Vitamin K and the Prevention of Fractures

Systematic Review and Meta-analysis of Randomized Controlled Trials

Sarah Cockayne, MSc; Joy Adamson, PhD; Susan Lanham-New, PhD; Martin J. Shearer, PhD, MRCPath; Simon Gilbody, DPhil; David J. Torgerson, PhD

**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. 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, we undertook a sensitivity analysis excluding data from this center. The OR for hip fractures 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).

**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. 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 and a trial of cholecalciferol alone among retired physicians in England noted a modest effect, 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. 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. Low vitamin K consumption or impaired vitamin K status is associated with a higher risk of hip fracture among older women and men, lower bone mass in older women and men, and increased bone turnover in girls. 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 K1), and...
multiple forms synthesized by bacteria (vitamins K2). The only synthetic forms of vitamin K available for supplementation are phytonadione and one member of the vitamin K2 series, menaquinone-4. In this article, the use of the term vitamin K2 in trials always denotes menaquinone-4.

**METHODS**

We searched the following electronic databases for RCTs: MEDLINE (1966 to June 2003), EMBASE (1980 to June 2003), the Cochrane Library (issue 2, 2003), the ISI Web of Science (1945 to June 2003), 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). We used the following keywords: "vitamin K", vitamin K2, vitamin K3, 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 I² statistic.19 The I² statistic has several advantages over other measures of heterogeneity (such as χ²), including greater statistical power to detect clinical heterogeneity when fewer studies are available. As a guide, I² 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 non-vertebral fractures.

352 Potentially Relevant Articles Identified and Screened for Retrieval

329 Articles Excluded on the Basis of Title and Abstract

70 Irrelevant Studies

54 Not Using Human Subjects

89 Not RCTs

37 Incorrect Interventions

2 Articles Written in Japanese

75 Duplicate Publications

1 Trial On-going

1 Crossover Trial

23 Articles Retrieved for More Detailed Evaluation

10 Articles Excluded

1 Unable to Obtain

1 Not an RCT

1 Unclear if an RCT

1 Intervention Not Long Enough

1 Expansion Study

3 Lacking Outcome Data

1 Duplicate Publication

13 Potentially Appropriate RCTs to Be Included in This Meta-analysis

8 RCTs Excluded From Meta-analysis

6 With No Fracture Data

7 RCTs to Be Included in Meta-analysis

Table 1

Table 2

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vertebra fractures (Figure 2). Menaquinone-4 supplementation was associated with a consistent reduction in all fracture types (OR_hip = 0.23; 95% confidence interval [CI], 0.12-0.47; OR_nonvertebral = 0.24; 95% CI, 0.19-0.35). There was no statistical evidence of heterogeneity among the fracture studies (I² = 0%; OR_hip = 0%; OR_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 (I² = 62%; OR_hip = 81%; and OR_nonvertebral = 84%).

In 3 trials, 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, we undertook a sensitivity analysis excluding data from this center. The OR for hip fractures 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_nonvertebral = 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
power of bias tests remains low to detect bias and funnel plot asymmetry (Egger test: $P_{\text{hip}}=.09$; $P_{\text{vertebral}}=.61$; $P_{\text{nonvertebral}}=.08$). Visual inspection of funnel plots showed no evidence of bias (data not shown).24 In terms of reporting quality, only 2 studies25,30 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.

Table 2. Trial Outcomes

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Randomized Patients</th>
<th>No. of Fractures/Total No. of Patients*</th>
<th>Difference in BMD, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braam et al,29 2003</td>
<td>61 (13)</td>
<td>66 (12)</td>
<td>1.3 (hip) (0.10 to 3.41); 0.9 (spine) (−0.70 to 2.23)</td>
</tr>
<tr>
<td>Ishida and Kawai,26 2004</td>
<td>66 (6)</td>
<td>68 (3)</td>
<td>17/66 (spine); 1/66 (hip); 3/66 (nonspine)</td>
</tr>
<tr>
<td>Iwamoto et al,27 1999</td>
<td>36 (0)</td>
<td>39 (0)</td>
<td>NA NA</td>
</tr>
<tr>
<td>Iwamoto et al,28 2000</td>
<td>49 (0)</td>
<td>48 (0)</td>
<td>NA NA</td>
</tr>
<tr>
<td>Iwamoto et al,29 2001</td>
<td>24 (0)</td>
<td>23 (0)</td>
<td>6/24 (spine) 2/23 (spine)</td>
</tr>
<tr>
<td>Braam et al,30 2003</td>
<td>≥42 (30†)</td>
<td>≤37 (30†)</td>
<td>NA NA</td>
</tr>
<tr>
<td>Nishiguchi et al,31 2001</td>
<td>15 (1)</td>
<td>15 (2)</td>
<td>1.3 (radius)</td>
</tr>
<tr>
<td>Sasaki et al,32 2005</td>
<td>10 (0)</td>
<td>10 (0)</td>
<td>1/10 (spine) 0/10 (spine)</td>
</tr>
<tr>
<td>Sato et al,33 1998</td>
<td>60 (6)</td>
<td>60 (6)</td>
<td>1/54 (hip) 1/54 (nonspine)</td>
</tr>
<tr>
<td>Sato et al,34 2002</td>
<td>60 (4)</td>
<td>60 (6)</td>
<td>8/56 (hip); 1/56 (nonspine)</td>
</tr>
<tr>
<td>Sato et al,35 2005</td>
<td>100 (12)</td>
<td>100 (10)</td>
<td>10/88 (hip); 22/88 (nonspine)</td>
</tr>
<tr>
<td>Shiraki et al,36 2000</td>
<td>121 (22)</td>
<td>120 (29)</td>
<td>30/121 (spine); 2/121 (hip); 5/121 (nonspine)</td>
</tr>
<tr>
<td>Sato et al,37 1999</td>
<td>50 (2)</td>
<td>52 (0)</td>
<td>NA NA</td>
</tr>
</tbody>
</table>

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.

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 conducted.

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 conducted.
Publication bias and heterogeneity of clinical populations. Publication bias can be detected using graphic techniques such as funnel and quantile normal plots. How-

ter, in this instance the number of studies is too small for such approaches to reliably detect publication bias (the minimum number of studies usually recom-
mended 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 phyto-

nadiene 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. Fi-

dinally, 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 K2 trials, patients with secondary osteoporosis (eg, those with stroke, Alzheimer disease, or Parkinson disease) had a lower vita-

min K status at baseline than either the community-recruited controls in the same studies or patients with involu-

tional osteoporosis in different studies.

There are at least 3 vitamin K–de-

pendent proteins present in bone and cartilage, namely, osteocalcin, matrix γ-carboxyglutamic acid pro-

tein, and protein S.11,12 Specifically, osteocalcin is the most abundant noncollagenous protein in bone and a recognized marker of bone forma-

tion. Exogenous vitamin K is re-

quired as an essential cofactor for an enzy-

matically active vitamin K–dependent carboxylation, whereby γ-carboxyglu-

tamic acid residues in osteocalcin are converted to γ-carboxy-

glutamic acid residues. Without this modification, osteocalcin lacks struc-

tural integrity and the ability to bind to the hydroxyapatite mineral.38 Evi-

dence demonstrates that the vita-

min K requirement for carboxyl-

ation of osteocalcin is not met by usual dietary intakes but that carboxylation readily responds to phyto-

nadiene or menaquinone supple-

mentation.12 Evidence supports a link between vitamin K insuffi-

ciency and osteoporosis, with low circulating vitamin K concentra-

tions in osteoporotic patients,46 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 K1), most trials to date have been performed with the vitamin K2 series called menaquinone-4. Menaquinone-4 is un-

usual because it is not a com-

mon bacterial form and is able to be synthe-

sized in the human body from dietary vitamin K1.42 Whether mena-

quinone-4 is more effective as an an-

tiosteoporotic agent than phytom-

dione remains to be established, but both forms can be used for carboxyla-

tion. There is some intriguing evidence that menaquinone-4 may possess other antiosteoporotic properties that are specifically associated with the geranylgeranyl side chain of this K2 vitamin.12

![Figure 3. Meta-analysis of treatment effects on hip fractures. Absolute risk difference with 95% confidence intervals (CIs).](image1)

![Figure 4. Meta-analysis of treatment effects with Sato et al.33,35 omitted. Peto odds ratio (OR) with 95% confidence intervals (CI).](image2)
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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Correspondence: David J. Torger-son, PhD, Department of Health Studies, University of York, Area 4, York Y010 5DD, England (dj6@york.ac.uk).
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REFERENCES