REVIEW ARTICLE

Fish Oil Supplementation in Type 2 Diabetes

A quantitative systematic review

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OBJECTIVE — To determine the effects of fish oil supplementation on lipid levels and glycemic control in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A comprehensive search of Medline, Embase, Lilacs, the Cochrane Clinical Trials Registry, bibliographies of relevant papers, and expert input updated through September 1998 was undertaken. All randomized placebo-controlled trials were included in which fish oil supplementation was the only intervention in subjects with type 2 diabetes. Three investigators performed data extraction and quality scoring independently with discrepancies resolved by consensus. Eighteen trials including 823 subjects followed for a mean of 12 weeks were included. Doses of fish oil used ranged from 3 to 18 g/day. The outcomes studied were glycemic control and lipid levels.

RESULTS — Meta-analysis of pooled data demonstrated a statistically significant effect of fish oil on lowering triglycerides (−0.56 mmol/l [95% CI −0.71 to −0.41]) and raising LDL cholesterol (0.21 mmol/l [0.02 to 0.41]). No statistically significant effect was observed for fasting glucose, HbA_{1c}, total cholesterol, or HDL cholesterol. The triglyceride-lowering effect and the elevation in LDL cholesterol were most marked in those trials that recruited hypertriglyceridemic subjects and used higher doses of fish oil. Heterogeneity was observed and explained by the recruitment of subjects with baseline hypertriglyceridemia in some studies.

CONCLUSIONS — Fish oil supplementation in type 2 diabetes lowers triglycerides, raises LDL cholesterol, and has no statistically significant effect on glycemic control. Trials with hard clinical end points are needed.

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The typical dyslipidemia associated with type 2 diabetes is a combination of hypertriglyceridemia, low levels of HDL cholesterol, and abnormal LDL composition (1). Several pharmacological approaches have been used to treat diabetic dyslipidemia (2). These include use of 3-hydroxy 3-methylglutaryl CoA (HMG-CoA) reductase inhibitors (3), fibric acid derivatives (4), and niacin (5). Standard dietary approaches focus on restriction of saturated fat and limitation of simple carbohydrate and alcohol intake (2). During the late 1980s, several investigators reported on the use of dietary supplementation with fish oil as a means of treating diabetic dyslipidemia (6,7).

The potential role of fish oil in cardiovascular disease risk reduction first came from observations involving Inuits in Greenland (8). Despite ingesting up to 40% of calories as fat (predominantly of marine origin), this population had a lower incidence of coronary heart disease than individuals with similar fat intake on a more conventional diet (9). Further evaluation revealed that dietary fish oil supplementation led to improvement in hypertriglyceridemia in nondiabetic individuals through lowering VLDL cholesterol synthesis (10,11). However, concern was raised in the initial nonrandomized studies in patients with type 2 diabetes that fish oil supplementation was associated with a deterioration in glycemic control (6,7). This concern continues to be mentioned in narrative reviews on the subject (12,13). The aim of the present study was to perform a systematic review of randomized controlled trials addressing the effects of fish oil supplementation in patients with type 2 diabetes. We were specifically interested in the effects of fish oil on lipid levels and glycemic control.

RESEARCH DESIGN AND METHODS

Identification and retrieval of primary studies

We conducted an electronic literature search from 1966 to September 1998 in Medline, Embase, Lilacs, Science Citation Index, and the Cochrane Controlled Trials Register using a protocol that included the Cochrane Collaboration's search strategy for randomized controlled trials (14) and the following terms: diabetes mellitus, type 2 diabetes, non-insulin dependent diabetes (NIDDM), fish oil, n-3 fatty acids, omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Hand searching of the bibliographic sections of all relevant articles was undertaken. Experts were consulted regarding unpublished or ongoing studies. Studies were included if they were randomized placebo-controlled trials that used fish oil supplementation as the only intervention in subjects with type 2 diabetes. Language was not an exclusion criterion.

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Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HMG-CoA, 3-hydroxy 3-methylglutaryl CoA.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many other substances.

Outcome measures and data extraction

Study selection, data extraction, and assigning of a quality score were undertaken independently by 3 investigators with discrepancies resolved by consensus. When data were not available in a published report, efforts were made to contact the primary investigators. Data related to the effects of fish oil and placebo on glycemic and lipid outcomes were extracted from each trial. One study reported total glycosylated hemoglobin; a formula was used to convert data to HbA_{1c} (15). Study quality was assessed using the score developed by Jadad et al. (16), which has a possible range of 0–5, with a cutoff of 2 used to designate studies of high versus low quality.

Data analysis and statistical methods

Extracted data were analyzed using the Review Manager 3.1 statistical software developed by the Cochrane Collaboration. A random-effects model was used to pool data. Effect sizes are presented as weighted mean differences with 95% CIs. Heterogeneity was assessed using the χ^2 method. Publication bias was evaluated using a funnel plot method (17). The method of Rosenthal (18) was used to estimate the number of unpublished studies with zero-effect that would be required to change a significant result from the meta-analysis into a nonsignificant result. Sensitivity analyses were planned a priori and undertaken for the following variables: study design, number of subjects, length of intervention, dose of fish oil, baseline triglyceride level, and study quality.

RESULTS

Search results

We obtained 158 citations, of which 64 were deemed relevant by title alone. Subsequent evaluation of the abstract and methods sections led to exclusion of 46 studies. Reasons for exclusion included the following: publications that did not assess fish oil supplementation (15 articles [19–33]), nonrandomized studies (11 articles [34–44]), the population had patients without diabetes or patients with type 1 diabetes (8 articles [45–52]), duplicate publications (7 articles [53–59]), studies that did not include a placebo arm (3 articles [60–62]), and 1 study that did not include human subjects (63). The 12-month follow-up report of the Italian Multicenter Fish Oil Study (64) was excluded because it is a nonrandomized non–placebo-controlled addition to the original study (65). Eighteen trials met inclusion criteria and were included in the review (65–82). The effect of fish oil on glycemic control and lipid levels was the focus of 17 of the included trials. One study was designed to assess the effect of fish oil supplementation on vascular physiology; however, these investigators also reported glycemic and lipid end points (73). Characteristics of the included studies are shown in Table 1.

Study characteristics

The 18 trials included 7 parallel group design and 11 crossover design studies. The parallel group trials ranged in duration from 3 to 24 weeks. The crossover studies had phases that ranged in duration from 2 to 24 weeks. None of the 11 crossover studies reported phase-specific data. Four studies had a washout period (3–8 weeks in duration) and 1 of these looked for but did not find a carryover effect (77). Of the 7 studies that did not have a washout period, 5 looked for and 2 found a carryover effect (66,72).

The interrater reliability for the assignment of a quality score was substantial (κ = 0.77). The studies could be classified by their quality scores into 8 studies of low quality ($\leq$2 points) (69–71,76,77,79, 80,82) and 10 studies of high quality ($>$2 points) (65–68,72–75,78,81). Because randomization was an inclusion criterion, all studies started with a score of 1. An additional point was usually assigned for the presence of blinding. Most of the articles of low quality failed to describe the method of randomization and/or blinding. Some failed to mask the odor of the fish oil supplement affecting blinding. In all of the trials, fish oil was added to the diet rather than being a replacement for some component of the dietary fat intake.

A total of 823 subjects were included in the 18 trials. The individual study sample size ranged from 8 to 418. The majority of participants were men between 55 and 65 years of age. Most participants had type 2 diabetes of 5–10 years' duration and were treated with diet or oral hypoglycemic agents. Few had diabetes-related complications. In 4 studies, all participants were hypertriglyceridemic (65,68,71,76). Two other studies included a subset of hypertriglyceridemic subjects, and these comprised 46% (69) and 10% (74) of all participants. Individual study exclusion criteria are outlined in Table 1.

The dose of fish oil ranged from 3 to 18 g (1.08–5.2 g EPA and 0.3–4.8 g DHA). The fish oil was usually given in capsules with the exception of 1 study, in which a liquid form was used (70). The dose of placebo was matched to the dose of fish oil. The placebo used was a vegetable oil with the exception of 1 study that used a saline solution (70).

Data synthesis

Glycemic control. Of the 18 trials included in the review, only 12 reported their fasting glucose results in a way that permitted pooling of data (Fig. 1). The pooled weighted mean difference for fasting glucose was 0.26 mmol/l (95% CI −0.08 to 0.60). Fifteen trials reported glycosylated hemoglobin data, and 11 of these were amenable to meta-analysis. The pooled weighted mean difference was 0.15% (−0.08 to 0.37). Of the 11 crossover studies, 8 reported glycosylated hemoglobin, and 5 had phase duration of $<$8 weeks.

Lipid profile. Fourteen trials reported data on triglycerides (Fig. 2). The pooled weighted mean difference was −0.56 mmol/l (−0.71 to −0.41). This effect was most marked in studies that recruited only hypertriglyceridemic subjects; the pooled weighted mean difference was −0.73 mmol/l (−0.95 to −0.51). When studies that used the higher doses of fish oil were analyzed, the pooled weighted mean difference was −0.85 mmol/l (−1.44 to −0.26). Thirteen trials reported data on total cholesterol. The pooled weighted mean difference was 0.007 mmol/l (−0.13 to 0.15). Ten trials reported data on LDL cholesterol. The pooled weighted mean difference was 0.21 mmol/l (0.02 to 0.41). The increase was most marked in the studies that administered the highest doses of fish oil (0.51 mmol/l [0.18–0.84]) and recruited subjects with baseline hypertriglyceridemia (0.60 mmol/l [0.16–1.04]). Twelve trials reported data on HDL cholesterol. The pooled weighted mean difference was 0.02 mmol/l (0.01–0.05).

Sensitivity analyses. The results for the test of heterogeneity for all outcomes studied were nonsignificant ($P > 0.1$ [Figs. 1 and 2]). As indicated above, most of the variation observed for the triglycerides and LDL cholesterol outcomes could be explained by the presence of 2 trials that recruited only hypertriglyceridemic patients and used the highest doses of fish oil (71,76). There was no association between the studies' design,

Table 1—*Characteristics of included studies*

		Population characteristics									
Study	Design	Subjects [*n* (% male)]	Mean age (years)	Type 2 diabetes duration (years)	Diabetes complications (%)	Diabetes therapy (*n*)	Htg. (%)	Subjects withdrawn (*n*)	EC	Interventions	Duration (weeks)
Annuzi et al. 1991 (79)	Crossover	8 (100)	51	9.8	NA	Diet: 1 Oral agents: 4 Insulin: 0	NA	0	Renal and hepatic failure	1.8/1.2 g EPA/ DHA vs. 10 g olive oil	2 weeks per phase, no washout
Axelrod et al. 1994 (78)	Parallel	20 (NA)	56	7.8	Microvascular (22), Macrovascular (22)	Diet: 4 Oral agents: 1 Insulin: 4	NA	2 (1 colon cancer, 1 noncompliance)	Bleeding diathesis, anemia, poorly controlled diabetes, proliferative retinopathy, use of ASA, NSAID, or steroids	1.1/1.5 EPA/ DHA vs. 5 g safflower oil	6 weeks
Boberg et al. 1992 (66)	Crossover	14 (86)	65	NA	CAD (7)	Diet: 1 Oral agents: 13 Insulin: 0	NA	0	Renal and hepatic failure, hypothyroidism	1.8/1.2 g EPA/ DHA vs. 10 g olive oil	8 weeks per phase, no washout
Borkman et al. 1989 (77)	Crossover	10 (70)	57	3.5	CAD (10)	Diet: 6 Oral agents: 4 Insulin: 0	NA	0	Renal or hepatic failure, microvascular	1.8/1.2 g EPA/ DHA vs. 10 g safflower oil	3 weeks per phase, 3-week washout
Connor et al. 1993 (76)	Crossover	16 (81)	58	NA	NA	Diet: 1 Oral agents: 10 Insulin: 5	100	0	NA	4.1/1.9 g EPA/ DHA vs. 15 g olive oil	24 weeks per phase, no washout
Goh et al. 1997 (75)*	Crossover	28 (NA)	57	8	CAD (0)	NA	NA	0	Heart disease, lipid-lowering agent	1.4/0.88 g EPA/ DHA vs. 35 mg/kg linseed oil	12 weeks per phase, no washout
Hendra et al. 1990 (81)	Parallel	80 (75)	56	6.7	Microvascular in control group (42.5), in fish oil (70); CAD in control group (35), in fish oil (7.5)	Diet: 8 Oral agents: 32 Insulin: 0	0	0	Pregnancy, oral contraceptives, dyslipidemia, recent myocardial infarction or stroke	1.8/1.2 g EPA/ DHA vs. 10 g olive oil	6 weeks
Luo et al. 1998 (74)	Crossover	12 (100)	54	6	NA	Diet: 2 Oral agents: 8 Insulin: 0	10	2 (protocol violations)	Hepatic or renal failure thyroid or gastrointestinal disorders	1.08/0.72 g EPA/ DHA vs. 6 g sunflower oil	9 weeks per phase, 9-week washout
McGrath et al. 1996 (73)	Crossover	23 (87)	53	NA	Macrovascular (0)	Diet: NA Oral agents: NA Insulin: 0	NA	0	Renal failure, stroke, cardio-vascular disease, hypertension, cardiovascular drugs, lipid-lowering agents or vitamins	1.8/1.2 g EPA/ DHA vs. 10 g olive oil	6 weeks per phase, 6-week washout
McManus et al. 1996 (72)	Crossover	11 (73)	62	7.7	NA	Diet: 7 Oral agents: 4 Insulin: 0	NA	0	No insulin use or lipid-lowering agents	1.8/1.2 g EPA/ DHA vs. 35 mg/kg linseed oil	3 weeks, no washout
Morgan et al. 1995 (71)†	Parallel	40 (50)	54	9.8	NA	Diet: 2 Oral agents: 2 Insulin: 16	100	0	NA	Low dose: 2.6/2.4 High dose: 5.2/4.8 vs. 9 or 18 g corn oil	12 weeks
Pelikanova et al. 1993 (70)	Parallel	20 (100)	51	NA	NA	Diet: 0 Oral agents: 10 Insulin: 0	0	0	Obesity, Htg., renal or hepatic failure	15 ml (3 g) fish oil vs. 15 ml saline	3 weeks

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Table 1—*Continued*

Study	Design	Population characteristics: Subjects [*n* (% male)]	Mean age (years)	Type 2 diabetes duration (years)	Diabetes complications (%)	Diabetes therapy (*n*)	Htg. (%)	Subjects withdrawn (*n*)	EC	Interventions	Duration (weeks)
Puhakainen et al. 1995 (82)	Crossover	9 (44)	53	13	0	Diet: 2 Oral agents: 7 Insulin: 0	NA	0	Macro-/microvascular complications, hepatic or renal failure, bleeding diathesis, insulin requirement hypothyroidism	2.16/1.44 g EPA/DHA vs. 6 g corn + 6 g olive oil	6 weeks per phase, no washout
Schectman et al. 1988 (69)	Crossover	13 (69)	52	NA	Macrovascular (15)	Diet: 2 Oral agents: 9 Insulin: 2	46	0	Hepatic failure, renal failure hypothyroidism, poorly controlled diabetes, lipid-lowering agents	2.6/1.4 g EPA/DHA vs. 12 g safflower oil	4 weeks per phase, 4-week washout
Silvis et al. 1990 (80)	Parallel	63 (46)	55	4.8	NA	Diet: 0 Oral agents: 11 Insulin: 13	NA	0 (7 not included in analysis: noncompliance	NA	1.4/0.3 g EPA/DHA vs. 12 g olive oil	8 weeks per phase, 8-week washout
Sirtori et al. 1997 (65)	Parallel	418 (62)	58	5	NA	Diet: NA Oral: NA Insulin: 0	100	4 (from treatment arm; volunteers' decision)	Obesity, malabsorption, duodenal ulcer, noncompliant or unreliable subject, epilepsy, alcoholism, insulin use, history of unstable angina or recent myocardial infarction, severe hypertension or severe dyslipidemia	1.14/0.8 g EPA/DHA‡ vs. 3 g olive oil	24 weeks
Vessby and Boberg 1990 (68)	Crossover	14 (78)	37–72	NA	NA	NA	100	0	Lipid-lowering agents	1.8/1.2 g EPA/DHA vs. 10 g olive oil	8 weeks per phase, no washout
Westerveld et al. 1993 (67)	Parallel	24 (62.5)	56	6.5	NA	Diet: 4 Oral agents: 3 Insulin: 0	NA	0	Hepatic or renal failure, bleeding diathesis, no cardiovascular disorder in last 3 months, no insulin use	1.8 g EPA vs. 1.6 g olive oil	8 weeks

*Subjects were classified as a low or a high P/S diet groups; groups were randomized separately. †The intervention group had a larger weight; they were divided into 4 groups: 2 doses of fish oil and 2 doses of placebo (10 per group). ‡Obtained from averaging the doses used: 1.5/1 g EPA/DHA for 2 months, then 1/0.7 g EPA/DHA for 6 months. ASA, acetyl salicylic acid; EC, exclusion criteria; Htg., hypertriglyceridemia; *n*, number randomized; NA, not available; NSAID, nonsteroidal anti-inflammatory drug.

duration, or quality and the direction or magnitude of the outcomes studied.

Publication bias. According to the funnel plot analysis, small studies showing small triglyceride-lowering treatment effect or no net effect are missing from this analysis as a result of either publication bias or nonexistence of such studies. Approximately 253 unpublished zero-effect studies would be needed to change the magnitude or direction of the effect observed for triglycerides.

CONCLUSIONS

— This systematic review pools 10 years of evidence and 18 randomized controlled trials of fish oil supplementation studying >800 subjects with type 2 diabetes. In the studies reviewed, fish oil supplementation had a statistically significant triglyceride-lowering effect. This effect was most marked in studies that recruited hypertriglyceridemic subjects.

Fish oil supplementation did not result in any statistically or clinically significant increase in fasting glucose or HbA_{1c}. A statistically significant increase in LDL cholesterol was especially noted in the studies recruiting hypertriglyceridemic subjects and using the highest doses of fish oil. None of the trials examined hard clinical end points such as cardiovascular events or death.

Several methodological challenges were encountered in the course of this review. Eleven of 18 trials used a crossover design, and phase-specific data were not available for any of these. There is no accepted method for pooling results from crossover and parallel group design studies. Ideally, individual patient data or at least phase-specific data should be available. In the absence of these data, 3 approaches are possible. The first approach is to not analyze data from crossover studies. The second is to pool parallel group design and crossover trials separately. The third is to treat data from crossover studies as data coming from parallel group design studies, pool these with data from parallel group design studies, and look for heterogeneity in the analysis. We adopted the latter approach, and our sensitivity analysis did not show any association between study design and direction or magnitude of effect. Use of the crossover design to study fish oil supplementation has other potential drawbacks. Fish oil is incorporated into biologic membranes and presumably would require washout periods of appropriate duration to minimize any carryover effect. In our review, only 4 of the 11 crossover studies had a washout period. Despite these limitations, the main findings of the review were similar if crossover studies were included or excluded from the analysis. HbA_{1c} provides an integrated measure of glycemic control over a period of ~12 weeks. The use of such measurements in studies of short duration will underestimate any effects on glycemic control. This may have occurred in several trials included in this review (Table 1). Sensitivity analysis showed that the study duration did not affect the pooled HbA_{1c} estimate.

It is interesting to compare the current systematic review with that of Friedberg et al. (44). Our review was limited to randomized trials involving patients with type 2 diabetes, whereas the earlier review included studies of varying designs and patients with both type 1 and type 2 diabetes. Our review is more current and includes published data up to September 1998, whereas the review by Friedberg et al. includes data up to June 1995. The large Italian Fish Oil Multicenter Study, which reported the effects of fish oil in 418 patients with type 2 diabetes, is included in our review (65). Our methods included an assessment for heterogeneity; the study by Friedberg et al. did not attempt to understand or explain heterogeneity. Despite these differences in design, the findings of the 2 reviews are similar, and both findings are keeping with the results of the largest trial performed in this area. Taken together, these similar results speak to the robustness of the findings that fish oil lowers triglycerides without adversely affecting glycemic control.

Our data are relevant to clinicians managing patients with type 2 diabetes. They indicate that, in normotriglyceridemic patients, dietary supplementation with fish oil leads to a modest lowering of triglycerides without any clinically significant effect on glycemic control. It is unlikely that fish oil will be prescribed in normotriglyc-

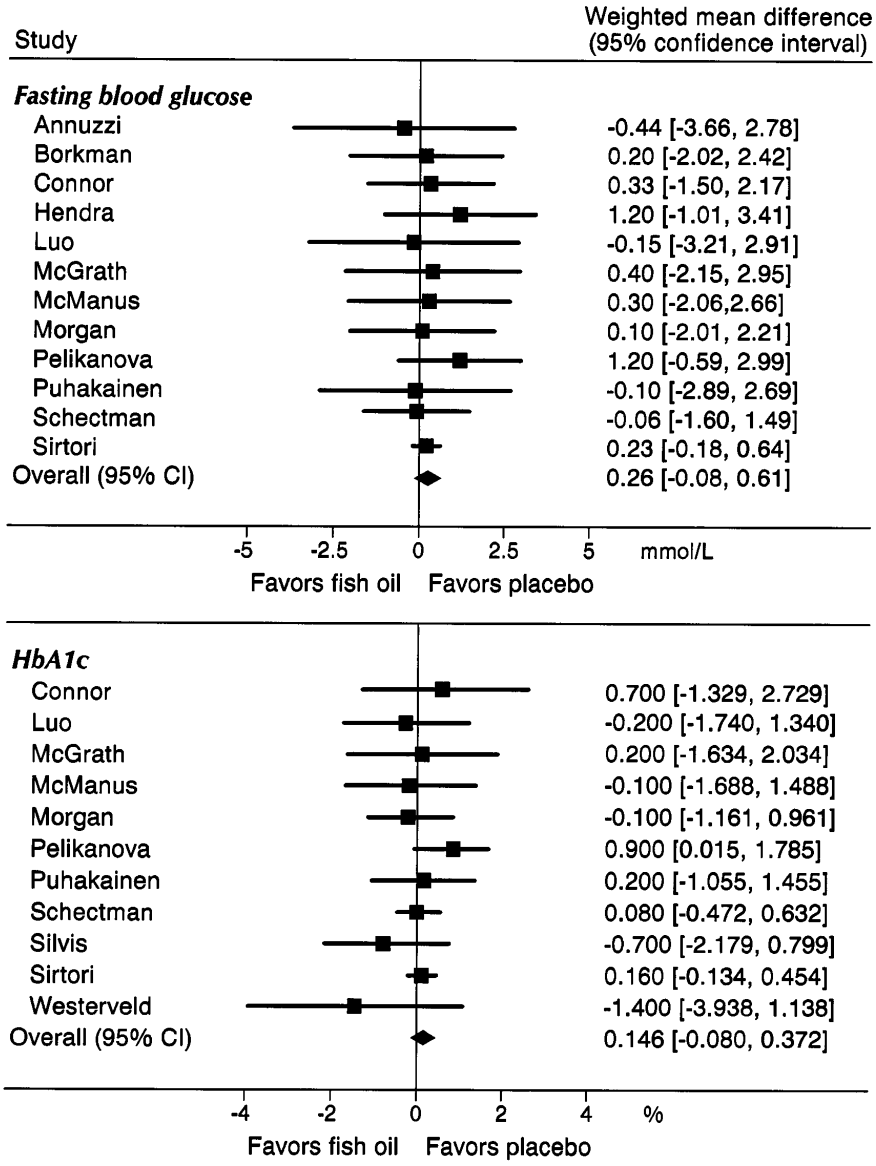

Figure 1—*Effect of fish oil supplementation on glycemic control in subjects with type 2 diabetes. Data shown represent the weighted mean difference (■) with 95% CI (—) using a random effects model. The overall weighted mean difference (◆) for fasting glucose was 0.26 mmol/l (95% CI −0.08 to 0.60) and for HbA_{1c} was 0.15% (−0.08 to 0.37). These results indicate that fish oil supplementation was associated with a nonsignificant increase in fasting blood glucose and HbA_{1c}. The results for the test of heterogeneity among studies were not significant (*P = 0.99 and 0.78, respectively).

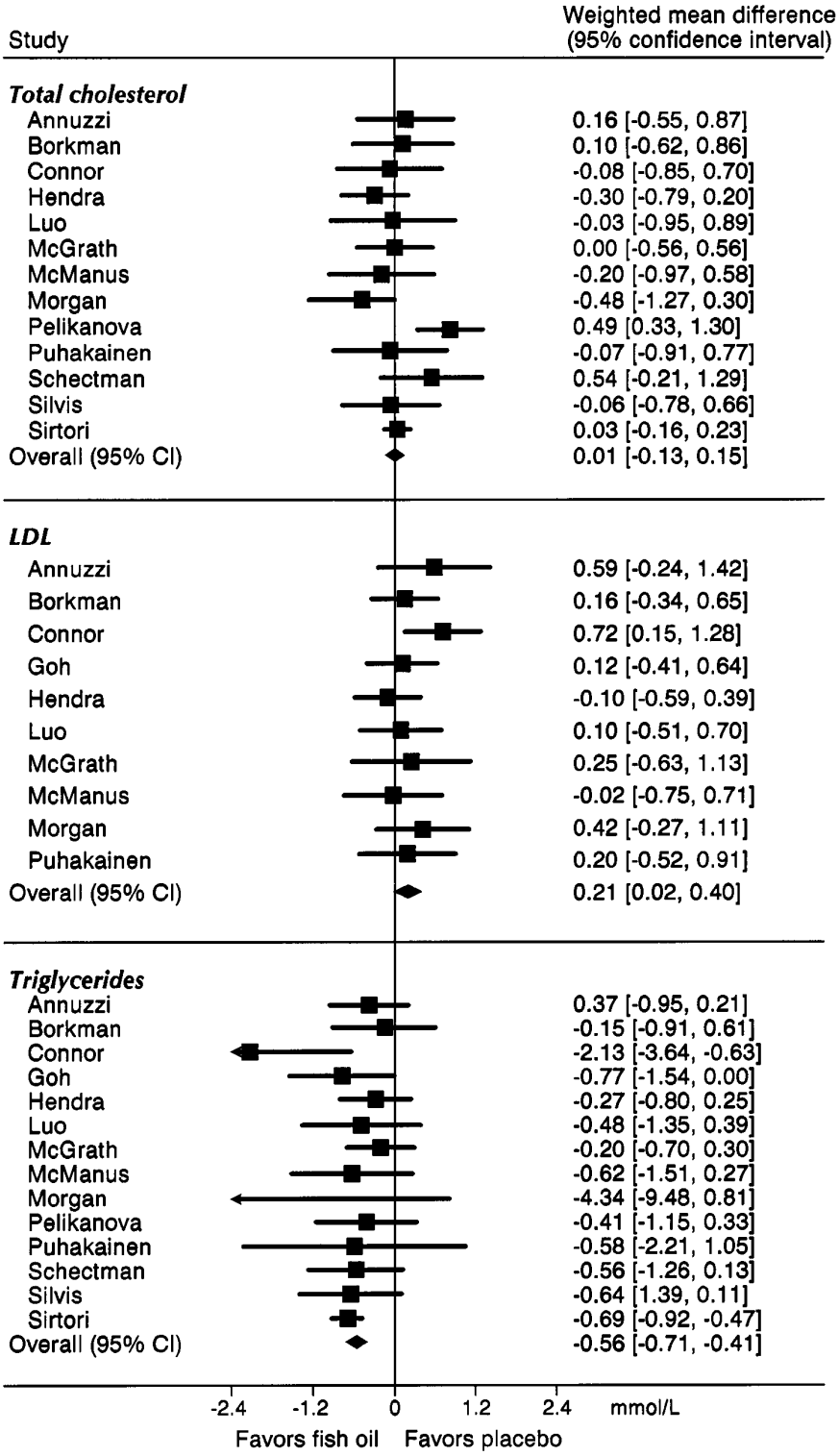

Figure 2—*Effect of fish oil supplementation on the lipid profile of subjects with type 2 diabetes. Data shown represent the weighted mean difference (■) with 95% CI (—) using a random effects model. Arrowheads represent CIs beyond the scale. The overall weighted mean difference (◆) for total cholesterol was 0.007 mmol/l (95% CI −0.13 to 0.15), for LDL cholesterol was 0.21 mmol/l (0.02 to 0.41), and for triglycerides was −0.56 mmol/l (−0.71 to −0.41). These results indicate that fish oil supplementation was associated with a nonsignificant change in total cholesterol levels, a significant triglyceride-lowering effect, and a significant increase in LDL cholesterol levels. The results for the test of heterogeneity among studies were not significant (cholesterol,* P *= 0.86; LDL cholesterol,* P *= 0.69; and triglycerides,* P *= 0.46).*

eridemic patients, but their use as over-the-counter preparations should not be discouraged, provided they are obtained from a reputable source. This recommendation is based partly on the fact that fish oil supplementation has been shown to have beneficial effects on other biologic systems (e.g., immune function [83]). Fish oil represents a reasonable therapeutic strategy in hypertriglyceridemic individuals. Very few studies have compared fish oil with fibric acid derivatives (62), and we are not aware of any studies assessing the combination of fish oil with other lipid-lowering drugs. The slight increase in LDL cholesterol seen with the use of fish oil can occur with other triglyceride-lowering agents. The mechanism of the LDL increase with fish oil has recently been elucidated (84). In addition, large buoyant LDL is known to be less atherogenic than small dense LDL, and this may be the type of LDL produced in response to fish oil (85). Since completion of our review, the Gruppo Italiano per lo Studio delia Sopravvivenza nell'infarto miocardico-Prevenzione Trial has published its findings on the administration of fish oil to 11,324 survivors of myocardial infarction (86). Although the analysis for the diabetes subgroup (15% of participants) has not yet been reported, the findings of reduced triglycerides, increased LDL cholesterol, and an overall beneficial effect on survival (relative risk reduction of 10% for the primary end point of death, nonfatal myocardial infarction, and stroke) are encouraging. We believe that further long-term studies assessing hard cardiovascular end points in patients with diabetes are needed.

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