Selenium for preventing Kashin-Beck osteoarthropathy in children: a meta-analysis

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CRD summary
The authors concluded that selenium supplementation was associated with decreased risk of Kashin-Beck disease in children living in areas with low selenium levels. The evidence was limited and further research was needed. Given methodological limitations in the available studies, small sample sizes and uncertainties around the meta-analysis, the reliability of the authors’ conclusions is unclear.

Authors’ objectives
To assess the efficacy of selenium supplementation in the prevention of Kashin-Beck osteoarthropathy (Kashin-Beck disease, KBD) in children living in areas with low levels of selenium.

Searching
Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, Chinese Biomedical Database, Chinese National Knowledge Infrastructure, Chinese Science and Technique Journals Database, Chinese Clinical Trials Register and clinicaltrials.gov were search. Search terms were reported. Search dates varied across the sources and spanned 1966 to July 2007. No language restrictions were applied. Seven relevant journals were handsearched from the earliest record to July 2007. Reference lists of included studies were handsearched.

Study selection
Randomised controlled trials (RCT) and prospective non-randomised controlled trials that investigated the effects of selenium supplementation through any route and at any dosage compared to placebo or no treatment on rates of Kashin-Beck disease in children with under 18 years were eligible for inclusion. Studies of selenium supplementation in conjunction with vitamin E, vitamin C or both combined were excluded. Studies of adult and child participants were included if it was possible to isolate the data on the children.

Included RCTs were of selenium tablets of varying dosages and unknown duration compared to placebo in children aged between three and 13 years from Kashin-Beck disease endemic areas with or without Kashin-Beck disease. Included RCTs reported Kashin-Beck disease incidence rates or the case number of Kashin-Beck disease diagnosed using X-ray or Yonghou Scientific Survey group diagnosis criteria. Follow up ranged from one to three years.

Included prospective non-RCTs were of selenium salt, selenium tablet, selenium-iodine salt, selenium water and selenium crop spraying or fertiliser in varying dosages and unknown duration compared to placebo or no treatment in children between birth and 16 years in Kashin-Beck disease endemic regions. Included studies reported on the number of participants with Kashin-Beck disease or the incidence of Kashin-Beck disease measured using X-ray or recognised criteria. Follow up ranged from 10 months to six years. Some studies also reported on adverse events.

Two reviewers independently selected the studies for the review at both abstract and full text stages. Disagreements were resolved by consensus.

Assessment of study quality
Methodological quality of the RCTs was assessed according to Cochrane guidelines focusing on randomisation, allocation concealment, blinding and follow-up using the description of blinding and allocation concealment by Wu and Liu (2007) (see Other Publications of Related Interest). The quality of non-RCTs was assessed using a checklist by Deeks et al (2003). At least two reviewers independently assessed the methodological quality of the included studies; the authors stated only that disagreements were resolved by consensus without explicitly reporting how many reviewers performed the quality assessment.

Data extraction
The number of cases of Kashin-Beck disease in previously healthy children was extracted for the treatment and control groups in each study and used to calculate the odds ratio with corresponding 95% confidence intervals (CI). Two
reviewers extracted the data. It was unclear whether extraction was conducted independently.

**Methods of synthesis**

The results were combined using a fixed-effects Peto-odds ratio with 95% confidence intervals. Heterogeneity was assessed using the $X^2$ test and quantified using the $I^2$ statistic. Where there was evidence of significant heterogeneity, a random-effects meta-analysis was planned. The number needed to treat was calculated. RCTs and non-RCTs were analysed separately. Meta-regression was used to explore the effect of the following variables on Kashin-Beck disease incidence: study design; year study started; region; administration route; and duration of follow up.

**Results of the review**

Fifteen studies were included in the review and 12 were included for the meta-analysis. Five RCTs ($n=542$) and 10 prospective non-RCTs ($n=at least 1,817; n$ missing for two studies). Methodological quality of the included studies was generally low.

When RCTs were analysed, selenium supplementation was associated with a significant reduction in the risk of Kashin-Beck disease compared to placebo (odds ratio 0.13, 95% CI: 0.04 to 0.47, $p=0.002$; four RCTs, $n=399$). The number needed to treat was 21. Selenium supplementation continued to be associated with a significant reduction in the risk of Kashin-Beck disease compared to placebo or no treatment when non-RCTs were analysed (odds ratio 0.16, 95% CI: 0.09 to 0.30, $p<0.00001$; eight studies, $n=1,817$). The number needed to treat was 26. There was no evidence of significant statistical heterogeneity for either meta-analysis.

Meta-regression revealed no significant effects of study design, study year, region, administration route and duration of follow up on the effects of selenium supplementation on incidence of Kashin-Beck disease. Two trials reported no adverse events. One trial reported that some participants had nausea and vomiting.

**Authors' conclusions**

Current evidence supported the use of selenium supplementation to prevent Kashin-Beck disease in children living in areas with low selenium levels, but the evidence was limited and further research was needed.

**CRD commentary**

The review addressed a clear question with well-defined inclusion criteria. Several relevant databases were searched for articles in any language, thereby minimising the risk of language bias. However, attempts did not appear to be made to identify unpublished data, therefore, publication bias cannot be ruled out. Appropriate attempts appeared to be made to minimise reviewer error and bias in the review process. It was unclear whether the data extraction was conducted independently, therefore, reviewer error and bias cannot be definitively ruled out. The methodological quality of included studies was evaluated using established criteria. Although Peto's odds ratio performs well when events are rare, the disparity in sample sizes between intervention and control groups (particularly in non-randomised studies) meant that this method of meta-analysis may not have been appropriate. Given methodological limitations in the available studies, small sample sizes and uncertainties around the meta-analysis, the reliability of the authors' conclusions is unclear.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further large well-designed trials were needed of healthy children with cluster-randomisation of samples of at least 20 at village, school or classroom level with adequate follow up time. The dosage and administration of selenium should be well-defined and measured using biomarkers. Standardised outcome assessment was needed using both X-ray and diagnostic criteria to assess the incidence of Kashin-Beck disease. Adverse effects should be noted. Future research should be reported in accordance with the CONSORT statement.

**Funding**

No funding was received.
Bibliographic details
Osteoarthritis and Cartilage 2009; 17(2): 144-151

PubMedID
18693119

DOI
10.1016/j.joca.2008.06.011

Original Paper URL
http://www.oarsijournal.com/article/S1063-4584(08)00207-0/abstract

Other publications of related interest
Wu TX, Liu GJ. The concepts, design, practice and report of allocation concealment and blinding (in Chinese). Chin J

Indexing Status
Subject indexing assigned by NLM

MeSH
Adolescent; Cartilage Diseases /prevention & control; Child; Child, Preschool; Dietary Supplements; Humans; Joint
Diseases /prevention & control; Randomized Controlled Trials as Topic; Research Design; Selenium /adverse effects
/therapeutic use; Treatment Outcome

AccessionNumber
12009103296

Date bibliographic record published
27/05/2009

Date abstract record published
19/08/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on
the reliability of the review and the conclusions drawn.