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Allam MF, Lucena RA

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Selenium supplementation for asthma.
Cochrane Database of Systematic Reviews 2004, Issue 2. Art. No.: CD003538.
DOI: 10.1002/14651858.CD003538.pub2.

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[Intervention Review]

Selenium supplementation for asthma

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Editorial group: Cochrane Airways Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.

Citation: Allam MF, Lucena RA. Selenium supplementation for asthma. *Cochrane Database of Systematic Reviews* 2004, Issue 2. Art. No.: CD003538. DOI: 10.1002/14651858.CD003538.pub2.

ABSTRACT

Background

Selenium deficiency may be important in chronic asthma. Observational studies have demonstrated that patients with chronic asthma may have lower levels of selenium than their control. Nevertheless, selenium supplementation has not been recommended with drug therapy for asthma. This review systematically examines RCTs that evaluated the role of selenium supplementation in chronic asthma.

Objectives

Recognition that chronic asthma can be associated with selenium deficiency has led to the investigation of the role of selenium supplementation in reducing the symptoms and impact of chronic asthma. The objective of this review was to assess the efficacy of selenium supplementation as an adjunct to medication for the treatment of chronic asthma.

Search methods

We searched the Cochrane Airways Group Specialised Register, MEDLINE/PubMed, and EMBASE. Searches were current as of August 2005.

Selection criteria

Randomised trials comparing patients with chronic asthma receiving selenium supplementation in conjunction with asthma medication, with patients taking asthma medication only.

Data collection and analysis

Two reviewers applied the study inclusion criteria

Main results

One trial with a total of 24 patients suffering from chronic asthma was included. The study reported significant clinical improvement in the selenium-supplemented group, as compared with the placebo group, in terms of a 'clinical evaluation'. However, this improvement could not be validated by significant changes in separate objective parameters of lung function and airway hyper-responsiveness.

Authors' conclusions

There is some indication that selenium supplementation may be a useful adjunct to medication for patients with chronic asthma. This conclusion is limited because of insufficient studies and lack of improvement in the clinical parameters of lung function.

PLAIN LANGUAGE SUMMARY

Selenium supplementation for asthma

Selenium is a trace mineral, and it is thought that deficiency of selenium may play some role in the development of asthma. Some studies suggest that selenium supplementation for people with chronic asthma may help to improve symptoms. This review found some evidence from only one small trial that selenium supplementation might help reduce symptoms of chronic asthma symptoms, but more research is needed to be certain.

BACKGROUND

Asthma, a chronic inflammatory disorder of the respiratory airways, is characterized by bronchial airway inflammation resulting in airway hyper-responsiveness, wheezing, coughing, and shortness of breath (BTS 2003; Miller 2001). Oxidative processes, mediated by free radical chemistry, are recognized to contribute to its inflammatory pathology (Greene 1995; Fenech 1998).

There is no fixed figure for normal serum selenium level. In 1986, a collaborative study was conducted to examine the levels of selenium in Europe. Serum samples was obtained from healthy individuals, aged between 20 and 65 years, from 17 locations in 10 different European countries. Mean serum selenium levels were ranged between 63 ± SD 14 µg/L in Greece to 109 ± SD 14 µg/L in London (Thorling 1986). Meanwhile, mean selenium levels of healthy subjects according to different epidemiological studies are: Kadrabova 1996: mean plasma Se (ng/ml) in control subjects 58.4 ± SD 1.2; Stone 1989: mean Plasma Se (µmol/L) in control subjects 1.19 ± SD 0.19; Flatt 1990; mean plasma Se (ng/ml) in control subjects 60.6 ± SEM 1.8; Fenech 1998: mean plasma Se (ng/ml) in control subjects 114.4 ± SD 4.7.

The accumulated data indicate that asthma is associated with reduced circulatory selenium status and lowered activity of the selenium-dependent enzyme glutathione peroxidase, which may have aetiological implications, considering its important role in the cellular elimination of hydroperoxides (Stone 1989; Hasselmark 1993). It has been suggested that a serum Selenium concentration less that 100 ng/ml would be suboptimal for saturation of glutathione peroxidase (Thomson 1977).

Several epidemiological studies have observed lowered selenium status in asthma patients (Stone 1989; Flatt 1990; Shaw 1994; Kadrabova 1996). In addition, it has been reported that selenium supplementation might be beneficial to patients with intrinsic asthma (Kadrabova 1996).

Although selenium may be safer than new agents especially in patients with other chronic diseases, it is still not used as supplementary treatment to steroids and beta agonists. The level of selenium deficiency that is associated with disease is not clearly established. Similarly, the ability of supplementation protocols to reverse this deficiency is also not well established.

To our knowledge there has been no systematic review of the use of supplementary selenium in the treatment of asthma.

OBJECTIVES

The aim of the review is to assess the efficacy of selenium supplementation in asthma.

METHODS

Criteria for considering studies for this review

Types of studies

The review was restricted to randomised controlled trials (RCTs), which studied the efficiency of selenium as supplementary treatment in chronic asthma. Double blinded trials were preferred, but single blind and open studies were also reviewed for possible inclusion. No restriction was placed on the language of publications.

Types of participants

Participants were adults or children (over the age of 2 years) with a diagnosis of asthma. Asthma was diagnosed by solely clinical diagnosis by physicians as well as specific objective criteria. All healthcare settings (community/primary care, hospital outpatient or long-stay institutional) were considered eligible.

Types of interventions

Selenium administered as a supplementary treatment for at least 2 weeks, versus placebo.

Types of outcome measures

The primary outcome measure considered was symptom score.

Secondary outcomes considered were:
1) Lung function (FEV1, % predicted FEV1, diary and clinic PEFR and PEFR variability).
2) Selenium level post-intervention (if available).
3) Selenium-dependent enzyme glutathione peroxidase function post-intervention (if available).

Search methods for identification of studies

An initial search was carried out using the Cochrane Airways Group Specialised Regsister of asthma trials. Additional and separate searches were carried out on MEDLINE (1966-2005), EMBASE (1980-2005), PubMed and also on all relevant respiratory journals that were available electronically.

For this review, the Specialised Register was searched using the term: selenium*

Review articles and bibliographies of each RCT identified were searched for additional references that contained further RCTs. Personal contact with colleagues, collaborators and other trialists working in the field of asthma were made to identify other published and unpublished relevant studies.

Update searches have been run up to August 2005.

Data collection and analysis

SELECTION OF TRIALS:
Abstracts of articles identified using the search strategy above were viewed, and articles that appear to fulfil the inclusion criteria were retrieved in full. Data on at least one of the outcome measures were included in the study.
Each article identified were reviewed and categorised into one of the following groups:
-included: RCT that met the described inclusion criteria and those where it was impossible to tell from the abstract, title or MESH headings;
-excluded: non RCT.

Two reviewers (MFA and RAL) reviewed 10 papers retrieved and discarded those that did not meet the inclusion criteria of RCTs. Only one trial was appropriate for inclusion (Hasselmark 1993).

DATA EXTRACTION:

Data were independently extracted by the two reviewers (MFA and RAL) and cross-checked. Data were entered into RevMan 4.2 where possible.

For continuous variables data were extracted and entered as WMD. For dichotomous variables, data were extracted and entered as Odds Ratios (OR). No data could be pooled but any heterogeneity identified in future updates of the review will be explored on the basis of asthma severity and dose of selenium.

RESULTS

Description of studies

The search strategy yielded a total of 20 references. Eleven papers were retrieved, of which ten were excluded as they were non-randomised studies (See Characteristics of Excluded Studies'). One trial met the inclusion criteria (Hasselmark 1993). For a full description please see 'Table of Characteristics of Included Studies'. An update search in August 2004 did not identify any new studies for inclusion or exclusion in the review.

- **Study design**

Hasselmark 1993 was a randomised placebo-controlled, double-blind trial.

- **Participants**

Twenty four participants were recruited to the study. Participants suffered from chronic intrinsic asthma. Patients were excluded if they had atopic disease. Patients with recent or acute infections were excluded. Participants were recruited from a chest clinic. None of the participants had taken oral steroids or antibiotics in the previous three months. Patients had not taken selenium or vitamin E preparations in the previous six months.

The patients were allowed to use their habitual asthma drugs, which included beta agonist, theophyllines, and inhaled corticosteroids, but when extra medication was needed, this was noted in a protocol.

- **Interventions**

After a pre-intervention period of 4 weeks, one group received a daily supplement of 100 microgram sodium selenite for 14 weeks, whereas the other group received placebo.

- **Outcomes**

The following outcomes were assessed in the study: Clinical evaluation (this was a composite score based on changes in vital capacity, forced expiratory volume/ 1 second, histamine challenge, morning/evening peak expiratory flow, need of extra medication, and subjective judgment of the patient. This was dichotomised as deterioration, unchanged, or improved); lung function; biochemical markers.

During the first 2 weeks of the pre-intervention period and the last 2 weeks of the intervention period, the patients took measurements of peak expiratory flow each morning and evening. Measurement was also taken of serum selenium concentrations and of glutathione peroxidase activity in platelets.

Risk of bias in included studies

The included study was randomised, controlled and double blinded. The method of randomisation was not reported.
After the experimental period, there had been drop out of one patient (with NSAID-intolerance) for the selenium group and two patients (without NSAID-intolerance) form the placebo group. The reasons for the dropouts were in two cases other somatic disease, and in one case domestic reasons.

Whilst the study was described as randomised, the methods used were not reported. In addition to this the study sample was small and all the participants recruited suffered from intrinsic asthma.

Effects of interventions

Data could not be pooled due to the absence of more than one data set. Results are summarised below under comparison and outcome.

- **Selenium plus conventional treatment versus placebo plus conventional treatment**

SYMPTOMS

No data were reported separately on symptom assessment.

MEDICATION USE

No data were reported separately on additional medication usage.

LUNG FUNCTION

There were no significant changes between the baseline and final values with regards the individual VC, FEV_1, histamine challenge test, and peak expiratory flow (no values presented).

ASSEMBLED CLINICAL EVALUATION

This was a composite score of several clinical and subjective outcomes (lung function (FVC, FEV_1, histamine challenge, morning/evening PEF and subjective judgement). In the assembled clinical evaluation made of each patient, seven were classified as improved after the intervention period, while the other 13 were judged to be clinically unchanged or deteriorated. Breaking the code revealed that in the group of patients classified as improved six were from the selenium group (two with NSAID (non-steroidal anti-inflammatory)-intolerance) and only one (with NSAID-intolerance) was from the placebo group, a difference in distribution which was statistically significant. ($P = 0.042$).

BIOCHEMICAL MEASURES

The were no significant differences regarding the basal values of either selenium or glutathione peroxidase activity in platelets between the selenium group and the placebo group. The authors also failed to find any differences in basal values between the patients with NSAID-intolerance, as compared with patients without NSAID-intolerance.

When the basal values were compared with the final values, there were significant increases in the selenium group both in the serum selenium and platelet glutathione peroxidase ($P < 0.001$), while no significant changes could be observed in the placebo group (no p values reported).

DISCUSSION

It must be noted that our systematic review concerns itself only with studies which have used selenium as an 'add-on' to usual treatment for chronic asthma and not as an alternative.

After a comprehensive search, we could localize only one RCT (Hasselmark 1993). To our knowledge, no other RCT intended to assess the value of selenium supplementation in chronic asthma since then. Professor Jon Ayres (Birmingham Heartlands Hospital, UK) planned a pilot study of supplementation with magnesium, selenium and vitamins A, C and E in subjects with type 1 brittle asthma in 1998. However, Professor Ayres and his colleagues decided not to proceed with the study because of the diverse confounding factors (personal communication).

Various case-control studies over the last fourteen years confirmed that asthmatic patients had lower level of selenium than their control. However, these studies did not determine the degree of selenium deficiency that is believed to be significant. Few of these studies reported the same for glutathione peroxidase function (Stone 1989; Flatt 1990; Hasselmark 1990; Pearson 1991; Shaw 1994; Kadrabova 1996; Misso 1996).

The only localized RCT reported significant clinical improvement in the selenium supplemented group, as compared with the placebo group, with regard to the assembled clinical evaluation made for each patient. However, this improvement could not be validated by significant changes in the separate clinical parameters of lung function and airway hyper-responsiveness. This could be explained by the small sample size of the study (selenium group N = 10; placebo group N = 10).

Another important finding is that in the selenium supplemented group when the basal values were compared with the values after 14 weeks of daily supplement of 100 mcg sodium selenite, there were significant increases both in serum selenium and platelet glutathione peroxidase ($p<0.001$).

It is possible that the supplemental dosage given was too low and that a supplemental dose of 200-250 mcg might be more beneficial (Miller 2001).

Jahnova 2002 examined the effects of selenium supplementation in corticosteroid dependant asthmatics with lowered circulatory selenium status. The asthmatics were receiving 200 mcg of selenium per day for a period of 6 months, in addition to regular treatment with inhaled corticosteroids and beta agonists. The expression of adhesion molecules on peripheral blood mononuclear cells of asthmatics before and after 3 and 6 months of selenium supplementation was assessed. The results of the study have demonstrated that selenium is able to affect the adhesion molecule expression that are crucial in the inflammatory process of asthma.

AUTHORS' CONCLUSIONS

Implications for practice

One small trial found that selenium supplementation produced improvement in subjective symptoms for patients with chronic asthma but this was not supported by significant benefit in objective measurements. There is insufficient evidence to assess the use of selenium in clinical practice.

Implications for research

This appears to be a field of treatment for asthma that warrants further research. This would require larger randomised trials, standardised rating scales and outcome measures, at similar time periods. Such studies are important in the light of the growing body of evidence supporting theories that the impact of asthma is not based upon molecular or organic processes alone, but involves a complex interrelationship between these and psychological phenomena.

ACKNOWLEDGEMENTS

Our thanks go to Steve Milan, Jane Dennis, Toby Lasserson and Karen Blackhall who have been enormously encouraging and helpful.

REFERENCES

References to studies included in this review

Hasselmark 1993 *{published data only}*

Hasselmark L, Malmgren R, Zetterstrom O, Unge G. [Selenium supplementation in intrinsic asthma]. *Allergy* 1993;**48**(1):30-6.

References to studies excluded from this review

Fenech 1998 *{published data only}*

Fenech AG, Ellul-Micallef R. [Selenium, glutathione peroxidase and superoxide dismutase in maltese asthmatic patients: effect of glucocorticoid administration.]. *Pulmonary Pharmacology & Therapeutics* 1998;**11**(4):301-8.

Flatt 1990 *{published data only}*

Flatt A, Pearce N, Thomson CD, Sears MR, Robinson MF, Beasley R. [Reduced selenium in asthmatic subjects in New Zealand]. *Thorax* 1990;**45**(2):95-9.

Gazdik 2002 *{published data only}*

* Gazdik F, Kadrabova J, Gazdikova K. Decreased consumption of corticosteroids after selenium supplementation in corticosteroid-dependent asthmatics. *Bratislavske Lekarske Listy* 2002;**103**(1):22-5.

Hasselmark 1990 *{published data only}*

Hasselmark L, Malmgren R, Unge G, Zetterstrom O. Lowered platelet glutathione peroxidase activity in patients with intrinsic asthma. *Allergy* 1990;**45**(7):523-7.

Jahnova 2002 *{published data only}*

Jahnova E, Horvathova M, Gazdik F, Weissova S. Effects of selenium supplementation of adhesion molecules in corticosteroid-dependent asthmatics. *Bratislavske Lekarske Listy* 2002;**103**(1):12-6.

Kadrabova 1996 *{published data only}*

Kadrabova J, Mad'aric A, Kovacikova Z, Podivinsky F, Ginter E, Gazdik F. [Selenium status is decreased in patients with intrinsic asthma]. *Biological Trace Elemement Research* 1996;**52**(3):241-8.

Misso 1996 *{published data only}*

Misso NL, Powers KA, Gillon RL, Stewart GA, Thompson PJ. Reduced platelet glutathione peroxidase activity and serum selenium concentration in atopic asthmatic patients. *Clinical Experimental Allergy* 1996;**26**(7):838-47.

Pearson 1991 *{published data only}*

Pearson DJ, Suarez-Mendez VJ, Day JP, Miller PF. Selenium status in relation to reduced glutathione peroxidase activity in aspirin-sensitive asthma. *Clinical Experimental Allergy* 1991;**21**(2):203-8.

Shaw 1994 *{published data only}*

Shaw R, Woodman K, Crane J, Moyes C, Kennedy J, Pearce N. [Risk factors for asthma symptoms in Kawerau children]. *New Zealand Medical Journal* 1994;**107**(987):387-91.

Stone 1989 *{published data only}*

Stone J, Hinks LJ, Beasley R, Holgate ST, Clayton BA. [Reduced selenium status of patients with asthma]. *Clinical Science* 1989;**77**(5):495-500.

Additional references

BTS 2003

Scottich Intercollegiate Guidelines Network/The British Thoracic Society. British Guideline on the Management of Asthma. *Thorax* 2003;**58**(Suppl 1):i1-i95.

Clarke 2001

Clarke M, Oxman AD. [Assessment of study quality]. In: Clarke M, Oxman AD editor(s). Cochrane Reviewers Handbook. Vol. **4.1.2 [updated March 2001], Section 4**, Oxford: Update Software, 2001.

Greene 1995

Greene LS. [Asthma and oxidant stress: nutritional, environmental, and genetic risk factors]. *Journal of the American College of Nutrition* 1995;**14**(4):317-24.

Miller 2001

Miller AL. The etiologies, pathophysiology, and alternative/complementary treatment of asthma. *Alternative Medicine Review* 2001;**6**(1):20-47.

Thomson 1977

Thomson CD, Rea HM, Doesburg VM, Robinson MF. Selenium concentrations and glutathione peroxidase activities in whole blood of New Zealand residents. *British Journal of Nutrition* 1977;**37**(3):457-60.

Thorling 1986

Thorling EB, Overvad K, Geboers J. Selenium status in Europe--human data. A multicenter study. *Annals of Clinical Research* 1986;**18**(1):3-7.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Hasselmark 1993

Methods	Randomised, double-blind trial. Run-in phase: 4 weeks.

Hasselmark 1993 *(Continued)*

Participants	A total of 24 patients (12 in each group) suffering from intrinsic asthma (14 men, 10 women) with age ranged between 18 and 75 years were selected for the study. Of these patients 7 had intolerance to non-steroid anti-inflammatory drugs which had been verified by challenge test or typical history. Patients with atopic disease were excluded from the study. Exclusion criteria were also acute or recent infections of less than 3 weeks and somatic diseases of clinical importance. None of the patients had received treatment with oral corticosteroids or antibiotics, or take any lipid preparation less than 3 months before the study. Nor had the patients taken any selenium or vitamin E tablets during the previous 6 months.
Interventions	100mcg sodium selenite or placebo, BID for 14 weeks
Outcomes	Symptoms (in house scale); medication usage; vital capacity and FEV1. Regular measurement were also made of serum selenium concentrations and of GSH-Px activity in platelet
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

BID = once daily

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

Study	Reason for exclusion
Fenech 1998	CCT
Flatt 1990	CCT
Gazdik 2002	Before and after study
Hasselmark 1990	CCT
Jahnova 2002	Before and after study
Kadrabova 1996	CCT
Misso 1996	CCT
Pearson 1991	CCT
Shaw 1994	CCT
Stone 1989	CCT

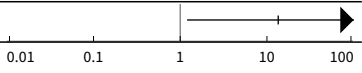
DATA AND ANALYSES

Comparison 1. Selenium plus usual care versus placebo plus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement (based on assembled clinical evaluation)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Selenium plus usual care versus placebo plus usual care, Outcome 1 Improvement (based on assembled clinical evaluation).

Study or subgroup	Selenium + UC n/N	Placebo + UC n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Hasselmark 1993	6/10	1/10		13.5[1.2,152.21]



WHAT'S NEW

Date	Event	Description
30 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2001
Review first published: Issue 2, 2004

Date	Event	Description
19 February 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Mohamed Farouk Allam: protocol initiation and development; assessing abstracts for suitability for inclusion; quality assessment and data extraction; interpretation and analysis.
Rosario Angulo Lucena: assessing abstracts for suitability for inclusion; quality assessment and data extraction; interpretation and analysis.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Asthma [*therapy]; Chronic Disease; Randomized Controlled Trials as Topic; Selenium [*administration & dosage] [deficiency]

MeSH check words

Humans