Fish oil and glycemic control in diabetes: a meta-analysis
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Authors' objectives
To estimate the size and direction of the effects of fish oil administration on both glycaemic control and lipid parameters in non-insulin dependent and insulin dependent diabetes mellitus (NIDDM and IDDM, respectively).

Searching
MEDLINE, Excerpta Medica and Current Contents were searched using the terms 'fish oil', 'w-3 polyunsaturated fatty acids' and 'n-3 polyunsaturated fatty acids' in combination with 'diabetes mellitus', 'insulin dependent diabetes mellitus' and 'non-insulin dependent diabetes mellitus'.

The reference lists of all traced articles and most of the general reviews were examined manually.

Study selection
Study designs of evaluations included in the review
Intervention studies that included more than 5 diabetic patients and aimed to assess the effect of fish oil on lipid and glycaemic parameters were included. Study designs were of the following types: double-blind parallel randomised; double-blind crossover randomised; single-blind parallel randomised; open parallel randomised; open crossover randomised; and open before-and-after. The duration of the studies ranged from 2 to 36 weeks.

Specific interventions included in the review
The following brands of fish oil were included: Maxepa, EpaE, Eskisol, Promega, Superepa, PGE, Feniko, Resq1000, Pikasol, cod-liver and Sardiniol. The components of fish oil included eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The doses of EPA ranged from 0.69 to 5.40 g/day, whilst the doses of DHA ranged from 0.14 to 3.00 g/day. The placebo oils included olive oil and safflower.

Participants included in the review
The participants were patients of both genders with NIDDM or IDDM. The treatment of NIDDM patients included diet alone, glucose-lowering drugs such as sulphonylurea derivatives and/or metformin, and insulin. The participants included were those who were instructed to adhere to a diet and those given no such instruction. The mean age of the patients in the primary studies ranged from 24 to 59 years. The mean baseline levels of participants were as follows: fasting blood glucose, 9.7 mmol/L (95% confidence interval, CI: 7.1, 15.4); haemoglobin A1c (HbA1c), 9.4% (95% CI: 7.4, 12.1); triglycerides, 2.02 mmol/L (95% CI: 0.93, 4.91); total cholesterol, 5.6 mmol/L (95% CI: 4.5, 7.1); low-density lipoprotein (LDL) cholesterol, 3.6 mmol/L (95% CI: 2.4, 4.6); and high-density lipoprotein (HDL) cholesterol, 1.17 mmol/L (95% CI: 0.79, 1.64).

Outcomes assessed in the review
The outcomes assessed included changes serum triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, fasting blood glucose concentration and HbA1c.

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

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The following data were extracted independently by two authors: design of trial; brand of fish oil; daily dosage of EPA and DHA; duration of trial; use of placebo, and brand and concentration of placebo if used; number, gender, mean age, and NIDDM or IDDM classification of participants; other medications taken by the participants; and data on outcomes. The changes in parameters were calculated according to study design.

**Methods of synthesis**

How were the studies combined?

The data were analysed by linear regression, weighted according to study size. The mean estimates and 95% CIs were calculated.

How were differences between studies investigated?

Baseline glucose and lipid parameters, and changes after intervention, were calculated for the whole group. They were also calculated separately for controlled (double-blind RCT, placebo-controlled, parallel or crossover) and uncontrolled (before-and-after) studies, and diabetic types (NIDDM and IDDM). The effects of various EPA and DHA concentrations, diabetic type and study duration on glucose, HbA1c, triglyceride, LDL cholesterol and total cholesterol levels, were examined.

**Results of the review**

A total of 26 studies (N=425) were included. There were 24 studies (N=395) of serum triglycerides, 23 studies (N=382) of total cholesterol, 19 studies (N=350) of LDL cholesterol, 21 studies (N=378) of HDL cholesterol, 15 studies (N=257) of fasting blood glucose, and 19 studies (N=258) of HbA1c. Randomised controlled trials (RCTs) accounted for 13 studies (N=274); 8 of these were double-blind (N=180).

The 8 double-blind RCTs differed in the type and age of the patients, and the use of other medications. The mean change on intervention was as follows.

For fasting blood sugar: all studies, -0.06 (95% CI: -0.71, +0.59); NIDDM, 9.11 (95% CI: 7.11, 13.1); IDDM, -1.86 (95% CI: -3.1, -0.61, P<0.05).

For HbA1c: all studies, 0.16 (95% CI: -0.10, +0.41); NIDDM, 0.14 (95% CI: -0.41, +0.68); IDDM, 0.17 (95% CI: -0.09, +0.43).

For triglycerides: all studies, -0.60 (95% CI: -0.84, -0.37, P<0.05); NIDDM, -0.81 (95% CI: -1.16, -0.46, P<0.05); IDDM, -0.29 (95% CI: -0.50, -0.07, P<0.05).

For total cholesterol: all studies, 0.02 (95% CI: -0.09, +0.14); NIDDM, -0.07 (95% CI: -0.24, +0.09); IDDM, 0.19 (95% CI: 0.04, 0.33, P<0.05).

For LDL cholesterol: all studies, 0.18 (95% CI: 0.04, 0.32, P=0.01), non significant increases in both controlled and uncontrolled trials; NIDDM, 0.20 (95% CI: 0.0, 0.40, P<0.05); IDDM, 0.13 (95% CI: -0.14, +0.41). Neither study duration nor baseline LDL had a significant effect on LDL.

For HDL cholesterol: all studies, 0.03 (95% CI: -0.02, +0.08); NIDDM, -0.01 (95% CI: -0.08, +0.05); IDDM, 0.08 (95% CI: 0.01, 0.16, P<0.05).

Fish oil, dose of EPA or DHA, and study duration had no effect on the total cholesterol levels.

A dose-response effect of EPA on LDL cholesterol was only demonstrated for all studies combined: for every increase in EPA of 1 g/day, LDL cholesterol increased by 0.14 mmol/L (95% CI: 0.002, 0.28, P<0.05).

In NIDDM, for every increase in EPA of 1 g/day, HbA1c increased by 0.38% (95% CI: 0.00, 0.76, P<0.05), and serum triglyceride decreased by 0.36 mmol/L (95% CI: -0.63, -0.09, P<0.05); for every increase in DHA of 1 g/day, fasting blood glucose increased by 0.74 mmol/L (95% CI: 0.16, 1.32, P<0.05), HbA1c increased by 0.6% (95% CI: 0.06, 1.15, P<0.05), and serum triglyceride decreased by 0.47 mmol/L (95% CI: -0.92, -0.02, P<0.05).
There were no significant dose-response effects between EPA and DHA and various parameters in IDDM.

No optimal dosage of fish oil could be calculated.

The effect of baseline triglyceride level on the triglyceride response to fish oil administration was only significant for all studies combined: -0.44 mmol/L (95% CI: -0.59, -0.30, P=0.000) for every 1 mmol/L increase in baseline triglyceride level.

The effect of study duration on the triglyceride response to fish oil administration was only significant for all studies combined: 0.05 mmol/L (95% CI: -0.10, +0.0001, P=0.05) for every 1-week increase in study duration.

**Authors’ conclusions**
The use of fish oil had no adverse effects on the HbA1c levels in diabetic patients and lowered the triglyceride levels effectively by 30%. However, this may be accompanied by a slight increase in LDL cholesterol concentration. Fish oil may be useful in treating dyslipidaemia in diabetics.

**CRD commentary**
The authors provided details of the inclusion criteria for the primary studies, the keywords used in the search strategy, the methods used to extract the data, and the data extracted. Changes in blood glucose and lipid parameters were calculated according to study design, diabetic type, study duration, and concentration of EPA and DHA. The authors acknowledged the following limitations of the review: some results were based on a small number of studies; there were a small number of trials in the control group; and the potential misclassification of lipid levels due to within person fluctuations was augmented by intra- and inter-laboratory differences.

More comprehensive details of the literature search would have been helpful, such as the dates during which the databases were searched and whether there were any language restrictions imposed on the retrieved studies. No details were given of the methods used to select relevant studies. The validity of the included studies was not assessed. Many of the studies were of a small sample size: only 4 out of the 26 studies contained more than 20 patients. There was no comment on, or statistical assessment of, the heterogeneity of results among studies. It was not stated whether the data were extracted on an intention to treat basis. Any conclusion from this review was weakened on the basis of these factors.

**Implications of the review for practice and research**
The authors suggest that future trials of combinations of fish oil and an LDL cholesterol-lowering drug, or fish oil and pravastatin, are needed to test their efficacy.

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