REVIEW ARTICLE

# Vitamin K and the Prevention of Fractures

## *Systematic Review and Meta-analysis of Randomized Controlled Trials*

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**Background:** Observational and some experimental data suggest that low intake of vitamin K may be associated with an increased risk of fracture.

**Objective:** To assess whether oral vitamin K (phytonadione and menaquinone) supplementation can reduce bone loss and prevent fractures.

**Data Sources:** The search included the following electronic databases: MEDLINE (1966 to June 2005), EMBASE (1980 to June 2005), the Cochrane Library (issue 2, 2005), the ISI Web of Science (1945 to June 2005), the National Research Register (inception to the present), Current Controlled Trials, and the Medical Research Council Research Register.

**Study Selection:** Randomized controlled trials that gave adult participants oral phytonadione and menaquinone supplements for longer than 6 months were included in this review.

**Data Extraction:** Four authors extracted data on changes in bone density and type of fracture. All articles were double screened and double data extracted.

**Data Synthesis:** Thirteen trials were identified with data on bone loss, and 7 reported fracture data. All studies but 1 showed an advantage of phytonadione and menaquinone in reducing bone loss. All 7 trials that reported fracture effects were Japanese and used menaquinone. Pooling the 7 trials with fracture data in a meta-analysis, we found an odds ratio (OR) favoring menaquinone of 0.40 (95% confidence interval [CI], 0.25-0.65) for vertebral fractures, an OR of 0.23 (95% CI, 0.12-0.47) for hip fractures, and an OR of 0.19 (95% CI, 0.11-0.35) for all nonvertebral fractures.

**Conclusions:** This systematic review suggests that supplementation with phytonadione and menaquinone-4 reduces bone loss. In the case of the latter, there is a strong effect on incident fractures among Japanese patients.

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FRAGILITY FRACTURES ARE AN important source of morbidity, mortality, and cost to society. Several pharmaceutical treatments have been shown to prevent vertebral and nonvertebral fractures in large randomized controlled trials (RCTs). For example, bisphosphonate therapy, parathyroid hormone, and strontium ranelate were demonstrated to be effective in reducing fractures.[1-4] In contrast, the evidence for supplementation with vitamin D (cholecalciferol) with or without calcium is equivocal. Although a large trial in France has shown a benefit of combined treatment among female nursing-home residents[5] and a trial of cholecalciferol alone among retired physicians in England noted a modest effect,[6] the more recent series of 3 large RCTs in England and the Women's Health Initiative in the United States found no statistically significant benefit.[7-10] The absence of a protective effect of cholecalciferol is particularly disappointing because this intervention is relatively inexpensive and has been widely used in the belief that it prevents fractures. Alternatively, evidence is increasing that suboptimal vitamin K status is associated with increased risk of fracture.[11,12] Low vitamin K consumption or impaired vitamin K status is associated with a higher risk of hip fracture among older women[13,14] and men,[14] lower bone mass in older women[15,16] and men,[16] and increased bone turnover in girls.[17] To assess whether phytonadione and menaquinone supplementation may have a role in the prevention of bone loss and fractures, we undertook a systematic review and meta-analysis. Vitamin K comprises a family of different molecular forms, a single form synthesized by plants (vitamin $K_1$), and multiple forms synthesized by bacteria (vitamins $K_2$). The only synthetic forms of vitamin K available for supplementation are phytonadione and one member of the vitamin $K_2$ se-

ries, menaquinone-4. In this article, the use of the term *vitamin* $K_2$ in trials always denotes menaquinone-4.

## METHODS

We searched the following electronic databases for RCTs: MEDLINE (1966 to June 2005), EMBASE (1980 to June 2005), the Cochrane Library (issue 2, 2005), the ISI Web of Science (1945 to June 2005), the National Research Register (inception to the present; http://www.update-software.com/National/), Current Controlled Trials (http://www.controlled-trials.com/), and the Medical Research Council Research Register (http://fundedresearch.cos.com/MRC/). We used the following keywords: *vitamin* $K_1$, *vitamin* $K_2$, *vitamin* $K_3$, *phylloquinone, Konakion, phytonadione, menadione, menaquinone, phytomenadione*, and *Mephyton*. We followed the Quality of Reporting of Meta-analyses statement when conducting our review.[18]

Any dose of oral phytonadione or menaquinone-4 in adults 18 years or older was permissible. Control treatments could include cholecalciferol with or without calcium or calcium alone, as well as placebo or no treatment. Outcomes were fractures of any type or changes in bone density. We compared the incidence of all fractures, vertebral fractures, and hip fractures between the supplemented and control groups. For any study we identified that did not report fractures, we e-mailed the corresponding author to ascertain whether any fractures had occurred within the study population. We excluded studies that had treated patients for less than 6 months on the basis that it was unlikely that an effect on fractures and bone mass would be seen in such a relatively short time. We also excluded 2 studies in Japanese patients, which we could not translate.

One of the authors (S.C.) developed the search strategy. Four authors (S.C., J.A., S.L.N., and D.J.T.) independently screened relevant abstracts, and potentially relevant articles were retrieved if at least 1 author thought that it should be included in the review. Identified articles were read by all the authors, and any disagreements at this stage were resolved by discussion.

### HETEROGENEITY

Between-study heterogeneity was assessed using the $I^2$ statistic.[19] The $I^2$ statistic has several advantages over other measures of heterogeneity (such as $\chi^2$), including greater statistical power to detect clinical heterogeneity when fewer studies are available. As a guide, $I^2$ values of 25% may be considered low, 50% moderate, and 75% high.

For homogeneous studies, we conducted a fixed-effects meta-analysis. Since the event rates for fractures were low and there were zero event rates in some studies, we added 0.5 to all cells in line with best practice within the Cochrane collaboration handbook.[20] The metric of choice was the Peto odds ratio (OR), which was empirically shown to be the most robust to zero event rates.[21] We also pooled absolute between-group differences in terms of the rate of fractures.

Studies that appeared to be homogeneous in terms of their clinical population were pooled in a meta-analysis. Studies that reported fracture data all involved older men and women at risk of fracture. Bone mineral density (BMD) studies were more heterogeneous. Therefore, we decided to pool only relatively clinically homogeneous studies; in practice this meant that only studies undertaken among older people at risk for fracture were combined. There was still some clinical heterogeneity, however. When there was obvious clinical heterogeneity among study participants, the robustness of our overall pooled result was established by the impact of inclusion and exclusion of these studies on our pooled effect size.

### QUALITY OF STUDIES

We looked for 2 measures of study quality: allocation concealment and attrition. Lack of adequate concealed allocation in particular has been shown to be strongly associated with study effect sizes.[22,23]

### PUBLICATION BIAS

To investigate the possibility of publication and small-study bias, we constructed funnel plots of effect size vs study precision and used the Egger weighted regression test to test for asymmetry.[24] All analyses were conducted with Stata statistical software, version 8 (StataCorp, College Station, Tex), with the user-written commands *metan* and *metabias*.

## RESULTS

**Figure 1** shows the number of studies we identified, excluded, and retrieved. Thirteen articles were included in the systematic review. All articles had data on bone loss, whereas 7 articles also recorded fracture data. We wrote to 4 authors and received replies from 2, who did not have fracture data available. **Table 1** gives the characteristics of the included studies. Most trials were conducted in Japan among postmenopausal women. All but 2 trials used menaquinone-4, with the remainder using phytonadione supplements. **Table 2** gives the sample sizes and outcomes of the trials. All studies but 1 showed an advantage of phytonadione and menaquinone-4 in terms of BMD. The exception was a German study among premenopausal athletic women given phytonadione supplements. All 7 studies that had fracture outcomes showed a benefit of menaquinone-4 supplements. We have combined these studies into 3 separate meta-analyses, looking at their effects on vertebral, hip, and all nonvertebra fractures (**Figure 2**). Menaquinone-4 supplementation was associated with a consistent

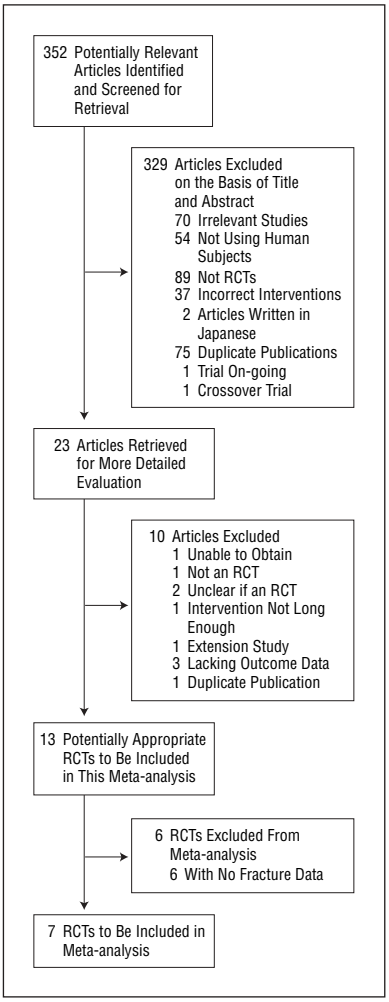


**Figure 1.** The Quality of Reporting of Meta-analyses statement flow diagram for vitamin K analysis. RCT indicates randomized controlled trial.

**Table 1. Description of Trials**

| Source | Trial Length, mo | Study Population | Age, Mean (Range), y | Daily Dose of Phytonadione or Menaquinone | Outcome Measures |
|---|---|---|---|---|---|
| Braam et al,[25] 2003 | 36 | Postmenopausal Dutch women with a BMD >2.5 SDs below the reference population | 55 (50-60) | 1 mg of phytonadione; both groups received cholecalciferol, calcium, zinc, and magnesium | BMD |
| Ishida and Kawai,[26] 2004 | 24 | Osteoporotic postmenopausal Japanese women | 70 (50-75) | 45 mg of menaquinone-4 | BMD and fractures |
| Iwamoto et al,[27] 1999 | 12 | Healthy postmenopausal Japanese women | 55 | 45 mg of menaquinone-4; half of controls received cholecalciferol | BMD |
| Iwamoto et al,[28] 2000 | 24 | Postmenopausal Japanese women with osteoporosis; baseline daily calcium intake of 505 mg | 64 | 45 mg of menaquinone-4; factorial trial, with half of controls and intervention group receiving cholecalciferol | BMD |
| Iwamoto et al,[29] 2001 | 24 | Postmenopausal Japanese women with osteoporosis; baseline daily calcium intake of 498 mg | 65 | 45 mg of menaquinone-4; all groups received calcium and cholecalciferol | BMD and fractures |
| Braam et al,[30] 2003 | 24 | Premenopausal German endurance athletes; baseline daily calcium intake of 781 mg | 29 (15-50) | 10 mg of phytonadione | BMD |
| Nishiguchi et al,[31] 2001 | 24 | Japanese women with biliary cirrhosis | 56 | 45 mg of menaquinone-4 | BMD |
| Sasaki et al,[32] 2005 | 12 | Japanese patients using oral steroids for kidney disease | 40 | 15 mg of menaquinone-4 | BMD and fractures |
| Sato et al,[33] 1998 | 12 | Male and female Japanese patients with stroke | 66 | 45 mg of menaquinone-4 | BMD and fractures |
| Sato et al,[34] 2002 | 12 | Elderly female Japanese patients with Parkinson disease; baseline daily cholecalciferol intake of 143 IU | 72 | 45 mg of menaquinone-4 | BMD and fractures |
| Sato et al,[35] 2005 | 24 | Elderly female Japanese patients with Alzheimer disease; baseline daily dietary intake of cholecalciferol, calcium, and phytonadione of 81 IU, 854 mg, and 103 µg, respectively | 78 | 45 mg of menaquinone-4; calcium and ergocalciferol given to both groups | BMD and fractures |
| Shiraki et al,[36] 2000 | 24 | Female Japanese patients with osteoporosis | 68 | 45 mg of menaquinone-4; both groups received calcium | BMD and fractures |
| Somekawa et al,[37] 1999 | 6 | Female premenopausal patients with endometriosis | 46 | 45 mg of menaquinone-4; factorial study, with half of intervention and control groups also receiving calcitriol | BMD |

Abbreviation: BMD, bone mineral density.

reduction in all fracture types ($OR_{hip}=0.23$; 95% confidence interval [CI], 0.12-0.47; $OR_{vertebral}=0.40$; 95% CI, 0.25-0.65; $OR_{all\ nonvertebral}=0.19$; 95% CI, 0.11-0.35). There was no statistical evidence of heterogeneity among the fracture studies ($I^2_{vertebral}=0\%$; $I^2_{hip}=0\%$; $I^2_{all\ nonvertebral}=0\%$).

When we assessed absolute differences in fracture rates, a significantly reduced rate was found at all fracture sites, with hip fractures reduced by 6% (95% CI, 3%-9%), vertebral fractures reduced by 13% (95% CI, 6%-21%), and all nonvertebral fractures by 9% (95% CI, 6%-12%) (**Figure 3**). However, variation in baseline risk among studies produced substantial between-study heterogeneity for the 2 nonvertebral fracture comparisons ($I^2_{vertebral}=0\%$, $I^2_{hip}=81\%$, and $I^2_{all\ nonvertebral}=84\%$).

In 3 trials,[33-35] BMD was measured at the metacarpals, and data were sufficient to calculate standardized effect sizes. All the studies showed a benefit of phytonadione and menaquinone-4 on BMD, with a standardized mean difference favoring the supplementation of 0.27 (95% CI, 0.03-0.50; $P=.02$). Because 1 of the centers provided most of the data for hip fractures and this center had included populations with a very high fracture risk,[33-35] we undertook a sensitivity analysis excluding data from this center. The OR for hip factures for the remaining 2 studies when combined was 0.30 (still a large effect); however, this finding was no longer statistically significant (95% CI, 0.05-1.74; $P=.18$) (**Figure 4**). The odds of vertebral and all nonvertebral fractures were both still statistically significant ($OR_{vertebral}=0.40$; 95% CI, 0.25-0.65; $OR_{nonvertebral}=0.24$; 95% CI, 0.07-0.84; $P<.001$ for both).

## PUBLICATION BIAS

When we checked for publication bias, no statistically significant evidence of bias was found, although with no more than 5 studies the

**Table 2. Trial Outcomes**

| Source | No. of Randomized Patients (Attrition Rate, %) | | No. of Fractures/ Total No. of Patients* | | Difference in BMD, % (95% CI) |
|---|---|---|---|---|---|
| | Control | Intervention | Control | Intervention | |
| Braam et al,[25] 2003 | 61 (13) | 66 (12) | NA | NA | 1.3 (hip) (0.10 to 3.41); 0.9 (spine) (–0.70 to 2.23) |
| Ishida and Kawai,[26] 2004 | 66 (6) | 68 (3) | 17/66 (spine); 1/66 (hip); 3/66 (nonspine) | 9/66 (spine); 0/66 (hip); 0/66 (nonspine) | 1.4 (radius) |
| Iwamoto et al,[27] 1999 | 35 (0) | 17 (0) | NA | NA | 2.0 (spine) |
| Iwamoto et al,[28] 2000 | 49 (0) | 43 (0) | NA | NA | 1.34 (spine) |
| Iwamoto et al,[29] 2001 | 24 (0) | 23 (0) | 6/24 (spine) | 2/23 (spine) | 1.6 (radius) |
| Braam et al,[30] 2003 | ≥42 (30†) | ≥37 (30†) | NA | NA | –0.1 (spine) –1.3 (hip) |
| Nishiguchi et al,[31] 2001 | 15 (1) | 15 (2) | NA | NA | 3.8 (spine) |
| Sasaki et al,[32] 2005 | 10 (0) | 10 (0) | 1/10 (spine) | 0/10 (spine) | Not possible to calculate |
| Sato et al,[33] 1998 | 60 (6) | 60 (4) | 1/54 (hip) | 0/54 (hip) | 1.8 (metacarpals) |
| Sato et al,[34] 2002 | 60 (4) | 60 (6) | 8/56 (hip); 10/56 (nonspine) | 1/54 (hip); 1/54 (nonspine) | 5.2 (metacarpals) |
| Sato et al,[35] 2005 | 100 (12) | 100 (10) | 15/88 (hip); 22/88 (nonspine) | 2/90 (hip) 3/90 (nonspine) | 7.5 (metacarpals) |
| Shiraki et al,[36] 2000 | 121 (22) | 120 (29) | 30/121 (spine); 2/121 (hip); 5/121 (nonspine) | 13/120 (spine); 0/120 (hip); 1/120 (nonspine) | 2.8 (spine) |
| Somekawa et al,[37] 1999 | 52 (0) | 52 (0) | NA | NA | 1.1 (spine) |

Abbreviations: BMD, bone mineral density; CI, confidence interval; NA, not applicable.
*Indicates number of patients who underwent follow-up for outcome.
†This is an estimated attrition rate.

power of bias tests remains low to detect bias and funnel plot asymmetry (Egger test: $P_{hip}$=.09; $P_{vertebral}$=.61; $P_{nonvertebral}$=.08). Visual inspection of funnel plots showed no evidence of bias (data not shown).[24] In terms of reporting quality, only 2 studies[25,30] reported that they had used a method of concealing the allocation mechanism. Attrition, another source of potential bias, ranged from 0% to as high as 30%.

## ADVERSE EVENTS

No study reported any serious adverse events associated with vitamin K. However, minor gastrointestinal problems were reported by some authors.

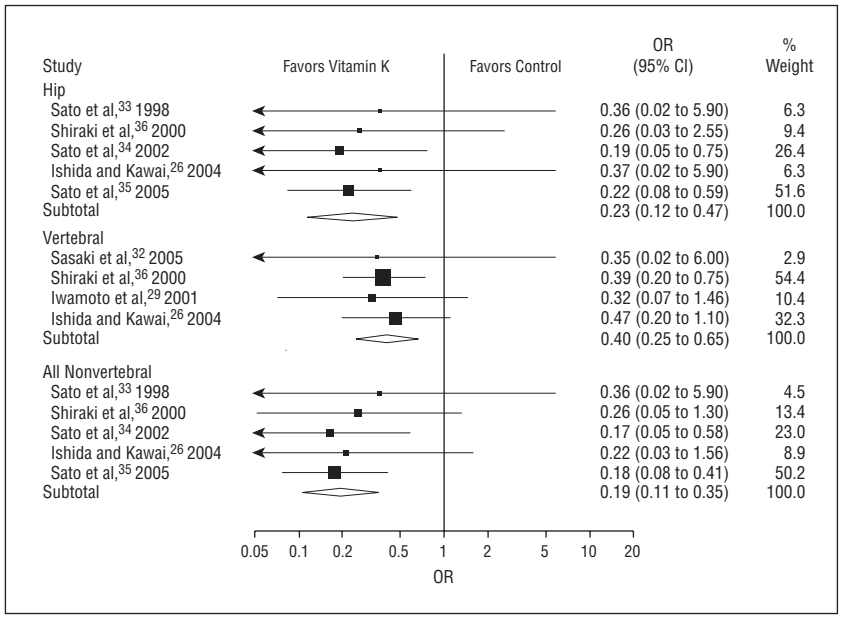


**Figure 2.** Meta-analysis of treatment effects on fractures. Peto odds ratios (ORs) with 95% confidence intervals (CIs).

## COMMENT

In this systematic review and meta-analysis, we have shown that supplementation with phytonadione and menaquinone, particularly menaquinone-4, is associated with increased BMD and reduced fracture incidence. The reduction in fracture incidence is particularly striking, with an approximate 80% reduction in hip fractures. Our findings should be treated cautiously, however, because the studies were not primarily designed to show a fracture effect. Another reason for caution is that the effect on fractures is much larger than with other treatments, such as bisphosphonates. Therefore, it is possible that such a large effect is due to chance or some other unidentified reason. In addition, all the studies with fracture outcomes were undertaken in Japan, and there may be dietary differences that could mean that these findings are not applicable elsewhere. The quality of many of the trials was not high. Few trials, none with fracture outcomes, reported how the randomization process was con-

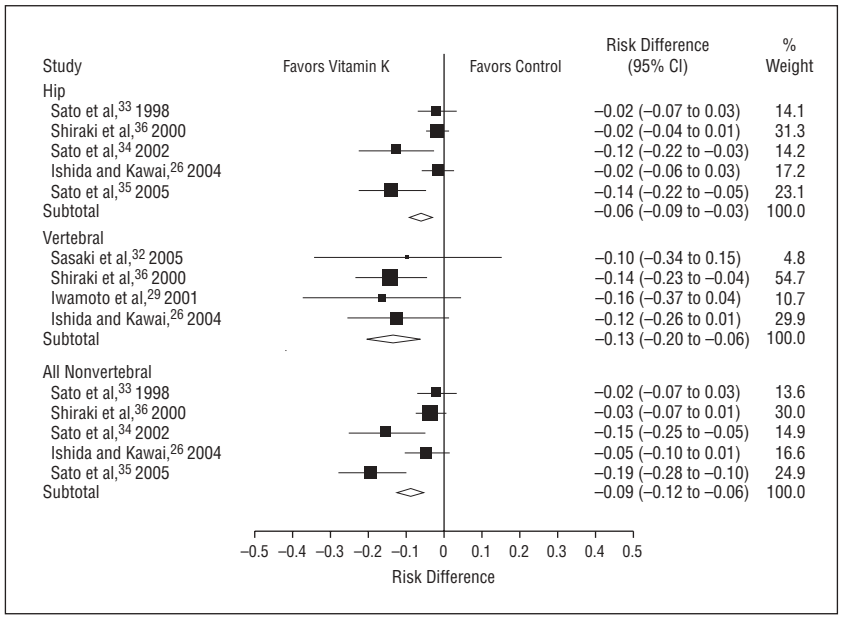


**Figure 3.** Meta-analysis of treatment effects on hip fractures. Absolute risk difference with 95% confidence intervals (CIs).

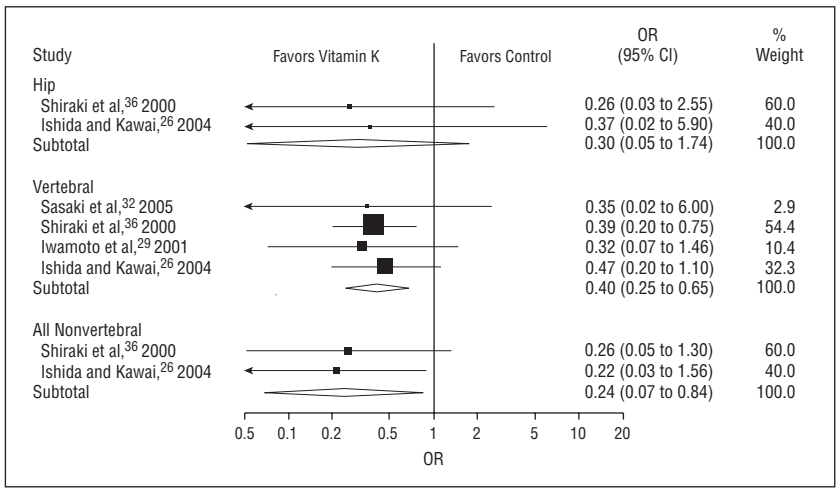


**Figure 4.** Meta-analysis of treatment effects with Sato et al[33-35] omitted. Peto odds ratio (OR) with 95% confidence intervals (CI).

cealed from those recruiting the participants, which could be a source of bias.[22,23] Attrition was also high in some trials; for instance, the trial with the largest weight in the meta-analysis of vertebral factures had an attrition rate of approximately 24%.[36] Other reasons for caution include publication bias and heterogeneity of the clinical populations. Publication bias can be detected using graphic techniques such as funnel and quantile normal plots. However, in this instance the number of studies of fractures is too small for such approaches to reliably detect publication bias (the minimum number of studies usually recommended for funnel plots is 10).[24] Although all the studies in the fracture meta-analysis were homogeneous in terms of the dose and type of phytonadione or menaquinone, they were different in terms of cosupplementation and their population. For example, the nonspine fracture rates of the control groups ranged from 4.1% to 25%, suggesting different fracture risk groups. Furthermore, the number of events, particularly the numbers of hip fractures, is small, which increases the element of chance, explaining our results. Finally, the few studies that reported baseline vitamin D and calcium status suggest that these populations tended to have low intakes of both (Table 1). When reported in the Japanese vitamin $K_2$ trials, patients with secondary osteoporosis (eg, those with stroke, Alzheimer disease, or Parkinson disease) had a lower vitamin K status at baseline than either the community-recruited controls in the same studies or patients with involutional osteoporosis in different studies.

There are at least 3 vitamin K–dependent proteins present in bone and cartilage, namely, osteocalcin, matrix γ-carboxyglutamic acid protein, and protein S.[11,12] Specifically, osteocalcin is the most abundant noncollagenous protein in bone and a recognized marker of bone formation. Exogenous vitamin K is required as an essential cofactor for an enzymatic carboxylation, whereby 3-glutamic acid residues in osteocalcin are converted to γ-carboxyglutamic acid residues. Without this modification, osteocalcin lacks structural integrity and the ability to bind to the hydroxyapatite mineral.[38] Evidence demonstrates that the vitamin K requirement for carboxylation of osteocalcin is not met by usual dietary intakes but that carboxylation readily responds to phytonadione or menaquinone supplementation.[12] Evidence supports a link between vitamin K insufficiency and osteoporosis, with low circulating vitamin K concentrations in osteoporotic patients,[39] and the finding that circulating Glu-osteocalcin is an independent risk predictor of bone fractures.[40,41]

Although the major dietary source of vitamin K is the plant form phytonadione (vitamin $K_1$), most trials to date have been performed with the vitamin $K_2$ series called menaquinone-4. Menaquinone-4 is unusual because it is not a common bacterial form and is able to be synthesized in the human body from dietary vitamin $K_1$.[42] Whether menaquinone-4 is more effective as an antiosteoporotic agent than phytonadione remains to be established, but both forms can be used for carboxylation. There is some intriguing evidence that menaquinone-4 may possess other antiosteoporotic properties that are specifically associated with the geranylgeranyl side chain of this $K_2$ vitamin.[12]

From a clinical perspective, the results of this review suggest that patients at risk for fracture should be encouraged to consume a diet rich in vitamin K, which is chiefly obtained from green leafy vegetables and certain vegetable oils. Routine supplementation, however, is not justified until these results are confirmed in a large pragmatic RCT with fractures as the main outcome.

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