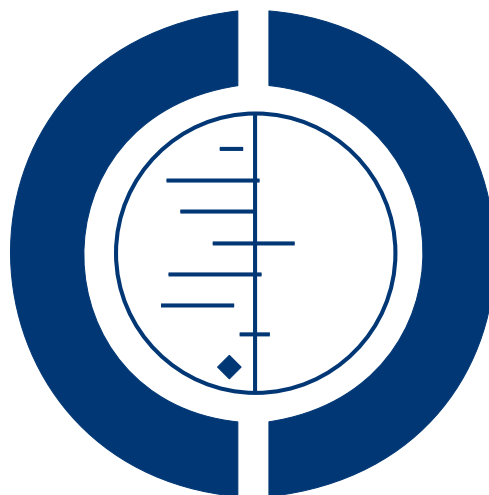


Vitamin A supplementation for cystic fibrosis (Review)

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[Intervention Review]

Vitamin A supplementation for cystic fibrosis

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ABSTRACT

Background

People with cystic fibrosis and pancreatic insufficiency are at risk of fat soluble vitamin deficiency as these vitamins (A, D, E and K) are co-absorbed with fat. Thus, some cystic fibrosis centres routinely administer these vitamins as supplements but the centres vary in their approach of addressing the possible development of deficiencies in these vitamins. Vitamin A deficiency causes predominantly eye and skin problems while supplementation of vitamin A to excessive levels may cause harm to the respiratory and skeletal systems in children. Thus a systematic review on vitamin A supplementation in people with cystic fibrosis would help guide clinical practice.

Objectives

To determine if vitamin A supplementation in children and adults with CF:

1. reduces the frequency of vitamin A deficiency disorders;
2. improves general and respiratory health;
3. increases the frequency of vitamin A toxicity.

Search methods

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

Date of the most recent search of the Group's Cystic Fibrosis Trials Register: 26 November 2009.

Selection criteria

All randomised or quasi-randomised controlled trials comparing all preparations of oral vitamin A used as a supplement compared to either no supplementation (or placebo) at any dose and for any duration, in children or adults with cystic fibrosis (defined by sweat tests or genetic testing) with and without pancreatic insufficiency.

Data collection and analysis

No relevant studies for inclusion were identified in the search.

Vitamin A supplementation for cystic fibrosis (Review)

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Main results

No studies were included in this review.

Authors' conclusions

As there were no randomised or quasi-randomised controlled trials identified, we cannot draw any conclusions on the benefits (or otherwise) of regular administration of vitamin A in people with cystic fibrosis. Until further data are available, country or region specific guidelines on the use of vitamin A in people with cystic fibrosis should be followed.

PLAIN LANGUAGE SUMMARY

The use of regular vitamin A preparations for children and adults with cystic fibrosis

Cystic fibrosis can cause certain vitamins, such as vitamin A, to be inadequately absorbed leading to problems caused by vitamin deficiency. Lack of vitamin A (vitamin A deficiency) can cause specific problems such as eye and skin problems. It can also be associated with poorer general and respiratory health. Thus people with cystic fibrosis are usually given regular vitamin A preparations from a very young age. However, excess vitamin A can also cause respiratory and bone problems. The review found no studies to show whether giving vitamin A regularly for people with cystic fibrosis is beneficial or not. The authors are unable to draw any conclusions regarding the routine administration of vitamin A supplements and recommend that until further evidence is available, local guidelines are followed regarding this practice.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a genetic disorder that affects multiple organs. Pancreatic insufficiency affects up to 90% of people with CF, whereby fat malabsorption occurs and pancreatic enzyme replacement is required to prevent steatorrhoea and malnutrition (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). Some CF centres routinely administer these vitamins as supplements from the neonatal period, whilst others administer them only later in life or when deficiencies are detected clinically or on routine monitoring. While deficiencies may occur from the disease process of CF and insufficient supplementation, vitamin toxicity may also occur from excess supplementation. Both deficiency and excess of these vitamins may lead to specific medical problems (Dodge 2006; Sethuraman 2006).

Vitamin A is an essential nutrient for epithelial cell maintenance and repair in the respiratory, urinary and intestinal tract, immune response, and bone growth (DAA 2006). Dietary vitamin A (retinol or retinol esters) is found in liver, beef, eggs, fish, the fat of dairy products and vitamin A fortified margarine. Beta- and alpha-carotene can act as precursors for the synthesis of vitamin A. The

dietary carotenoid (beta-carotene) is found in red, orange, yellow and leafy green vegetables (e.g. carrots, sweet potato, silverbeet) and red and orange fruit (e.g. mangos, oranges).

Vitamin A deficiency can be defined as serum retinol (SROL) concentration less than 0.70 $\mu\text{mol/L}$ (less than 20 $\mu\text{g/dl}$) (West 2003). However, SROL levels may be influenced by albumin and retinol binding protein (RBP) as well as acute illnesses with infection and inflammation (Napoli 1996; Stephensen 1994). SROL levels should be measured during clinical stability (DAA 2006). The major consequence of vitamin A deficiency is ocular (eye) with abnormal dark adaptation (night blindness), conjunctival and corneal xerosis (thickening) which can lead to blindness (DAA 2006; West 2003). Another consequence of vitamin A deficiency is the skin condition phrynoderma (a form of follicular hyperkeratosis associated with some micronutrient deficiencies). Vitamin A deficiency has also been linked to impaired mechanisms of host resistance to infection, poor growth and increased mortality in a study of mothers and children (West 2003).

Description of the intervention

Vitamin A is available as a sole supplement as well as in combination form with other vitamins.

How the intervention might work

Normalisation of vitamin A levels may avoid the afore-mentioned problems. However supplementation of these vitamins to excessive levels may cause harm to the respiratory system, the skeletal system (osteoporosis and fractures) and liver abnormality (Penniston 2006) in children with and without CF (Graham-Maar 2006; Sethuraman 2006).

Why it is important to do this review

The approach of addressing the possibility of the development deficiency of these fat soluble vitamins is variable among CF centres. Thus a systematic review on the efficacy of vitamins A, D, E and K supplementation in children and adults with CF in preventing effects of the deficiency of these vitamins would help guide clinical practice. Supplementation of vitamins D, E and K will be addressed in other Cochrane Systematic Reviews (Ferguson 2008; Shamseer 2008). This review will evaluate vitamin A supplementation in children and adults with CF.

OBJECTIVES

To determine if vitamin A supplementation in children and adults with CF:

1. reduces the frequency of vitamin A deficiency disorders;
2. improves general and respiratory health;
3. increases the frequency of vitamin A toxicity.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised (RCTs) and quasi-randomised trials (controlled clinical trials).

Types of participants

Children or adults with CF (defined by sweat tests or genetic testing) with and without pancreatic insufficiency.

Types of interventions

All preparations of oral vitamin A used as a supplement compared to either no supplementation or placebo at any dose for at least three months.

Types of outcome measures

We planned to obtain data on at least one of the following outcome measures:

Primary outcomes

1. Vitamin A deficiency disorders
 - i) visual impairment
 - ii) any other ocular dysfunction
 - iii) skin manifestations (e.g. phrynoderma)
2. Growth and nutritional status (e.g. weight, height, body mass index, z score for weight, etc.)
3. Mortality

Secondary outcomes

1. Respiratory outcomes
 - i) bronchiectasis severity control (e.g. Likert scale, visual analogue scale or radiological score (Marchant 2001))
 - ii) lung function indices (spirometry e.g. FEV₁ and FVC)
 - iii) proportions of participants who had respiratory exacerbations or hospitalisations or both
 - iv) total number of hospitalised days or days off work or school
 2. Quality of life
 3. Adverse events (e.g. vomiting, loss of appetite, osteoporosis, fractures or any other adverse event noted)
 4. Possible toxicity events (e.g. liver dysfunction)
 5. Measured levels of vitamin A
- We planned to evaluate outcomes based on
1. short term (12 months or less), and
 2. medium to long term (longer than one year)

Search methods for identification of studies

Electronic searches

We attempted to identify relevant studies from the Group's Cystic Fibrosis Trials Register using the term 'vitamin A'. The Cystic Fibrosis Trials Register 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 through 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 most recent search of the Group's Cystic Fibrosis Trials Register: 26 November 2009.

Searching other resources

Searches of bibliographies and texts of selected studies were also conducted to identify additional studies.

Data collection and analysis

The authors did not apply the process described below since no studies were identified. In future updates of this review, the authors will apply the following methods if studies are identified:

Selection of studies

From the title, abstract, or descriptors, two authors will independently review results of the literature searches to identify studies potentially relevant to the review according to our inclusion criteria for further assessment. From these studies, the same two authors will independently examine the papers in further detail in order to select studies for inclusion using the criteria stated before. The authors will resolve disagreement by consensus.

Data extraction and management

The authors will review studies that satisfy the inclusion criteria for the review and independently extract data on the outcomes described as follows: study setting; year of study; source of funding; participant recruitment details (including number of eligible participants); inclusion and exclusion criteria; randomisation and allocation concealment method; numbers of participants randomised; blinding (masking) of participants, care providers and outcome assessors; dose and type of intervention; duration of therapy; co-interventions; numbers of participants not followed up; reasons for withdrawals from study protocol (clinical, side effects, refusal and other); side effects of therapy; and whether intention-to-treat analyses were possible.

Assessment of risk of bias in included studies

In order to assess the risk of bias, two review authors will independently assess the quality of the studies included in the review according to the criteria described by Jüni ([Jüni 2001](#)):

Allocation concealment

Allocation concealment in each study will be assessed as follows:

1. Adequate, if the allocation of participants involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed opaque envelopes;
2. Unclear, if the method used to conceal the allocation was not described;
3. Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

Generation of the allocation sequence

Each study will be graded for allocation concealment as follows:

1. Adequate, if methods of randomisation include using a random number table, computer-generated lists or similar methods;
2. Unclear, if the study is described as randomised, but no description of the methods used to allocate participants to treatment group was described;
3. Inadequate, if methods of randomisation include alternation; the use of case record numbers, dates of birth or day of the week, and any procedure that is entirely transparent before allocation.

Blinding (or masking)

Each study will be graded for blinding as follows:

1. blinding of clinician (person delivering treatment) to treatment allocation;
2. blinding of participant to treatment allocation;
3. +blinding of outcome assessor to treatment allocation.

Follow up

Each study will be graded as to whether numbers of and reasons for dropouts and withdrawals in all intervention groups were described; or if it was specified that there were no dropouts or withdrawals.

We will also report on whether the investigators had performed a sample-size calculation and if they used an intention-to-treat (ITT) analysis.

Measures of treatment effect

The results from studies that meet the inclusion criteria and reports any of the outcomes of interest will be included in the subsequent meta-analyses if any data are applicable.

For the dichotomous outcome variables of each individual study, we will calculate the odds ratio (OR) using a modified ITT analysis, i.e. if the original investigators did not use ITT analysis, we

will consider dropouts to be failures. We will also calculate the summary weighted odds ratios and 95% confidence intervals (CIs) (fixed-effect model) using the Cochrane Collaboration's statistical package (RevMan 2008). Numbers needed to treat (NNT) and their 95% CIs will be calculated from the pooled OR and its 95% CI for a specific baseline risk, which is the sum of all the events in the control groups (in all studies) divided by the total participant numbers in control groups in all studies using an online calculator (Cates 2003).

For continuous outcomes, we will record the mean relative change from baseline for each group or mean post-treatment or post-intervention values and standard deviation. If standard errors are reported, we will calculate the standard deviations. We will then calculate a pooled estimate of treatment effect by the weighted mean difference and 95% confidence interval (fixed-effect model) again using RevMan (RevMan 2008).

Unit of analysis issues

For cross-over studies, we will calculate the mean treatment differences where possible and enter these using the fixed-effect generic inverse variance (GIV) analysis in RevMan, to provide summary weighted differences and 95% CIs (RevMan 2008). In cross-over studies, if we believe there is a carryover effect which will outlast any washout period included in the study, we will include only data from the first arm in the meta-analysis (Elbourne 2002).

If studies report outcomes using different measurement scales, we will estimate the standardised mean difference and 95% CIs.

Dealing with missing data

The authors will request further information from the primary investigators where required.

Assessment of heterogeneity

We will describe any heterogeneity between the study results and test this to see if it reached statistical significance using the chi-squared test. We will consider heterogeneity to be significant when the P value is less than 0.10 (Higgins 2006). We also plan to use the I² statistic where heterogeneity is categorised such that a value of under 25% is considered low, around 50% is considered moderate and over 75% is considered a high degree of heterogeneity (Higgins 2003).

Data synthesis

We will include the 95% CI, estimated using a fixed-effect model. However the random-effects model will be utilised whenever there are concerns about statistical heterogeneity.

Subgroup analysis and investigation of heterogeneity

We plan to perform the following a priori subgroup analyses to investigate any heterogeneity which has been identified.

1. children (aged 18 years or less) and adults (over 18 years);
2. formulations of the vitamin (single or multivitamin);
3. presence of significant liver synthetic dysfunction (low baseline albumin);
4. presence of previous bowel resections;
5. presence of pancreatic insufficiency;
6. method of CF diagnosis (i.e. screening versus symptomatic diagnosis).

Sensitivity analysis

Sensitivity analyses are also planned to assess the impact of the potentially important factors on the overall outcomes:

1. analysis using a random-effects model;
2. analysis by "treatment received" (as opposed to ITT analysis).

RESULTS

Description of studies

See: [Characteristics of excluded studies](#).

Results of the search

We identified a single study in our searches (Wood 2003).

Excluded studies

The only study identified was excluded because it was not placebo controlled (see [Characteristics of excluded studies](#)).

Risk of bias in included studies

We did not find any eligible studies that fulfilled the inclusion criteria.

Effects of interventions

We did not find any eligible studies that fulfilled the inclusion criteria.

DISCUSSION

Daily vitamin A supplementation is almost universally recommended for people with CF who are pancreatic insufficient. However, it is unfortunate that there are no controlled studies that have examined this. The appropriate dose and frequency of vitamin A supplementation is also unknown. Furthermore while vitamin A deficiency causes eye and skin disorders, excess vitamin A can also cause problems (Griffiths 2000; Penniston 2006). Indeed, increasingly data on micronutrients have shown that micronutrient supplementation is only beneficial in states of deficiency and harmful when no deficiency exists (Chang 2006; Shenkin 2006). For vitamin A, Griffiths has termed this the 'vitamin A paradox' as vitamin A supplementation is likely to be "protective against pneumonia in malnourished children (who are likely to be vitamin A-deficient) and is paradoxically detrimental for adequately nourished children" (Griffiths 2000). It is well accepted that people with cystic fibrosis and pancreatic insufficiency are at risk of vitamin A deficiency. However, it is also biologically plausible that currently, with improved pancreatic replacement therapies and attention to macro nutrition and caloric supplements, the majority of people with CF are vitamin A sufficient and may not require daily vitamin A supplementation. Daily supplementation in these situations at best causes no harm, but it adds a further burden to the daily medical regimen of people with CF and it is possible that it may be biologically harmful.

AUTHORS' CONCLUSIONS

Implications for practice

As there were no randomised or quasi-randomised controlled trials identified, we cannot draw any conclusions on the benefits (or

otherwise) of regular administration of vitamin A in people with cystic fibrosis. Until further data are available, country or region specific guidelines (e.g. UK CF Trust Nutrition Guidelines (CF Trust 2002)) on the use and monitoring of vitamin A in people with cystic fibrosis should be followed.

Implications for research

The need for a well-designed, parallel, adequately-powered, multicentre, randomised controlled trial to assess if vitamin A supplementation in children and adults with cystic fibrosis is beneficial or otherwise, is obvious. The study should examine if vitamin A supplementation positively or negatively influences the frequency of symptoms of vitamin A deficiency or general and respiratory outcomes. The possible negative effects should be examined in light of recent data showing possible harm when micronutrients are used in people who are not micronutrient-deficient. Safety monitoring during such a study would be important as the current practice is to use supplementation of vitamin A in people with CF. Vitamin A levels should be measured before and during the studies when clinically stable and related to serum albumin and retinol binding protein. Studies involving both children and adults are required and results should be related to nutritional status and pancreatic status. Data relating to appropriate dose and frequency of supplementation are also needed.

AUTHORS' CONCLUSIONS

ACKNOWLEDGEMENTS

We thank Nikki Jahnke and Dr Gerard Ryan from the Cochrane Cystic Fibrosis & Genetic Disorders Group for their advice, supportive role and comments to the protocol and review and to Natalie Yates for help with the searches.

Implications for practice

As there were no randomised or quasi-randomised controlled trials identified, we cannot draw any conclusions on the benefits (or

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Wood 2003	Non-placebo controlled trial. This trial examined outcomes of forty-six CF patients randomly assigned to either group A [low dose of supplement (10 mg vitamin E and 500 micro g vitamin A)] or group B [high dose of supplement (200 mg vitamin E, 300 mg vitamin C, 25 mg beta-carotene, 90 micro g Se, and 500 micro g vitamin A)]

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 25 November 2009.

Date	Event	Description
1 December 2009	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified a single reference which was excluded (Wood 2003).

HISTORY

Protocol first published: Issue 4, 2007

Review first published: Issue 1, 2008

Date	Event	Description
12 August 2009	Amended	Contact details updated.
10 April 2008	Amended	Converted to new review format.
10 April 2008	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any trials which might be eligible for inclusion in this review

CONTRIBUTIONS OF AUTHORS

Protocol: CO and AC wrote the protocol. ES reviewed the protocol.

Review: When any studies are identified, CO and AC will select relevant studies, perform data extraction and analysis and write the review. ES will contribute to writing of the review.

DECLARATIONS OF INTEREST

There is no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Royal Children's Hospital Foundation, Brisbane, Australia.

External sources

- National Health and Medical Research Council, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Cystic Fibrosis [*complications]; Vitamin A [adverse effects; *therapeutic use]; Vitamin A Deficiency [prevention & control]; Vitamins [adverse effects; *therapeutic use]

MeSH check words

Humans