Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis

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CRD summary
This review concluded that fish oil supplementation resulted in clinically significant reductions in blood triglyceride levels, but had little effect on cholesterol, in hyperlipidaemic patients. A lack of reporting of some of the review methods and quality assessment, plus the levels of heterogeneity, warrant cautious interpretation of these results.

Authors’ objectives
To evaluate the benefits of fish oil supplementation for blood lipid management in hyperlipidaemic patients.

Searching
MEDLINE, EMBASE, Current Contents, CINAHL, AMED, DARE, Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews were searched from 1996 to March 2008. Search terms were reported. In addition, trial registers of National Institute of Health, National Research Register and Current Controlled Trials were scanned. Reference lists were also searched manually. There were no language restrictions.

Study selection
Randomised controlled trials (RCTs) of adults with cardiovascular risk factors (hyperlipidaemia, diabetes, acute myocardial infarction, coronary heart disease) that compared omega-3 supplements (eicosapentaenoic acid or docosahexaenoic acid) with placebo and that reported on lipid biomarkers (high-density lipoprotein, low-density lipoprotein, total cholesterol, triglycerides) were eligible. RCTs not using a parallel design, in normolipidaemic individuals, or evaluating omega-3 supplied through diet were excluded.

The included trials were conducted between 1985 and 2007 with most populations being either hyperlipidaemic or having coronary heart disease. Some trials were only in patients with insulin or non-insulin dependent diabetes. The included trials mainly compared fish oil (eicosapentaenoic acid or docosahexaenoic acid) with olive oil, sunflower oil, evening primrose oil or placebo. Most of the trials (72%) had participants that were male, with a mean age of 49 years. The mean duration of treatment was 24 weeks (range four to 260 weeks).

The authors did not state how studies were selected for the review.

Assessment of study quality
Trial quality was assessed using criteria recommended by the Cochrane Collaboration which assessed randomisation, allocation concealment, outcome assessor blinding and completeness of follow-up.

The authors did not report how many reviewers performed the quality assessment.

Data extraction
The mean difference (MD) between fish oil and control for total cholesterol, high-density lipoprotein, low-density lipoprotein and triglyceride levels were extracted for each trial. Data on adverse events were also extracted. Trial authors were contacted for clarification where necessary.

Data were extracted by two reviewers independently with disagreements resolved by consensus.

Methods of synthesis
Results were pooled using a DerSimonian-Laird random-effects model. Heterogeneity was assessed using Cochran's Q statistic and the I² statistic. Subgroup analyses were used to explore differences in outcome measures by age, gender, fish oil formulation and fish oil dose. Meta-regression was also used to look at the effects of age, fish oil dose, baseline triglyceride level, patient compliance and trial duration. Sensitivity analyses compared results from those trials that did or did not satisfy quality criteria for randomisation, allocation concealment or blinding. Publication bias was assessed.
using a funnel plot and Egger's regression model.

**Results of the review**

Forty-seven RCTs were included (n=16,511 participants). Eight trials tested docosahexaenoic acid; 39 trials tested eicosapentaenoic acid fish oil. Most trials were rated as being of excellent quality; six did not reporting allocation concealment or blinding.

Compared with placebo, fish oil supplementation produced a statistically significant reduction in fasting blood triglyceride levels of -0.34mmol/L (95% CI -0.41 to -0.27) from a mean baseline level of 2.44mmol/L. There was a small statistically significant increase in low-density lipoprotein cholesterol after fish oil supplementation (MD 0.06mmol/L, 95% CI 0.03 to 0.09). There were no significant statistical differences for total cholesterol or high-density lipoprotein cholesterol.

Clinically significant triglyceride lowering appeared to be for a mean daily dose of 3.25g/day (1.9g/day of eicosapentaenoic acid and 1.35g/day of docosahexaenoic acid). The percentage reduction in triglycerides was related to the baseline triglyceride level (p<0.001) and the fish oil dose (p=0.01). Patient age, treatment compliance and treatment duration did not explain any of the variation in outcomes. Forty-five percent of trials reported adverse events in the fish oil groups; 29% reported them in the placebo groups. Most adverse events were gastrointestinal. No significant adverse events were reported.

Publication bias was suspected for the high-density lipoprotein, low-density lipoprotein and triglyceride outcomes. Egger's regression model was used to impute values for the potentially missing trials; the results were similar for high-density lipoprotein and low-density lipoprotein cholesterol. This suggested that the efficacy of fish oils for reducing triglyceride levels might be over-estimated by a small amount (-0.09).

**Authors’ conclusions**

Fish oil supplementation produced a clinically significant dose-dependent reduction of fasting blood triglyceride levels, but not total, high-density lipoprotein or low-density lipoprotein cholesterol levels in patients with hyperlipidaemia.

**CRD commentary**

This review had a clearly stated aim. It specified inclusion and exclusion criteria regarding study design, participants, interventions and outcomes. The literature search appeared to be comprehensive and there were no language restrictions, which reduced the risk of publication bias, an aspect of the review which the authors explored. Data extraction was performed by two reviewers independently to reduce the possibility of error and bias. However, it was not reported whether study selection and validity assessment were performed in the same way.

The authors stated that all the included trials were of good quality but did not report the details for each trial. The meta-analyses seemed to have been conducted using appropriate methods but, even though they reported it in the methods, no details of the amount of statistical heterogeneity have been reported. All outcomes, except total cholesterol, seemed to be very heterogeneous, so the pooled values may not be robust. The authors also referred to the observed values as being clinically significant without providing any details to or references of how a minimal clinical difference was defined.

Given the lack of detail about some aspects of this review, the conclusion should be interpreted with caution.

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

The authors did not state any recommendations for practice or research.

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