



Long-term effects of fish oil on lipoprotein subfractions and low density lipoprotein size in non-insulin-dependent diabetic patients with hypertriglyceridemia

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Abstract

The effects of fish oil on lipoprotein subfractions and low density lipoprotein (LDL) size in non-insulin-dependent diabetes mellitus (NIDDM) patients with hypertriglyceridemia are unknown. To elucidate this, 16 NIDDM hypertriglyceridemic patients (plasma triglyceride 2.25–5.65 mmol/l, plasma cholesterol ≤ 7.75 mmol/l) were randomly assigned to a 6-month period with either moderate amounts of fish oil ($n = 8$) or placebo ($n = 8$) after 4 weeks of wash-out and 3 weeks of run-in. Diet and hypoglycemic treatment were unchanged throughout the experiment. LDL size were evaluated at baseline and after 6 months. Three VLDL and LDL subfractions were measured at the end of the two periods. The total lipid concentration of all very low density lipoprotein (VLDL) subfractions was lower at the end of fish oil treatment compared with placebo (large VLDL 124.3 ± 19.7 mg/dl vs 156.7 ± 45.5 mg/dl; intermediate VLDL 88.5 ± 9.5 mg/dl vs 113.9 ± 23.2 mg/dl; small VLDL 105.9 ± 9.7 mg/dl vs 128.9 ± 40.7 mg/dl) (mean \pm SEM), although the difference was not statistically significant. Moreover, at the end of the two treatments, the percentage distribution of VLDL subfractions was very similar (large $37.5 \pm 3.3\%$ vs $37.6 \pm 2.6\%$, intermediate $27.6 \pm 0.9\%$ vs $31.0 \pm 2.4\%$; small $34.9 \pm 3.7\%$ vs $31.4 \pm 2.1\%$). Concerning LDL, no significant change in LDL size was observed after the two treatments (255.4 ± 2.2 Å vs 254.2 ± 1.7 Å, fish oil; 253.7 ± 2.0 Å vs 253.3 ± 1.7 Å, placebo). LDL subfraction distribution was also very similar (large $17 \pm 3\%$ vs $17 \pm 2\%$; intermediate $62 \pm 3\%$ vs $65 \pm 3\%$; small $21 \pm 3\%$ vs $18 \pm 2\%$), at the end of the two periods, confirming the lack of effects on LDL size. In conclusion, our study indicates that in NIDDM patients with hypertriglyceridemia, fish oil does not induce any improvement in LDL distribution and LDL size despite its positive effects on plasma triglycerides. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Fish oil; Non-insulin-dependent diabetes mellitus; Lipoprotein subfractions; Low density lipoprotein size

1. Introduction

There is growing evidence on the importance of the composition and distribution of lipoprotein subfractions in the etiology of cardiovascular disease [1–6]. As a matter of fact, the hypothesis that smaller very low density lipoprotein (VLDL) and low density lipoprotein (LDL) particles are more atherogenic has been supported by cross-sectional as well as by the more recent prospective studies [3,4,6]. NIDDM is frequently

associated with an abnormal triglyceride metabolism; this also leads to an increase in small LDL [7–9], which could explain, at least in part, the very high cardiovascular risk for these patients. This evidence underlines the clinical relevance of any intervention that could have beneficial effects not only on lipoprotein concentrations, but also on lipoprotein subfraction distribution and, in particular, LDL size. Nevertheless, the data on the effects of dietary and/or drug treatments in non-insulin-dependent diabetes mellitus (NIDDM) patients on this issue are still scanty. There is a wealth of literature on the effects of fish oil on different cardiovascular risk factors and one of the most consistent beneficial effects of fish oil is a clear reduction of

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triglyceride levels [10–13]. Since plasma triglyceride levels are among the main determinants of the formation of smaller LDL [1,14,15], it is reasonable to believe that fish oil could also decrease the concentration of smaller LDL. Nonetheless, despite the importance of this issue, there is little information on the influence of ω -3 fatty acids on either VLDL or LDL subfraction profile, or LDL particle size in both non-diabetic and diabetic individuals. Considering the importance of these variables as cardiovascular risk factors, the aim of our study was to evaluate the effects of long-term fish oil supplementation on VLDL and LDL subfractions as well as on LDL size in NIDDM patients with hypertriglyceridemia. For the purpose of our study, we chose NIDDM hypertriglyceridemic patients as we feel they are the best candidates to benefit from a fish oil treatment.

2. Research design and methods

2.1. Subjects

Sixteen hypertriglyceridemic NIDDM patients (World Health Organisation criteria) [16] with type IIB or IV hyperlipidemia (Fredrikson's classification), whose clinical characteristics have been described in Table 1, were enrolled after giving their written informed consent. The study was part of a multicenter trial on the effects of fish oil on plasma lipids and blood glucose control [17]. The patients were all selected from the diabetic clinic of our department according to the following criteria: (1) NIDDM duration of at least 2 years; (2) almost stable metabolic control for the 3 months prior to enrollment; (3) no significant changes in body weight during the 3 months before enrollment; (4) fasting plasma triglycerides between 2.25 and 5.56 mmol/l, and cholesterol levels ≤ 7.75 mmol/l in the absence of any hypolipidemic drug for at least 4 weeks; (5) age between 40 and 75 years; (6) as to women, only

those in the post-menopausal phase not on hormone replacement therapy.

Patients with mild hypertension could be enrolled, provided that they were well controlled by calcium antagonists or angiotensin converting enzyme (ACE) inhibitors.

2.2. Study protocol

The study followed a randomized double-blind, placebo-controlled design with parallel groups. After a wash-out period of 4 weeks, during which all hypolipidemic drugs were withdrawn and patients were stabilized on their own isoenergetic diet and previous hypoglycemic treatment (only sulfonylureas were admitted), there was a run-in period of 3 weeks during which patients received three capsules per day of placebo. At the end of the run-in period, patients were randomized to receive either fish oil or placebo capsules. Eight patients followed the fish oil treatment and eight received placebo. The study lasted 6 months, during which the patients were seen monthly on an outpatient basis; all patients completed the study. During the first 2 months, the patients took three capsules of fish oil daily (2.5 g ω -3 fatty acids/day) or placebo (3 g olive oil/day). Thereafter and for the remaining 4 months, the dosage was reduced to two capsules per day, equal to 1.7 g ω -3 fatty acids or 2 g olive oil. Both fish oil and placebo capsules were provided by Pharmacia, Farmitalia Carlo Erba (Milan, Italy).

Throughout the experiment, the patients followed a standardized isoenergetic diet for diabetes (carbohydrate 50%, fat 35%—mostly monounsaturated, protein 15%); their habitual consumption of fish was, on average, one serving of fish per week. Compliance to the diet was checked by semiquantitative dietary questionnaires at the beginning and at the end of the study and was estimated to be good. Compliance to treatment was analyzed by the fatty acids spectrum of red blood cells; results of these parameters have been reported else-

Table 1
Clinical characteristics and metabolic parameters of the participants at baseline and after 6 months on fish oil or placebo in hypertriglyceridemic NIDDM patients^a

	Fish oil (<i>n</i> = 8)		Placebo (<i>n</i> = 8)	
	Baseline	6 months	Baseline	6 months
Age (years)	56 ± 3	–	57 ± 2	–
Sex (f/m)	5/3	–	4/4	–
Weight (kg)	69 ± 5	70 ± 5	74 ± 3	74 ± 4
Fasting plasma glucose (mmol/l)	10.2 ± 1.2	10.9 ± 0.5	9.2 ± 0.6	10.3 ± 1.0
HbA _{1c} (%)	7.3 ± 0.4	8.3 ± 0.5	6.9 ± 0.6	7.7 ± 0.5
Plasma cholesterol (mmol/l)	6.27 ± 0.57	5.71 ± 0.26	5.76 ± 0.29	6.21 ± 0.44
Plasma triglycerides (mmol/l)	3.85 ± 0.32	2.92 ± 0.23*	3.29 ± 0.38	3.14 ± 0.33
HDL cholesterol (mmol/l)	0.88 ± 0.04	0.89 ± 0.05	0.93 ± 0.07	0.95 ± 0.10

^a Data are mean ± SEM. *P* < 0.01 vs baseline.

where [13]. Hypoglycemic and antihypertensive treatment were left unchanged throughout the experiment.

The study was approved by the ethical committee of the Federico II University and each patient gave his/her informed consent to participate.

2.3. Laboratory procedures

2.3.1. Lipoprotein subfractions

Blood samples were collected at the end of fish oil and placebo treatments by vein puncture without stasis, after an overnight fast (12–14 h), and allowed to clot. Serum was separated by low-speed centrifugation (3000 rpm for 10 min) and added with EDTA-Na₂ (final concentration, 0.05%).

VLDL and LDL were isolated by sequential preparative ultracentrifugation under standard conditions [18].

2.3.2. VLDL subfractions

A discontinuous density gradient preparative ultracentrifugation (DGPU) procedure was used to subfractionate VLDL using the method of Redgrave and Carlson [19], with small modifications [20]. Three VLDL subfractions of decreasing size (large, intermediate, and small) were separated by three consecutive runs: (1) 105 min at 40 000 rpm (large VLDL, Svedberg flotation unit $S_f > 400-175$); (2) 80 min at 40 000 rpm (intermediate VLDL, $S_f = 175-100$); (3) 18 h at 37 000 rpm (small VLDL, $S_f = 100-20$). Centrifugation was carried out in a Beckman SW40 Ti rotor at 20°C on a Centrikon T2060 ultracentrifuge (Kontron Instruments, Zurich, Switzerland) with operating mode preselection keys set at 'vertical on-off'. This key allows the slowest acceleration up to 800 rpm; at the end of the run, the brake is automatically switched off at 800 rpm and the rotor coasts to a standstill.

2.3.3. LDL subfractions

Three LDL subfractions of increasing density and decreasing size were separated by density gradient ultracentrifugation on the LDL fraction obtained by sequential ultracentrifugation, according to the method described by Griffin et al. [21] and modified by Tilly-Kiesi et al. [22]. Tubes were centrifuged for 24 h at 23°C using the same rotor and ultracentrifuge apparatus as for VLDL subfractions. After centrifugation, the tubes were emptied from the top using an ISCO density gradient flow cell and fractionator system, a WIZ Peristaltic pump, Fluorinert FC-40 d 1.85 g/ml, absorbance detector UA-6 (ISCO, Lincoln, Nebraska, USA). Densities were checked by a Digital Density Meter DMA-48 (Anton Paar, Graz, Austria). Three LDL subfractions of increasing density (large, $d = 1.024-1.031$ g/ml; intermediate, $d = 1.031-1.040$ g/ml; small, $d = 1.040-1.060$ g/ml) were collected in a volume of 1.5 ml each by a Retriever II fraction collector (ISCO, Nebraska, USA).

2.3.4. LDL size

LDL particle size (diameter in Å of the major LDL peak) was assessed on serum by non-denaturing polyacrylamide gradient gel electrophoresis using commercially available 2.5–16% gels (ISOLAB; Akron, OH, USA), with a minor modification of the method of McNamara et al. [23,24]. Briefly, samples were pre-stained with Sudan Black B lipid stain and scanned at 633 nm on a LKB Ultrosan XL laser densitometer (Pharmacia LKB Biotechnology, Piscataway, NY). Gels were calibrated using serum calibrators, whose size was confirmed by analytical ultracentrifugation. The coefficient of variation for control pools was 1.8–3.6%.

LDL subclass pattern was characterized according to the criteria of Austin et al. [25]: LDL pattern A consisting of a major peak with LDL particle diameter > 255 Å, LDL pattern B consisting of a major peak with LDL particle diameter ≤ 255 Å.

2.3.5. Other measurements

Total cholesterol, triglycerides, and phospholipids were assayed on each subfraction by enzymatic colorimetric methods [26–29], using commercially available kits (Boehringer Mannheim, Mannheim, Germany), adequately modified in order to obtain a high sensitivity also at low concentrations, on a COBAS MIRA auto-analyzer (Roche, Basle, CH). Quality control of lipid analysis is regularly ensured in our laboratory by the WHO Prague Reference Centre [30]. Recovery of single constituents in VLDL and LDL (sum of the concentration in VLDL and LDL subfractions as percentage of the concentration in total VLDL and LDL) was, respectively, $97 \pm 1.2\%$ and $94 \pm 3.1\%$ for cholesterol, $96 \pm 1.2\%$ and $91 \pm 2.7\%$ for triglycerides, $98 \pm 1.0\%$ and $95 \pm 2.2\%$ for phospholipids, without difference between placebo or fish oil treatments.

At baseline and after 6 months of either fish oil or placebo, blood samples for the measurement of lipoprotein lipase (LPL) and hepatic lipase (HL) activities were collected in tubes containing EDTA-K3, 15 min after intravenous administration of heparin (100 IU/kg body weight). Plasma was immediately separated by centrifugation at 4°C and stored at -25°C . LPL and HL activities were evaluated according to Nilsson-Ehle and Ekman [31], using as substrate a (³H) trioleoylglycerol emulsion by di-oleoyl phosphatidyl choline, as previously described in detail [20]. Coefficients of variation were 6.3 and 2.4% (intra-assay), and 8.9 and 4.6% (inter-assay) for LPL and HL, respectively.

2.4. Statistical analysis

Data are expressed as mean \pm SEM, unless otherwise specified.

In order to try to minimize the great variability in triglyceride levels, fasting plasma triglycerides and

Table 2

Lipid concentrations of VLDL subfractions and their percentage composition after 6 months on fish oil or placebo in hypertriglyceridemic NIDDM patients^a

	Fish oil (n = 8)	Placebo (n = 8)
Large VLDL (mg/dl)	124.3 ± 19.7	156.7 ± 45.5
%CHOL	11.1 ± 0.5	10.8 ± 0.8
%TG	72.8 ± 0.8	73.4 ± 0.7
%PL	16.1 ± 0.8	15.8 ± 0.2
Intermediate VLDL (mg/dl)	88.5 ± 9.5	113.9 ± 23.2
%CHOL	16.4 ± 0.3	17.3 ± 1.4
%TG	63.8 ± 0.4	63.1 ± 2.1
%PL	19.8 ± 0.2	19.6 ± 0.8
Small VLDL (mg/dl)	105.9 ± 9.7	128.9 ± 40.7
%CHOL	25.4 ± 1.0	25.1 ± 2.1
%TG	51.4 ± 0.9	51.8 ± 2.8
%PL	23.2 ± 0.6	23.1 ± 0.9

^a Data are mean ± SEM.

Table 3

Percentage distribution of VLDL and LDL subfractions after 6 months of fish oil or placebo in hypertriglyceridemic NIDDM patients^a

	VLDL (n = 8)		LDL (n = 8)	
	Fish oil	Placebo	Fish oil	Placebo
% Large	37 ± 3	38 ± 3	17 ± 3	17 ± 2
% Intermediate	28 ± 1	31 ± 3	62 ± 3	65 ± 3
% Small	35 ± 4	31 ± 2	21 ± 3	18 ± 2

^a Data are mean ± SEM.

Table 4

Lipid concentrations of LDL subfractions and their percentage composition after 6 months on fish oil or placebo in hypertriglyceridemic NIDDM patients^a

	Fish oil (n = 8)	Placebo (n = 8)
Large LDL (mg/dl)	30.9 ± 5.1	28.9 ± 2.4
%Chol	55.6 ± 1.6	52.1 ± 2.7
%TG	13.4 ± 2.0	18.6 ± 2.7
%PL	31.0 ± 1.8	29.3 ± 1.4
Intermediate LDL (mg/dl)	113.7 ± 12.0	120.4 ± 15.7
%Chol	53.4 ± 1.4	52.5 ± 1.3
%TG	11.1 ± 1.2	13.3 ± 2.6
%PL	35.5 ± 0.7	34.2 ± 1.3
Small LDL (mg/dl)	36.5 ± 3.7	34.3 ± 8.0
%Chol	55.8 ± 0.8*	50.1 ± 2.3
%TG	10.6 ± 0.7	14.8 ± 2.5
%PL	33.6 ± 0.8	35.1 ± 2.0

^a Data are mean ± SEM.

* $P < 0.05$.

cholesterol concentrations represent the mean of three samples taken on three consecutive days. Variables that were not uniformly distributed were log-transformed before statistical analysis. Statistical analysis was performed according to standard methods [32] using the

Statistical Package for Social Sciences (SPSS/PC) Software.

Baseline data were compared using Student's *t*-test for unpaired data. The effect of treatment was analyzed by comparing the results within each group at baseline and at 6 months with Student's *t*-test for paired data. Moreover, comparisons between the two treatments were performed using Student's *t*-test for unpaired data on differences between 6 months and baseline values. For variables analyzed only at the end of the two study periods, statistical evaluation was performed using Student's *t*-test for unpaired data. $P < 0.05$ was considered as statistically significant (two tails).

3. Results

The main clinical characteristics of the two groups of patients at baseline were not significantly different (Table 1); there was no difference in body weight, fasting plasma glucose and HbA_{1c} between baseline and the end of the treatment in either group of patients (Table 1). Moreover, fish oil induced a significant decrease in total serum triglycerides and no significant change either in total serum cholesterol or in HDL cholesterol (Table 1).

3.1. VLDL subfractions

The total lipid concentration (sum of cholesterol, triglyceride and phospholipids) of each VLDL subfraction was lower after fish oil treatment compared with placebo (large, 124.3 ± 19.7 mg/dl vs 156.7 ± 45.5 mg/dl; intermediate, 88.8 ± 9.5 mg/dl vs 113.9 ± 23.2 mg/dl; small, 105.9 ± 9.7 mg/dl vs 128.9 ± 40.7 mg/dl), but the difference was not statistically significant (Table 2). In any case, since the effect of fish oil was similar on each of the three isolated subfractions, their percentage distribution (lipid concentration of each VLDL subfraction expressed as the percentage of the total VLDL lipid concentration) was also very similar at the end of both periods (large, 37.5 ± 3.3% vs 37.6 ± 2.6%; intermediate, 27.6 ± 0.9% vs 31.0 ± 2.4%; small, 34.9 ± 3.7% vs 31.4 ± 2.1%) (Table 3). Moreover, there was no change in the lipid composition of each VLDL subfraction (Table 2).

3.2. LDL subfractions and LDL size

Table 4 reports the total lipid concentration of LDL subfractions and their relative composition at the end of the two periods of treatment. The total lipid concentrations were very similar (large, LDL 30.9 ± 5.1 mg/dl vs 28.9 ± 2.4 mg/dl; intermediate, 113.4 ± 12.0 mg/dl vs 120.4 ± 15.7 mg/dl, small, 36.5 ± 3.7 mg/dl vs 34.3 ± 8.0 mg/dl); on the other hand, at the end of the fish oil

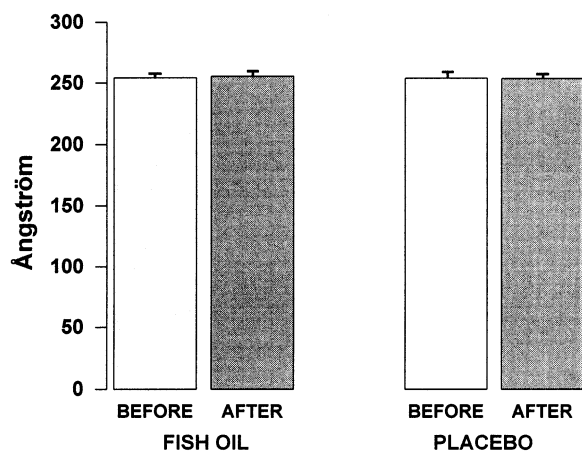


Fig. 1. LDL size (mean diameter in Å of the major LDL peak) before and after 6 months on fish oil ($n = 7$) or placebo ($n = 8$) in hypertriglyceridemic NIDDM.

treatment, the percentage of cholesterol content was higher in all the LDL subfractions compared with placebo, even if this increase was statistically significant only for the small LDL (percent cholesterol, 55.8 ± 0.8 vs 50.1 ± 2.3 ; $P < 0.05$) (Table 4).

The effects of treatment on LDL size are shown in Fig. 1. There were no changes at all in LDL size between baseline values and those at 6 months in either the fish oil period (254.2 ± 1.7 Å vs 255.4 ± 2.2 Å; ns; $\Delta 1.11 \pm 2.58$ Å; 95% CI, -7.44 to 5.21) or the placebo period (253.7 ± 2.0 Å vs 253.3 ± 1.7 Å; ns; $\Delta -0.38 \pm 1.36$; 95% CI, -2.84 to 3.59). The lack of effect on LDL size was confirmed by the data on the percentage distribution of LDL subfractions, separated by DGPU; the data at the end of fish oil and placebo periods fully overlapped (large, LDL $17 \pm 3\%$ vs $17 \pm 2\%$; intermediate, $62 \pm 3\%$ vs $65 \pm 3\%$; small, LDL $21 \pm 3\%$ vs $18 \pm 2\%$) (Table 3).

3.3. Lipolytic activities

There was no change in post heparin plasma lipoprotein and hepatic lipase activities in either the fish oil or the placebo group between baseline and 6 months (Table 5).

4. Discussion

The main findings of our study are as follows: (1) fish oil induces no significant change in either VLDL subfraction distribution or composition; (2) despite the relevant reduction in triglycerides (about 45%), supplementation of fish oil induces no significant change in either distribution of LDL subfractions or LDL size.

Although the literature is full of studies on the effects of fish oil on lipid metabolism [10–13], data on VLDL subfraction distribution—especially in diabetic patients—are not available. However, since some of the studies do report a major effect of fish oil on VLDL triglycerides compared with VLDL cholesterol [33], it has been postulated that fish oil treatment could lead to an increase in smaller VLDL [34], which may be more atherogenic [6]. Our study, instead, indicates, for the first time, that VLDL subfractions distribution is not affected by fish oil treatment. These results, together with our data on lipolytic activities (Table 4) and on the significant reduction in plasma free fatty acids induced by fish oil [13], support the hypothesis that fish oil acts principally by reducing VLDL synthesis [33], and suggest that this reduction involves the whole particle—not only its triglyceride content.

A preponderance of small, dense LDL particles has been reported to be an independent predictor of CV risk by some, but not all authors [2,35], and is present not only in NIDDM patients, but also in subjects characterized by insulin resistance [36]. Moreover, one of the main determinants of smaller LDL particles is represented by the level of plasma triglycerides, inasmuch as the higher the level of plasma triglycerides, the higher the percentage of small LDL and the smaller the size of the predominant LDL particle [37]. Therefore, since one of the most consistent effects of fish oil is a reduction in plasma triglycerides, it is reasonable to expect an increase in LDL size. Our data on LDL subfraction distribution and, more specifically, on LDL size do not support this hypothesis. The data in the literature on this aspect are rather scanty [38,39] and no studies have been performed in diabetic patients with hypertriglyceridemia, who are characterized by a predominance of smaller LDL [7–9] and in whom, therefore, a shift toward larger LDL could be very important from a clinical point of view.

Table 5
Post heparin plasma lipase activities before and after 6 months of fish oil or placebo in hypertriglyceridemic NIDDM patients^a

	Fish oil ($n = 6$)		Placebo ($n = 7$)	
	Baseline	6 months	Baseline	6 months
Lipoprotein lipase (mU/ml)	57.7 ± 12.7	63.4 ± 6.4	51.6 ± 10.9	53.1 ± 7.4
Hepatic lipase (mU/ml)	270.2 ± 33.2	280.2 ± 42.0	261.8 ± 34.3	261.4 ± 33.0

^a Data are mean \pm SEM.

The results of the few studies on this topic are controversial and, moreover, in the one showing a significant increase in LDL size [39], this increase is far from being striking (from 12.42 to 12.58 nm); although this result could be significant from a statistical point of view, it is unlikely to be clinically relevant.

The lack of any effect of fish oil on LDL size could be interpreted in different ways. First, it may be that the hypotriglyceridemic effect (a 45% reduction) induced by fish oil in our patients is not sufficient to change LDL size. However, against this point is the consideration that a smaller or equal reduction in triglycerides obtained with fibrates was able to significantly change LDL size by about 20% [40,41]. More than to the magnitude of the decrease, importance could be given to the levels of plasma triglycerides reached, especially considering that only levels of plasma triglycerides below 1.3 mmol/l are associated with a very low formation rate of small LDL [14]. In our hypertriglyceridemic diabetic patients, fish oil was indeed able to decrease plasma triglycerides but failed to fully normalize them. Further studies in patients with milder hypertriglyceridemia and in whom fish oil is able to normalize plasma triglyceride levels are needed to clarify this point.

The most plausible explanation for the lack of effects of fish oil on LDL size, compared with other hypotriglyceridemic agents, could be linked to its particular mechanism of action. As a matter of fact, fish oil acts quite exclusively on VLDL synthesis, and does not seem to have major effects on the VLDL catabolic pathways [38], as confirmed also by our negative findings on plasma lipolytic activities. Fibrates, instead, act by both reducing VLDL synthesis and increasing their catabolism [42,43]. It is possible that if a reduction in the VLDL pool is not associated with important changes in the catabolic pathway, especially with regard to HL activities, the complex mechanism involved in the regulation of LDL subfraction distribution will not be sufficiently affected.

Finally, the increase in small LDL is strictly linked to the level of insulin resistance. We have previously shown that fish oil is totally unable to modify the level of insulin resistance in the patients of the present study [13]. Therefore, the lack of changes in LDL size may also reflect the inability of fish oil to act on insulin resistance, considered by many authors to be the common pathogenetic mechanism of different metabolic abnormalities, including hypertriglyceridemia and high levels of small LDL [36,44].

Moreover, our patients present an enrichment in the cholesterol content of LDL and their subfractions, especially the smallest ones, after fish oil treatment. This enrichment is likely to be due to the reduction in VLDL particles with a subsequent decrease in CETP-mediated exchange of cholesterol and triglyceride between VLDL

and LDL, as reported to occur in IDDM patients treated with fish oil [45].

In conclusion, our study shows that in NIDDM patients with hypertriglyceridemia, the positive hypotriglyceridemic effect of fish oil is not associated with any unfavorable effect on VLDL subfraction distribution; neither does it improve LDL distribution pattern, which, instead, would be very useful for these patients, who are characterized by a predominance of small LDL.

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