Fish Oil and Glycemic Control in Diabetes

A meta-analysis

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OBJECTIVE — Hypertriglyceridemia is associated with cardiovascular disease in diabetes. Fibrates effectively lower, but do not always normalize, serum triglyceride levels. Fish oil supplements may then be added to lower serum triglyceride levels. Doubt remains whether the net effect of fish oil intake on glycemic control is beneficial in diabetes. We therefore performed a meta-analysis from published clinical trials.

RESEARCH DESIGN AND METHODS — Data sources were Medline (Cologne, Germany), Excerpta Medica, Current Contents, review articles, and published reference lists. Publications of 26 trials were selected, and all trials included more than five diabetes (IDDM and NIDDM) patients and addressed the effects of fish oil (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) on serum lipids and glucose tolerance. We (C.E.F., M.J.F.M.J.) extracted data independently based on predetermined criteria. Studies were classified according to design.

RESULTS — All studies combined showed a decrease in mean triglyceride concentrations in association with fish oil: −0.60 mmol/l (95% CI, −0.84 to −0.33, $P < 0.01$) and a slight but significant increase in serum LDL cholesterol: 0.18 mmol/l (95% CI, 0.04−0.32, $P = 0.01$), with both findings most prominent in NIDDM. No significant changes in HbA_{1c} percentages occurred in diabetic subjects treated with fish oil. Fasting blood glucose levels were increased with borderline significance in NIDDM subjects (0.43 mmol/l [95% CI, 0.00−0.87], $P = 0.06$) and were significantly lower in IDDM subjects (−1.86 mmol/l [95% CI, −3.1 to −0.61], $P < 0.05$). Significant dose-response effects of EPA (g/day) on HbA_{1c} and triglycerides and of DHA (g/day) on fasting blood glucose levels, HbA_{1c}, and triglycerides were demonstrated only in NIDDM subjects.

CONCLUSIONS — The use of fish oil has no adverse affects on HbA_{1c} in diabetic subjects and lowers triglyceride levels effectively by almost 30%. However, this may be accompanied by a slight increase in LDL cholesterol concentration. Fish oil may be useful in treating dyslipidemia in diabetes.

Debate remains about the net benefits of administering fish oil to diabetic patients. A link between diabetes and fish oil intake was first proposed during the 1960s and 1970s by Danish researchers, who reported a remarkably lower incidence of diabetes and cardiovascular disease in Greenland Eskimos compared with the general Danish population (1,2). Bang et al. (3) attributed this to differences in diet: the Eskimos consumed more fish (containing polyunsaturated fatty acids, mainly of the ω-3 class) and less saturated fat. Later epidemiological studies in other populations also showed fish consumption to be inversely related to cardiovascular mortality (4,5) and to glucose intolerance (6).

The high cardiovascular mortality rate in diabetes has been partly attributed to an unfavorable lipoprotein profile. This profile is characterized by increased serum triglyceride concentrations, mainly of serum VLDL triglyceride, and a low HDL cholesterol concentration (7). Fish oil has been shown to induce a decrease in serum triglycerides, sometimes accompanied by an increase in LDL and HDL cholesterol levels. Variable effects on glucose tolerance have also been reported; moreover, results in NIDDM and IDDM patients seem to diverge (8). These discrepancies may result from differences in such factors as trial design, type of patient studied (NIDDM or IDDM), and fish oil dosage. Reaching clear-cut conclusions about the efficacy of fish oil administration in diabetes is therefore difficult, and clinicians may be underutilizing the potentially beneficial effects of fish oil. We therefore performed a meta-analysis to estimate the size and direction of the effects of fish oil administration on both glycemic control and lipid parameters in NIDDM and IDDM patients.

RESEARCH DESIGN AND METHODS

Data sources

To identify all publications containing discussions of fish oil administration to diabetic patients, we (C.E.F, M.J.F.M.J.) conducted a computer search through Medline (Cologne, Germany), Excerpta Medica, and Current Contents using the terms fish oil, ω-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 general reviews of this topic (8–13) were examined manually.

Study selection and data extraction

The publications selected were of intervention studies that included more than five diabetic (IDDM and NIDDM) patients and that aimed to assess the effect of fish oil on lipid and/or glycemic parameters. In June 1995, this search had resulted in 61 publications (9,14–73). Of these, 36 publications did not meet our criteria: 5 did not concern diabetes (9,14–17); 16 were reviews or

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Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

commentaries (18–33); 2 described the same patients mentioned in other selected studies (34,35); 6 had final results missing (36–38), had baseline (39) or postintervention (40) results missing, or had outcomes that resulted from two different treatment dosages used (41); 6 did not involve administration of fish oil (42–46) or involved external use of fish oil (47); and 1 was a case report (48). Our meta-analysis summarized the results of the remaining 26 studies (49–74), classified by trial design.

We (C.E.F., M.J.F.M.J.) recorded the following characteristics from these trials independently:

1. Design of the trial (whether trial is open, single-blind, or double-blind; whether a parallel-group, crossover, or before-after design was used; and whether the trial was randomized).
2. Brand of fish oil, daily dosage of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), duration of the trial (expressed in weeks), use of placebo, and brand and concentration of placebo if used.
3. Number, sex, mean age, and NIDDM or IDDM classification of participants in the study and which other medications, if any, were being taken by study participants.
4. Changes recorded in the following parameters during the intervention period: serum triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, fasting blood glucose concentration, and HbA_{1c}.

Calculations of the changes in parameters depended on the design of the trial. In before-after trials, the difference between baseline level and the end of the intervention period was calculated. In parallel trials, the differences between the results of the intervention period (before and after the intervention) and the placebo period (before and after the placebo period) were calculated, after which the change during the placebo period was subtracted from that during the intervention period. In crossover trials, first the difference between the end of the intervention period and the baseline period was calculated, then the difference between placebo period and baseline period was calculated, and finally the change in the placebo period was subtracted from that in the intervention period.

About one-third of the 26 selected reports did not report SDs or other measures of variance of one or more of the study parameters. Weighting according to variance was therefore impossible, and it was decided to weight the studies by number of participants. Two studies (51,60) had a three-parallel-groups design. Because of the small number of studies with this design, no separate analysis has been performed for these studies, and they were included as two-parallel-groups trials.

Statistical analysis

Data were analyzed using weighted linear regression analysis (Stata; Stata, College Station, TX). Because no individual data were available, the meta-analysis was based on aggregate data from published trials. The data-analytic approach was determined by the study with the most limited set of information. For this reason, the only weight used in the regression analyses was the size of the study (n). Mean estimates were calculated with corresponding 95% CIs. Analyses were performed for all studies combined, and separately for controlled studies (those with a double-blind, randomized, placebo-controlled, parallel, or crossover design) and uncontrolled studies (those with a before-after design), because we assumed heterogeneity for the fish oil effect by study design. Baseline glucose and lipid parameters and changes after intervention were calculated for the whole group, and separately for controlled and uncontrolled study designs and diabetes types (NIDDM and IDDM).

The effects of various EPA and DHA concentrations (g/day), diabetes type (NIDDM or IDDM), and study duration (expressed in weeks) on glucose, HbA_{1c}, triglyceride, LDL cholesterol, and total cholesterol concentrations were examined, and results for the whole group and the respective subgroups of trials were compared.

RESULTS

Trial characteristics

A summary of the design and selected clinical characteristics from all 26 trials is presented in Table 1. Some clinical data were missing, and not all study parameters were available from all included trials. Serum triglycerides were not measured in 2 trials (59,60), total cholesterol was not measured in 3 trials (59,60,62), LDL cholesterol was not measured in 7 trials (52,59,62,68,71,73,74), HDL cholesterol was not measured in 5 trials (52,59,62,71,74), fasting blood glucose was not measured in 11 trials (51,52,57,59,60,62,65,66,68,73,74), and HbA_{1c} was not measured in 7 trials (49,51,52,55,60,61,64). In 13 trials, treatment allocation was randomized (49–61), but only 8 of these trials (49–56) were executed in a double-blind fashion.

Even though these eight studies are comparable in design and dose of fish oil given (in general, ~1.8 g of EPA and 1.2 g of DHA), they differed in the type of patients included, NIDDM (49,50,52,54–56) or IDDM (51,53), and, consequently, in age of patient and the use of other medications. The NIDDM patients were treated for their diabetes with diet alone, with glucose-lowering drugs (sulfonylurea derivatives [55] and/or metformin [49,52]), or with insulin (50). One study did not state which medication was used (54). One study (55) used safflower oil, and all other studies used olive oil, as the placebo oil. In four studies (51,52,55,56), subjects were instructed to adhere to a diet, and their adherence was tested, but this instruction was not given in the other studies (49,50,53,54).

The effect of fish oil administration on the mean weighted differences of the various parameters, for the 26 studies combined and for NIDDM and IDDM studies considered separately, is summarized in Table 2. There was no effect of fish oil consumption on HbA_{1c} percentages in either NIDDM or IDDM subjects. Fish oil administration resulted in a tendency for fasting blood glucose levels to be higher in NIDDM subjects (0.43 mmol/l [95% CI, 0.00–0.87], $P = 0.06$) and to be significantly lower in IDDM patients (−1.86 mmol/l [95% CI, −3.1 to −0.61], $P < 0.05$). This difference in fasting blood glucose responses to fish oil between NIDDM and IDDM subjects was significant ($P < 0.01$). Fish oil consumption lowered serum triglycerides significantly by 25–30% in both types of subjects and resulted in a slight but significant increase in LDL cholesterol levels in NIDDM subjects only.

Dose-response curves were calculated for all studies combined and for the two diabetes groups separately. A dose-response effect of EPA on LDL cholesterol levels could be demonstrated only in all studies combined: for every increase in EPA dose of 1 g/day, LDL cholesterol concentrations increased by 0.14 mmol/l (95% CI, 0.002–0.28, $P < 0.05$). In NIDDM subjects, for every increase in EPA dose of 1 g/day, the HbA_{1c} increased by 0.38% (95% CI, 0.00–0.76, $P < 0.05$), and serum triglyc-

Table 1—*Design and clinical characteristics of 26 studies*

Study (reference number)	Study design	Fish oil dosage (brand)*	Placebo oil dosage (type)*	Duration (weeks)	EPA/DHA (g/day)	*n* (male/female)	Diabetes type	Age (years) (means ± SD)
Hendra et al. (49)	D,P,R	10.0 (Maxepa)	10.0 (olive)	6	1.80/1.20	80 (55/25)	NIDDM	56 ± 2
Westerveld et al. (50)	D,P,R	1.8 (EpaE)	1.7 (olive)	8	1.80/NP	16 (10/6)	NIDDM	59†
Mori et al. (51)	D,P,R	15.0 (Maxepa)	15.0 (olive)	3	2.84/1.83	18 (18/0)	IDDM	34 ± 6
Annuzzi et al. (52)	D,X,R	10.0 (Maxepa)	10.0 (olive)	2	1.80/1.20	8 (8/0)	NIDDM	51 ± 5
Jensen et al. (53)	D,X,R	21 ml/day (Eskisol)	21 ml/day (olive)	8	2.00/2.60	18 (14/4)	IDDM	37†
Vessby et al. (54)	D,X,R	10.0 (Maxepa)	10.0 (olive)	8	1.80/1.20	14 (11/3)	NIDDM	39–72 (range)
Borkman et al. (55)	D,X,R	10.0 (Maxepa)	10.0 (safflower)	3	1.80/1.20	10 (7/3)	NIDDM	57 ± 7
Connor et al. (56)	D,X,R	15.0 (Promega)	15.0 (olive)	24	4.10/1.90	16 (13/3)	NIDDM	59 ± 8
Haines et al. (57)	S,P,R	15.0 (Maxepa)	0.6 (olive)	6	2.70/1.90	41 (30/11)	IDDM	42 ± 9
Schectman et al. (58)	S,X,R	12.0 (Maxepa)	12.0 (safflower)	4	2.60/1.40	13 (9/4)	NIDDM	52 ± 4
Tariq et al. (59)	O,P,R	20.0 (Maxepa)	20.0 (olive)	36	3.60/2.40	8 (5/3)	IDDM	25†
Mori et al. (60)	O,P,R	15.0 (Maxepa)	NP	3	2.70/1.70	22 (22/0)	IDDM	33 ± 2
Zambon et al. (61)	O,X,R	15.0 (Superepa)	NP	8	4.50/3.00	10 (10/0)	NIDDM	64 ± 19
Spannagl et al. (62)	O,B	21.6 (PGE)	NP	4	5.40/2.30	13 (10/3)	IDDM	29 ± 8
Rillaerts et al. (63)	O,B	9.0 (Maxepa)	NP	10	1.80/0.90	12 (6/6)	IDDM	42 ± 11
Herrmann et al. (64)	O,B	6.0 (Feniko)	NP	12	1.80/1.20	19 (19/0)	NIDDM	48 ± 8
Friday et al. (65)	O,B	15.0 (Resq1000)	NP	8	4.50/3.00	8 (8/0)	NIDDM	64 ± 5
Mori et al. (66)	O,B	15.0 (Maxepa)	NP	3	2.67/1.72	10 (10/0)	IDDM	33 ± 7
Schmidt et al. (67)	O,B	4.0 (Pikasol)	NP	6	1.34/0.14	10 (4/6)	IDDM	31†
Schimke et al. (68)	O,B	6.8 (cod-liver)	NP	2	NP	20 (20/0)	IDDM	24 ± 2
Glauber et al. (69)	O,B	18.0 (Maxepa)	NP	4	3.30/2.20	6 (6/0)	NIDDM	59 ± 10
Miller et al. (70)	O,B	20.0 (Maxepa)	NP	8	4.00/—	5 (2/3)	IDDM	42†
Popp-Snijders et al. (71)	O,B	6 (Superepa)	NP	8	1.87/1.13	6 (3/3)	NIDDM	64 ± 5
Kasim et al. (72)	O,B	9.0 (Maxepa)	NP	8	1.62/1.08	22 (20/2)	NIDDM	62 ± 8
Bagdade et al. (73)	O,B	12.0 (Superepa)	NP	12	3.60/2.40	8 (0/8)	IDDM	30 ± 5
Kamada et al. (74)	O,B	2.7 (Sardinoil)	NP	8	0.69/0.20	12 (3/9)	NIDDM	60 ± 7

B, before-after; D, double-blind; NP, not present; O, open; P, parallel; R, randomized; S, single-blind; X, crossover. *Data for fish oil and placebo oil dosages are expressed in grams per day unless otherwise noted; †SD not given.

erides decreased by 0.36 mmol/l (95% CI, −0.63 to −0.09, $P < 0.05$). In NIDDM subjects, DHA had a significant influence on fasting blood glucose concentrations, HbA_{1c}, and serum triglycerides: for every increase in DHA dose of 1 g/day, fasting glucose concentrations increased by 0.74 mmol/l (95% CI, 0.16–1.32, $P < 0.05$), HbA_{1c} increased by 0.6% (95% CI, 0.06–1.15, $P < 0.05$), and serum triglycerides decreased by 0.47 mmol/l (95% CI, −0.92 to −0.02, $P < 0.05$). In IDDM subjects, there were no significant dose-response effects between EPA and DHA and various parameters. One study (74) reported an unlikely combination of values for total and LDL cholesterol. However, when this study was excluded from the analysis for these lipid fractions, the results remained essentially unchanged. Because of the divergent effects of EPA and DHA in NIDDM, and the narrow range of administered dosages in IDDM, no optimal dosage of fish oil could be calculated.

A significant influence of baseline triglyceride level on triglyceride responses to fish oil administration was demonstrated only when all studies were combined (−0.44 mmol/l [95% CI, −0.59 to −0.30], $P = 0.000$ per increase in baseline triglyceride level of 1 mmol/l). Study duration had a small effect, again only when all studies were combined; for every 1-week increase in study duration, triglyceride levels decreased by 0.05 mmol/l (95% CI, −0.10 to 0.0001, $P = 0.05$). The combined results further showed a significant increase in LDL cholesterol levels of 0.18 mmol/l (95% CI, 0.04–0.32, $P = 0.01$), with nonsignificant increases in both controlled and uncontrolled trials. Neither study duration nor baseline LDL cholesterol had a modifying effect on LDL cholesterol concentration after fish oil administration. No effect on HDL cholesterol could be found in the combined studies: 0.03 mmol/l (95% CI, −0.02 to 0.07, $P = 0.25$). No effect of fish oil, dose of EPA and DHA, or study duration on total cholesterol concentrations could be demonstrated, regardless of whether the results of the whole group or of the two designs, considered separately, were analyzed. In summary, trial design did not result in significant differences between measured parameters.

CONCLUSIONS — The results of this meta-analysis showed no deleterious effects of fish oil administration on glycemic control in NIDDM or IDDM subjects. NIDDM subjects showed a tendency to increase fasting blood glucose levels whereas IDDM subjects showed a significant decrease in fasting glucose levels. A profound triglyceride-lowering effect of fish oil, most prominent in NIDDM subjects, was confirmed by our analyses. The combined results of all studies indicate a slight but significant increase in LDL cholesterol levels but no changes in total and HDL cholesterol levels.

Table 2—*Combined (weighted) results of all 26 studies and of NIDDM and IDDM studies considered separately*

	Fasting blood glucose (mmol/l)	HbA_{1c} (%)	Triglycerides (mmol/l)	Total cholesterol (mmol/l)	LDL cholesterol (mmol/l)	HDL cholesterol (mmol/l)
All studies						
Mean baseline level (range)	9.7 (7.11–15.4)	9.4 (7.4–12.1)	2.02 (0.93–4.91)	5.6 (4.5–7.1)	3.6 (2.44–4.64)	1.17 (0.79–1.64)
Mean change on intervention (95% CI)	−0.06 (−0.71 to 0.59)	0.16 (−0.10 to 0.41)	−0.60* (−0.84 to −0.37)	0.02 (−0.09 to 0.14)	0.18* (0.04–0.32)	0.03 (−0.02 to 0.08)
NIDDM studies						
Mean baseline level (range)	9.11 (7.11–13.1)	8.8 (7.7–12.1)	2.6 (1.73–4.91)	5.8 (4.94–7.13)	3.7 (2.8–4.64)	1.01 (0.79–1.18)
Mean change on intervention (95% CI)	0.43 (0.0–0.87)	0.14 (−0.41 to 0.68)	−0.81* (−1.16 to −0.46)	−0.07 (−0.24 to 0.09)	0.20* (0.0–0.40)	−0.01 (−0.08 to 0.05)
IDDM studies						
Mean baseline level (range)	11.9 (9.9–15.4)	9.8 (7.4–11.1)	1.17 (0.93–1.47)	5.1 (4.48–6.26)	3.3 (2.44–4.53)	1.38 (1.08–1.64)
Mean change on intervention (95% CI)	−1.86* (−3.1 to −0.61)	0.17 (−0.09 to 0.43)	−0.29* (−0.50 to −0.07)	0.19* (0.04–0.33)	0.13 (−0.14 to 0.41)	0.08* (0.01–0.16)

*$P < 0.05$.

The results of this meta-analysis also suggest a dose-response relationship, especially in NIDDM, between EPA and DHA on various parameters (fasting blood glucose levels, HbA_{1c}, and serum triglyceride levels. A fish oil dosage of 3 g/day of **ω**-3 fatty acids (1.8 g/day of EPA and 1.2 g/day of DHA) was most commonly used. Fish oil consumption had no effect on glycemia in NIDDM in our meta-analysis and resulted in a significant decrease in mean serum triglyceride levels. These findings suggest that 3 g/day of **ω**-3 fatty acids is a safe and effective dosage for lowering triglyceride levels in NIDDM. Some changes in LDL cholesterol levels were so small that they may not have warranted treatment, but when treatment was indicated, a statin could be given. One must consider, however, that results were sometimes based on a small number of studies.

If our findings are to be accepted, we need to address some limitations of the analyses. We have done our utmost to include all published studies to avoid selection bias and confirmatory bias (which tend to emphasize one's preconceived perspective). Because heterogeneity of the results according to study design was expected, the trials were classified accordingly in different design groups and were evaluated separately. However, any difference we found between the overall results and the results of the controlled trials was probably due to the small number of trials in the controlled group ($n = 8$) rather than to real differences. Despite the obvious importance of controlled observations, no clear difference between controlled and uncontrolled studies could be shown in this meta-analysis of limited size. Misclassification of lipid levels is always a serious problem in intervention trials. Variability of lipoprotein concentrations can range from 5 to >20% (75,76). This variability is caused mainly by within-person fluctuations but is augmented by intra- and interlaboratory differences. The large fluctuations in biologic parameters serve as a good reason to perform a meta-analysis and thus enhance precision.

Comparison of our results with conclusions of narrative reviews (8,10–13, 77,78) showed that the latter (except for one [13]) tend to exaggerate the adverse influence of fish oil administration on glycemic control. In general, the authors of these reviews report a decrease in serum triglycerides and an increase in total and LDL cholesterol concentrations.

It is now well established that fish oil induces a decrease in triglyceride concentrations by decreasing the hepatic production of VLDL triglycerides (79,80). The triglyceride-depleted VLDL particles show a flux toward LDL, thereby increasing LDL cholesterol levels (81). A reduction in the number of LDL receptors in the liver (82) and peripheral tissues (83) also contributes to this increase. Fish oil may also increase gluconeogenesis from glycerol, but not total hepatic glucose production (84); consequently, one would not expect glycemic parameters to alter. Increased caloric intake by increased **ω**-3 fat intake (55) may explain the deterioration of fasting blood glucose levels reported in some studies. The evidence for the differing effects of EPA and DHA on serum lipids is fragmentary. In most studies, fish oil is used instead of the purified components EPA and DHA. Several studies suggest that EPA could be responsible for the lipoprotein changes associated with fish oil consumption (85–87). In normolipidemic subjects, EPA decreased triglyceride levels and increased LDL cholesterol concentrations (87). However, in hypertriglyceridemic NIDDM subjects, pure EPA showed no hypotriglyceridemic effect and only induced an increase in LDL cholesterol (50). Pure DHA did not show a hypotriglyceridemic effect in rats (88).

Hypertriglyceridemia is associated with cardiovascular disease in diabetes. How should it be treated? The first approach in the NIDDM patient should be optimization of diabetes control with diet, exercise, and, when indicated, oral hypoglycemic agents and/or insulin (89). In the IDDM patient, optimization of glycemic control with insulin therapy is mandatory. If hypertriglyceridemia is still present, fibric acid derivatives should be used. These agents, however, may not always normalize triglyceride levels. Fish oil supplements could then be added to lower triglyceride levels in both NIDDM and IDDM patients. Nicotinic acid is not recommended as first-line therapy because it could deteriorate glycemic control and the role of acipimox (a nicotinic acid analog, not yet registered in the U.S.) is uncertain. The combined hyperlipidemia common in diabetes (90) may be treated with a combination of fish oil and an LDL cholesterol–lowering drug such as a 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase inhibitor. The combination of fibrates plus HMG-CoA reductase inhibitors carries an increased risk of myopathy (91). The combination of pravastatin and fish oil has been shown during a short-term trial to be a very effective therapy with few side effects in patients with primary combined hyperlipidemia (92). Future trials

in diabetic patients are needed to test the efficacy of both combination therapies.

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