Effect of alpha linolenic acid on cardiovascular risk markers: a systematic review

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CRD summary
This review studied the effects of dietary supplementation with alpha linolenic acid (ALA) on cardiovascular risk markers. It concluded that although ALA may cause small decreases in fibrinogen and fasting blood glucose, most cardiovascular markers are not affected, and that further trials are needed. The limited reporting makes it difficult to assess the reliability of the review's findings.

Authors' objectives
To investigate the impact of dietary supplementation with alpha linolenic acid (ALA) on established and emerging cardiovascular risk markers.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched for published studies, while the meta Register of Controlled Trials was searched for unpublished studies; the search terms were reported. Reference lists were searched and no language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with parallel (at least 4 weeks' treatment) or crossover (with a washout period of at least 4 weeks) designs were eligible for inclusion. Only data for the first treatment period of crossover trials were used if the results for both treatment periods were reported.

Specific interventions included in the review
Studies of ALA were eligible. The included treatments were ALA, linolenic acid, docosahexaenoic acid, arachidonic acid, eicosapentaenoic acid, gamma linolenic acid, fish oil, and various forms of vegetable oil such as olive and sunflower. These were most commonly consumed in the form of margarine, but also in bread products or as capsules. The control arms were placebo, although olive oil was used as a placebo in one study. Treatment duration ranged from 4 weeks to 2 years; most studies had a 4- to 6-week treatment period.

Participants included in the review
Studies of human participants were eligible. The participants varied across studies and included postmenopausal women, overweight men, healthy men and women, and men and women with cardiovascular risk factors such as high cholesterol, dyslipidaemia and non-insulin dependent diabetes. Average ages ranged from 24 to over 60 years.

Outcomes assessed in the review
Eligible outcomes were measures of cardiovascular risk markers. The outcomes included in the review were: changes in very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and total cholesterol; tryglycerides; fibrinogen; fasting plasma glucose; body mass index (BMI); weight; systolic and diastolic blood-pressure (BP); and various plasma markers such as tumour necrosis factor alpha.

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
Studies were assessed for validity on the basis of the randomisation method, blinding or objective measurements, loss to follow-up, and whether there were systematic differences in care between the treatment groups.
The authors did not state how many reviewers performed the validity assessment.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The change in the means of each outcome between the start and end of treatment were calculated. The corresponding standard deviations were estimated from the 95% confidence intervals (CIs) or standard errors if they were not reported directly.

**Methods of synthesis**

How were the studies combined?
The studies were combined in a meta-analysis using a fixed-effect model. If statistically significant heterogeneity was detected, a random-effects model was used. Weighted mean differences (WMDs) and 95% CIs were calculated for each outcome. Publication bias was assessed using funnel plots.

How were differences between studies investigated?
Heterogeneity was assessed using a chi-squared test at a 10% significance level. Subgroup analyses by ALA dose and placebo type were conducted.

**Results of the review**
Fourteen RCTs (n=1,235), of which two (n=57) were crossover trials, were included.

**Cholesterol and triglycerides.**
There was no significant difference between ALA and placebo for change in total cholesterol (WMD -0.01 mmol/L, 95% CI: -0.08, 0.06), based on 11 studies with significant heterogeneity (P<0.05). There was a statistically significant but clinically unimportant decrease in HDL cholesterol with ALA supplementation (WMD -0.01 mmol/L, 95% CI: -0.02, 0.00), based on 10 studies with no evidence of heterogeneity. There were no significant differences observed for LDL or VLDL cholesterol or for triglycerides.

**Body weight and BP.**
There was no significant difference between ALA and placebo for change in BMI (WMD -0.04 kg/m2, 95% CI: -0.11, 0.03; 3 studies) or weight (WMD -0.18 kg, 95% CI: -0.72, 0.36; 3 studies). There were also no differences for systolic BP (WMD -0.72 mmHg, 95% CI: -2.01, 0.58; 3 studies) or diastolic BP (WMD -0.17 mmHg, 95% CI: -0.82, 0.48; 3 studies). There was no evidence of heterogeneity for any of these outcomes.

**Glucose and fibrinogen.**
There was a significant reduction in fasting plasma glucose after ALA supplementation (WMD -0.20 mmol/L, 95% CI: -0.30, -0.10; 2 studies). There was also a significant reduction in fibrinogen (WMD -0.17 micromol/L, 95% CI: -0.30, -0.04; 3 studies). There was no evidence of heterogeneity for either outcome.

**Emerging cardiovascular risk markers.**
One study reported changes in plasma markers. Vascular cell adhesion molecule 1 was the only marker that was significantly different between treatments.

**Other analyses.**
Subgroup analyses by placebo type or ALA dose did not show any significant differences (results not presented). Funnel plots suggested no evidence of publication bias (plots not presented).
Authors' conclusions
ALA supplementation may lead to small decreases in fibrinogen concentrations and fasting blood glucose levels, but most established or emerging cardiovascular risk factors do not appear to be affected. Further trials are needed but, on the basis of this meta-analysis, ALA supplementation to reduce cardiovascular disease cannot be recommended.

CRD commentary
The lack of detail reported by this review makes it difficult to assess its reliability. The research question was clear, the databases searched were appropriate and no language restrictions were applied. However, only limited details of the review methodology and included studies were reported. In particular, no details of the quality or results of individual studies were presented. A forest plot was presented for only one of the outcomes. The authors' conclusions are cautious and recommend the need for further research, but the brief reporting of this review prevents independent endorsement of its findings.

Implications of the review for practice and research
Practice: The authors stated that, based on the findings of this meta-analysis, dietary supplementation with ALA for cardiovascular disease cannot be recommended.

Research: The authors stated that further trials of ALA supplementation are needed.

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