (60) emphasize the potential role of MK-4 as an adjunct therapy, they conclude that the evidence supporting high doses of MK-4 for prevention of vertebral fractures are from smaller, nondefinitive studies, and the efficacy has not been established for prevention of hip fractures or nonvertebral fractures.

ROLE OF VITAMIN K IN VASCULAR CALCIFICATION

Although a role for vitamin K in the regulation of vascular calcification was proposed more than 30 years ago (78–80), the evidence in humans to date has been limited. Vascular smooth muscle cells, which have a central role in calcification, synthesize the VKDP, matrix Gla protein (MGP). As reviewed elsewhere (95), MGP inhibits vascular calcification through a variety of mechanisms, including the binding of calcium ions and crystals, and extracellular matrix. It has been shown that the calcium-regulation activity of MGP depends upon the VKD γ-carboxylation of specific Glu residues that confer a conformational change in the protein (86). In mice, targeted deletion of the MGP gene causes extensive calcification of the elastic lamellae of the abdominal aorta (82). In humans, mutations in the gene encoding MGP resulting in the production of nonfunctional or absent MGP are responsible for Keutel syndrome and are characterized by

abnormal cartilage and arterial calcification (58). MGP has been detected in human atherosclerotic plaques (109), with the uncarboxylated form present in the calcified regions of the vasculature (107). Given the recent identification of two more VKDPs involved in extracellular calcium regulation (36, 130), it will be of interest to see if these proteins also contribute to regulation of vascular calcification. Others have proposed that the VKDP growth arrest–specific gene 6 product (Gas-6) is also implicated in vascular calcification through its role in vascular smooth muscle cell apoptosis and movement (39).

Serum MGP concentrations have been reported by some to be elevated in individuals with high amounts of coronary calcium deposits (22, 89), although concentrations have been inversely correlated with the severity of coronary artery calcification (CAC) by others (62). Expression of MGP increases in calcified regions of the vascular wall, and MGP has been shown to accumulate at sites of calcification (94). It is thought that increased accumulation of MGP slows the progression of calcification, and that a fraction of this increased synthesis escapes to serum, where it causes an elevation in serum MGP (95). However, increased serum concentrations of MGP failed to rescue vascular calcification in mice due to targeted MGP deletion (86), which challenges the utility of serum MGP concentrations. MGP is a VKDP, and as such, must be γ-carboxylated to be functional. The majority of currently available MGP assays measure total serum MGP and do not discriminate between the ucMGP and carboxylated forms of MGP, making the interpretation of these findings more difficult. The inconsistencies in the associations between serum MGP and CAC underscore the conclusions of some authors that serum total MGP is not a robust biochemical measure for vascular calcification (89).

In the absence of a direct measure of vitamin K status in the vessels of healthy individuals, it is assumed that any dietary role of vitamin K in slowing the progression of calcification is mediated through the carboxylation of MGP. Vitamin K antagonism with warfarin inhibits VKD γ-carboxylation of MGP, leading to arterial calcification in rats (94). Furthermore, diets high in vitamin K have been shown to reverse aortic calcification and improve arterial elasticity in warfarin-treated rats (106). However, data to support the potential role for vitamin K intake in the protection against vascular calcification in humans are limited.

Observational Studies

High phylloquinone intake has generally not been associated with low risk of cardiovascular disease in population studies once the statistical analysis is controlled for other dietary and lifestyle factors associated with coronary heart disease (CHD) (43) (**Table 3**). It was suggested that higher menaquinone intakes, primarily in the form of MK-4, were associated with a lower risk of CHD mortality and a lower risk of severe aortic calcification (50) (**Table 3**). The intake of menaquinones was very low compared to that of phylloquinone, and based on our current understanding of vitamin K, one would assume that any putative beneficial effect of menaquinones on CHD risk would be also conferred by phylloquinone intake because there is a tissue-specific conversion of phylloquinone to MK-4. However, phylloquinone intakes in this study were not associated with a protective effect on CHD risk (50). Unlike phylloquinone, various menaquinones are generally not detectable in circulation in response to dietary intakes, and currently no alternative biomarkers are available that are specific for validation of estimated menaquinone intakes. Given that phylloquinone intake is a marker of a heart-healthy diet and that assessment of dietary menaquinone intakes is problematic in terms of validation, the role of vitamin K in the progression of vascular calcification and CHD risk needs to be assessed in clinical trials.

Randomized Controlled Trials

In a single randomized controlled trial that assessed the effect of phylloquinone on vascular health in postmenopausal women, three-year

Table 3 Vitamin K intake and atherosclerosis outcomes (adapted with permission from Reference 43)[a]

Setting	Subjects	Diet or intervention	Outcome	Main results	Reference
Calcification outcomes					
Population-based sample	n = 113 postmenopausal women	Phylloquinone	Presence of abdominal aorta calcification	Lower phylloquinone intake in women aged 60–69 with calcifications than those without calcification; no differences in any other age group	(61)
Clinical intervention, duration 3 years	n = 108 postmenopausal women	Minerals + vitamin D versus Phylloquinone + minerals + vitamin D	Carotid intima-media thickness	No differences	(23)
		Minerals + vitamin D versus Phylloquinone + minerals + vitamin D	Vessel wall elasticity	Phylloquinone + control has improved elasticity compared with control	
Cross-sectional	n = 807 U.S. Army personnel, 39–45 years	Phylloquinone in quartiles	Coronary artery calcification score	No association	(131)
PROSPECT Study, cross-sectional	n = 1689 women, 49–70 years	Phylloquinone and menaquinone in quartiles	Presence of breast artery calcification	No association	(84)
Coronary heart disease (CHD) and stroke outcomes					
				Relative risk in highest compared to lowest intake category	
Rotterdam Study, 7- to 10-year follow-up	n = 4807 men and women, >55 years	Phylloquinone and menaquinone in tertiles	Total CHD	Phylloquinone: 0.89 (0.63–1.25)	(50)
			Total CHD	Menaquinones: 0.59 (0.40–0.86)	
			Fatal CHD	Phylloquinone: 1.02 (0.61–1.69)	
			Fatal CHD	Menaquinones: 0.43 (0.24–0.77)	
Nurses' Health Study, 16-year follow-up	n = 72,874 women, 38–65 years	Phylloquinone in quintiles	Total CHD	0.84 (0.71–1.00)	(45)
			Fatal CHD	0.90 (0.65–1.23)	
			Stroke	1.04 (0.83–1.31)	
Health Professionals Follow-up Study, 14-year follow-up	n = 40,087 men, 40–75 years	Phylloquinone in quintiles	Total CHD	0.91 (0.77–1.06)	(44)
			Fatal CHD	0.81 (0.62–1.05)	
			Stroke	1.01 (0.76–1.35)	

[a]Abbreviations: CHD, coronary heart disease; PROSPECT, Predictors of Response to Cardiac Resynchronization Therapy.

phylloquinone, calcium, and vitamin D supplementation improved elasticity and compliance in the common carotid artery compared to women taking the supplement without phylloquinone (23). The authors speculate that the improvement resulted from an increase in the vitamin K–dependent carboxylation of MGP, leading to a decrease in vascular calcium deposition. However, neither MGP nor vascular calcification was measured directly (23). Furthermore, there was no beneficial effect of phylloquinone on carotid thickness (**Table 3**). To the best of our knowledge, menaquinone supplementation has not been assessed in terms of vascular calcification progression in humans.

GENETIC INTERACTIONS WITH VITAMIN K

As previously reviewed in this journal, single nucleotide polymorphisms (SNPs) in genes encoding components of single nutrients have the potential to modulate disease risk, and may partially explain the disparity of findings among the various studies examining disease risk in response to a given nutrient (35, 57). Little is known about the role of genetic variation at candidate loci in the variability in individual response to vitamin K supplementation and corresponding disease risk. Therefore, it is plausible that potential genetic determinants of vitamin K metabolism include variation in genes involved in the transport or uptake of vitamin K into the tissues, tissue-specific availability and recycling of vitamin K, and proteins that are direct targets of the VKD γ-carboxylation.

It is well documented that a large interindividual variation exists with respect to vitamin K status (20). In one observational study of community-based Caucasian men and women, variability in biomarkers of vitamin K status was attributed to nongenetic factors, such as triglycerides and phylloquinone intake (110). In contrast, heritability estimates for these vitamin K status biomarkers were not statistically significant, which implied limited genetic contribution to variability in vitamin K status. The heritability estimates were based on biochemical measures obtained from a single blood draw and may have limited the authors' ability to accurately assess variability in plasma phylloquinone or serum %ucOC. However, heritability estimates for the vitamin D biomarker, plasma 25(OH)D, were statistically significant in this same study, despite the study design limitations (110).

Polymorphisms in the vitamin K epoxide reductase complex subunit 1 (*VKORC1)* and γ-carboxylase (*GGCX)* genes have been shown to contribute to the interindividual variability in response to the vitamin K antagonist, warfarin (69, 132), and differences in vascular disease risk (133), although not consistently (134). In one study, it was reported that homozygous carriers of a minor allele of a different SNP in the VKORC1 gene had significantly higher concentrations of plasma phylloquinone and lower %ucOC than did carriers of the C allele (38). This suggests adequate availability of reduced substrate for γ-carboxylation in extrahepatic tissues. However, the variation in this gene did not predict changes in vitamin K status in response to phylloquinone supplementation in older men and women. Furthermore, polymorphisms in VKORC1 were not found to be associated with prothrombin time or bone mineral density in 40 mouse priority strains, despite reports that warfarin resistance in both humans and rodents is attributed to polymorphisms in the VKORC1 gene (114).

Even less is known about the influences of *GGCX* polymorphisms on vitamin K status, although the limited findings to date are consistent. In a study of older Caucasian men and women, individual *GGCX* SNPs were found to influence %ucOC but not plasma phylloquinone concentrations (38). These data suggest that the association between these *GGCX* SNPs and %ucOC is due to a direct influence on the γ-carboxylation of OC. These findings are consistent with a recent report that a functional SNP in the GGCX, compared to the more common variant, was associated with forearm BMD that was lower among women older than 75 years, a finding that the authors attribute

to the lower carboxylase activity with the functional SNP (39).

The apoE genotype, which influences serum cholesterol and triglycerides, has been suggested to influence skeletal health through the transport of vitamin K to bone (74). More specifically, it has been shown that individuals who carry the apoE4 allele and have a rapid hepatic clearance of chylomicron remnants and lower serum cholesterol and triglyceride concentrations also have lower bone mineral density BMD and increased risk for fracture (142). Some have attributed this increased fracture risk to inadequate vitamin K transport to the skeletal tissue (30, 74), although there is little evidence that apoE is a modifier of any putative effect of vitamin K on bone among Caucasians. In a recent population-based study of Scottish women, phylloquinone intake was not associated with change in BMD after 5–7 years of follow-up, nor was there an effect modification by apoE genotype (85). Similarly, Booth et al. (19) observed an increased risk for hip fracture associated with lower phylloquinone intake in men and women participating in the Framingham Heart Study (mean age 75) over seven years of follow-up, with no effect modification by apoE genotype. Several small studies comparing vitamin K status as stratified by apoE genotype among different populations suggest that there may be some gene-environment interactions that influence vitamin K status beyond that which can be identified through individual SNP and vitamin K biomarker association studies (7, 137). As recommended by others in a review in this journal, there is a need to consider interactions among multiple genes, dietary components, and risk factors to understand the complexity of gene-nutrient interactions (35), including those that may explain the role of vitamin K in modulating disease risk.

Recent studies suggest that there is a strong genetic component to the development of arterial calcification. Genetic variability in MGP is of particular interest because of its role as an inhibitor of calcification. In vitro studies suggest that SNPs in MGP are associated with altered promoter activity (46, 56, 72). In addition, there is some evidence that MGP SNPs are associated with arterial calcification (37, 56), although these results are not consistent (73, 120). Inconsistent findings may be attributable to differences in the age of the cohorts studied, with younger cohorts less likely to have sufficient calcification to detect differences when stratified by MGP SNPs, and to differences in the sensitivity of the methods used to detect calcification. There are also ethnic differences in the calcification prevalence and burden (26). In the study by Crosier et al. (37), which was limited to Caucasian men and women, significant associations were found in men only. Men initiate vascular calcification earlier in life than women, so it is plausible that the associations between these MGP SNPs and CAC may manifest only in individuals with high amounts of calcification. Currently, it is not known if associations between MGP SNPs and CAC are due to functional consequences of these polymorphisms or if these polymorphisms are in linkage with other functional loci. Clearly, larger population studies and well-designed intervention studies are required to evaluate the role of genetic variation at candidate loci in the variability in individual response to vitamin K supplementation and corresponding disease risk.

EMERGING ROLES FOR VITAMIN K IN ENERGY METABOLISM AND INFLAMMATION

As previously reviewed in this journal, diet and lifestyle play an important role in the progress of insulin resistance, a metabolic disorder characterized by diminished hepatic and peripheral tissue sensitivity to insulin (97). With respect to micronutrients, a potential protective role for vitamin K against insulin resistance has been proposed (99–101, 140, 141).

Rats fed a low phylloquinone-containing diet had higher glucose concentrations and a delayed insulin response to glucose infusion compared to rats fed a high phylloquinone-containing diet (101). Similar findings were reported in a small metabolic study of young men (99). More recently, it was reported that higher

phylloquinone intakes had a beneficial effect on insulin resistance, as defined by fasting and two-hour post oral glucose tolerance insulin levels and the homeostasis model assessment of insulin resistance (HOMA-IR) in community-dwelling men and women (140). Since major sources of phylloquinone in the diet are green leafy vegetables, higher phylloquinone intakes are generally associated with healthier lifestyle and dietary habits (43), which may contribute to the reduced insulin resistance. However, it was subsequently reported that phylloquinone supplementation (500 μg/d) for three years resulted in less progression of insulin resistance among older men, as indicated by lower HOMA-IR, compared to a control group (141). Of interest was the observation that among women, there was no beneficial effect of phylloquinone supplementation on HOMA-IR. However, because this study was not designed for examining the effect of phylloquinone on insulin resistance, and state-of-the art techniques were not used for outcome measures, the findings are considered as hypothesis generating.

The potential mechanisms underlying this possible role for vitamin K and insulin resistance may relate to the carboxylation of OC and/or inflammation. Two forms of vitamin K, phylloquinone and MK-4, are found in the human pancreas and liver (122), and both forms act as a cofactor for the carboxylation of the VKDPs (**Figure 2**). Of these, prothrombin and protein S are both present in liver and pancreas and are involved in coagulation (115). More recently, it has been suggested that OC may function as a hormone in the regulation of energy metabolism. In a series of in vitro and animal studies, OC was reported to influence β-cell function, insulin sensitivity, adiponectin production, energy expenditure, and adiposity (47, 77). OC regulated insulin sensitivity through an effect on an adipocyte-derived hormone, adiponectin, rather than through a direct effect on insulin (77).

In circulation, OC is detectable in both the carboxylated and uncarboxylated forms. However, it has been proposed that the ucOC form alone functions hormonally in the regulation of glucose homeostasis and energy metabolism (47, 77). This is in contrast to the role of OC in bone, in which the carboxylated form of osteocalcin is thought to confer functionality to the protein. Furthermore, the hypothesis that only the ucOC form functions in the regulation of glucose homeostasis is a direct contradiction to the findings of Yoshida et al. (140, 141) because higher intakes of vitamin K result in greater carboxylation of OC (13). That only the ucOC form regulates glucose homeostasis would imply that high intakes of vitamin K would be detrimental to glucose homeostasis. This apparent contradiction in the functions of OC, based on current knowledge, highlights the need for more research to elucidate the underlying mechanisms.

Alternatively, vitamin K may be influencing glucose homeostasis through mechanisms beyond its classic role as an enzyme cofactor. Low-grade inflammation has been implicated in the development of insulin resistance (124), and associations between OC and inflammation have also been reported (105). In vitro studies have shown that vitamin K decreases proinflammatory cytokines (76, 90, 98). Vitamin K supplementation of human fibroblasts inhibits IL-6 production independent of γ-carboxylation (98). A recent observational study has shown that low vitamin K status, as assessed by both biochemical and dietary markers, was inversely associated with circulating measures of inflammation (112). The mechanism underlying the potential influence of vitamin K on inflammatory cytokine production is unclear, although it may be through the regulation by MK-4 of the transcription factor, nuclear factor kappa B (NFKB). More specifically, in vitro treatment with MK-4 inhibited the phosphorylation and degradation of the inhibitory-subunit (IkBα), thereby preventing the translocation of NFKB into the nucleus, where it regulates gene expression (90). As IL-6 gene expression is regulated by NFKB (6), the inhibitory influence of MK-4 on NFKB may lead to a decrease in expression of IL-6 and other cytokines regulated by NFKB. Alternatively, since markers

of vitamin K status are reflective of an overall healthy diet, the cross-sectional observations may reflect a general influence of healthy dietary patterns on serum IL-6, osteoprotegerin, and C-reactive protein. The potential influence of different doses and forms of vitamin K on inflammatory cytokine production merits further investigation.

CONCLUSIONS

It has been proposed that vitamin K has multiple roles beyond coagulation, both dependent and independent of its known biochemical function as an enzyme cofactor. This expanded scope of potential functions of vitamin K in the maintenance of human health has been accompanied by a substantial number of observational studies and, to a lesser extent, randomized controlled trials designed to isolate the role(s) of vitamin K in the prevention of specific chronic diseases, including osteoporosis and cardiovascular disease. Observational studies were used as evidence to support the hypothesis that vitamin K has a protective influence on the prevention of age-related bone loss. However, the current evidence is equivocal, particularly as the results of the randomized control trials using different forms of vitamin K emerge. The roles of phylloquinone and menaquinones in the etiology of vascular diseases in humans also remain ambiguous. Even though a biologically plausible mechanism has been proposed through its critical role in the γ-carboxylation of MGP, the data from observational studies refer to a role for vitamin K as a marker for a heart-healthy diet rather than an independent factor in the progress of multifactorial vascular diseases. Clinical trials assessing the response of supplementation of different vitamin K forms in relation to cardiovascular diseases are needed to further explore the field. Preliminary studies also suggest roles for vitamin K in the regulation of inflammation and energy metabolism that appear to be independent of its role as an enzyme cofactor. However, the evidence to date can be best viewed as hypothesis generating, with inadequate knowledge available at this time to elucidate the underlying putative mechanisms.

DISCLOSURE STATEMENT

The author is not aware of any biases that might be perceived as affecting the objectivity of this review.

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LITERATURE CITED

1. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. 2001. Washington, DC: Inst. Med., Natl. Acad. Press
2. Arbour NC, Darwish HM, DeLuca HF. 1995. Transcriptional control of the osteocalcin gene by 1,25-dihydroxyvitamin D-2 and its 24-epimer in rat osteosarcoma cells. *Biochim. Biophys. Acta* 1263:147–53
3. Arjmandi BH, Getlinger MJ, Goyal NV, Alekel L, Hasler CM, et al. 1998. Role of soy protein with normal or reduced isoflavone content in reversing bone loss induced by ovarian hormone deficiency in rats. *Am. J. Clin. Nutr.* 68:1358–63S
4. Ashwell M, Stone E, Mathers J, Barnes S, Compston J, et al. 2008. Nutrition and bone health projects funded by the UK Food Standards Agency: Have they helped to inform public health policy? *Br. J. Nutr.* 99:198–205

5. Avgeri M, Papadopoulou A, Platokouki H, Douros K, Rammos S, et al. 2008. Assessment of bone mineral density and markers of bone turnover in children under long-term oral anticoagulant therapy. *J. Pediatr. Hematol. Oncol.* 30:592–97
6. Barnes PJ, Karin M. 1997. Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. *N. Engl. J. Med.* 336:1066–71
7. Beavan SR, Prentice A, Stirling DM, Dibba B, Yan L, et al. 2005. Ethnic differences in osteocalcin gamma-carboxylation, plasma phylloquinone (vitamin K1) and apolipoprotein E genotype. *Eur. J. Clin. Nutr.* 59:72–81
8. Binkley N, Harke J, Krueger D, Engelke J, Vallarta-Ast N, et al. 2008. Vitamin K treatment reduces undercarboxylated osteocalcin but does not alter bone turnover, density or geometry in healthy postmenopausal North American women. *J. Bone Miner. Res.* Epub ahead of print
9. Binkley NC, Krueger DC, Kawahara TN, Engelke JA, Chappell RJ, Suttie JW. 2002. A high phylloquinone intake is required to achieve maximal osteocalcin gamma-carboxylation. *Am. J. Clin. Nutr.* 76:1055–60
10. Bolton-Smith C, McMurdo ME, Paterson CR, Mole PA, Harvey JM, et al. 2007. Two-year randomized controlled trial of vitamin K1 (phylloquinone) and vitamin D3 plus calcium on the bone health of older women. *J. Bone Miner. Res.* 22:509–19
11. Bolton-Smith C, Price RJ, Fenton ST, Harrington DJ, Shearer MJ. 2000. Compilation of a provisional UK database for the phylloquinone (vitamin K1) content of foods. *Br. J. Nutr.* 83:389–99
12. Booth S, Broe K, Gagnon D, Tucker K, Hannan M, et al. 2003. Vitamin K intake and bone mineral density in women and men. *Am. J. Clin. Nutr.* 77:512–16
13. Booth SL, Al Rajabi A. 2008. Determinants of vitamin K status in humans. *Vitam. Horm.* 78:1–22
14. Booth SL, Broe KE, Peterson JW, Cheng DM, Dawson-Hughes B, et al. 2004. Associations between vitamin K biochemical measures and bone mineral density in men and women. *J. Clin. Endocrinol. Metab.* 89:4904–9
15. Booth SL, Dallal G, Shea MK, Gundberg C, Peterson JW, Dawson-Hughes B. 2008. Effect of vitamin K supplementation on bone loss in elderly men and women. *J. Clin. Endocrinol. Metab.* 93:1217–23
16. Booth SL, Martini L, Peterson JW, Saltzman E, Dallal GE, Wood RJ. 2003. Dietary phylloquinone depletion and repletion in older women. *J. Nutr.* 133:2565–69
17. Booth SL, O'Brien-Morse ME, Dallal GE, Davidson KW, Gundberg CM. 1999. Response of vitamin K status to different intakes and sources of phylloquinone-rich foods: comparison of younger and older adults. *Am. J. Clin. Nutr.* 70:368–77
18. Booth SL, Suttie JW. 1998. Dietary intake and adequacy of vitamin K. *J. Nutr.* 128:785–88
19. Booth SL, Tucker KL, Chen H, Hannan MT, Gagnon DR, et al. 2000. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. *Am. J. Clin. Nutr.* 71:1201–8
20. Booth SL, Tucker KL, McKeown NM, Davidson KW, Dallal GE, Sadowski JA. 1997. Relationships between dietary intakes and fasting plasma concentrations of fat-soluble vitamins in humans. *J. Nutr.* 127:587–92
21. Boskey AL, Gadaleta S, Gundberg C, Doty SB, Ducy P, Karsenty G. 1998. Fourier transform infrared microspectroscopic analysis of bones of osteocalcin-deficient mice provides insight into the function of osteocalcin. *Bone* 23:187–96
22. Braam LA, Dissel P, Gijsbers BL, Spronk HM, Hamulyak K, et al. 2000. Assay for human matrix Gla protein in serum: potential applications in the cardiovascular field. *Arterioscler. Thromb. Vasc. Biol.* 20:1257–61
23. Braam LA, Hoeks AP, Brouns F, Hamulyak K, Gerichhausen MJ, Vermeer C. 2004. Beneficial effects of vitamins D and K on the elastic properties of the vessel wall in postmenopausal women: a follow-up study. *Thromb. Haemost.* 91:373–80
24. Braam LA, Knapen MH, Geusens P, Brouns F, Hamulyak K, et al. 2003. Vitamin K1 supplementation retards bone loss in postmenopausal women between 50 and 60 years of age. *Calcif. Tissue Int.* 73:21–26
25. Braam LA, Knapen MH, Geusens P, Brouns F, Vermeer C. 2003. Factors affecting bone loss in female endurance athletes: a two-year follow-up study. *Am. J. Sports Med.* 31:889–95

26. Budoff MJ, Nasir K, Mao S, Tseng PH, Chau A, et al. 2006. Ethnic differences of the presence and severity of coronary atherosclerosis. *Atherosclerosis* 187:343–50
27. Cairns JR, Price PA. 1994. Direct demonstration that the vitamin K-dependent bone Gla protein is incompletely gamma-carboxylated in humans. *J. Bone Miner. Res.* 9:1989–97
28. Caraballo PJ, Gabriel SE, Castro MR, Atkinson EJ, Melton LJ 3rd. 1999. Changes in bone density after exposure to oral anticoagulants: a meta-analysis. *Osteoporos. Int.* 9:441–48
29. Cashman KD, O'Connor E. 2008. Does high vitamin K1 intake protect against bone loss in later life? *Nutr. Rev.* 66:532–38
30. Cauley JA, Zmuda JM, Yaffe K, Kuller LH, Ferrell RE, et al. 1999. Apolipoprotein E polymorphism: a new genetic marker of hip fracture risk—The Study of Osteoporotic Fractures. *J. Bone Miner. Res.* 14:1175–81
31. Chawla D, Deorari AK, Saxena R, Paul VK, Agarwal R, et al. 2007. Vitamin K1 versus vitamin K3 for prevention of subclinical vitamin deficiency: a randomized controlled trial. *Indian Pediatr.* 44:817–22
32. Cheung AM, Tile L, Lee Y, Tomlinson G, Hawker G, et al. 2008. Vitamin K supplementation in postmenopausal women with osteopenia (ECKO Trial): a randomized controlled trial. *PLoS Med.* 5:e196
33. Cockayne S, Adamson J, Lanham-New S, Shearer MJ, Gilbody S, Torgerson DJ. 2006. Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. *Arch. Intern. Med.* 166:1256–61
34. Conway SP, Wolfe SP, Brownlee KG, White H, Oldroyd B, et al. 2005. Vitamin K status among children with cystic fibrosis and its relationship to bone mineral density and bone turnover. *Pediatrics* 115:1325–31
35. Corella D, Ordovas JM. 2005. Single nucleotide polymorphisms that influence lipid metabolism: interaction with dietary factors. *Annu. Rev. Nutr.* 25:341–90
36. Coutu DL, Wu JH, Monette A, Rivard GE, Blostein MD, Galipeau J. 2008. Periostin, a member of a novel family of vitamin K-dependent proteins, is expressed by mesenchymal stromal cells. *J. Biol. Chem.* 283:17991–8001
37. Crosier MD, Booth SL, Peter I, Dawson-Hughes B, Price PA, et al. 2009. Matrix Gla polymorphisms are associated with coronary artery calcification in men. *J. Nutr. Sci. Vitaminol. (Tokyo)*. In press
38. Crosier MD, Peter I, Booth SL, Bennett G, Dawson-Hughes B, Ordovas JM. 2009. Association of sequence variations in vitamin K epoxide reductase and gamma-glutamyl carboylase genes with biochemical measures of vitamin K status. *J. Nutr. Sci. Vitaminol.* (*Tokyo*). In press
39. Danziger J. 2008. Vitamin K-dependent proteins, warfarin, and vascular calcification. *Clin. J. Am. Soc. Nephrol.* 3:1504–10
40. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. 1997. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N. Engl. J. Med.* 337:670–76
41. Ducy P, Desbois C, Boyce B, Pinero G, Story B, et al. 1996. Increased bone formation in osteocalcin-deficient mice. *Nature* 382:448–52
42. Elder SJ, Haytowitz DB, Howe J, Peterson JW, Booth SL. 2006. Vitamin K contents of meat, dairy, and fast food in the U.S. diet. *J. Agric. Food Chem.* 54:463–67
43. Erkkila AT, Booth SL. 2008. Vitamin K intake and atherosclerosis. *Curr. Opin. Lipidol.* 19:39–42
44. Erkkila AT, Booth SL, Hu FB, Jacques PF, Lichtenstein AH. 2007. Phylloquinone intake and risk of cardiovascular diseases in men. *Nutr. Metab. Cardiovasc. Dis.* 17:58–62
45. Erkkila AT, Booth SL, Hu FB, Jacques PF, Manson JE, et al. 2005. Phylloquinone intake as a marker for coronary heart disease risk but not stroke in women. *Eur. J. Clin. Nutr.* 59:196–204
46. Farzaneh-Far A, Davies JD, Braam LA, Spronk HM, Proudfoot D, et al. 2001. A polymorphism of the human matrix gamma-carboxyglutamic acid protein promoter alters binding of an activating protein-1 complex and is associated with altered transcription and serum levels. *J. Biol. Chem.* 276:32466–73
47. Ferron M, Hinoi E, Karsenty G, Ducy P. 2008. Osteocalcin differentially regulates beta cell and adipocyte gene expression and affects the development of metabolic diseases in wild-type mice. *Proc. Natl. Acad. Sci. USA* 105:5266–70
48. Feskanich D, Weber P, Willett WC, Rockett H, Booth SL, Colditz GA. 1999. Vitamin K intake and hip fractures in women: a prospective study. *Am. J. Clin. Nutr.* 69:74–79
49. Fewtrell MS, Benden C, Williams JE, Chomtho S, Ginty F, et al. 2008. Undercarboxylated osteocalcin and bone mass in 8–12-year-old children with cystic fibrosis. *J. Cyst. Fibros.* 7:307–12

50. Geleijnse JM, Vermeer C, Grobbee DE, Schurgers LJ, Knapen MH, et al. 2004. Dietary intake of menaquinone is associated with a reduced risk of coronary heart disease: the Rotterdam Study. *J. Nutr.* 134:3100–5
51. Gundberg CM, Nieman SD, Abrams S, Rosen H. 1998. Vitamin K status and bone health: an analysis of methods for determination of undercarboxylated osteocalcin. *J. Clin. Endocrinol. Metab.* 83:3258–66
52. Hamilton DW. 2008. Functional role of periostin in development and wound repair: implications for connective tissue disease. *J. Cell Commun. Signal.* 2:9–17
53. Hara K, Akiyama Y, Nakamura T, Murota S, Morita I. 1995. The inhibitory effect of vitamin K2 (menatetrenone) on bone resorption may be related to its side chain. *Bone* 16:179–84
54. Harrington DJ, Booth SL, Card DJ, Shearer MJ. 2007. Excretion of the urinary 5C- and 7C-aglycone metabolites of vitamin K by young adults responds to changes in dietary phylloquinone and dihydrophylloquinone intakes. *J. Nutr.* 137:1763–68
55. Heiss C, Hoesel LM, Wehr U, Wenisch S, Drosse I, et al. 2008. Diagnosis of osteoporosis with vitamin K as a new biochemical marker. *Vitam. Horm.* 78:417–34
56. Herrmann SM, Whatling C, Brand E, Nicaud V, Gariepy J, et al. 2000. Polymorphisms of the human matrix Gla protein (MGP) gene, vascular calcification, and myocardial infarction. *Arterioscler. Thromb. Vasc. Biol.* 20:2386–93
57. Hesketh J. 2008. Nutrigenomics and selenium: gene expression patterns, physiological targets, and genetics. *Annu. Rev. Nutr.* 28:157–77
58. Hur DJ, Raymond GV, Kahler SG, Riegert-Johnson DL, Cohen BA, Boyadjiev SA. 2005. A novel MGP mutation in a consanguineous family: review of the clinical and molecular characteristics of Keutel syndrome. *Am. J. Med. Genet. A* 135:36–40
59. Ikeda Y, Iki M, Morita A, Kajita E, Kagamimori S, et al. 2006. Intake of fermented soybeans, natto, is associated with reduced bone loss in postmenopausal women: Japanese Population-Based Osteoporosis Study (JPOS). *J. Nutr.* 136:1323–28
60. Iwamoto J, Takeda T, Sato Y. 2006. Role of vitamin K2 in the treatment of postmenopausal osteoporosis. *Curr. Drug Saf.* 1:87–97
61. Jie KS, Bots ML, Vermeer C, Witteman JC, Grobbee DE. 1995. Vitamin K intake and osteocalcin levels in women with and without aortic atherosclerosis: a population-based study. *Atherosclerosis* 116:117–23
62. Jono S, Ikari Y, Vermeer C, Dissel P, Hasegawa K, et al. 2004. Matrix Gla protein is associated with coronary artery calcification as assessed by electron-beam computed tomography. *Thromb. Haemost.* 91:790–94
63. Kalkwarf HJ, Khoury JC, Bean J, Elliot JG. 2004. Vitamin K, bone turnover, and bone mass in girls. *Am. J. Clin. Nutr.* 80:1075–80
64. Kamao M, Suhara Y, Tsugawa N, Uwano M, Yamaguchi N, et al. 2007. Vitamin K content of foods and dietary vitamin K intake in Japanese young women. *J. Nutr. Sci. Vitaminol. (Tokyo)* 53:464–70
65. Kameda T, Miyazawa K, Mori Y, Yuasa T, Shiokawa M, et al. 1996. Vitamin K2 inhibits osteoclastic bone resorption by inducing osteoclast apoptosis. *Biochem. Biophys. Res. Commun.* 220:515–19
66. Katsuyama H, Ideguchi S, Fukunaga M, Saijoh K, Sunami S. 2002. Usual dietary intake of fermented soybeans (natto) is associated with bone mineral density in premenopausal women. *J. Nutr. Sci. Vitaminol. (Tokyo)* 48:207–15
67. Katsuyama H, Otsuki T, Tomita M, Fukunaga M, Fukunaga T, et al. 2005. Menaquinone-7 regulates the expressions of osteocalcin, OPG, RANKL and RANK in osteoblastic MC3T3E1 cells. *Int. J. Mol. Med.* 15:231–36
68. Kawana K, Takahashi M, Hoshino H, Kushida K. 2001. Circulating levels of vitamin K1, menaquinone-4, and menaquinone-7 in healthy elderly Japanese women and patients with vertebral fractures and patients with hip fractures. *Endocr. Res.* 27:337–43
69. Kimura R, Miyashita K, Kokubo Y, Akaiwa Y, Otsubo R, et al. 2007. Genotypes of vitamin K epoxide reductase, gamma-glutamyl carboxylase, and cytochrome P450 2C9 as determinants of daily warfarin dose in Japanese patients. *Thromb. Res.* 120:181–86

70. Knapen MH, Nieuwenhuijzen-Kruseman AC, Wouters RSME, Vermeer C. 1998. Correlation of serum osteocalcin fractions with bone mineral density in women during the first 10 years after menopause. *Calcif. Tissue Int.* 63:375–79
71. Knapen MH, Schurgers LJ, Vermeer C. 2007. Vitamin K2 supplementation improves hip bone geometry and bone strength indices in postmenopausal women. *Osteoporos. Int.* 18:963–72
72. Kobayashi M, Hara K, Akiyama Y. 2004. Effects of vitamin K2 (menatetrenone) and alendronate on bone mineral density and bone strength in rats fed a low-magnesium diet. *Bone* 35:1136–43
73. Kobayashi N, Kitazawa R, Maeda S, Schurgers L, Kitazawa S. 2004. T-138C polymorphism of matrix Gla protein promoter alters its expression but is not directly associated with atherosclerotic vascular calcification. *Kobe J. Med. Sci.* 50:69–81
74. Kohlmeier M, Salomon A, Saupe J, Shearer MJ. 1996. Transport of vitamin K to bone in humans. *J. Nutr.* 126:1192–96S
75. Koshihara Y, Hoshi K, Ishibashi H, Shiraki M. 1996. Vitamin K2 promotes 1alpha,25(OH)2 vitamin D3-induced mineralization in human periosteal osteoblasts. *Calcif. Tissue Int.* 59:466–73
76. Koshihara Y, Hoshi K, Shiraki M. 1993. Vitamin K2 (menatetrenone) inhibits prostaglandin synthesis in cultured human osteoblast-like periosteal cells by inhibiting prostaglandin H synthase activity. *Biochem. Pharmacol.* 46:1355–62
77. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, et al. 2007. Endocrine regulation of energy metabolism by the skeleton. *Cell* 130:456–69
78. Levy RJ, Lian JB, Gallop P. 1979. Atherocalcin, a gamma-carboxyglutamic acid containing protein from atherosclerotic plaque. *Biochem. Biophys. Res. Commun.* 91:41–49
79. Levy RJ, Zenker JA, Lian JB. 1980. Vitamin K-dependent calcium binding proteins in aortic valve calcification. *J. Clin. Invest.* 65:563–66
80. Lian JB, Skinner M, Glimcher MJ, Gallop P. 1976. The presence of gamma-carboxyglutamic acid in the proteins associated with ectopic calcification. *Biochem. Biophys. Res. Commun.* 73:349–55
81. Lukacs JL, Booth S, Kleerekoper M, Ansbacher R, Rock CL, Reame NE. 2006. Differential associations for menopause and age in measures of vitamin K, osteocalcin, and bone density: a cross-sectional exploratory study in healthy volunteers. *Menopause* 13:799–808
82. Luo G, Ducy P, McKee MD, Pinero GJ, Loyer E, et al. 1997. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. *Nature* 386:78–81
83. Luukinen H, Kakonen SM, Pettersson K, Koski K, Laippala P, et al. 2000. Strong prediction of fractures among older adults by the ratio of carboxylated to total serum osteocalcin. *J. Bone Miner. Res.* 15:2473–78
84. Maas AH, Van Der Schouw YT, Beijerinck D, Deurenberg JJ, Mali WP, et al. 2007. Vitamin K intake and calcifications in breast arteries. *Maturitas* 56:273–79
85. Macdonald HM, McGuigan FE, Lanham-New SA, Fraser WD, Ralston SH, Reid DM. 2008. Vitamin K1 intake is associated with higher bone mineral density and reduced bone resorption in early postmenopausal Scottish women: no evidence of gene-nutrient interaction with apolipoprotein E polymorphisms. *Am. J. Clin. Nutr.* 87:1513–20
86. Murshed M, Schinke T, McKee MD, Karsenty G. 2004. Extracellular matrix mineralization is regulated locally; different roles of two Gla-containing proteins. *J. Cell Biol.* 165:625–30
87. Nakao M, Nishiuchi Y, Nakata M, Kimura T, Sakakibara S. 1994. Synthesis of human osteocalcins: gamma-carboxyglutamic acid at position 17 is essential for a calcium-dependent conformational transition. *Pept. Res.* 7:171–74
88. O'Connor E, Molgaard C, Michaelsen KF, Jakobsen J, Lamberg-Allardt CJ, Cashman KD. 2007. Serum percentage undercarboxylated osteocalcin, a sensitive measure of vitamin K status, and its relationship to bone health indices in Danish girls. *Br. J. Nutr.* 97:661–66
89. O'Donnell CJ, Shea MK, Price PA, Gagnon DR, Wilson PW, et al. 2006. Matrix Gla protein is associated with risk factors for atherosclerosis but not with coronary artery calcification. *Arterioscler. Thromb. Vasc. Biol.* 26:2769–74
90. Ohsaki Y, Shirakawa H, Hiwatashi K, Furukawa Y, Mizutani T, Komai M. 2006. Vitamin K suppresses lipopolysaccharide-induced inflammation in the rat. *Biosci. Biotechnol. Biochem.* 70:926–32

91. Okano T, Shimomura Y, Yamane M, Suhara Y, Kamao M, et al. 2008. Conversion of phylloquinone (vitamin K1) into menaquinone-4 (vitamin K2) in mice: two possible routes for menaquinone-4 accumulation in cerebra of mice. *J. Biol. Chem.* 283:11270–79
92. Philip WJ, Martin JC, Richardson JM, Reid DM, Webster J, Douglas AS. 1995. Decreased axial and peripheral bone density in patients taking long-term warfarin. *QJM* 88:635–40
93. Presse N, Shatenstein B, Kergoat MJ, Ferland G. 2008. Low vitamin K intakes in community-dwelling elders at an early stage of Alzheimer's disease. *J. Am. Diet. Assoc.* 108:2095–99
94. Price P, Faus S, Williamson M. 1998. Warfarin causes rapid calcification of the elasetic lamellae in rat arteries and heart valves. *Arterioscler. Thromb. Vasc. Biol.* 18:1400–7
95. Proudfoot D, Shanahan CM. 2006. Molecular mechanisms mediating vascular calcification: role of matrix Gla protein. *Nephrology* 11:455–61
96. Prynne CJ, Thane CW, Prentice A, Wadsworth ME. 2005. Intake and sources of phylloquinone (vitamin K(1)) in 4-year-old British children: comparison between 1950 and the 1990s. *Public Health Nutr.* 8:171–80
97. Reaven GM. 2005. The insulin resistance syndrome: definition and dietary approaches to treatment. *Annu. Rev. Nutr.* 25:391–406
98. Reddi K, Henderson B, Meghji S, Wilson M, Poole S, et al. 1995. Interleukin 6 production by lipopolysaccharide-stimulated human fibroblasts is potently inhibited by naphthoquinone (vitamin K) compounds. *Cytokine* 7:287–90
99. Sakamoto N, Nishiike T, Iguchi H, Sakamoto K. 1999. Relationship between acute insulin response and vitamin K intake in healthy young male volunteers. *Diabetes Nutr. Metab.* 12:37–41
100. Sakamoto N, Nishiike T, Iguchi H, Sakamoto K. 2000. Possible effects of one week vitamin K (menaquinone-4) tablets intake on glucose tolerance in healthy young male volunteers with different descarboxy prothrombin levels. *Clin. Nutr.* 19:259–63
101. Sakamoto N, Wakabayashi I, Sakamoto K. 1999. Low vitamin K intake effects on glucose tolerance in rats. *Int. J. Vitam. Nutr. Res.* 69:27–31
102. Sato Y, Honda Y, Hayashida N, Iwamoto J, Kanoko T, Satoh K. 2005. Vitamin K deficiency and osteopenia in elderly women with Alzheimer's disease. *Arch. Phys. Med. Rehabil.* 86:576–81
103. Sato Y, Honda Y, Kunoh H, Oizumi K. 1997. Long-term oral anticoagulation reduces bone mass in patients with previous hemispheric infarction and nonrheumatic atrial fibrillation. *Stroke* 28:2390–94
104. Schaafsma A, Muskiet FA, Storm H, Hofstede GJ, Pakan I, Van Der Veer E. 2000. Vitamin D(3) and vitamin K(1) supplementation of Dutch postmenopausal women with normal and low bone mineral densities: effects on serum 25-hydroxyvitamin D and carboxylated osteocalcin. *Eur. J. Clin. Nutr.* 54:626–31
105. Schett G, Kiechl S, Weger S, Pederiva A, Mayr A, et al. 2006. High-sensitivity C-reactive protein and risk of nontraumatic fractures in the Bruneck study. *Arch. Intern. Med.* 166:2495–501
106. Schurgers LJ, Spronk HM, Soute BA, Schiffers PM, DeMey JG, Vermeer C. 2007. Regression of warfarin-induced medial elastocalcinosis by high intake of vitamin K in rats. *Blood* 109:2823–31
107. Schurgers LJ, Teunissen KJ, Knapen MH, Kwaijtaal M, van Diest R, et al. 2005. Novel conformation-specific antibodies against matrix gamma-carboxyglutamic acid (Gla) protein: undercarboxylated matrix Gla protein as marker for vascular calcification. *Arterioscler. Thromb. Vasc. Biol.* 25:1629–33
108. Schurgers LJ, Vermeer C. 2000. Determination of phylloquinone and menaquinones in food. Effect of food matrix on circulating vitamin K concentrations. *Haemostasis* 30:298–307
109. Shanahan CM, Cary NR, Metcalfe JC, Weissberg PL. 1994. High expression of genes for calcification-regulating proteins in human atherosclerotic plaques. *J. Clin. Invest.* 93:2393–402
110. Shea MK, Benjamin EJ, Dupuis J, Massaro JM, Jacques PF, et al. 2007. Genetic and non-genetic correlates of vitamins K and D. *Eur. J. Clin. Nutr.* doi:10.1038/sj.ejcn.1602959
111. Shea MK, Booth SL. 2008. Update on the role of vitamin K in skeletal health. *Nutr. Rev.* 66:549–57
112. Shea MK, Dallal GE, Dawson-Hughes B, Ordovas JM, O'Donnell CJ, et al. 2008. Vitamin K, circulating cytokines, and bone mineral density in older men and women. *Am. J. Clin. Nutr.* 88:356–63
113. Shearer MJ, Newman P. 2008. Metabolism and cell biology of vitamin K. *Thromb. Haemost.* 100:530–47

114. Song Y, Vera N, Kohn MH. 2008. Vitamin K epoxide reductase complex subunit 1 (Vkorc1) haplotype diversity in mouse priority strains. *BMC Res. Notes* 1:125
115. Stenberg LM, Nilsson E, Ljungberg O, Stenflo J, Brown MA. 2001. Synthesis of gamma-carboxylated polypeptides by alpha-cells of the pancreatic islets. *Biochem. Biophys. Res. Commun.* 283:454–59
116. Suttie JW. 1995. The importance of menaquinones in human nutrition. *Annu. Rev. Nutr.* 15:399–417
117. Szulc P, Chapuy MC, Meunier PJ, Delmas PD. 1993. Serum undercarboxylated osteocalcin is a marker of the risk of hip fracture in elderly women. *J. Clin. Invest.* 91:1769–74
118. Szulc P, Chapuy MC, Meunier PJ, Delmas PD. 1996. Serum undercarboxylated osteocalcin is a marker of the risk of hip fracture: a three year follow-up study. *Bone* 18:487–88
119. Tamura T, Morgan SL, Takimoto H. 2007. Vitamin K and the prevention of fractures. *Arch. Intern. Med.* 167:94
120. Taylor BC, Schreiner PJ, Doherty TM, Fornage M, Carr JJ, Sidney S. 2005. Matrix Gla protein and osteopontin genetic associations with coronary artery calcification and bone density: the CARDIA study. *Hum. Genet.* 116:525–28
121. Thane CW, Bolton-Smith C, Coward WA. 2006. Comparative dietary intake and sources of phylloquinone (vitamin K1) among British adults in 1986-7 and 2000-1. *Br. J. Nutr.* 96:1105–15
122. Thijssen HH, Drittij-Reijnders MJ. 1996. Vitamin K status in human tissues: tissue-specific accumulation of phylloquinone and menaquinone-4. *Br. J. Nutr.* 75:121–27
123. Thijssen HH, Vervoort LM, Schurgers LJ, Shearer MJ. 2006. Menadione is a metabolite of oral vitamin K. *Br. J. Nutr.* 95:260–66
124. Tilg H, Moschen AR. 2008. Insulin resistance, inflammation, and non-alcoholic fatty liver disease. *Trends Endocrinol. Metab.* 19:371–79
125. Tsugawa N, Shiraki M, Suhara Y, Kamao M, Ozaki R, et al. 2008. Low plasma phylloquinone concentration is associated with high incidence of vertebral fracture in Japanese women. *J. Bone Miner. Metab.* 26:79–85
126. Vallarta-Ast N, Kreuger D, Suttie J, Binkley N. 2008. Vitamin K treatment for one year does not alter femure geometry in postmenopausal women. *J. Bone Miner. Res.* 23:S217
127. van Summeren MJ, van Coeverden SC, Schurgers LJ, Braam LA, Noirt F, et al. 2008. Vitamin K status is associated with childhood bone mineral content. *Br. J. Nutr.* 100:852–58
128. Vergnaud P, Garnero P, Meunier PJ, Breart G, Kamihagi K, Delmas PD. 1997. Undercarboxylated osteocalcin measured with a specific immunoassay predicts hip fracture in elderly women: the EPIDOS Study. *J. Clin. Endocrinol. Metab.* 82:719–24
129. Vermeer C, Jie KS, Knapen MH. 1995. Role of vitamin K in bone metabolism. *Annu. Rev. Nutr.* 15:1–22
130. Viegas CS, Simes DC, Laize V, Williamson MK, Price PA, Cancela ML. 2008. GLA-rich protein (GRP): a new vitamin K-dependent protein identified from sturgeon cartilage and highly conserved in vertebrates. *J. Biol. Chem.* 283:36655–64
131. Villines TC, Hatzigeorgiou C, Feuerstein IM, O'Malley PG, Taylor AJ. 2005. Vitamin K1 intake and coronary calcification. *Coron. Artery Dis.* 16:199–203
132. Wadelius M, Chen LY, Downes K, Ghori J, Hunt S, et al. 2005. Common VKORC1 and GGCX polymorphisms associated with warfarin dose. *Pharmacogenomics J.* 5:262–70
133. Wang Y, Zhang W, Zhang Y, Yang Y, Sun L, et al. 2006. VKORC1 haplotypes are associated with arterial vascular diseases (stroke, coronary heart disease, and aortic dissection). *Circulation* 113:1615–21
134. Watzka M, Nebel A, El Mokhtari NE, Ivandic B, Muller J, et al. 2007. Functional promoter polymorphism in the VKORC1 gene is no major genetic determinant for coronary heart disease in Northern Germans. *Thromb. Haemost.* 97:998–1002
135. Woo C, Chang LL, Ewing SK, Bauer DC. 2008. Single-point assessment of warfarin use and risk of osteoporosis in elderly men. *J. Am. Geriatr. Soc.* 56:1171–76
136. Yaegashi Y, Onoda T, Tanno K, Kuribayashi T, Sakata K, Orimo H. 2008. Association of hip fracture incidence and intake of calcium, magnesium, vitamin D, and vitamin K. *Eur. J. Epidemiol.* 23:219–25
137. Yan L, Zhou B, Greenberg D, Wang L, Nigdikar S, et al. 2004. Vitamin K status of older individuals in northern China is superior to that of older individuals in the UK. *Br. J. Nutr.* 92:939–45

138. Yasui T, Uemura H, Tomita J, Miyatani Y, Yamada M, et al. 2007. Change in serum undercarboxylated osteocalcin concentration in bilaterally oophorectomized women. *Maturitas* 56:288–96
139. Yasui T, Uemura H, Tomita J, Umino Y, Yamada M, et al. 2006. Different effects of oral conjugated equine estrogens and transdermal estrogen on undercarboxylated osteocalcin concentration in postmenopausal women. *Menopause* 13:651–59
140. Yoshida M, Booth SL, Meigs JB, Saltzman E, Jacques PF. 2008. Phylloquinone intake, insulin sensitivity, and glycemic status in men and women. *Am. J. Clin. Nutr.* 88:210–15
141. Yoshida M, Jacques PF, Meigs JB, Saltzman E, Shea MK, et al. 2008. Effect of vitamin K supplementation on insulin resistance in older men and women. *Diabetes Care* 31:2092–96
142. Zajickova K, Zofkova I, Hill M, Horinek A, Novakova A. 2003. Apolipoprotein E 4 allele is associated with low bone density in postmenopausal women. *J. Endocrinol. Invest.* 26:312–15

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Errata

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