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Vitamin K supplementation for cystic fibrosis (Review)

Jagannath VA, Fedorowicz Z, Thaker V, Chang AB



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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	3
METHODS	3
RESULTS	6
Figure 1.	8
Figure 2.	8
DISCUSSION	10
AUTHORS' CONCLUSIONS	11
ACKNOWLEDGEMENTS	11
REFERENCES	11
CHARACTERISTICS OF STUDIES	13
DATA AND ANALYSES	20
Analysis 1.1. Comparison 1 Comparison of 1 mg/day vs 5 mg/day oral vitamin K, Outcome 1 Serum undercarboxylated osteocalcin levels.	20
Analysis 1.2. Comparison 1 Comparison of 1 mg/day vs 5 mg/day oral vitamin K, Outcome 2 Serum vitamin K levels.	21
ADDITIONAL TABLES	21
APPENDICES	23
WHAT'S NEW	23
HISTORY	24
CONTRIBUTIONS OF AUTHORS	24
DECLARATIONS OF INTEREST	24
SOURCES OF SUPPORT	25
INDEX TERMS	25

[Intervention Review]

Vitamin K supplementation for cystic fibrosis

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ABSTRACT

Background

Cystic fibrosis is a genetic disorder which can lead to multiorgan dysfunction. Malabsorption of fat and fat-soluble vitamins (A, D, E, K) may occur and can cause subclinical deficiencies of some of these vitamins. Vitamin K is known to play an important role in both blood coagulation and bone formation. Supplementation with vitamin K appears to be one way of addressing the deficiency, but there is very limited agreement on the appropriate dose and frequency of use of these supplements.

Objectives

To assess the effects of vitamin K supplementation in people with cystic fibrosis and to determine the optimal dose and route of administration of vitamin K for both routine and therapeutic use.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.

Most recent search: 15 April 2010.

Selection criteria

Randomised and quasi-randomised controlled trials of all preparations of vitamin K used as a supplement compared to either no supplementation (or placebo) at any dose or route and for any duration, in children or adults diagnosed with cystic fibrosis (by sweat test or genetic testing).

Data collection and analysis

Two authors independently screened papers, extracted trial details and assessed their risk of bias.

Main results

Two trials (total of 32 participants) were included in the review and were assessed as having a moderate risk of bias. One was a dose-ranging parallel group trial; and the other had a cross-over design, but no separate data were reported for the first intervention period. Neither of the trials addressed any of the primary outcomes (coagulation, bone formation and quality of life). Both trials reported the restoration of serum vitamin K and undercarboxylated osteocalcin levels to the normal range after one month of daily supplementation with 1 mg of vitamin K.

Authors' conclusions

Evidence from randomised controlled trials on the benefits of routine vitamin K supplementation for people with CF is currently weak and limited to two small trials of short duration. However, no harm was found and until further evidence is available, the present recommendations should be adhered to.

PLAIN LANGUAGE SUMMARY

Vitamin K supplementation for cystic fibrosis

Cystic fibrosis is an inherited condition causing disease most noticeably in the lungs, digestive tract and pancreas. People with cystic fibrosis often have pancreatic insufficiency which may be linked to deficiencies of fat-soluble vitamins like vitamin K. Vitamin K is needed for adequate blood clotting, bone formation and some metabolic functions.

This review looked at giving vitamin K supplements to address the effects of deficiency on blood clotting, bone strength and quality of life in people with cystic fibrosis. We tried to determine the optimal dosage required to prevent this deficiency.

Data from two small trials did not clearly indicate whether giving vitamin K supplements will improve blood clotting, bone strength or quality of life in people with cystic fibrosis. We were not able to draw firm conclusions from this review and advise that the current recommendations from the Cystic Fibrosis Foundation and the European Cystic Fibrosis Society should be followed until further evidence becomes available.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a multisystem disorder that primarily affects the respiratory and gastrointestinal (GI) systems (Morgan 1999). It is caused by homozygous presence of a mutation in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein.

In the UK there are over 8000 people affected by CF and in the United States of America this figure is approximately 30,000; most are diagnosed by six months of age and the median survival has reached the fifth decade of life (Davis 2006; Goss 2004; Staab 2004). It is the most common, life-threatening, autosomal-recessively inherited disease in the white population, with a carrier rate of 1 in 25 and an incidence of 1 in 2500 live births (Ratjen 2003); CF is less common in other ethnic groups, approximately 1 in 46 Hispanics, 1 in 65 Africans and 1 in 90 Asians carry at least one abnormal CFTR gene (Bobadilla 2002).

The CFTR protein is a chloride ion channel, important in tissues that produce sweat, digestive juices and mucus. The dominant symptoms of CF relate to the respiratory and GI systems (Wagener 2003). In the GI system, liver dysfunction, intestinal obstruction and exocrine pancreatic insufficiency are the most common morbidities. Pancreatic insufficiency (PI) affects up to 90% of people

with CF and causes fat malabsorption (Dodge 2006). Fat-soluble vitamins (A, D, E and K) are co-absorbed with fat and thus deficiency of these vitamins may occur (Dodge 2006). Hence, vitamin K deficiency is well recognised in patients with CF and PI. While deficiencies may occur from the disease process of CF and from insufficient supplementation, another additional co-factor is the long-term use of certain types of antibiotics. These can put some individuals at additional risk of vitamin K deficiency by altering intestinal flora which produce vitamin K (Conway 2005). Long-term effects of bowel resection, an intervention required for intestinal obstruction in some newborns with CF and varying degrees of liver dysfunction can pose a further additional risk for vitamin K deficiency (Fuchs 1998).

The manifestations of vitamin K deficiency can range from a mild subclinical identification (e.g. low levels of vitamin K in the blood) to widespread coagulopathy (defect in the body's mechanism for blood clotting). Such manifestations may include mucosal bleeding (e.g. in the nose, gastro-intestinal system, and in the urine) and subcutaneous bleeding (e.g. oozing from venipuncture sites and susceptibility to bruising). Vitamin K is also involved in the calcium binding proteins in the bone and its deficiency is implicated in defective bone remineralization and thus osteoporosis (Conway 2005).

The majority of CF centres routinely administer vitamins A, D, and E as supplements from the neonatal period. Vitamin K ad-

ministration is usually prescribed when clinical deficiencies are detected or following routine investigations. The limited storage capacity and rapid metabolic turnover of vitamin K (Olsen 1994) supports the recommendations for daily rather than weekly supplementation of vitamin K (Beker 1997).

Description of the intervention

Two forms of vitamin K (K1 and K2) occur naturally and synthetic forms of the vitamin (K3, K4, and K5) are also available. Naturally occurring vitamin K is found in green vegetables i.e. kale, collards, spinach and salads (K1 -phytonadione) and a small amount is made in human gut by bacteria (K2-menaquinones). Therapeutic vitamin K is available in both water soluble and insoluble forms (Durie 1994). The enteral forms of vitamin K supplementation are commonly prescribed. These can be in tablet, ampoule (Borowitz 2002; Cystic Fibrosis Trust 2007) or multivitamin preparations (Durie 1994). Vitamin K can also be administered by intramuscular (Shearer 1995) or intravenous injections (Verghese 2003).

How the intervention might work

Vitamin K functions as the cofactor of the enzyme vitamin K-dependent carboxylase. This enzyme catalyses the post-translation formation of gamma-carboxyglutamyl (Gla) residues in specific proteins. Vitamin K-dependent proteins are: blood coagulation factors (prothrombin and Factors VII, IX and X); other plasma proteins (protein C, protein S and protein Z); two proteins from bone (osteocalcin and matrix Gla-protein); and proteins from lung, kidney, spleen, testis, placenta and other tissues (Uotila 1990).

Blood coagulation requires activation of inactive proenzymes, hence vitamin K is a vital factor in synthesis of clotting factors and causes haemostasis in vitamin K-dependant bleeding manifestations.

Vitamin K-related carboxylation allows the activation of the bone matrix protein, osteocalcin, resulting in osteoblast function and bone formation; vitamin-K deficiency impairs this process and thus impairs bone formation (Okano 2005).

Why it is important to do this review

Vitamin K deficiency is common in CF patients with pancreatic insufficiency. Supplementation (often oral and occasionally parenteral) appears to be the most immediate measure to address the deficiency, although there is limited consensus on the dose and frequency of supplements for routine or therapeutic use (Rashid 1999). In 1992 the Consensus Committee of the Cystic Fibrosis Foundation (CFF) suggested a particular dosage (Ramsey 1992); but the recommendations were later proved ineffectual by another study (Beker 1997). The 2002 American Consensus Committee

recommended a low-dose supplementation of vitamin K for all ages (0.3 to 0.5 mg/day), but emphasized that no adverse effects had been reported at any dosage level of vitamin K (Borowitz 2002). Recent recommendations from Europe and the UK have suggested varying dose regimens ranging from 0.3 to 1 mg/day to 10 mg/week (Cystic Fibrosis Trust 2002; Sinaasappel 2002). There is a suggestion from a recent study that only a higher level of supplementation can normalise vitamin K levels in people with CF (Dougherty 2010).

There is no uniform consensus on routine or at-risk vitamin K supplementation in individuals with CF. There is increasing evidence that the prevalence of vitamin K deficiency in CF is associated with an increased morbidity (Rashid 1999). Thus, a systematic review on vitamin K supplementation in people with CF could provide evidence to guide clinical practice.

OBJECTIVES

To determine the effects of vitamin K supplementation on the morbidities in people with CF.

To investigate the hypotheses that vitamin K will decrease deficiency-related coagulopathy, increase bone mineral density, decrease risk of fractures and improve quality of life in people with CF.

To determine the optimal dose and route of administration of vitamin K for people with CF (for both routine and therapeutic use).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials and quasi-randomised controlled trials.

Types of participants

Children and adults with a diagnosis of CF (defined by sweat test or genetic testing or both).

Exclusion criteria: Any intervention which may affect the interpretation of the effects of vitamin K or any allergy to vitamin K:

- any anticoagulation in the past three months (will make interpretation of vitamin K effects on blood coagulation difficult);

- bisphosphonates in the past six months (will make interpretation of vitamin K effects on bone metabolism difficult);
- allergy to vitamin K.

Types of interventions

All preparations of vitamin K used as a supplement compared to placebo or no supplementation at any dose and for any duration. Studies comparing different doses and regimens of vitamin K were considered.

Types of outcome measures

Primary outcomes

1. Clinical outcomes related to coagulopathy (Sutor 1995)
 - i) time to cessation of bleeding manifestations (symptomatic coagulopathy)
 - ii) time to normalisation of sub-therapeutic international normalized ratio (INR) (asymptomatic or sub-clinical coagulopathy)
2. Bone formation outcome measures
 - i) bone mineral density at the spine (L1-L4) and the total hip (measured by dual energy X-ray absorptiometry (DEXA) scans with z score compared to reference population) (Borowitz 2002)
 - ii) reduction in risk of bone fractures
3. Quality of life (e.g. the CFQ-R (Quittner 2000) and the CFQoL (Gee 2000))

Secondary outcomes

1. Nutritional parameters (including z scores or centiles)
 - i) weight
 - ii) height
 - iii) body mass index (BMI)
2. Adverse events
 - i) mild (not requiring intervention)
 - ii) moderate (requiring treatment)
 - iii) severe (life threatening or requiring hospitalisation)
3. Serum levels
 - i) serum undercarboxylated osteocalcin (ucOC)
 - ii) ucOC/cOC (carboxylated osteocalcin) ratio (UCR)
4. Vitamin K-specific laboratory outcomes
 - i) plasma level of vitamin K1 (measured by high performance liquid chromatography (HPLC) and fluorescence detection (Wang 2004)
 - ii) proteins induced by vitamin K absence or antagonism factor II (PIVKA II) levels (measured by enzyme-linked immunosorbent assay (ELISA)) (Belle 1991; Belle 1995)

Search methods for identification of studies

Electronic searches

We identified relevant trials from the Group's Cystic Fibrosis Trials Register using the term: 'vitamin K'.

A systematic search without language restrictions was conducted using the optimally sensitive strategy developed for the Cochrane Collaboration to identify all relevant published and unpublished randomised controlled trials (Lefebvre 2009) in the Cystic Fibrosis Trials Register which is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (Clinical Trials) (updated each new issue of *The Cochrane Library*), quarterly searches of MEDLINE, a search of EMBASE to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the [Cystic Fibrosis and Genetic Disorders Group Module](#).

Date of the latest search: 15 April 2010.

Searching other resources

The following additional resources were used:

1. the bibliographical references of identified studies were searched for citations to additional studies;
2. personal contact with corresponding authors of relevant trials or reviewers and other experts;
3. clinical trials registries: [clinicaltrials.gov](#); [Current Controlled Trials](#).

Data collection and analysis

Selection of studies

Two review authors (Vanitha Jagannath (VJ) and Zbys Fedorowicz (ZF)) independently assessed the abstracts of trials resulting from the searches. We obtained full text copies of all relevant and potentially relevant trials, those appearing to meet the inclusion criteria, and those for which there was insufficient detail in the title and abstract to make a clear decision. The two authors then independently assessed the full text papers. There were no disagreements; however, if there are any disagreements on the eligibility of trials in the future, we will resolve these through discussion and consensus, or through a third party (Vidhu Thaker (VT)). All irrelevant records were excluded and details of the trials and the reasons for their exclusion were noted in the tables ([Characteristics of excluded studies](#)) in RevMan 5 (RevMan 2008).

Data extraction and management

We entered details for the included trials into the tables ([Characteristics of included studies](#)) in RevMan 5 ([RevMan 2008](#)) and collected outcome data using a pre-determined form designed for this purpose. Two review authors (VJ, ZF) extracted data independently and in duplicate and only included these if there was a consensus; there were no disagreements; if these occur in the future, we will resolve them by consulting with a third review author (VT).

The authors extracted the following details.

1. Trial methods
 - i) method of allocation;
 - ii) masking of participants, trialists and outcome assessors;
 - iii) exclusion of participants after randomisation and proportion and reasons for losses at follow-up.
2. Participants
 - i) country of origin and study setting;
 - ii) sample size;
 - iii) age;
 - iv) gender;
 - v) inclusion and exclusion criteria.
3. Intervention
 - i) type;
 - ii) dose and frequency;
 - iii) duration of intervention in follow-up.
4. Control
 - i) type;
 - ii) dose and frequency;
 - iii) duration of intervention in follow-up.
5. Outcomes: primary and secondary outcomes mentioned in the [Types of outcome measures](#) section of this review and categorised and grouped accordingly: short term (less than 12 months) data at 3, 6 and 12 months and medium to long term (over 1 year).

If stated in the trial reports, we recorded the sources of funding of any of the included studies.

The review authors used this information to help them assess clinical heterogeneity and the external validity of any included trials.

Assessment of risk of bias in included studies

Two authors (VJ, ZF) independently graded the selected trials using a simple contingency form and followed the domain-based evaluation described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0 ([Higgins 2009a](#)). The authors compared evaluations and discussed and resolved any inconsistencies in these evaluations.

The authors assessed the following domains as 'Yes' (i.e. low risk of bias), 'Unclear' (uncertain risk of bias) or 'No' (i.e. high risk of bias):

1. sequence generation;

2. allocation concealment;
3. blinding (of participants, personnel and outcome assessors);
4. incomplete outcome data addressed;
5. free of selective outcome reporting;
6. free of other bias.

The authors categorised the risk of bias in any included studies according to the following:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria met;
- unclear risk of bias (plausible bias that raises some doubt about the results) if one or more criteria assessed as unclear; or
- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria not met.

We report these assessments for each trial in the tables ([Risk of bias in included studies](#)) in the review.

Measures of treatment effect

For dichotomous outcomes, we planned to express results as odds ratios (OR) with 95% confidence intervals (CI). For continuous outcomes, we calculated the mean difference (MD); we would have calculated the standardized mean difference (SMD) if different measurement scales had been used. We planned to express any time-to-event outcomes data as ORs or hazards ratios.

Unit of analysis issues

We included trials with a parallel group design, such that participants were randomised to either intervention or control with subsequent analysis at individual allocation level. Unit of analysis issues can arise with cross-over trials and therefore we decided not to include end-of-trial data from these trials because the effects of vitamin K on bone metabolism are likely to be long-term and an appropriate wash-out period cannot be defined. However, we planned to include any data reported from the first intervention period.

Dealing with missing data

We were only able to contact the investigators from one of the trials ([Drury 2008](#)). We obtained individual patient data which we have included in the analysis.

Assessment of heterogeneity

As we were only able to include two trials in this review, we did not assess heterogeneity; but in future updates of this review, if we are able to include further trials, we will apply the following methods of assessment.

We will assess clinical diversity between the trials by examining the trial characteristics, the similarity between the types of participants, the interventions and the outcomes as specified in the inclusion criteria.

We will assess statistical heterogeneity using a Chi² test and the I² statistic, where I² values of 30% to 60% indicate moderate to high, 50% to 90% substantial and 75% to 100% considerable heterogeneity. We will consider heterogeneity to be significant when the P value is less than 0.10 (Higgins 2003).

Assessment of reporting biases

The paucity of trials included in this review did not permit an assessment of publication bias. If we had identified a sufficient number of trials for inclusion in this review (at least 10), we would have assessed publication bias according to the recommendations on testing for funnel plot asymmetry as described in section 10.4.3.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.0 (updated September 2009) (Higgins 2009b). If we had then identified asymmetry, we would have tried to assess other possible causes and explored these further in the Discussion section of the review, if appropriate.

Data synthesis

Two review authors (VJ and ZF) analysed the data in Review Manager 5 (RevMan 2008) and reported them as specified in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0 (updated September 2009) (Higgins 2009c).

Although we included two trials in this review, we were only able to report reliable data from one of them (Drury 2008) and therefore did not carry out a meta-analysis. If at a later date we include further trials in this review, we will apply the following methods of data synthesis. When we include sufficient numbers of trials investigating similar interventions, we will conduct the analysis in RevMan (RevMan 2008). In general, we will use the fixed-effect model; but if there is substantial clinical diversity, we will use the random-effects model with trials grouped by action.

Subgroup analysis and investigation of heterogeneity

Lack of data did not permit a subgroup analysis, but in future updates and if further data become available we plan to carry out the following subgroup analyses:

1. cumulative dose (as per kg body weight per day) of vitamin K2;
2. route of administration (oral or parenteral);
3. baseline plasma level of vitamin K1 (subnormal versus normal);
4. presence or absence of any of the following: pancreatic insufficiency, liver dysfunction, bowel resection or prolonged usage of antibiotics and chronic steroid administration;
5. mean 25OH vitamin D level.

Sensitivity analysis

In view of the low number of trials included in this review, a sensitivity analysis was not possible. For future updates and if we are able to include sufficient trials, we will undertake sensitivity analyses to assess the robustness of our review results by repeating the analysis with the following adjustments:

- exclusion of trials with unclear or inadequate allocation concealment;
- exclusion of trials with unclear or inadequate blinding of outcomes assessment;
- exclusion of trials with unclear or inadequate completeness of follow-up;
- exclusion of quasi-randomised trials.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#).

Results of the search

The electronic searches retrieved references to nine trials. After examination of the titles and abstracts of these references, all of those which did not match our inclusion criteria and were clearly ineligible were eliminated from the review. Full text copies of the remaining potentially eligible trials were obtained and subjected to further evaluation. The review authors discussed the eligibility of these trials, resolved any remaining uncertainties by consensus. Two trials were included (Beker 1997; Drury 2008), five trials were excluded (Cornelissen 1992; Grey 2008; Mosler 2003; Nicolaidou 2006; Wilson 2001), and two trials are awaiting classification until we obtain further information from the trialists (van Hoorn 2003; van Hoorn 2008).

Our search of the clinical trials database (clinicaltrials.gov) retrieved an additional ongoing trial which will be assessed for inclusion as soon as it has been published (Kuitert 2010).

Included studies

Two trials, neither of which addressed any of our primary outcomes and only reported on two of the secondary outcomes were included in this review. Albeit these two trials were assessed as having a moderate risk of bias, and provided limited data, it was considered that their inclusion and the reporting of their results would provide at least some evidence towards answering this research question.

One of the trials was cross-over in design, but did not include a wash-out period and thus the potential risk of bias as a consequence of the carry-over of treatment effect could not be ruled out (Beker 1997). Although trials with a cross-over design were eligible for inclusion in this review, we had specified that only data from the first intervention period would be used. Unfortunately, the trial investigators only provided an analysis across both treatment periods and, even though we were unable to contact the authors to obtain the first period data, this trial has been included in the review but it has not been possible to enter the data into a meta-analysis.

The second trial included in this review was a dose-ranging randomised controlled trial which reported some data for two of our secondary outcomes, but these were presented as graph-plots from which we were unable to obtain precise data (Drury 2008). After successful contact with the principal investigator via electronic mail we received the relevant individual patient data for these two outcomes and have presented them in this review.

Characteristics of the trial setting and investigators

Both were single centre trials, one was conducted at the Montreal Children's Hospital CF Clinic in Canada (Drury 2008), and the other was carried out at the CF Clinic of the Children's National Medical Center (CNMC), Washington DC, USA (Beker 1997). Although the overall duration of the two trials differed, the active treatment period was the same (i.e. one month). Thus, in the cross-over trial, the participants were allocated to either active intervention or no-treatment control for a four-week period and then crossed over for a further four weeks but without undergoing a wash-out period (Beker 1997).

The providers of care in both trials were hospital staff and the assessors of outcomes were the investigators and other healthcare providers (Beker 1997; Drury 2008).

Characteristics of the participants

The total sample size comprised of 32 participants between the ages of 8 and 35 years. In the Beker study, the diagnosis of CF was confirmed by duplicate sweat test (Beker 1997). Although Drury did not report the method used to confirm the diagnosis of CF, it is most probable that participants with CF were enrolled in this trial (Drury 2008).

All of the participants in the Beker trial were pancreatic insufficient, as documented by previous fecal fat measurement, and they received replacement therapy of 750 to 200 units of lipase/kg of body weight at meal times during the course of the trial (Beker 1997). The investigators in the Drury trial reported that only pancreatic insufficient participants were included, but provided no further details (Drury 2008). Participants with liver disease (diagnosed by ultrasound, liver function tests or hepatomegaly or both) and those who were taking supplemental therapeutic vitamin K to

treat coagulopathies at enrolment were excluded from both trials (Beker 1997; Drury 2008).

Characteristics of the interventions

The active intervention in the Beker trial consisted of 5 mg oral vitamin K1 supplementation per week and the control was no supplementation for four weeks; participants then crossed over for a second four-week period (Beker 1997). Compliance with the intervention by participants was verified by the trial coordinator at each visit. Oral antibiotic medications of cephalosporin; sulfamethoxazole; erythromycin as well as concomitant usage of bronchodilators and standard multivitamins and 200 to 400 IU vitamin E were allowed during the course of the trial.

The participants in the Drury trial were randomised to either the orally administered injectable formulation of vitamin K1 phytonadione of 1 mg/day (diluted to 1 mg/ml) or the 5 mg/day dose (Drury 2008).

Characteristics of the outcome measures

None of the primary outcomes specified in the protocol for the review were considered in either of the included trials (Beker 1997; Drury 2008). Both trials carried out assessments of plasma Vitamin K1 levels and serum undercarboxylated osteocalcin levels; these were measured at entry and at the completion of the trial by Drury (Drury 2008), and at the end of each period by Beker (Beker 1997). Dietary intake records to estimate the extent of dietary contribution of Vitamin K1 were maintained by the participants in one trial (Beker 1997). The vitamin K1 data of foods were analysed using Nutritionist III software, the database, however, did not have complete vitamin K1 data for many foods.

Excluded studies

Five trials were excluded from the review since these were not randomised controlled trials. Further information about the reasons for exclusion of trials is available in the Excluded studies table.

Risk of bias in included studies

The risks of bias for the two included trials in this review were classified as previously described (*Assessment of risk of bias in included studies*).

Both included trials were judged as having an 'unclear' risk of bias overall (Beker 1997; Drury 2008). These assessments were to a certain extent based on the inadequate reporting of several of the criteria that are considered to be important in the evaluation of methodological rigour in terms of trial design and conduct.

For further details see the risk of bias tables in *Characteristics of included studies*, the risk of bias graph (Figure 1) and the risk of bias summary (Figure 2).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

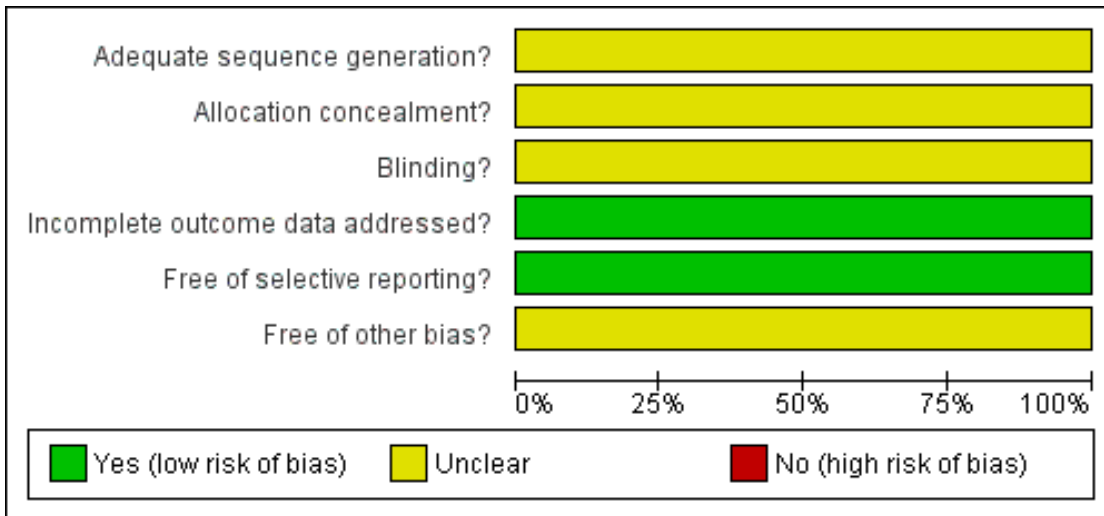


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Beker 1997	?	?	?	+	+	?
Drury 2008	?	?	?	+	+	?

Allocation

The methods used to generate the allocation sequence were not reported in either trial. Moreover, neither of the trials described how the allocation sequence was concealed, which did not allow us to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment. Inadequate reporting quality did not permit a clear judgement to be made for both domains in either of the included trials (Beker 1997; Drury 2008).

Blinding

The measures used to blind trial participants and personnel from knowledge of which intervention a participant received or any information relating to whether the intended blinding was effective were not reported in either trial (Beker 1997; Drury 2008). However, whilst it may be accepted that blinding of participants and investigators in the Beker trial may not have been feasible, it was unclear if the assessors of the outcomes were adequately blinded (Beker 1997). Therefore the judgement given for this domain in both trials was 'unclear'.

Incomplete outcome data

There were no withdrawals and no missing or incomplete data in the Beker trial (Beker 1997); and the only missing data in the Drury trial was as a result of the inability of the investigators to make the final outcome assessment for one participant (Drury 2008). Therefore, we judge there to be a low risk of bias from incomplete outcome data in both trials.

Selective reporting

Although neither trial protocols were available, based on information presented in the methods sections of each of the reports, the investigators appear to have reported on all of their stated objectives and expected outcomes, a number of which were pre-specified inclusion criteria for this systematic review (Beker 1997; Drury 2008). We therefore judge there to be a low risk of bias from selective reporting for these trials.

Other potential sources of bias

Insufficient information was provided in the reports to assess whether any other important risk of bias exists, and therefore the judgement for this domain in both trials was 'unclear' (Beker 1997; Drury 2008).

Effects of interventions

Primary outcomes

None of the primary outcomes specified in the protocol for this review were considered in either of the included trials (Beker 1997; Drury 2008).

Secondary outcomes

1. Nutritional parameters

These were not considered in either of the included trials (Beker 1997; Drury 2008).

2. Adverse events

No adverse events were reported in either of the trials (Beker 1997; Drury 2008).

3. Serum levels

The Drury trial was under-powered (Drury 2008). Even though we had managed to obtain individual patient data, the small number of participants and the degree of baseline imbalance in vitamin K and undercarboxylated osteocalcin levels (both within and between the groups) did not support analysis of the magnitude of individual response to treatment or control, i.e. the measure of change from baseline. Although it is likely that baseline imbalance may reflect the clinical variability of CF, neither report provided sufficient clinical detail of the participants to enable any assessment of the degree of variability in presentation of CF (Beker 1997; Drury 2008). Therefore, the data for both of these outcomes have been presented in the analysis as the end of trial mean response for the total number of participants in each of the treatment and control groups. We also report the baseline means and SDs alongside the end of trial values in the additional tables (Table 1; Table 2).

In the Beker trial, the data for this outcome were analysed across both treatment periods and therefore we only report the end of trial data narratively (Beker 1997). We advise caution in its interpretation and in any comparison with data from the other trial included in this review.

a. Serum undercarboxylated osteocalcin (ucOC)

In the Drury trial, all of the participants had elevated (in excess of 21%) concentrations of ucOC before supplementation, but these levels were reduced after one month of vitamin K1 supplementation (Drury 2008). The overall level of ucOC decreased from a median of 46.8% to 29.1%, and the undercarboxylated osteocalcin levels decreased and returned to levels within the normal range in three (one in the 5 mg/day group, two in the 1 mg/day group) out of the 13 participants by the end of the trial. The mean end of trial difference in ucOC between the two intervention groups was -2.20 (95% CI -14.33 to 9.93) (Analysis 1.1).

There was no evidence of any difference between the 5 mg/day and the 1 mg/day vitamin K dosage in terms of statistically significant

effect on ucOC levels at the end of the one-month trial period (Drury 2008).

In the Beker trial, all of the participants had increased serum undercarboxylated osteocalcin concentrations (ucOC) at enrolment and prior to supplementation (Beker 1997). It was reported that following supplementation and by the end of the trial the majority had successfully achieved the normal reference mean levels (21%) of ucOC (Beker 1997).

b. ucOC/cOC (carboxylated osteocalcin) ratio (UCR)

This was not evaluated in either of the trials (Beker 1997; Drury 2008).

4. Vitamin K-specific laboratory outcomes

a. Plasma level of vitamin K1

In the Drury trial, the baseline vitamin K levels in seven out of the 14 participants were sub-optimal (defined as less than 0.3 nmol/L) (Drury 2008). The paper reported that serum vitamin K levels appeared to improve significantly ($P < 0.001$) with supplementation, rising into the normal range in all of the participants who were below the optimum level. There was no statistically significant difference in effect between the 5 mg/day and the 1 mg/day vitamin K dose; MD -4.46 (95% CI -12.65 to 3.73) (Analysis 1.2).

In the Beker trial, a substantial number of the participants had below normal serum vitamin K levels at trial entry (Beker 1997). Although the mean concentration of plasma vitamin K was higher in the supplemented group, in only less than half of the total number of participants were these levels reportedly brought into the normal range after supplementation with the 5 mg dose (Beker 1997).

b. Proteins induced by vitamin K absence or antagonism factor II (PIVKA II) levels

Drury did not consider or report on this outcome (Drury 2008). In the Beker trial PIVKA-II concentrations were elevated prior to supplementation and almost one third of the participants had PIVKA-II levels within the normal range (≤ 2 ng/ml) following supplementation (Beker 1997).

DISCUSSION

Summary of main results

The results from both of the included trials could not be pooled and entered into a meta-analysis; however, both trials reported an

increase in serum vitamin K levels, and a decrease in the undercarboxylated osteocalcin levels which returned to normal following supplementation with oral vitamin K 1 mg/day for one month. There did not appear to be any significant difference in these outcomes when a dose of 1 mg/day was compared with 5 mg/day in the Drury trial (Drury 2008). The PIVKA levels also showed a decrease and a return to normal in the Beker trial following supplementation (Beker 1997).

Overall completeness and applicability of evidence

The noticeable absence in the included trials of any assessments of important clinical outcomes related to coagulopathy or growth and improvement in quality of life as a result of vitamin K supplementation does somewhat limit the overall completeness and ultimately the generalisability of the evidence to the wider CF population. Equally, the short duration and follow-up of the included trials does not permit any conclusions to be made about the longer-term benefits and any potential harms of vitamin K supplementation.

Future research should aim to close this gap in the evidence by focusing more closely on some of the patient-relevant and preferred outcomes rather than solely on biochemical laboratory analyses.

Quality of the evidence

The two trials included in this review were underpowered and of short duration which was illustrated by the wide confidence intervals in the comparisons of treatment effect and reflected the degree of imprecision in these results (Beker 1997; Drury 2008). Some of the practical and methodological difficulties faced by investigators of this research question were highlighted in these trials. The key factors which are likely to have had a degree of impact on the quality level of the evidence for the outcomes sought in this review can be linked to the design and implementation of the included trials, and in particular to the effective concealment of the allocation sequence and adequate blinding of investigators and outcome assessors.

Potential biases in the review process

Although it would be not unreasonable to assume that the comprehensive electronic searches employed in this review will have identified all existing randomised controlled trials and thereby helped to limit bias in the conduct of this review, the absence of any other published randomised trials over the intervening ten years between the two included trials and their scant contribution to the outcomes specified for this review, might presuppose an indication of publication bias.

Agreements and disagreements with other

studies or reviews

Several trials have indicated a degree of support for the requirement of supplementation in addition to emphasising the comparative safety of oral supplementation with vitamin K in people with CF (Beker 1997; Borowitz 2002; Ramsey 1992; Sinaasappel 2002); but there is no agreement amongst the trials about the dosage of supplementation. However, there is some concern that the adequacy of dosing based on measurement of vitamin K levels may be inaccurate and that PIVKA levels and ucOC levels may be better indicators of effectiveness of supplementation. Some trials suggest a complimentary role for quantified dietary intake of vitamin K in people with CF (Dougherty 2010). This review did not show anything conclusively to agree or disagree with these trials.

AUTHORS' CONCLUSIONS

Implications for practice

People with CF are at risk of vitamin K deficiency. Routine supplementation along with the other fat soluble vitamins is common clinical practice; however, there appears to be very little consensus about the exact dosage that should be prescribed. Until further evidence is available supplementation should continue to follow published ECFS and CFF guidelines (Borowitz 2002; Cystic Fibrosis Trust 2002; Sinaasappel 2002) and be guided by monitoring of the PIVKA or ucOC levels at annual clinical reviews.

Implications for research

There is now a better understanding of the important effect of

vitamin K on gamma-carboxylation of osteocalcin synthesized in the bones over and above its well-acknowledged requirement for synthesis of coagulation proteins in the liver. Well-designed randomised controlled trials are still needed to determine the impact of vitamin K on the outcomes relevant to bone health in addition to routine supplementation and its benefits in people with CF. Research in this area is currently limited and long-term and large-scale trials are needed to provide clear answers to these issues. Additional issues that need to be considered are the sensitivity and reliability of markers for vitamin K deficiency, as well as the diagnostic accuracy and associated costs of laboratory equipment and tests.

Thus randomised controlled trials of vitamin K supplementation should be placebo-controlled trials of parallel-design involving both children and adults (considered separately). Outcomes should include clinical measures (e.g. coagulation effects), bone measures (density scans) and biochemical markers. In addition patient-orientated measures such as quality of life and patient satisfaction should also be evaluated. Possible adverse events should also be specifically recorded and reported.

Further research recommendations based on the EPICOT format (Brown 2006) are presented in the additional tables (Table 3).

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Beker 1997

Methods	Randomised cross-over trial (2 periods of 4 weeks). CF Clinic Children's National Medical Center (CNMC), Washington DC. No date specified.
Participants	Randomised: N = 18 (8 male, 10 female); mean age 20 years (Range 13 - 35 years) Inclusion criteria <ul style="list-style-type: none"> • confirmed diagnosis of CF by duplicate sweat test • clinically stable as determined by physical exam; afebrile • moderate lung disease based on an average radiograph score of 15 using the Brasfield scoring method <ul style="list-style-type: none"> • within or above the fifth NCHS height percentile for age and body mass index (BMI) ≥ 20 • AST/ALT levels within the normal range, and normal plasma albumin levels Exclusion criteria <ul style="list-style-type: none"> • without cholestasis or overt liver disease • elevated AST/ALT Withdrawal or loss to follow-up: None reported.
Interventions	Intervention: 5 mg oral vitamin K1 supplementation per week. Control: no supplementation. 4 weeks of first treatment then crossed over to the other treatment for a second 4-week period Concomitant medications permitted: cephalosporin (13); sulfamethoxazole (3); erythromycin (1); bronchodilators; standard multivitamins and 200 - 400 IU vitamin E
Outcomes	Primary outcomes: none reported Secondary outcomes (assessments at entry and end of each trial period) <ul style="list-style-type: none"> • plasma vitamin K1 and vitamin K1-2,3 epoxide • plasma PIVKA-II • serum osteocalcin 3-day dietary intake records were completed during each treatment period, but these did not correspond with the nutritional parameters sought as secondary outcomes for this review Patient compliance was verified by the trial coordinator at each visit
Notes	Randomised cross-over trial, vitamin K supplementation compared with no treatment. No wash-out period with a potential carry-over of treatment effect. No first-period data available "Supported in part by grants from the Board of Lady Visitors, Children's National Medical Center, Washington, DC, and the University of Maryland, College Park, Maryland." "

Risk of bias

Bias	Authors' judgement	Support for judgement
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Beker 1997 (Continued)

Adequate sequence generation?	Unclear risk	Quote: “randomly assigned” Page 512 Comment: insufficient information to make a clear judgement of ‘Yes’ or ‘No’
Allocation concealment?	Unclear risk	Not reported. Probably not done.
Blinding? All outcomes	Unclear risk	Participants: not possible; control was ‘no treatment’. Healthcare providers: not possible; control was ‘no treatment’ Outcomes assessors and data analysts: unclear. Comment: overall judgement unclear.
Incomplete outcome data addressed? All outcomes	Low risk	There were no withdrawals and no missing or incomplete data.
Free of selective reporting?	Low risk	Although the protocol was not available all relevant outcomes appear to have been addressed
Free of other bias?	Unclear risk	Quote: “Supported in part by grants from the Board of Lady Visitors, Children’s National Medical Center, Washington, DC, and the University of Maryland, College Park, Maryland.” Comment: it is unclear to what extent the support provided may have had on the results of this study. Insufficient information to assess whether an important risk of bias exists

Drury 2008

Methods	Randomised control trial over 1-month period. Montreal Children’s Hospital Cystic Fibrosis Clinic, Canada. Date not specified.
Participants	Randomised: N = 14; 8 to 18 years, gender unspecified. Inclusion criteria <ul style="list-style-type: none"> • CF with pancreatic insufficiency. Method of CF diagnosis unreported Exclusion criteria: <ul style="list-style-type: none"> • known liver disease (diagnosed by ultrasound, liver function tests and/or hepatomegaly) • supplemental therapeutic vitamin K to treat coagulopathies Withdrawal or loss to follow-up: missing data (1) from 5 mg group at final assessment.

Drury 2008 (Continued)

Interventions	Intervention: oral administration of injectable formulation of vitamin K1 phytonadione (Sandoz Canada, Boucherville, Qc) diluted 1 mg/1 ml. Dose 1 mg/day for 1 month. Control: identical but dose 5 mg/day for 1 month.
Outcomes	Primary outcomes: none reported Secondary outcomes <ul style="list-style-type: none"> • plasma vitamin K1 levels • serum undercarboxylated osteocalcin levels Measured at the beginning of the trial and at the end of 1 month
Notes	This project was funded by the Canadian CF Foundation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Quote: "were randomised to receive either 1 mg/day, or 5 mg/day" Page 458 Comment: insufficient information to make a clear judgement of 'Yes' or 'No'
Allocation concealment?	Unclear risk	Not reported. Probably not done.
Blinding? All outcomes	Unclear risk	Participants: not reported. Healthcare providers: unclear. Outcomes assessors and data analysts: unclear. Comment: overall judgement unclear.
Incomplete outcome data addressed? All outcomes	Low risk	Quote "One subject in the 5 mg group lost consciousness at the time of the second blood procurement". Pg 458 Comment: incomplete data for one participant.
Free of selective reporting?	Low risk	The stated objectives of the trial appear to match the listed outcomes. There was no evidence of selective reporting of outcomes
Free of other bias?	Unclear risk	Quote: "This project was funded by the Canadian CF Foundation". Comment: it is unclear to what extent the support provided may have had on the results of this trial. Insufficient information to assess whether an important risk of bias exists

ALT: alanine aminotransferase
 AST: aspartate aminotransferase
 BMI: body mass index
 CF: cystic fibrosis
 IU: international units
 NCHS: National Center for Health Statistics
 PIVKA-II: proteins induced by vitamin K absence or antagonism factor II
 RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cornelissen 1992	Non-RCT.
Grey 2008	Non-RCT.
Mosler 2003	Non-RCT.
Nicolaidou 2006	Non-RCT, non-CF control group.
Wilson 2001	Uncontrolled study, non-RCT.

CF: cystic fibrosis
 RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

van Hoorn 2003

Methods	Case controlled study
Participants	CF patients
Interventions	Vitamin K in 3 different groups - no supplements, low supplements or high supplements
Outcomes	serum ucOC level
Notes	Awaiting inclusion until the response form the authors about randomisation in the study

van Hoorn 2008

Methods	Randomised controlled study
Participants	26 patients not receiving vitamin K supplementation before
Interventions	0.1 mg and 1 mg vitamin K supplementation for 2 years
Outcomes	ucOC levels and BMD
Notes	Only abstract is available now, likely to be included, but we will consider after we get further information from the investigators

BMD: bone mineral density

CF: cystic fibrosis

ucOC: undercarboxylated osteocalcin

Characteristics of ongoing studies [ordered by study ID]**Kuitert 2010**

Trial name or title	Investigating the effect of vitamin K supplementation on markers of bone turnover and bone density in adolescents and adults with CF
Methods	RCT
Participants	Patients with a diagnosis of CF (positive sweat test or genotype testing) aged over 16 years (post pubertal-stage IV Tanner), either sex, pancreatic insufficient (i.e. with a positive faecal elastase test, and requiring pancreatic enzyme supplementation) and no overt liver disease
Interventions	10 mg of menadiol phosphate (water soluble form of vitamin K) once daily orally for 12 months versus placebo
Outcomes	<ul style="list-style-type: none"> ● difference in the ratio of undercarboxylated osteocalcin to total osteocalcin, measured prior to supplementation starting and at the end of the 12 months supplementation ● total osteocalcin ● undercarboxylated osteocalcin ● N Terminal X (marker of bone resorption) ● bone specific alkaline phosphatase ● serum vitamin D ● calcium ● DEXA scan z and t scores of lumbar spine and femoral neck (scores adjusted for age, height and sex) measured prior to supplementation starting and at the end of the 12 months supplementation
Starting date	09/05/2008
Contact information	Lieske Kuitert, Department of Respiratory Medicine, London Chest Hospital, Bonner Road, E2 9JX, London, United Kingdom

Notes

CF: cystic fibrosis

DEXA: dual energy x-ray absorptiometry

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Comparison of 1 mg/day vs 5 mg/day oral vitamin K

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum undercarboxylated osteocalcin levels	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Serum vitamin K levels	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Comparison of 1 mg/day vs 5 mg/day oral vitamin K, Outcome 1 Serum undercarboxylated osteocalcin levels.

Review: Vitamin K supplementation for cystic fibrosis

Comparison: 1 Comparison of 1 mg/day vs 5 mg/day oral vitamin K

Outcome: 1 Serum undercarboxylated osteocalcin levels

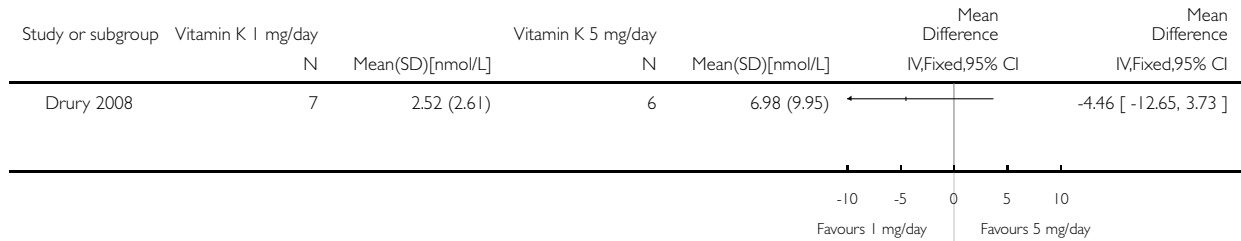
Study or subgroup	Vitamin K 1 mg/day		Vitamin K 5 mg/day		Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)[percentage]	N	Mean(SD)[percentage]		
Drury 2008	7	28 (8.26)	6	30.2 (13.09)	-2.20 [-14.33, 9.93]	

Analysis 1.2. Comparison 1 Comparison of 1 mg/day vs 5 mg/day oral vitamin K, Outcome 2 Serum vitamin K levels.

Review: Vitamin K supplementation for cystic fibrosis

Comparison: 1 Comparison of 1 mg/day vs 5 mg/day oral vitamin K

Outcome: 2 Serum vitamin K levels



ADDITIONAL TABLES

Table 1. Serum undercarboxylated osteocalcin (ucOC) percentage (Drury 2008)

Dose	n	UcOC % Baseline mean (SD)	UcOC % End of study mean (SD)
1 mg/day	7	46 (14.4)	28 (8.26)
5 mg/day	6	47.6 (9.45)	30.2 (13.09)

SD: standard deviation

ucOC: undercarboxylated osteocalcin

Table 2. Serum vitamin K levels (Drury 2008)

Dose	n	Serum vitamin K levels (nmol/L) Baseline mean (SD)	Serum vitamin K levels (nmol/L) End of study mean (SD)
1 mg/day	7	0.28 (0.25)	2.52 (2.61)
5 mg/day	6	0.15 (0.19)	6.98 (9.95)

SD: standard deviation

Table 3. Research recommendations based on a gap in the evidence on Vitamin K supplementation for cystic fibrosis

Core elements	Issues to consider	Status of research for this review
Evidence (E)	What is the current state of evidence?	A systematic review found only limited high quality evidence in relation to the effectiveness or otherwise of vitamin K supplementation for people with CF
Population (P)	Diagnosis, disease stage, comorbidity, risk factor, sex, age, ethnic group, specific inclusion or exclusion criteria, clinical setting	Any age group with a diagnosis of CF (defined by sweat test or genetic testing or both). Pancreatic insufficient
Intervention (I)	Type, prognostic factor	All preparations of vitamin K used as a supplement at any dose and for any duration
Comparison (C)	Type, prognostic factor	Placebo with a dose, frequency, duration comparable to the intervention, or no supplementation. Trials comparing different doses and dose regimens of vitamin K will also be considered. Compliance to be recorded via pill counts and any concomitant medications
Outcome (O)	Which clinical or patient related outcomes will the researcher need to measure, improve, influence or accomplish? Which methods of measurement should be used?	Clinical outcomes related to: <ul style="list-style-type: none"> • coagulopathy • bone formation ie bone mineral density, DEXA scans • nutritional parameters; weight, height, BMI Biochemical analysis: <ul style="list-style-type: none"> • serum levels: serum ucOC/cOC ratio • vitamin K-specific laboratory outcomes: plasma level of vitamin K1 (measured by HPLC), PIVKA II levels (measured by ELISA) Quality of life: <ul style="list-style-type: none"> • CFQ-R (Quittner 2000) • CFQoL (Gee 2000) Adverse events Data type: continuous and dichotomous
Time stamp (T)	Date of literature search or recommendation	15 April 2010.
Study type	What is the most appropriate study design to address the proposed question?	RCT (adequately powered/large sample size, sufficient duration) Methods: concealment of allocation sequence Blinding: participants and investigators, but if not feasible then outcomes assessors and data analysts should be blinded. Setting: CF Clinic

BMI: body mass index

CF: cystic fibrosis

cOC: carboxylated osteocalcin
 DEXA: dual energy X-ray absorptiometry
 ELISA: enzyme-linked immunosorbent assay
 HPLC: high performance liquid chromatography
 PIVKA-II: proteins induced by vitamin K absence or antagonism factor II
 RCT: randomised controlled trial
 ucOC: undercarboxylated osteocalcin

APPENDICES

Appendix I. Glossary

Term	Meaning
bisphosphonate	a class of drugs that prevent the loss of bone mass, used to treat osteoporosis and similar diseases
carboxylation	a chemical reaction in which a carboxylic acid group is introduced in a substrate
coagulopathy	a defect in the body's mechanism for blood clotting
cofactor	a non-protein chemical compound that is bound to a protein and is required for the protein's biological activity
gamma-glutamyl carboxylase	an enzyme that catalyses the gamma-carboxylation of glutamic acid residues in bone matrix proteins such as osteocalcin
haemostasis	a complex process which causes the bleeding process to stop
homozygous	in genetics having identical alleles for a single characteristic
mucosal bleeding	bleeding in mucus membranes
osteoblast	mononucleate cells that are responsible for bone formation
post-translational modification	the chemical modification of a protein after its translation (the production of proteins by decoding messenger RNA); the post-translational modification extends the range of functions of the protein
subclinical	describes an early stage or mild form of a medical condition, where no symptoms are detectable
subcutaneous bleeding	bleeding under the skin

WHAT'S NEW

Last assessed as up-to-date: 14 October 2010.

Date	Event	Description
22 May 2012	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2010

Review first published: Issue 1, 2011

CONTRIBUTIONS OF AUTHORS

VJ, ZF and VT were responsible for:

- organising the retrieval of papers;
- writing to authors of papers for additional information;
- screening search results;
- screening retrieved papers against inclusion criteria;
- appraising the quality of papers;
- data collection for the review;
- extracting data from papers; and
- obtaining and screening data on unpublished trials;
- the analysis and interpretation of data.

VJ and VT were responsible for :

- designing the review;
- co-ordinating the review;and
- data extraction and management for the review.

All review authors contributed to writing the review.

VJ conceived the idea for the review and is the guarantor of the review.

DECLARATIONS OF INTEREST

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INDEX TERMS

Medical Subject Headings (MeSH)

Blood Coagulation [drug effects]; Cystic Fibrosis [*blood; complications]; Dietary Supplements; Osteogenesis [drug effects]; Quality of Life; Randomized Controlled Trials as Topic; Vitamin K [*administration & dosage]; Vitamin K Deficiency [complications; *drug therapy]; Vitamins [*administration & dosage]

MeSH check words

Humans