Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials
Cockayne S, Adamson J, Lanham-New S, Shearer M J, Gilbody S, Torgerson D J

CRD summary
This review investigated the effects of oral vitamin K supplements on bone mineral density and fractures. The authors concluded that supplementation may reduce bone loss and that an effect on fractures has been shown in Japanese patients. The cautious conclusions reflect the limitations of the available evidence and appear appropriate.

Authors' objectives
To determine whether oral vitamin K supplements can reduce bone loss and prevent fractures.

Searching
MEDLINE (1966 to June 2005), EMBASE (1980 to June 2005), the Cochrane Library (Issue 2, 2005), ISI Web of Science (1945 to June 2005), National Research Register, Current Controlled Trials and the MRC Funded Research database were searched; the search terms were reported.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies of synthetic vitamin K supplements (phytonadione and menaquinone-4) given at any dose for at least 6 months were eligible for inclusion. The daily doses used in the included studies were 1 or 10 mg of phytonadione and 15 or 45 mg of menaquinone-4. In some included studies one or both groups received other supplements such as calcium or cholecalciferol.

Participants included in the review
Studies of adults aged 18 years or older were eligible for inclusion. The participants in the included studies were postmenopausal women with or without osteoporosis, endurance athletes, and people with various medical conditions such as biliary cirrhosis, kidney disease, stroke, Parkinson's disease, Alzheimer's disease and endometriosis. The mean age of the participants ranged from 29 to 72 years. Most of the participants were Japanese.

Outcomes assessed in the review
The outcomes of interest were fractures of any kind and changes in bone mineral density (BMD). The studies had to report bone loss data to be included in the review.

How were decisions on the relevance of primary studies made?
Four authors independently screened papers for inclusion in the review. Any disagreements were resolved by discussion.

Assessment of study quality
The authors assessed the included studies for adequacy of allocation concealment and attrition rate. The authors did not state how the validity assessment was performed.

Data extraction
The data extraction was performed in duplicate. Data on the numbers of all fractures, vertebral fractures and hip
fractures in the intervention and control groups were used to calculate odds ratios (ORs) and absolute risk differences, both with associated 95% confidence intervals (CIs). Data on differences in BMD between groups and adverse events were also extracted. For studies that did not report fractures, corresponding authors were contacted for fracture data.

Methods of synthesis
How were the studies combined?
Studies that appeared homogeneous were pooled by meta-analysis using a fixed-effect model for hip fractures, vertebral and nonvertebral fractures. Pooled Peto ORs and risk differences were calculated for fracture rates, and a standardised mean difference (SMD) for changes in BMD. Publication bias was investigated using funnel plots; the Egger weighted regression test was used to test for asymmetry.

How were differences between studies investigated?
Heterogeneity between the studies was assessed using the I-squared statistic. A sensitivity analysis was undertaken to assess the effects of excluding data from one centre that had included populations with a particularly high fracture risk.

Results of the review
Thirteen RCTs (n=1,366) were included in the review.

Only 2 studies reported using a method of allocation concealment. Attrition rates ranged from 0 to 30%. No evidence of significant publication bias was found.

Fractures (7 RCTs).
Vitamin K supplementation significantly reduced hip (OR 0.23, 95% CI: 0.12, 0.47), vertebral (OR 0.40, 95% CI: 0.25, 0.65) and all nonvertebral (OR 0.19, 95% CI: 0.11, 0.35) fractures. Pooled absolute risk differences also showed a significant positive effect of supplementation. When the data from the high-risk populations were removed, the effects on hip fracture were not statistically significant, but those on vertebral (4 RCTs; OR 0.40, 95% CI: 0.25, 0.65) and all nonvertebral fractures (2 RCTs; OR 0.24, 95% CI: 0.07, 0.84) were significant. There was no evidence of heterogeneity among studies for the OR, but there was heterogeneity for risk differences in nonvertebral fractures.

BMD.
All except one of the included studies showed an advantage of vitamin K supplementation in terms of BMD. Pooled data from 3 studies of BMD measured at the metacarpals showed a significant positive effect of supplementation (SMD 0.27, 95% CI: 0.03, 0.50).

Adverse events.
No study reported any serious adverse events associated with vitamin K supplementation.

Authors’ conclusions
Supplementation with phytonadione and menaquinone-4 may reduce bone loss, while the latter reduced fractures in Japanese patients.

CRD commentary
This review addressed a well-defined question and the inclusion criteria were clear. The authors searched a range of relevant sources. It was unclear whether any language restrictions were imposed, although two potentially relevant studies published in Japanese were excluded, which could have affected the results of the review. Publication bias was assessed using standard methods and no indication of bias was found. The study selection and data extraction were performed by two or more independent reviewers, thereby reducing the risk of bias and errors during the review process. Study quality was assessed in terms of two features known to be associated with risk of bias.
Relevant details of the included primary studies were presented. The studies were combined by meta-analysis, with clinical and statistical heterogeneity being assessed. The generalisability of the results is unclear as the majority of included studies were conducted in Japanese samples with osteoporosis or other risk factors. The authors' conclusions reflect the limitations of the evidence and appear appropriately cautious.

**Implications of the review for practice and research**
Practice: The authors stated that patients at risk for fracture should be encouraged to consume a diet rich in vitamin K, but routine supplementation is not justified until these results are confirmed.

Research: The authors stated that a large pragmatic RCT of vitamin K supplements with fractures as the main outcome is required.

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