Vitamin K supplementation for cystic fibrosis

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[Intervention Review]

Vitamin K supplementation for cystic fibrosis

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ABSTRACT

Background

Malabsorption and deficiency of fat-soluble vitamins K may occur in cystic fibrosis, a genetic disorder affecting multiple organs. Vitamin K is known to play an important role in both blood coagulation and bone formation, hence the role of supplementation of vitamin K in this category needs to be reviewed. This is an updated version of the review.

Objectives

To assess the effects of vitamin K supplementation in people with cystic fibrosis and 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. Also to determine the optimal dose and route of administration of vitamin K for people with CF (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: 12 August 2019.

Selection criteria

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 patients with cystic fibrosis.

Data collection and analysis

Two authors independently screened papers, extracted trial details and assessed their risk of bias. The quality of the evidence was assessed using the GRADE criteria.

Main results

Three trials (total 70 participants, aged 8 to 46 years) assessed as having a moderate risk of bias were included. One trial compared vitamin K to placebo, a second to no supplementation and the third compared two doses of vitamin K. No trial in either comparison reported our primary outcomes of coagulation and quality of life or the secondary outcomes of nutritional parameters and adverse events.

Vitamin K versus control

Two trials compared vitamin K to control, but data were not available for analysis. One 12-month trial (n = 38) compared 10 mg vitamin K daily or placebo in a parallel design and one trial (n = 18) was of cross-over design with no washout period and compared 5 mg vitamin K/week for four-weeks to no supplementation for four-weeks. Only the 12-month trial reported on the primary outcome of bone formation; we are very uncertain whether vitamin K supplementation has any effect on bone mineral density at the femoral hip or lumbar spine (very low-quality evidence). Both trials reported an increase in serum vitamin K levels and a decrease in undercarboxylated osteocalcin levels. The cross-over trial also reported that levels of proteins induced by vitamin K absence (PIVKA) showed a decrease and a return to normal following supplementation, but due to the very low-quality evidence we are not certain that this is due to the intervention.

High-dose versus low-dose vitamin K

One parallel trial (n = 14) compared 1 mg vitamin K/day to 5 mg vitamin K/day for four weeks. The trial did report that there did not appear to be any difference in serum undercarboxylated osteocalcin or vitamin K levels (very low-quality evidence). While the trial reported that serum vitamin K levels improved with supplementation, there was no difference between the high-dose and low-dose groups.

Authors' conclusions

There is very low-quality evidence of any effect of vitamin K in people with cystic fibrosis. While there is no evidence of harm, until better evidence is available the ongoing recommendations by national CF guidelines should be followed.

PLAIN LANGUAGE SUMMARY

Vitamin K supplementation for cystic fibrosis

Review question

We reviewed the evidence to see whether supplementing vitamin K in people with cystic fibrosis counteracts the effects of deficiency on blood clotting, bone strength and quality of life in people with cystic fibrosis. We tried to determine the best dose needed to prevent this deficiency. This is an update of an earlier review.

Background

Cystic fibrosis is an inherited condition which causes disease, most noticeably in the lungs, digestive system and pancreas. In people with cystic fibrosis, the pancreas often does not produce enough enzymes to allow the body to absorb digested food properly and this may also 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.

Search date

The evidence is current to: 12 August 2019.

Study characteristics

We included three trials (total of 70 participants aged between 8 and 46 years) in the review.

Two trials compared vitamin K to a control. In the first trial all 18 people taking part (aged 13 to 35 years) were given 5 mg oral vitamin K supplement once a week or nothing for a total duration of one month and then they swapped to the other group for another month. Unfortunately, we could not analyse the data from this trial because the investigators did not report data just from the first part of the trial (only from the end of the trial when everyone taking part had been in both groups), so we could not tell if the effects were due to supplements or no supplements. In the second trial a total of 38 people aged 16 to 45 years took part. They were given either 10 mg vitamin K or placebo (a dummy supplement not containing any vitamin K) every day for 12 months, but the investigators did not state how many people were in each group so we could not analyse the results.

In the third trial (14 children aged 8 to 18 years old) participants were given oral vitamin K supplements, half of them at a dose of 1 mg every day and the other half were given 5 mg every day for one month.

Key results

No trial in either comparison reported our primary outcomes of blood clotting and quality of life or the secondary measures of nutrition and adverse events.

Vitamin K versus control

Only the 12-month trial reported on the primary outcome of bone formation; we are very uncertain whether vitamin K supplementation has any effect on bone mineral density measured at the hip or lower back (very low-quality evidence). Both trials reported an increase in vitamin K levels in the blood and a decrease in undercarboxylated osteocalcin levels (this is an indicator of the risk of hip fracture). The

four-week trial also reported that levels of proteins induced by vitamin K absence (PIVKA) dropped and returned to normal levels, but due to the very low-quality evidence we are not certain that this is due to supplementation.

High-dose versus low-dose vitamin K

The trial reported that while vitamin K levels improved there did not seem to be any difference between the high-dose and low-dose groups. There also did not seem to be any difference in undercarboxylated osteocalcin levels (very low-quality evidence).

Quality of the evidence

The overall quality of the evidence was judged to be very low due to risks of bias in the design of all trials and the low numbers of participants.

Summary of findings 1. Vitamin K compared to control for people with cystic fibrosis

Vitamin K compared to control for people with cystic fibrosis

Patient or population: people with cystic fibrosis
Setting: community or health care facilities
Intervention: vitamin K
Comparison: placebo or no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo	Risk with Vitamin K				
Time to cessation of bleeding **Follow-up**: 12 months	Outcome not reported.					
Bone mineral density: lumbar spine z score **Follow-up**: 12 months	The mean (SD) change in the placebo group in z score at the lumbar spine was 0.041 (0.15) g/cm^3 and in the treatment group it was -0.073 (0.30) g/cm^3.			38 (1)	Very low ⊕⊖⊖⊖[a,b]	The trial authors also reported mean change in z score in those participants 25 or under and those that were over 25 years. They concluded that vitamin K had no significant effect except in participants that were over 25 years. where vitamin K may have a protective effect against decline in BMD (Kuitert 2010). The mean (SD) change in the placebo group at the femoral hip z score was 0.053 (0.19) g/cm^3 and in the treatment group was -0.20 (0.31) g/cm^3. The mean change in femoral hip z score ≤ 25, but there is not enough information to comment on the statistical significance of this. The authors report no significant effect of vitamin K on bone mineral density.
QoL: CFQ-R **Follow-up**:12 months	Outcome not reported.					
QoL: CFQoL	Outcome not reported.					

Follow-up: 12 months				
Adverse events **Follow-up**: 12 months	Outcome not reported.			
PIVKA II levels: change in PIVKA II (ng/mL) **Follow-up**: 12 months	Mean (SD) PIVKA-II concentrations increased significantly when participants were not supplemented (5.1 (3.2) ng/mL in the supplemented group and 21.8 (3.2) ng/mL in the unsupplemented group) and almost one third (5 out of 18) of the participants had PIVKA-II levels within the normal range (≤ 2 ng/mL) following supplementation.	18 (1 study)	Very low ⊕⊖⊖⊖[b,c]	
Uncarboxylated osteocalcin: change in carboxylation of osteocalcin (% Glu-OC) **Follow-up**: 1 month	See comments.			Two studies (total n = 56) narratively reported that vitamin K improved carboxylation of osteocalcin (Beker 1997; Kuitert 2010).

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **CFQoL**: Cystic Fibrosis Quality of Life; **CFQ-R**: Cystic Fibrosis Questionnaire - Revised; **PIVKA-II**: proteins induced by vitamin K absence; **SD**: standard deviation.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate.The true effect is likely to be substantially different from the estimate of effect

[a] Downgraded twice due to an unclear risk of bias in one RCT, particularly for the domains of randomisation, allocation concealment and blinding.
[b] Downgraded once due to imprecision as numbers were too low to meet the optimal information size.
[c] Downgraded twice due to risk of bias within one RCT. The randomisation and allocation concealment processes were unclear and it wasn't possible to blind either participants or healthcare providers. It was unclear whether the outcome assessors were blinded.

Summary of findings 2. Comparison of different vitamin K doses for people with cystic fibrosis

High-dose vitamin K compared to low-dose vitamin K for people with cystic fibrosis

Patient or population: people with cystic fibrosis

Setting: community or health care facilities
Intervention: high-dose vitamin K
Comparison: low-dose vitamin K

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with low-dose vitamin K	Risk with high-dose vitamin K				
Time to cessation of bleeding **Follow-up**: 12 months	Outcome not reported.					
Bone mineral density: lumbar spine z score **Follow-up**: 12 months	Outcome not reported.					
QoL: CFQ-R **Follow-up**:12 months	Outcome not reported.					
QoL: CFQoL **Follow-up**: 12 months	Outcome not reported.					
Adverse events **Follow-up**: 12 months	Outcome not reported.					
PIVKA II levels: change in PIVKA II (ng/mL) **Follow-up**: 12 months	Outcome not reported.					
Uncarboxylated osteocalcin: change in carboxylation of osteocalcin level (% Glu-OC) **Follow-up**: 1 month	Uncarboxylated osteocalcin was 2.20% lower in the 1 mg group than in the 5 mg group (14.33% lower to 9.93% higher).			13 (1 study)	Very low ⊕⊖⊖⊖[a,b]	

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **CFQoL**: Cystic Fibrosis Quality of Life; **CFQ-R**: Cystic Fibrosis Questionnaire - Revised; **PIVKA-II**: proteins induced by vitamin K absence; **SD**: standard deviation.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate.The true effect is likely to be substantially different from the estimate of effect

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[a] Downgraded once due to imprecision as numbers were too low to meet the optimal information size.
[b] Downgraded twice due to risk of bias within the single RCT. There was an unclear risk of bias across four of the six domains, particularly around randomisation, allocation concealment and blinding. This was a cross-over trial with no wash-out period and there was therefore a potential carry-over of treatment effect. No first-period data were 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; and over 100,000 people worldwide, most are diagnosed by six months of age and the median survival has reached the fifth decade of life (Davis 2006; Goss 2004; Klimova 2017; 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; Krzyzanowska 2018).

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 people 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 reduced bone mineral density (BMD) and thus osteopenia and osteoporosis (Conway 2005).

The majority of CF centres routinely administer vitamins A, D, and E as supplements from the neonatal period. Vitamin K administration 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 people with CF with pancreatic insufficiency. In a recent study of people with CF, the pathological proteins induced by vitamin K absence (PIVKA)-II concentration (≥ 2 ng/mL) was found in 42.8% of the population studied and an abnormal percentage of osteocalcin (≥ 20%) in 35.7% of people studied (Krzyzanowska 2015). 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 one study that only a higher level of supplementation can normalise vitamin K levels in people with CF (Dougherty 2010). Another study found that vitamin K deficiency occurs in people with CF despite applied supplementation (Krzyzanowska 2010). The study authors suggested that an accurate supplementation dose should be estimated individually and the assessment of its effectiveness

requires studies allowing investigators to determine the real body resources of vitamin K.

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.

This is an update of previous review versions (Jagannath 2010; Jagannath 2011; Jagannath 2013; Jagannath 2015; Jagannath 2017).

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 BMD, decrease risk of fractures and improve quality of life (QoL) 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 (RCTs) and quasi-RCTs.

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. RCTs comparing different doses and regimens of vitamin K were also considered.

Types of outcome measures

Primary outcomes

1. Clinical outcomes related to coagulopathy (Sutor 1995)
   a. time to cessation of bleeding manifestations (symptomatic coagulopathy)
   b. time to normalisation of sub-therapeutic international normalized ratio (INR) (asymptomatic or sub-clinical coagulopathy)
2. Bone formation outcome measures
   a. BMD 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)
   b. reduction in risk of bone fractures
3. QoL (e.g. the CFQ-R (Quittner 2000) and the CFQoL (Gee 2000))

Secondary outcomes

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

Search methods for identification of studies

There are no restrictions regarding language or publication status.

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 (CENTRAL) (updated each new issue of the Cochrane Library), weekly 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 website.

Date of the latest search: 12 August 2019.

We also searched online clinical trials registries (Appendix 1).

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.

Data collection and analysis

Selection of studies

Up to the 2017 update, two review authors (Vanitha Jagannath (VJ) and Zbys Fedorowicz (ZF)) independently assessed the abstracts of trials resulting from the searches. For 2020 update two review authors (VJ and Vidhu Thaker (VT)) independently assessed the abstracts for inclusion in the review. 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 Amy Price (AP). 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 (RevMan 2014).

Data extraction and management

We collected outcome data using a predetermined form designed for this purpose and entered details for the included trials into the tables in RevMan (Characteristics of included studies; RevMan 2014).

The authors extracted the following details.

1. Trial methods
   a. method of allocation
   b. masking of participants, investigators and outcome assessors
   c. exclusion of participants after randomisation and proportion and reasons for losses at follow-up
2. Participants
   a. country of origin and study setting
   b. sample size
   c. age
   d. gender
   e. inclusion and exclusion criteria
3. Intervention
   a. type
   b. dose and frequency
   c. duration of intervention in follow-up
4. Control
   a. type
   b. dose and frequency
   c. 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 outcomes (less than 12 months) and medium- to long-term outcomes (over 12 months)

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

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

The review authors have presented the comparison of vitamin K versus control separately to the comparison of high-dose versus low-dose vitamin K.

Assessment of risk of bias in included studies

For the original review, 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* (Higgins 2011). 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 RCTs 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 in the review (Risk of bias in included studies).

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 attempted to contact the authors of any trials where we needed clarification of trial design or results (at all stages of the review and updates). We have only received a response from the investigators of one of the trials which reported some data for two of our secondary outcomes, but presented these 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.

Assessment of heterogeneity

As we were only able to include three trials in this review and have not been able to combine data in a meta-analysis, 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 Chi^2 test and the I^2 statistic, where I^2 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 chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011). 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

For the original review, two review authors (VJ and ZF) analysed the data in Review Manager (RevMan 2014) and reported them as specified in chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Although we included three RCTs 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 2014). 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.

Summary of findings

We have prepared a summary of findings table according to GRADEpro guidelines to summarise the effect of supplementation of vitamin K compared with placebo in people with CF (Schünemann 2017a; Schünemann 2017b). We have included the outcomes of time to cessation of bleeding, BMD (lumbar spine z score), QoL measured using both CFQ-R and CFQOL, adverse events and the laboratory parameters of PIVKA and undercarboxylated osteocalcin (Summary of findings 1).

RESULTS

Description of studies

Results of the search

The electronic searches retrieved references to 10 trials. After examination of the titles and abstracts of these references, we planned to eliminate trials that did not match our inclusion criteria and were clearly ineligible. This was not the case and we obtained full text copies of the potentially eligible trials, which we subjected to further evaluation. The review authors discussed the eligibility of these trials, resolved any remaining uncertainties by consensus. We included three trials (Beker 1997; Drury 2008; Kuitert 2010), excluded five trials (Cornelissen 1992; Grey 2008; Mosler 2003; Nicolaidou 2006; Wilson 2001), and have listed two trials as awaiting classification until we obtain further information from the trialists (van Hoorn 2003; van Hoorn 2008).

Included studies

Three trials are included in the review; two of these did not address any of our primary outcomes and only reported on two of the secondary outcomes, while one trial reported on a primary outcome (BMD). Albeit the 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.

Vitamin K versus control

Characteristics of the trial

Two trials compared vitamin K to control; one was of parallel design (Kuitert 2010). One of the trials was cross-over in design, but did not include a washout 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.

Both were single-centre trials; one was carried out at the CF Clinic of the Children's National Medical Center (CNMC), Washington DC, USA (Beker 1997) and one was conducted at CF clinics of Barts and the London, Kings College Hospital and Lewisham University NHS Trusts (Kuitert 2010).

The duration of two trials differed. 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 washout period (Beker 1997). In the parallel trial the treatment period was 12 months (Kuitert 2010).

The providers of care in both trials were hospital staff and the assessors of outcomes were the investigators and other healthcare providers (Beker 1997; Kuitert 2010).

Characteristics of the participants

The total sample size comprised of 56 participants between the ages of 8 and 46 years (Beker 1997; Kuitert 2010).

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). 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 this trial (Beker 1997). Unfortunately, such details are not currently available from the remaining trial (Kuitert 2010).

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 second trial randomised participants to either 10 mg/day vitamin K or placebo (Kuitert 2010).

Characteristics of the outcome measures

One trial reported on one primary outcome BMD (z scores of femur, hip and lumbar spine) and also a secondary outcome of osteocalcin levels; however, since there is only an abstract available we do not have complete information (Kuitert 2010).

None of the primary outcomes specified in the protocol for the review were considered in the second trial (Beker 1997). This cross-over trial did, however, assess plasma vitamin K1 levels and serum undercarboxylated osteocalcin levels at the end of each period (Beker 1997). Dietary intake records to estimate the extent of dietary contribution of vitamin K1 were also maintained by the participants; 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 (Beker 1997).

High-dose vitamin K versus low-dose vitamin K

Characteristics of the trial

One parallel dose-ranging trial lasting one month compared different doses of vitamin K (Drury 2008). It was a single-centre trial conducted at the Montreal Children's Hospital CF Clinic in Canada. The providers of care were hospital staff and the assessors of outcomes were the investigators and other healthcare providers (Drury 2008).

Characteristics of the participants

The total sample size comprised 14 participants. The investigators reported that only pancreatic insufficient participants were included, but provided no further details; 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 (Drury 2008).

Characteristics of the interventions

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

This RCT did not report any of the primary outcomes specified in the protocol for the review. It did, however, report 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). These assessments were of plasma vitamin K1 levels and serum undercarboxylated osteocalcin levels measured at the completion of the trial (Drury 2008).

Excluded studies

Five trials were excluded from the review since these were not RCTs. Further information about the reasons for exclusion of trials is available in the tables (Characteristics of excluded studies).

Risk of bias in included studies

All included trials were judged as having an 'unclear' risk of bias overall (Beker 1997; Drury 2008; Kuitert 2010). 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.

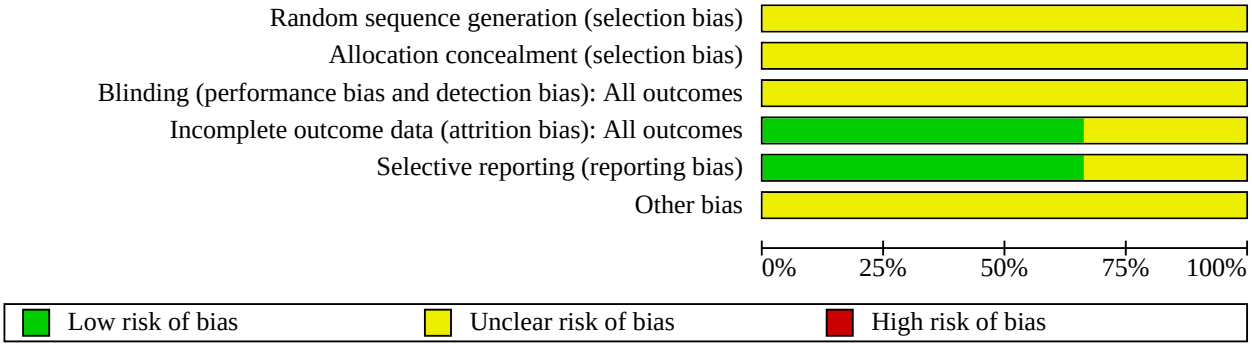
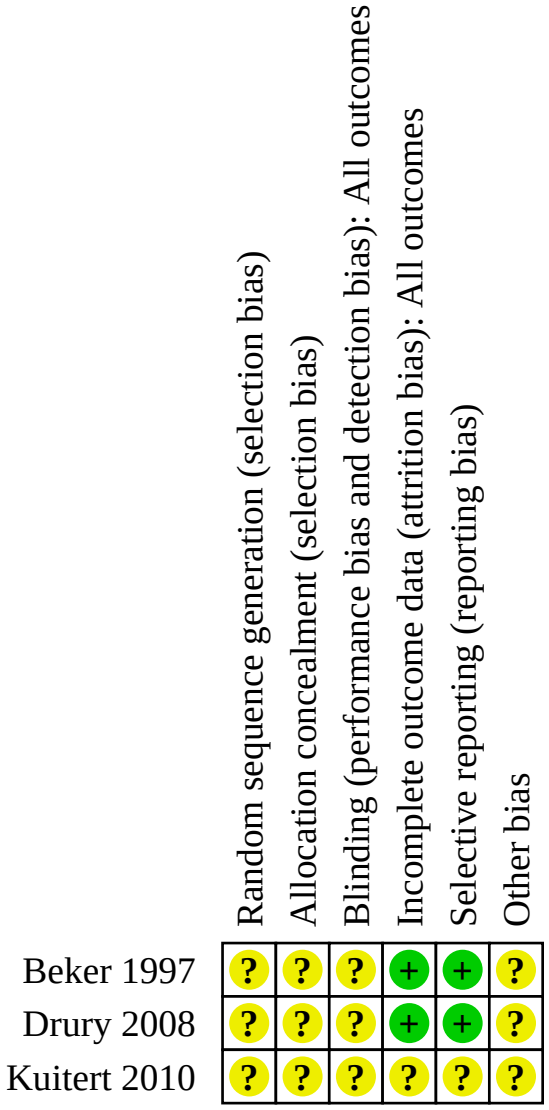


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The methods used to generate the allocation sequence were not reported in any trial. Moreover, none 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 any of the included trials (Beker 1997; Drury 2008; Kuitert 2010).

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 any trial (Beker 1997; Drury 2008; Kuitert 2010). 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 all 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 of these trials. The judgement for the remaining trial was unclear in view of limited information obtained in the abstract (Kuitert 2010).

Selective reporting

Although trial protocols were not available for two trials, 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. For the remaining trial we judged the risk of bias to be unclear since although the protocol was available on trials registries, there was limited information reported in the abstract (Kuitert 2010).

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; Kuitert 2010).

Effects of interventions

See: **Summary of findings 1** Vitamin K compared to control for people with cystic fibrosis; **Summary of findings 2** Comparison of different vitamin K doses for people with cystic fibrosis

In the summary of findings table, the quality of the evidence has been graded for pre-defined outcomes (see above) and definitions of these gradings are provided within the table (Summary of findings 1; Summary of findings 2).

Vitamin K versus control

Two trials (n = 56) reported on this comparison (Beker 1997; Kuitert 2010).

Primary outcomes

1. Clinical outcomes related to coagulopathy

Neither trial reported on this outcome (Beker 1997; Kuitert 2010).

2. Bone formation outcome measures

One trial reported on bone formation outcome measures (Kuitert 2010). The data on number of participants in each group could not be obtained from the abstract and hence we report the relevant details here narratively. We graded the quality of the evidence as very low.

At baseline, 20% in the placebo group and 16.7% in the treatment group had femoral hip z scores less than -1.0 and 30% in the placebo group and 33.3% in the treatment group had lumbar spine z scores less than -1.0. One participant had a z score consistent with osteoporosis at the lumbar spine.

At 12 months the mean (SD) change in the placebo group at the femoral hip z score was 0.053 (0.19) g/cm^3 and in the treatment group was -0.20 (0.31) g/cm^3. At the same time point, the mean (SD) change in the placebo group in z score at the lumbar spine was 0.041 (0.15) g/cm^3 and in the treatment group it was -0.073 (0.30) g/cm^3 (Kuitert 2010).

3. QoL

Neither trial reported on this outcome (Beker 1997; Kuitert 2010).

Secondary outcomes

1. Nutritional parameters

Neither trial reported on this outcome (Beker 1997; Kuitert 2010).

2. Adverse events

Neither trial reported on this outcome (Beker 1997; Kuitert 2010).

3. Serum levels

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 trials included in this review.

a. % ucOC level

In the Beker trial, all of the participants had increased serum ucOC concentrations 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 of ucOC (21%) (Beker 1997).

The second trial reported that supplementation with vitamin K improved carboxylation of osteocalcin (P = 0.007), but we do not have data for analysis (Kuitert 2010).

b. ucOC/cOC ratio

One trial reported the mean (SD) reduction in ucOC to cOC of 14.02% (15.94) in the treatment group compared to 3.69% (20.59) in the placebo group (Kuitert 2010).

4. Vitamin K-specific laboratory outcomes

a. Plasma level of vitamin K1

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. PIVKA or antagonism factor II levels

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) (very low-quality evidence).

High-dose vitamin K versus low-dose vitamin K

Only one trial (n = 14) reported on this comparison (Drury 2008).

Primary outcomes

The included trial did not report on any of the primary outcomes specified in the protocol for this review (Drury 2008).

Secondary outcomes

1. Nutritional parameters

These were not assessed in the included trial (Drury 2008).

2. Adverse events

No adverse events were reported in the included trial (Drury 2008).

3. Serum levels

The Drury trial was underpowered (Drury 2008). Despite obtaining 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, the report did not provide sufficient clinical detail of the participants to enable any assessment of the degree of variability in presentation of CF. 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).

a. % ucOC level

In the Drury trial, all of the participants had elevated % ucOC levels before supplementation (in excess of 21%), 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 % ucOC levels decreased and returned to within the normal range in three out of the 13 participants by the end of the trial (one in the 5 mg/day group, two in the 1 mg/day group). The mean end of trial difference in % ucOC between the two intervention groups was MD -2.20 (95% CI -14.33 to 9.93) (Analysis 1.1) (very low-quality evidence).

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).

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

This outcome was not assessed in the included trial (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, -4.96 (95% CI -12.65 to 3.73) (Analysis 1.2).

b. PIVKA or antagonism factor II levels

This outcome was not assessed in the included trial (Drury 2008).

DISCUSSION

Summary of main results

There are three trials included in this review; two of these (n = 56) compare vitamin K to control (placebo or no supplementation) and one (n = 14) compares different doses of vitamin K. The results from the included trials could not be pooled and entered into a meta-analysis.

Vitamin K versus control

Only one trial (n = 38) reported on any of our primary outcomes and found no changes in BMD after 12 months of vitamin K supplementation in one trial (Kuitert 2010). Neither trial reported on nutritional parameters or adverse events, however, the trials reported an increase in serum vitamin K levels, and a decrease in the ucOC levels which returned to normal following supplementation with oral vitamin K (Beker 1997; Kuitert 2010). The PIVKA levels also showed a decrease and a return to normal in the Beker trial following supplementation (Beker 1997).

High-dose vitamin K versus low-dose vitamin K

The only trial (n = 14) comparing different doses of vitamin K (1 mg/day versus 5 mg/day) did not report on any of our primary outcomes, or the secondary outcomes of nutritional parameters and adverse events (Drury 2008). The trial did report that there did not appear to be any significant difference in serum ucOC or vitamin K levels, but the quality of the evidence was very low (Drury 2008). While the trial reported that serum vitamin K levels improved with supplementation, there was no difference between the high-dose and low-dose groups.

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 QoL 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 two included trials and the limited data from the longest (12-month trial) 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

Some of the practical and methodological difficulties faced by investigators of this research question were highlighted in these trials and the quality of the evidence across all outcomes assessed was very low (Summary of findings 1; Summary of findings 2). The key factors which are likely to have had a degree of impact on the quality level of the evidence for the outcomes assessed in this review can be linked to the design and implementation of the included trials, and in particular to the concealment of the allocation sequence and blinding of investigators and outcome assessors. The trials included in this review were underpowered and of short duration (the longest being 12 months) which was illustrated by the wide CIs in the comparisons of treatment effect

and reflected the degree of imprecision in these. In addition there were issues due to different scales of measurement for the outcomes and unavailable complete data.

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 RCTs and thereby helped to limit bias in the conduct of this review, the absence of any other published RCTs over the intervening 13 years between the earliest and latest of the 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 need for 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 most appropriate dosage. However, there is some concern that the adequacy of dosing based on the 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 cystic fibrosis (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 European Cystic Fibrosis Society and Cystic Fibrosis Foundation guidelines (Borowitz 2002; Cystic Fibrosis Trust 2002; Sinaasappel 2002) and be guided by monitoring of the proteins induced by vitamin K absence (PIVKA) or undercarboxylated osteocalcin 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.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Beker 1997

Study characteristics	
Methods	RCT. Cross-over design. Duration: 2 periods of 4 weeks. Location: 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** • 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 • 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** • 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) • 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. Participant 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	

Beker 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned" Page 512. Comment: insufficient information to make a clear judgement of 'Yes' or 'No'.
Allocation concealment (selection bias)	Unclear risk	Not reported. Probably not done.
Blinding (performance bias and detection bias) 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 (attrition bias) All outcomes	Low risk	There were no withdrawals and no missing or incomplete data.
Selective reporting (reporting bias)	Low risk	Although the protocol was not available all relevant outcomes appear to have been addressed.
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

Study characteristics	
Methods	RCT. Parallel design. Duration: 1 month. Location: Montreal Children's Hospital Cystic Fibrosis Clinic, Canada. Date not specified.
Participants	Randomised: n = 14; 8 to 18 years, gender unspecified. **Inclusion criteria** • CF with pancreatic insufficiency; method of CF diagnosis unreported **Exclusion criteria** • 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.
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.

Drury 2008 *(Continued)*

	Control: oral administration of injectable formulation of vitamin K1 phytonadione (Sandoz Canada, Boucherville, Qc) diluted 1 mg/1 mL; dose 5 mg/day for 1 month.
Outcomes	**Primary outcomes**: none reported **Secondary outcomes** • 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
Random sequence generation (selection bias)	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 (selection bias)	Unclear risk	Not reported. Probably not done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Participants: not reported. Healthcare providers: unclear. Outcomes assessors and data analysts: unclear. Comment: overall judgement unclear.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote "One subject in the 5 mg group lost consciousness at the time of the second blood procurement". Page 458. Comment: incomplete data for one participant.
Selective reporting (reporting bias)	Low risk	The stated objectives of the trial appear to match the listed outcomes. There was no evidence of selective reporting of outcomes.
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.

Kuitert 2010

Study characteristics

Methods	RCT. Parallel. Duration: 12 months. Location: CF clinics at Barts and the London, Kings College Hospital and Lewisham University NHS Trusts, UK.

Kuitert 2010 *(Continued)*

Participants	Participants 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), no overt liver disease and not taking vitamin K. 38 participants recruited. Age: 16 - 43 years.
Interventions	**Intervention**: 10 mg of menadiol phosphate (water soluble form of vitamin K) once daily orally. **Control**: placebo.
Outcomes	• 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
Notes	Trial was undertaken at CF clinics at Barts and the London, Kings College Hospital and Lewisham University NHS Trusts, UK. The trial details could only be obtained as an abstract of poster presentation of conference proceedings or entries on trials registries. An electronic mail communication with the trial author could not obtain any further information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no further details given in the published abstract.
Allocation concealment (selection bias)	Unclear risk	Details not available/published in the abstract.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Details not available/published, although the abstract describes the control as "placebo".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details not available/published.
Selective reporting (reporting bias)	Unclear risk	Protocol available on trial registry websites, but limited results only published in abstract form and not a full paper.
Other bias	Unclear risk	Insufficient detail available to make a judgement.

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 classification *[ordered by study ID]*

van Hoorn 2003

Methods	Case-controlled trial.
Participants	People with CF.
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 trial.

van Hoorn 2008

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

BMD: bone mineral density
CF: cystic fibrosis
ucOC: undercarboxylated osteocalcin

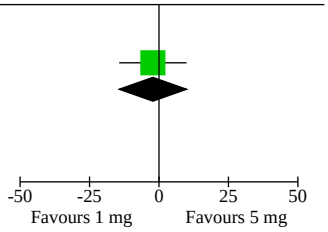
DATA AND ANALYSES

Comparison 1. 1 mg versus 5 mg oral vitamin k

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Serum % uncarboxylated osteocalcin	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 Short term (up to 12 months)	1	13	Mean Difference (IV, Fixed, 95% CI)	-2.20 [-14.33, 9.93]
1.2 Serum vitamin k levels	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 Short term (up to 12 months)	1	13	Mean Difference (IV, Fixed, 95% CI)	-4.46 [-12.65, 3.73]

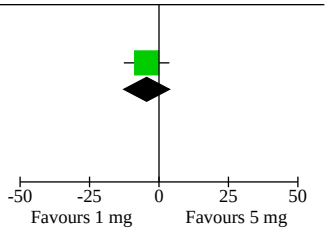
Analysis 1.1. Comparison 1: 1 mg versus 5 mg oral vitamin k, Outcome 1: Serum % uncarboxylated osteocalcin

	Vitamin K 1mg			Vitamin K 5mg				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.1.1 Short term (up to 12 months)									
Drury 2008	28	8.26	7	30.2	13.09	6	100.0%	-2.20 [-14.33 , 9.93]	
Subtotal (95% CI)			**7**			**6**	**100.0%**	**-2.20 [-14.33 , 9.93]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.36 (P = 0.72)									



Analysis 1.2. Comparison 1: 1 mg versus 5 mg oral vitamin k, Outcome 2: Serum vitamin k levels

	Vitamin K 1 mg			Vitamin K 5 mg				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.2.1 Short term (up to 12 months)									
Drury 2008	2.52	2.61	7	6.98	9.95	6	100.0%	-4.46 [-12.65 , 3.73]	
Subtotal (95% CI)			**7**			**6**	**100.0%**	**-4.46 [-12.65 , 3.73]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.07 (P = 0.29)									



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)

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

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

APPENDICES

Appendix 1. Electronic search strategies of online trials registries

Trials registry	Search terms	Date last searched
ClinicalTrials.gov (clinicaltrials.gov)	vitamin K AND cystic fibrosis	12 August 2019
International Standard Randomised Controlled Trials Number (ISRCTN) Registry (www.isrctn.com/)	vitamin K AND cystic fibrosis	12 August 2019
WHO International Clinical Trials Registry Platform (ICTRP) (WHO ICTRP)	vitamin K AND cystic fibrosis	12 August 2019

Appendix 2. 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

(Continued)

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

Date	Event	Description
7 May 2020	New citation required but conclusions have not changed	Despite the inclusion of results from a further study (n = 38) in the review, our conclusions remain the same.
7 May 2020	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register identified two new references potentially eligible for inclusion in the review which were found to be trial registry entries for a study already listed as ongoing and which has now been included (Kuitert 2010). A summary of findings table has been included at this update.

HISTORY

Protocol first published: Issue 4, 2010
Review first published: Issue 1, 2011

Date	Event	Description
20 June 2017	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register did not identify any new references potentially eligible for inclusion in this review.
20 June 2017	New citation required but conclusions have not changed	A former co-author, Prof Zbys Fedorowicz, has stepped down from the review and been replaced by Dr Amy Price. No new studies have been included in this updated review, therefore our conclusions remain the same.
13 April 2015	Amended	Contact details updated.

Date	Event	Description
4 February 2015	Amended	Source of support for author VT clarified and added.
18 December 2014	New citation required but conclusions have not changed	We have not been able to include any new information, hence our conclusions remain the same.
18 December 2014	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register did not identify any potentially eligible references for this review.
21 January 2013	New citation required but conclusions have not changed	No new information has been added to the review, therefore the conclusions have not changed.
21 January 2013	New search has been performed	A search of the Group's Cystic Fibrosis Register identified a single new reference to an ongoing study already listed in the review (Kuitert 2010a).
22 May 2012	Amended	Contact details updated.

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

Anne Chang declares she has received multiple grants from the National Health and Medical Research Council (Australia), but none of these relate to the subject matter of this review.

The remaining authors declare no financial conflicts of interest and that they do not have any associations with any parties who may have vested interests in the results of this review.

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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

Adolescent; Adult; Child; Humans