# Effect of Fish Oil Versus Corn Oil Supplementation on LDL and HDL Subclasses in Type 2 Diabetic Patients

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**OBJECTIVE** — The increased risk of coronary heart disease associated with type 2 diabetes may be partially explained by dyslipidemia characterized by high plasma triacylglycerol (TAG), low HDL cholesterol, and a predominance of atherogenic small dense LDLs. Fish oil reduces plasma TAG and has previously been shown to improve the distribution of LDL subclasses in healthy subjects and might, therefore, be a good nonpharmacological treatment for type 2 diabetic patients. In the present study, we investigate the effect of fish oil supplementation on the fasting lipid profile, including LDL and HDL subclasses.

**RESEARCH DESIGN AND METHODS** — A total of 42 type 2 diabetic patients were randomized to supplementation (capsules) with 4 g daily of either fish oil ($n = 20$) or corn oil ($n = 22$) for 8 weeks preceded by a 4-week run-in period of corn oil supplementation. Blood was drawn before and after the 8-week intervention period. Plasma lipoproteins, including LDL and HDL subclasses, were separated by ultracentrifugation.

**RESULTS** — Fish oil lowered TAG (group difference: $P = 0.025$) and raised HDL-2b cholesterol ($P = 0.012$) and HDL-2a cholesterol ($P = 0.007$) concentrations as compared with corn oil. We observed no significant effects of fish oil on LDL cholesterol, HDL cholesterol, or the concentration of small dense LDL particles.

**CONCLUSIONS** — Fish oil supplementation may partially correct the dyslipidemia of type 2 diabetic patients. However, the putative very important aspect of diabetic dyslipidemia—the predominance of small dense LDL particles—was unaffected by fish oil.

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Type 2 diabetes is associated with dyslipidemia characterized by increased plasma triacylglycerol (TAG), reduced HDL cholesterol, and an increased number of small dense LDL particles (1). This atherogenic lipoprotein profile probably contributes to the very high cardiovascular risk of type 2 diabetic patients (2–5).

Plasma TAG seems to be a major determinant of the LDL and HDL subclass profile because high TAG concentrations are typically associated with an increase in the number of small dense LDL and HDL particles. This association seems explained by increased cholesterol ester transfer protein (CETP)-mediated TAG-enrichment of LDL and HDL particles. Small dense LDL and HDL particles are formed during the subsequent TAG depletion catalyzed by hepatic lipase (1). Fish oil is known to reduce plasma TAG; therefore, fish oil supplementation might be a good nonpharmacological method to correct the atherogenic lipid profile of type 2 diabetic patients. Earlier studies in nondiabetic individuals have demonstrated that fish oil supplementation may reduce the number of small dense LDL and HDL particles and thus improve the LDL and HDL subclass profile (6).

In the present study, we describe the effect of moderate fish oil supplementation on the fasting lipid profile with special reference to the effect on LDL and HDL subclasses in type 2 diabetic patients. Precise and detailed information on the concentration and density distribution of LDL and HDL subclasses was obtained by the use of preparative density-gradient ultracentrifugation.

## RESEARCH DESIGN AND METHODS

— A total of 49 moderately hypertriglyceridemic type 2 diabetic patients were recruited from the Steno Diabetes Center. The inclusion criteria were *1*) known type 2 diabetes for >2 years, *2*) fasting plasma TAG >1.5 mmol/l at screening, *3*) diabetes onset at >30 years of age, *4*) no use of lipid-lowering drugs, *5*) no use of dietary supplements with fish oil or garlic, *6*) low or moderate alcohol intake (<5 drinks/day), and *7*) no use of hormone replacement therapy (women). Before entering the study, the patients were told about the nature of the study and written consent was obtained. Seven patients did not complete the study. Two dropped out during the run-in phase: one was hospitalized and another experienced weight gain. One patient could not participate in the last blood sampling due to pneumonia. Three subjects were excluded due to possible illness at the time of blood sampling based on increased levels of C-reactive protein in plasma (>10 mg/l). One subject was excluded because she was not fasting at time of blood sampling. Thus, this aticle is based on 42 patients, 20 from the fish oil group and 22 from the corn oil group. Baseline characteristics and

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**Abbreviations:** apo, apolipoprotein; CETP, cholesterol ester transfer protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IDL, intermediate-density lipoprotein; TAG, triacylglycerol.

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

**Table 1—*Fatty acid composition of the corn oil and fish oil capsules**

| Fatty acid | Corn oil (mol %) | Fish oil (mol %) |
|---|---|---|
| C14:0 | 0.0 | 0.9 |
| C16:0 | 12.1 | 1.6 |
| C16:1 | 0.1 | 0.8 |
| C18:0 | 1.8 | 2.5 |
| C18:1n-9 | 28.1 | 4.0 |
| C18:1n-7 | 0.6 | 1.6 |
| C18:2n-6 | 55.9 | 0.8 |
| C18:3n-3 | 0.0 | 1.3 |
| C20:0 | 0.4 | 0.9 |
| C20:1n-11 | 0.8 | 2.9 |
| C20:2n-6 | 0.0 | 0.5 |
| C22:0 | 0.0 | 2.3 |
| C22:1n-11 | 0.0 | 2.5 |
| C20:4n-3 | 0.0 | 3.0 |
| C20:5n-3 (EPA) | 0.0 | 40.2 |
| C22:4n-6 | 0.0 | 0.8 |
| C22:5n-6 | 0.0 | 2.1 |
| C22:5n-3 | 0.0 | 6.1 |
| C22:6n-3 (DHA) | 0.0 | 25.4 |

*Both capsules contained 13.4 mg/g oil.

treatment assignments in the subjects who dropped out were similar to those who completed the study.

### Study design

The study was a randomized, double-blind, placebo-controlled, parallel study. During a 4-week run-in phase, all subjects took four placebo (corn oil) capsules (4 g/day). After run-in, the patients were randomized to fish oil or corn oil treatment after stratification for total TAG (<3 mmol/l or 3 mmol/l) and smoking habits (smoking or nonsmoking). The fish oil group took four capsules of fish oil/day (Futura 1000; Dansk Droge) (4 g fish oil containing 2.6 g eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), and the corn oil group took four capsules of corn oil per day. Both capsules were provided by Dansk Droge and contained 13.4 mg vitamin E. The fatty acid composition of the capsules is shown in Table 1. The subjects were not told about the run-in period until after study termination. We advised the subjects to keep their level of physical activity and dietary habits, especially fish intake, constant during the study. The fish and alcohol intake of the subjects was assessed by a food frequency questionnaire completed in the beginning and at the end of the study period.

### Compliance

Compliance was assessed by measurement of LDL fatty acid composition and from counting the leftover capsules.

### Blood sampling and lipoprotein fractionation

After a 12-h overnight fast, venous blood was drawn in the morning. Blood was collected in tubes containing 0.1% EDTA and centrifuged at 3,000*g* for 15 min at 20°C. A 3-mg sample of EDTA plasma was stored at 5°C, and ultracentrifugation was started within a maximum of 72 h. VLDL (<1.006 g/ml), intermediate-density lipoprotein (IDL) (1.006–1.019 g/ml), LDL (1.019–1.063 g/ml), and HDL (1.063–1.210 g/ml) were separated by ultracentrifugation according to Lindgreen et al. (7). In addition, LDL and HDL particles were separated into subclasses as described (8), with slight modification. We used a 50.4 Ti rotor with 4-ml open top tubes. The density intervals of the LDL subclasses were slightly changed: LDL-1 1.019–1.031, LDL-2 1.031–1.034, LDL-3 1.034–1.037, LDL-4 1.037–1.039, LDL-5 1.039–1.042, and LDL-6 1.042–1.063 g/ml. The density intervals of the HDL subclasses were unchanged: HDL-2b 1.063–1.100, HDL-2a 1.100–1.125, and HDL-3 1.125–1.210 g/ml. The density intervals were determined by precision refractometry of blank gradients. Blood for determination of LDL fatty acid composition was drawn in tubes containing EDTA and spun at 3,000*g* for 15 min at 5°C and stored at −80°C until isolation of LDL. The LDL fraction was isolated by density ultracentrifugation for 18 h at 40,000 rpm and 4°C in Sw40 ultraclear 14 × 89 tubes (Ramcon) using a SW 40-ti rotor (Beckman) in a L8–70M ultracentrifuge (Beckman) and stored at −80°C until analysis.

### Lipid and apolipoprotein analysis

The concentration of TAG and cholesterol was determined in plasma and lipoprotein fractions (including subclasses) by enzymatic kits from Boehringer Mannheim (Mannheim, Germany). In plasma VLDL, IDL, and LDL particles, apolipoprotein (apo) B was determined, and in plasma and HDL particles, apo A-1 was determined. Apo concentrations were measured with immunological kits from Roche (Basel). All analyses were done on a Cobas Mira analyzer from Roche.

### Fatty acid composition of LDL

The lipid fraction of LDL was extracted by dissolving a 100-μl LDL sample in cholorform:methanol (2:1), to which 100 μl fatty acid (C21:0) was added as external standard. The fatty acid composition was determined as described (9).

### Fatty acid composition of the oil capsules

A drop of oil was dissolved in 10 ml heptane. The sample was methylated with 60 μl KOH (2 mol/l in MeOH). The sample was evaporated in a vacuum centrifuge and reconstituted in 1 ml heptane. The fatty acid composition was determined as described (9).

### Other measurements

Serum C-reactive protein was analyzed with an immunological kit from Roche. Blood glucose concentration was measured in capillary blood using a One-Touch Instrument (Life Scan, Milpalaz,

**Table 2—*Characteristics of the patients at baseline***

| | Fish oil | Corn oil |
|---|---|---|
| *n* | 20 | 22 |
| Age (years) | 63.5 (39–76) | 62.2 (33–85) |
| Sex (M/F) | 12/8 | 14/8 |
| Diabetes duration (years) | 9.2 (2–31) | 9.8 (2–27) |
| Diabetes treatment (tablets/insulin/diet %) | 70/40/5 | 55/59/9 |
| BMI (kg/m$^2$) | 29.6 ± 5.2 | 30.2 ± 5.5 |
| Waist-to-hip ratio | 0.93 ± 0.06 | 0.95 ± 0.07 |
| Fasting blood glucose (mmol/l) | 7.7 ± 2.5 | 8.1 ± 1.3 |
| $HbA_{1c}$ (%) | 8.1 ± 1.3 | 8.1 ± 1.3 |
| Systolic blood pressure (mmHg) | 150 ± 24.0 | 149 ± 22.7 |
| Diastolic blood pressure (mmHg) | 83.5 ± 10.7 | 85.0 ± 9.7 |

Data are means ± SE or mean (range).

**Table 3—*Effect of 8-week intervention with fish oil or corn oil capsules (4 g/day) on the fasting lipid profile***

| | Fish oil | Corn oil | *P** |
|---|---|---|---|
| *n* | 20 | 22 | |
| Total TAG (mmol/l) | | | |
| Before | 2.35 ± 0.27 | 2.76 ± 0.46 | 0.459 |
| After | 1.81 ± 0.20† | 2.72 ± 0.49 | 0.105 |
| Change | −0.54 ± 0.13 | −0.04 ± 0.17 | 0.025 |
| Total cholesterol (mmol/l) | | | |
| Before | 5.95 ± 0.21 | 5.51 ± 0.23 | 0.166 |
| After | 5.87 ± 0.23 | 5.43 ± 0.20 | 0.162 |
| Change | −0.08 ± 0.13 | −0.08 ± 0.09 | 0.966 |
| LDL cholesterol (mmol/l) | | | |
| Before | 3.29 ± 0.15 | 2.79 ± 0.16 | 0.032 |
| After | 3.43 ± 0.17 | 2.87 ± 0.18 | 0.031 |
| Change | 0.14 ± 0.10 | 0.08 ± 0.09 | 0.645 |
| HDL cholesterol (mmol/l) | | | |
| Before | 1.22 ± 0.05 | 1.12 ± 0.05 | 0.195 |
| After | 1.28 ± 0.06 | 1.11 ± 0.06 | 0.062 |
| Change | 0.06 ± 0.03 | −0.01 ± 0.03 | 0.094 |
| LDL-1 apo B (mg/dl) | | | |
| Before | 9.15 ± 0.69 | 8.58 ± 0.68 | 0.565 |
| After | 9.13 ± 0.59 | 8.08 ± 0.62 | 0.232 |
| Change | −0.02 ± 0.53 | −0.50 ± 0.48 | 0.501 |
| LDL-2 apo B (mg/dl) | | | |
| Before | 4.33 ± 0.33 | 4.50 ± 0.50 | 0.785 |
| After | 5.14 ± 0.51‡ | 4.95 ± 0.53 | 0.794 |
| Change | 0.81 ± 0.31 | 0.45 ± 0.23 | 0.346 |
| LDL-3 apo B (mg/dl) | | | |
| Before | 6.03 ± 0.57 | 5.83 ± 0.67 | 0.828 |
| After | 7.15 ± 0.83‡ | 6.67 ± 0.74 | 0.670 |
| Change | 1.12 ± 0.48 | 0.84 ± 44 | 0.669 |
| LDL-4 apo B (mg/dl) | | | |
| Before | 9.78 ± 0.90 | 8.20 ± 0.79 | 0.193 |
| After | 10.56 ± 1.12 | 9.52 ± 0.99 | 0.487 |
| Change | 0.78 ± 0.58 | 1.32 ± 0.64 | 0.540 |
| LDL-5 apo B (mg/dl) | | | |
| Before | 14.46 ± 0.85 | 11.52 ± 1.09 | 0.045 |
| After | 13.67 ± 0.89 | 11.77 ± 1.10 | 0.172 |
| Change | −0.79 ± 0.70 | 0.25 ± 0.71 | 0.306 |
| LDL-6 apo B (mg/dl) | | | |
| Before | 26.58 ± 3.10 | 22.07 ± 1.78 | 0.198 |
| After | 26.86 ± 3.53 | 20.66 ± 1.74 | 0.127 |
| Change | 0.28 ± 1.70 | −1.41 ± 1.11 | 0.396 |
| HDL-2b cholesterol (mmol/l) | | | |
| Before | 0.26 ± 0.02 | 0.26 ± 0.02 | 0.890 |
| After | 0.31 ± 0.02§ | 0.26 ± 0.02 | 0.165 |
| Change | 0.05 ± 0.01 | 0.00 ± 0.01 | 0.012 |
| HDL-2a cholesterol (mmol/l) | | | |
| Before | 0.39 ± 0.02 | 0.36 ± 0.02 | 0.500 |
| After | 0.37 ± 0.03 | 0.30 ± 0.03† | 0.057 |
| Change | −0.02 ± 0.01 | −0.06 ± 0.01 | 0.007 |
| HDL-3 cholesterol (mmol/l) | | | |
| Before | 0.57 ± 0.03 | 0.50 ± 0.02 | 0.055 |
| After | 0.59 ± 0.02 | 0.56 ± 0.03† | 0.434 |
| Change | 0.02 ± 0.02 | 0.06 ± 0.01 | 0.089 |

Data are means ± SE. *Fish oil versus corn oil; †$P < 0.001$, ‡$P < 0.05$, §$P < 0.01$ vs. before.

CA). $HbA_{1c}$ was measured with ion-exchange high-performance liquid chromatography (Bio-Rad Variant) (ref. interval 4.1–6.4%). Blood pressure was measured digitally using an instrument from A & D (Tokyo, Japan). Waist and hip circumference were measured according to previously described guidelines (10). Body weight was measured at blood sampling with the subjects wearing light clothing on a calibrated digital scale.

### Statistics

Data were tested for normal distribution by the Shapiro-Wilks test. Paired *t* tests, unpaired *t* tests, and Pearson's correlation analysis were used as appropriate for normally distributed data. For not normally distributed data, the Mann-Whitney *U* test (unpaired samples) or Wilcoxon's signed-rank test (paired samples) were used. Normally distributed data are presented as means ± SE. Data not normally distributed are expressed as median (25–75 percentiles). A *P* value <0.05 was considered statistically significant. We used SPSS version 10.0 (SPSS, Chicago) for statistical analyses.

## RESULTS

— The fish oil and corn oil groups were comparable at baseline, except for LDL cholesterol (Tables 2 and 3). Regarding LDL subclasses, the type 2 diabetic patients, characteristically, had an overabundance of small dense particles.

### Compliance

The fatty acid composition of LDL particles measured before and after the intervention indicates that good compliance was obtained (Table 4). Concentrations of EPA and DHA increased significantly in the fish oil group ($P < 0.001$). Counting of leftover capsules showed that participants consumed an average of 98% (±2%) of the planned number of capsules, confirming that good compliance was obtained. Body weight increased insignificantly in both groups (0.3 ± 0.3 kg in the fish oil group and 0.8 ± 0.3 kg in the corn oil group, $P = 0.32$). There was no significant difference in the consumption of fish and alcohol between the two groups, and there was no change during the intervention within any of the two groups (data not shown).

### Fasting lipid profile

Total TAG was significantly lower in the fish oil than in the corn oil group ($P =$

**Table 4—*Concentration of EPA and DHA in LDL particles before and after the intervention***

| | Fish oil (mol %) ($n$ = 20) | | | Corn oil (mol %) ($n$ = 22) | | |
|---|---|---|---|---|---|---|
| Fatty acid | Before | After | $P$ | Before | After | $P$ |
| EPA | 1.20 ± 0.16 | 3.83 ± 0.34 | <0.001 | 1.09 ± 0.13 | 1.11 ± 0.16 | NS |
| DHA | 1.65 ± 0.23 | 2.71 ± 0.25 | <0.001 | 1.66 ± 0.25 | 1.73 ± 0.27 | NS |

Data are means ± SE.

0.025). HDL-2b cholesterol was higher in the fish oil group than in the corn oil group ($P$ = 0.012). Finally, the reduction in HDL-2a cholesterol was smaller in the fish oil than in the corn oil group ($P$ = 0.007). We found no further group differences with respect to any other lipid or lipoprotein variables, including LDL subclasses (Table 3).

### Correlations

At baseline, total TAG and the concentration of small dense LDL particles (LDL-6 apo B) correlated positively ($r$ = 0.37, $P$ = 0.017; $n$ = 42), but we observed no association between the changes in total TAG and changes in the concentration of the small dense LDL particles ($r$ = 0.17, $P$ = 0.279; $n$ = 42).

We observed no significant changes in blood glucose, $HbA_{1c}$, or blood pressure (data not shown).

**CONCLUSIONS** — The lipid profile of our volunteers was characterized by increased total TAG (selection criterion) and an increased number of small dense LDL and HDL particles, as expected for type 2 diabetic patients. Fish oil supplementation caused a marked 23% decrease in plasma TAG similar to what was reported from earlier trials of healthy (6) and diabetic subjects (11–13). Contrary to our expectations, the TAG lowering was not accompanied by detectable changes in the LDL subclass profile. In the only previous trial dealing with this issue in diabetic subjects, LDL size was unaffected despite of a significant fish oil–mediated TAG lowering (−24%). That study determined LDL subclasses by gradient gel electrophoresis (14). In contrast, Suzukawa et al. (6) observed a favorable shift in LDL subclass distribution after a 24% fish oil–mediated TAG lowering in healthy volunteers, suggesting that diabetic patients may be more resistant to dietary improvement of their LDL subclass profile than nondiabetic subjects. This difference could be explained by abnormal lipase activity in diabetes (15). Some studies indicate that the LDL subclass distribution of diabetic subjects may be improved with TAG lowerings larger than those that can generally be achieved by fish oil alone. Halle et al. (16) obtained a 35% decline in TAG with diet and physical exercise, and Lahdenperä et al. (17) produced a 38% decrease in TAG with fibrates. In both studies, LDL subclass profiles improved. In our data, we saw some indications that individuals with larger TAG reductions were more prone to improve their LDL subclass profile (data not shown).

According to the review by Harris (18), fish oil supplementation could be expected to lead to minor increments in HDL and LDL cholesterol. We found only trends in that direction. However, the total/LDL cholesterol ratio was unaffected by treatment (−5.5% on fish oil and −4.6% on corn oil), whereas the total/HDL cholesterol ratio was reduced by 6% on fish oil and 0.6% on corn oil. Similarly, the LDL/HDL cholesterol ratio was reduced by 0.7% on fish oil but increased 4.0% on corn oil. These data suggest that fish oil had a beneficial effect for HDL cholesterol. Plasma HDL-2a and HDL-2b cholesterol concentrations were both significantly increased by fish oil as compared with corn oil. The finding of a specific HDL-2 raising effect of fish oil was also reported by others (19,20,21). At the same time, HDL-3 tended to decline after fish oil, suggesting a shift in the HDL profile in the direction of larger and less dense particles.

In conclusion, fish oil supplementation was found to partially correct the dyslipidemia of type 2 diabetes. However, the putative very important aspect of diabetic dyslipidemia—the predominance of small dense LDL particles—was unaffected by fish oil.

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