Oral essential fatty acid supplementation in atopic dermatitis: a meta-analysis of placebo-controlled trials

Van Gool C J, Zeegers M P, Thijs C

CRD summary
This review assessed the effects of essential fatty acid (EFA) supplements on atopic dermatitis (AD). The authors concluded that there was no evidence that EFA supplements improve AD. Full details of the review methods were not reported, but the authors' conclusions appear to follow from the evidence presented.

Authors' objectives
To compare essential fatty acid (EFA) supplements with placebo for the treatment of atopic dermatitis (AD).

Searching
MEDLINE, EMBASE and Current Contents were searched from 1966 to April 2002 for reports in any language; the search terms were reported. The reference lists in published reports and reviews were checked.

Study selection
Study designs of evaluations included in the review
Parallel or crossover controlled trials were eligible for inclusion. If randomisation was not mentioned, the review considered the studies to be non-randomised controlled trials (CCTs). These studies were still eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared EFAs with placebo were eligible for inclusion. The included studies used supplements with high gamma-linoleic acid (GLA) or fish oil content. GLA was given at doses of 90 to 480 mg/day for children and from 132 to 720 mg in adults, for 3 to 24 weeks, in the form of borage oil, evening primrose oil or blackcurrant seed oil. Fish oil supplements contained EPA (presumably eicosapentaenoic acid; 204 to 3,060 mg) and docosahexaenoic acid (132 to 1,920 mg) and were given for 12 to 16 weeks. The studies used placebo controls that generally contained liquid paraffin, olive oil or palm kernel oil.

Participants included in the review
Studies of patients with AD were eligible for inclusion. The included studies were conducted in children and/or adults.

Outcomes assessed in the review
The inclusion criteria were not explicitly defined in terms of outcomes. The primary review outcome was AD severity, as assessed using a published scale, physician's judgement regarding change from baseline to end point, and/or patient or parents' self-reported overall improvement.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The studies were assessed for inclusion and exclusion criteria, characteristics of the participants, baseline comparability of the treatment groups, blinding of patients and outcome assessors, compliance, co-supplements, loss to follow-up, outcome measures, and the use of intention-to-treat analysis. Three reviewers independently assessed validity. Two reviewers were blinded to the year of publication, authors, affiliations, funding and results. Any disagreements were resolved through discussion.
Data extraction
Three reviewers extracted the data listed under validity criteria, while one reviewer extracted data on the characteristics of the interventions. Indications of competing interest were extracted for each study, including affiliations with or funding by manufacturers and sponsorship through donation of supplements.

For studies not reporting overall severity of AD, the reviewers pooled data from reported subscales using a fixed-effect model to give one measure of AD severity for each study (assuming independence between subscales). The mean improvement in AD severity in each treatment group was calculated as the mean value at the longest end point (while patients remained on allocated treatment) minus the mean baseline value. For each study, an effect size (ES) with 95% confidence interval (CI) was calculated using a correction for small sample size and with variances estimated where not reported (details of the methods used were reported). The data were estimated from graphs where necessary.

Methods of synthesis
How were the studies combined?
Studies reporting adequate data were pooled using a random-effects meta-analysis, weighted by estimates of between-study variances. The other studies were combined in a narrative. Publication bias was assessed visually using a funnel plot and tested using Egger's test.

How were differences between studies investigated?
For studies of GLA, a meta-regression was used to explore the influence on AD severity of study design, competing interest, age of the patients, duration of supplementation and source of GLA. There were too few studies to use meta-regression to explore influences on the results for studies of fish oil supplementation. Sensitivity analysis was performed using different values (0.2 to 0.6) for the correlation between subscales to calculate an overall severity of AD. The meta-analysis was repeated after excluding each study in turn.

Results of the review
Twenty-two controlled trials were included. Of these, 12 randomised controlled trials (n=623), 5 crossover studies (n=326) and 2 CCTs (n at least 62) assessed GLA. Four randomised controlled trials (n=328), of which two had a treatment arm with GLA treatment, and 1 CCT (n=48) assessed fish oils.

GLA (19 studies).
There was no significant difference in AD severity between GLA and placebo; the ES (11 trials) was 0.15 (95% CI: -0.02, 0.32).

The results among the 8 studies that reported inadequate data for meta-analysis were mixed: 2 studies found GLA significantly improved some aspect of AD compared with placebo, two found a non-statistically significant improvement with GLA, and two found no statistically significant difference between the treatments. Two studies reported no conclusions.

The meta-regression showed no influence on AD severity of study design (P=0.25), competing interest (P=0.21), age of the patients (P=0.44), duration of supplementation (P=0.33), or source of GLA (P=0.83).

Fish oil (4 studies).
There was no significant difference in AD severity between fish oil and placebo; the ES (3 trials) was -0.01 (95% CI: -0.37, 0.30).

Studies assessing component subscales generally found no statistically significant improvements with treatment compared with placebo.

The funnel plot was mildly suggestive of publication bias (under-representation of high precision studies), but Egger's test showed no evidence for publication bias (P=0.15).
The omission of each study in turn did not influence the results.

**Authors’ conclusions**

There was no evidence that EFA supplements improve AD. The treatment may be successful in subgroups such as young children, but there was insufficient evidence to assess this.

**CRD commentary**

The review question was clear in terms of the study design, intervention and participants. Three databases were searched and attempts were made to minimise language bias. No attempt was made to locate unpublished studies, thus raising the possibility of the omission of relevant data and publication bias. However, the reviewers did assess the potential for publication bias. The methods used to select the studies were not described, so it is not known whether any efforts were made to reduce errors and bias; methods were used to minimise bias in the validity assessment and some of the data extraction. Validity was assessed using established criteria, and some additional methodological limitations of the included studies were discussed in the text of the review.

Adequate information on the included studies was presented. Studies reporting adequate data were combined in a meta-analysis and meta-analysis graphs were presented for GLA studies. The influence of various factors on the results was explored. The authors’ conclusions appear to follow from the evidence presented.

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

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

Research: The authors stated that studies should assiduously report baseline values and report in full the overall severity of AD or component subscales.

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