n–3 Fatty acids do not lead to an increased diabetic risk in patients with hyperlipidemia and abnormal glucose tolerance1–3

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ABSTRACT  A multicenter, randomized, double-blind, placebo-controlled study evaluated the possible worsening of glycemic control after a moderate daily intake of n–3 fatty acid ethyl esters in patients with hypertriglyceridemia and without glucose intolerance or diabetes. A total of 935 patients of both sexes in 63 Italian clinical centers were selected; 55% had either impaired glucose tolerance or non-insulin-dependent diabetes mellitus (NIDDM). They received for 2 mo either 1 g n–3 ethyl esters three times a day or a corresponding placebo, followed by 4 mo of either 1 g n–3 ethyl esters twice a day or placebo. In addition to the complete lipid and lipoprotein evaluation, patients with impaired glucose tolerance also underwent an oral-glucose-tolerance test; in patients with NIDDM, serum insulin and glycated hemoglobin (Hb A1c) concentrations were determined. Plasma triacylglycerol concentrations decreased significantly, up to 21.53% at 6 mo compared with baseline (decreased 15% compared with placebo), with a tendency toward a progressive reduction with time. There was no evidence for a different response in patients with either NIDDM or impaired glucose tolerance. Among NIDDM patients, the triacylglycerol reduction was greater in those with high-density-lipoprotein cholesterol ≤ 0.91 mmol/L. There was no alteration in the major glycemic indexes: fasting glucose, Hb A1c, insulinemia, and oral glucose tolerance in patients with impaired glucose tolerance or NIDDM after treatment with n–3 ethyl esters. Treatment with a moderate daily dose of n–3 ethyl esters over a prolonged period of time significantly reduced triacylglycerol concentrations without any worsening of glucose tolerance in patients with hypertriglyceridemia and without impaired glycemic regulation. Am J Clin Nutr 1997:65:1874–81.

KEY WORDS  n–3 Fatty acids, fish oil, hypertriglyceridemia, impaired glucose tolerance, non-insulin-dependent diabetes mellitus, insulin resistance, syndrome X

INTRODUCTION

Several clinical, experimental, and epidemiologic studies have confirmed that the intake of n–3 polyunsaturated fatty acids from fish oil exerts a favorable effect on atherosclerosis development and progression (1–3). This protective effect is believed to be mediated by changes in plasma lipids, particularly triacylglycerols (4); changes in prostaglandin metabolism, with a relative increase in the formation of the antithrombotic prostaglandin I2 (5); by reduced formation of growth factors (6); and by stimulated endothelial relaxation (7).

Despite these favorable lipid, prostaglandin, and tissue changes, caution has been suggested for the use of n–3 fatty acids in patients with glucose intolerance or clearly diabetic conditions (8, 9). In these patients, significant increases were reported in plasma glucose, at times requiring increased doses of insulin or hypoglycemic agents (10–12). On the basis of animal studies, a suggested mechanism has been adipocyte enlargement after prolonged intake of large doses of n–3 fatty acids, leading to insulin resistance (13). Several clinical reports, however, have shown that n–3 fatty acids do not impair glycemic control either in insulin-dependent (14) or non-insulin-dependent diabetes mellitus (NIDDM) (15–17) or in essential hypertension (18). It has been suggested moreover that enrichment of human cell membranes with n–3 fatty acids may lead to improved peripheral insulin action (19, 20). The evidence for and against a worsening action of n–3 fatty acids on glycemic control was reviewed recently (21).

n–3 Fatty acids are frequently used in patients with lipid disorders characterized by hypertriglyceridemia. In these patients, the altered lipid and lipoprotein concentrations may be accompanied frequently by hyperinsulinemia or insulin resistance and arterial hypertension (syndrome X) (22). For this reason, a large controlled multicenter study was designed in patients with hypertriglyceridemia (Fredrickson types IIB and IV), a large percentage of whom had either impaired glucose tolerance or definite NIDDM. They were randomly assigned to receive in double-blind conditions either n–3 fatty acids as ethyl esters or a corresponding placebo. Therefore, the primary aim of this study was the evaluation of the effects of low-dose n–3 fatty acid treatment on lipid and lipoprotein concentra-

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tions. As a secondary aim, the study evaluated the concomitant effects on the clinical abnormalities of hypertriglyceridemia, particularly altered glucose metabolism and arterial hypertension, thus offering a clue as to the potential influence of preexisting conditions on the risk factor change induced by n−3 ethyl ester administration.

PATIENTS AND METHODS

Patients

The study protocol allowed the selection of patients of both sexes, males aged 45–75 y and females aged 55–80 y, with hyperlipoproteinemia type IIB or IV (23) associated with at least one additional risk factor: impaired glucose tolerance, NIDDM, or arterial hypertension. Ethics Committees of all participating centers approved the protocol.

Diagnostic criteria

Hyperlipoproteinemia

Patients with significant and stable triacylglycerol elevations (> 2.26 mmol/L, or 200 mg/dL) were selected. These were defined as type IIB if serum total cholesterol was > 7.21 mmol/L (270 mg/dL) and type IV if cholesterol was ≤ 7.21 mmol/L (270 mg/dL). Patients with total cholesterol concentrations > 7.76 mmol/L (300 mg/dL) with triacylglycerol concentrations ≥ 4.52 mmol/L (400 mg/dL) were excluded for ethical reasons.

Impaired glucose tolerance

Patients with fasting glucose < 7.7 mmol/L (140 mg/dL) and altered oral glucose tolerance (diagnostic criteria proposed by the National Diabetes Data Group) were defined as having impaired glucose tolerance (24).

Non-insulin-dependent diabetes mellitus

Patients who had been diagnosed as having diabetes for ≥ 2 y, who were in satisfactory metabolic control with or without pharmacologic treatment (fasting glucose < 7.7 mmol/L, or 140 mg/dL, and postprandial glucose < 11.1 mmol/L, or 200 mg/dL) were defined as having NIDDM. Patients taking insulin were excluded.

Arterial hypertension

Patients treated with antihypertensive drugs or who on more than one occasion in the past year had had a systolic blood pressure (SBP) ≥ 160 mm Hg, a diastolic blood pressure (DBP) ≥ 95 mm Hg, or both, independent of drug treatment, were considered to have arterial hypertension.

Exclusion criteria

Patients with severe intercurrent ailments, kidney or renal disease, intestinal malabsorption, duodenal ulcer not responsive to therapy, obese individuals with a body mass index (in kg/m²) ≥ 30, as well as noncompliant or unreliable patients were excluded from the study. All patients with a history of vascular or nonvascular brain disease (including epilepsy and alcoholism), severe hyperlipidemia needing drug treatment, severe hypertension (DBP > 110 mm Hg, SBP > 180 mm Hg under antihypertensive treatment), myocardial infarction in the preceding 3 mo, or unstable angina were excluded.

Randomization and sample size

The multicenter study involved 63 clinical groups distributed throughout Italy. To have a power of 0.90 (1−β), a difference in triacylglycerol reduction of ≥ 0.25 of the variability of the phenomenon (SD of the change before compared with after), 450 patients were necessary per treatment arm for an unpaired t test performed at a significance level with α = 0.01. In addition, this sample size allowed us to show, with a power of 0.90, a potential rise of plasma glucose of 0.15 of the variability of the phenomenon (change before compared with after) for a paired t test carried out at the significance level of α = 0.01 within each treatment.

The selected centers were invited to treat the first 16–20 patients (within a selected time frame) who met the admission requirements of the study. To control the variability inherent to a study of this type, randomization was achieved by keeping each center a unit, with separate lists of random numbers for each. The lists were constructed in such a way as to balance the number of patients allocated to each treatment with the randomized-block technique.

Treatments and protocol

The study design did not foresee standard treatment criteria for each single risk factor because it was not the study’s objective to interfere with the normal behavior of each single participating clinician, except for the use of n−3 ethyl esters or the placebo.

The start of the active treatment or placebo period was preceded by a run-in and wash-out period of ≥ 4 wk, during which patients followed an isocaloric diet to maintain a stable body weight; concomitant therapy (eg, hypotensive or antidiabetic) was stabilized and no hypolipidemic drugs were prescribed. After this, a double-blind phase was started. In the first 2 mo, all patients received their conventional therapy with the addition of an n−3 ethyl ester preparation three times a day (Esapent; Pharmacia, Milan, Italy), corresponding to a total of 1530 mg eicosapentaenoic acid (EPA) and 1050 mg docosahexaenoic acid (DHA), or a corresponding placebo (olive oil) also given three times a day. The daily amount of EPA + DHA administered corresponded to the amount found in ~150 g fresh salmon or in 300 g albacore tuna.

After the first 2 mo, the doses of both EPA + DHA and placebo were reduced to one capsule twice a day (1020 mg EPA and 700 mg DHA) up to the end of the sixth month. Patients were advised to swallow the capsules before their main meals.

The use of hypolipidemic (both hypotriglyceridemic and hypcholesterolemic) agents was restricted in all participating centers. No change in the dose schedule of oral hypoglycemic or antihypertensive medications was allowed during the 6 mo of controlled investigation. If patients needed insulin, they were excluded from the study. Any necessary changes were indicated in the clinical chart. Furthermore, all patients received dietary instructions, including the reduction of arachidonic acid–rich food items such as eggs and pluck (heart, liver, and lungs). These could not be eaten more than once a week. All patients gave written consent to participate in the study, and
the responsible clinician had the ability to interrupt treatment at any time for major events.

Clinical and laboratory measurements
All patients underwent a complete laboratory evaluation, including urine and hematologic analysis, at baseline and at the end of the sixth month of the controlled investigation. At all visits (basal, 2, 4, and 6 mo), they underwent a complete lipid and lipoprotein evaluation, including total cholesterol and triglyceride concentrations by enzyme kit methods (Boehringer Mannheim, Mannheim, Germany), HDL cholesterol by selective precipitation with dextran-MgCl2, standardized in all centers (25), followed by calculation of low-density lipoprotein (LDL)-cholesterol concentrations with the Friedewald formula (26) [no patient with a triglyceride concentration > 4.52 mmol/L (400 mg/dL), which would have invalidated the formula, was admitted into the study], and fasting glucose concentrations. An oral-glucose-tolerance test with 75 g glucose was carried out only in the group with impaired glucose tolerance (24), with determination of glucose concentrations at all time points (30, 60, 90, and 120 min). In patients with NIDDM, glycated hemoglobin (Hb A1c) concentrations were determined by HPLC (27) and serum insulin by radioimmunoassay (Serono Kits, Saluggia, Italy) (28). Blood pressure was measured three times in the sitting position by the auscultatory technique. The numerical value of each measurement was recorded in the clinical chart with the means for the final calculation.

Concentrations of EPA and DHA in plasma and red blood cells (RBCs) were monitored in all patients in three participating centers. Fatty acids were analyzed by gas-liquid chromatography after chloroform-methanol extraction and transmethylation as described by Marangoni et al (29).

Statistical analysis
Analyses of data were performed both according to “intention-to-treat,” ie, by evaluating all patients, including those not satisfying the inclusion criteria, and also according to “per-protocol” criteria, for which patients without the additional cardiovascular risk factor or with other exclusion criteria at the first visit were not considered. For patients with a study period < 6 mo, the last value was considered (LOCF, last observation carried forward). For the analysis of the temporal trend, patients without values at all the scheduled visits were excluded. Data are presented as means ± SDs. Inferential analysis was performed by mixed-factorial analysis of variance for repeated-measures analysis of variance.

RESULTS
The 63 participating centers provided a total of 935 patients, 470 assigned to n-3 ethyl esters and 465 to placebo. Of all patients included in the study, 67 interrupted treatment for various reasons, 28 in the n-3 ethyl ester group and 39 in the placebo group. In the majority of cases, drop outs were consequent to a voluntary decision to interrupt the study. In the per-protocol analysis 10 patients were excluded: 7 for the absence of the additional cardiovascular risk factor, 2 because of the concomitant intake of a hypolipidemic drug; and 1 because the selected patient was already receiving n-3 fatty acid treatment and was randomly assigned to active treatment. In this last patient treatment was not stopped. Otherwise, the treatment was well tolerated, with an overall compliance > 90%, as assessed by pill counting. Twenty-five patients in the n-3 ethyl ester group and 20 in the placebo group did not adhere satisfactorily to treatment. Only 39 patients had a total of 46 side effects, mainly mild gastrointestinal disturbances: 21 side effects in 18 patients treated with n-3 ethyl esters and 25 in 21 patients taking the placebo. Similarly, there were no significant changes in the major laboratory measures, either biochemical or hematologic.

The distribution of patients by age, sex, height, and body weight is reported in Table 1. The majority (62.4%) of the patients were men, distributed similarly between the two treatment groups. Mean age was also similar in the two groups and body weight, mostly within normal limits, was evenly distrib-

### Table 1
Characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>EPA + DHA (n = 294 M, 176 F)</th>
<th>Placebo (n = 289 M, 176 F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>62.1 ± 7.12*</td>
<td>61.8 ± 7.06</td>
</tr>
<tr>
<td>Men</td>
<td>55.8 ± 9.35</td>
<td>57.0 ± 9.54</td>
</tr>
<tr>
<td>̄x</td>
<td>58.2 ± 9.09</td>
<td>58.8 ± 8.99</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>74.0 ± 10.44</td>
<td>73.7 ± 10.08</td>
</tr>
<tr>
<td>6 mo</td>
<td>73.5 ± 10.38</td>
<td>73.2 ± 10.10</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.3 ± 8.68</td>
<td>166.8 ± 8.38</td>
</tr>
<tr>
<td>Type of hypercholesterolemia (% of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type IIb</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Type IV</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Additional risk factors (% of patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIDDM</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>68</td>
<td>68</td>
</tr>
</tbody>
</table>

* EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; NIDDM, non-insulin-dependent diabetes mellitus.

* ̄x ± SD.
uted; no significant differences in weight were observed during all later visits, confirming good compliance with the dietary guidelines. Hyperlipidemias were again evenly distributed between the n-3 ethyl ester and placebo groups. The majority of patients had type IIB hyperlipoproteinemia (65%), whereas 35% had type IV. Fifty-five percent of the selected patients, evenly distributed between the two treatment groups, had pathologic glycemic control, 11% with impaired glucose tolerance and 44% with NIDDM (>50% with a disease duration < 5 y) (Table 1).

Among hypertensive patients, 99% had mild-to-moderate disease (SBP < 190 mm Hg and DBP < 110 mm Hg) and 73.8% had been receiving antihypertensive therapy before random assignment; the distribution between the groups was superimposable (Table 2).

Plasma lipid changes

The treatments had no significant effect on total cholesterol, both when examined according to intention-to-treat or per protocol (data not shown). The calculated LDL-cholesterol concentrations before and after 6 mo of treatment tended to rise, both in patients taking placebo (3.0%) and, to a slightly larger extent, in those taking n-3 ethyl esters (6.0%) (Figure 1). Comparison of the two groups showed a significant difference at the end of 6 mo (P = 0.048).

Conversely, triacylglycerol concentration was significantly lower (~21.53% compared with ~6.54% in the placebo group after 6 mo; P < 0.0001), with the largest reduction occurring in the first 2 mo, followed by a progressive lowering later on (Figure 2). Patients with impaired glucose tolerance or NIDDM did not show a different triacylglycerol response from normoglycemic subjects (data not shown).

When patients were divided into those with and without LDL-cholesterol concentrations (≤0.91 mmol/L), n-3 ethyl esters reduced triacylglycerol concentrations significantly in both, but in NIDDM patients the percentage triacylglycerol reduction was greater in those with HDL cholesterol ≤0.91 mmol/L (~23.3%) than in those with HDL cholesterol > 0.91 mmol/L (~16.9%; P < 0.05) (Figure 3). Evaluation of normoglycemic patients at the same criteria did not show any HDL-related difference in triacylglycerol response (data not shown).

Overall, there was a small increase in HDL cholesterol, both in the placebo and in the n-3 ethyl esters group (5% for both) (Figure 1). However, the increase of HDL-cholesterol concentrations in male patients with impaired glucose tolerance or NIDDM treated with n-3 ethyl esters was greater than that observed in normoglycemic males (8.31% compared with 4.35% for the corresponding placebo, respectively, P < 0.05).

Glycemic control and blood pressure changes

No effect of n-3 ethyl ester treatment was observed on any of the major glycemic indexes: fasting glucose, Hb A1c, insulinemia, and oral glucose tolerance. These were essentially identical before and after treatment in patients with impaired glucose tolerance or NIDDM (Tables 3 and 4). In addition, mean values of SBP and DBP were not modified either during or at the end of the 6-mo treatment in the whole group or in the patients with impaired glucose tolerance or NIDDM (data not shown).

Plasma and red blood cell fatty acid profiles

In three participating centers EPA and DHA concentrations were monitored in plasma and RBCs. Plasma and RBC concentrations of EPA and DHA were similar at baseline in all three centers. Six months of treatment with EPA + DHA resulted in significant changes in the n-3 fatty acid content of both plasma and RBCs. In plasma, the mean rise in EPA was 43% and that of DHA was 16%. Similarly, in RBC membranes, EPA showed a more significant rise (214%; P < 0.0001 compared with baseline) than did DHA (31%; P < 0.001 compared with baseline). All of these significant changes con-

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**TABLE 2**

Baseline lipid, fasting glucose, and blood pressure concentrations in all patients

<table>
<thead>
<tr>
<th></th>
<th>EPA + DHA (n = 470)</th>
<th>Placebo (n = 465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>6.05 ± 0.84</td>
<td>6.04 ± 0.86</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/L)</td>
<td>1.03 ± 0.25</td>
<td>1.03 ± 0.25</td>
</tr>
<tr>
<td>Triacylglycerol (mmol/L)</td>
<td>3.32 ± 0.89</td>
<td>3.36 ± 0.96</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>6.6 ± 2.1</td>
<td>6.7 ± 2.0</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>145.7 ± 14.5</td>
<td>144.8 ± 14.9</td>
</tr>
<tr>
<td>Diastolic</td>
<td>86.5 ± 8.2</td>
<td>85.5 ± 8.1</td>
</tr>
</tbody>
</table>

χ ± SD. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
firm the more marked influence of EPA than of DHA intake, resulting from the lower circulating and tissue pools of EPA in humans (30).

DISCUSSION

The increasing use of n-3 fatty acids, especially the ethyl ester preparation which is effective at low daily doses, has made it mandatory to clarify some major issues emerging from recent and earlier studies. Concern has been raised recently about possible damage from an increased intake of dietary fish among middle-aged men by the reported increase in cardiovascular morbidity in subjects with the highest n-3 fatty acid consumption in the Health Professionals’ Follow-up Study (31). Although there is no question that the intake of fish and particularly of n-3 fatty acids may be associated with a reduction of both basal and postprandial concentrations of triacylglycerol and very-low-density-lipoprotein cholesterol (4, 32), reduced platelet aggregability (33), and improved vasodilatation (7), the analysis of the direct effects of n-3 intake on variables underlying glycemic control has found divergent responses.

Studies in diabetic patients receiving either diet or sulfonylureas, were often characterized by a rise in glyceria, at times associated with reduced insulinemia. These findings led in some cases to the suggestion that n-3 fatty acid intake should be restricted in diabetics (8, 12). As for the molecular basis for these findings, Ezaki et al (13) suggested that n-3 fatty acid intake might initially improve muscle and fat transporter (GLUT-4) activity in adipocytes; the transient improvement of GLUT-4 activity would, however, be followed over time by a loss of activity, thus leading to increased cell size and consequent peripheral insulin resistance. The animal findings have been partially supported by studies with large doses of n-3 ethyl esters (> 9 g/d) (10), both in normal and diabetic persons, indicative of altered insulin secretion with a rise in the daily insulin requirements in insulin-dependent diabetes mellitus. Animal and human studies thus suggest that membrane changes at the adipocyte or liver levels may affect substrate disposal along the different metabolic routes. The chemical composition of fatty acids taken up by the liver might quantitatively affect hepatic glucose output by redirecting one or more substrates from lipid synthesis to gluconeogenesis in hypertriglyceridemic patients with either type of diabetes, for example after n-3–enriched diets (34, 35).

These biochemical hypotheses were contradicted by the data from Storelil et al (36, 37), who showed that n-3 fatty acid incorporation into skeletal muscle is inversely related to local lipid accumulation and may be associated with an improvement of peripheral insulin action. This hypothesis was corroborated recently by findings indicating a positive correlation in humans between insulin sensitivity and muscular concentrations of polyunsaturated fatty acids, particularly n-3 fatty acids (38). In addition, rats fed n-3 fatty acids tended to gain less weight at the abdominal level, a possible indication of improved peripheral insulin sensitivity (39).

Indeed, relatively lower daily doses of n-3 fatty acids, in proportions similar to those in the present study, failed to cause
significant changes in glycemic control (14–20), with the possible exception of a small reduction of fasting insulin in n-3 fatty acid–treated, moderately hypertriglyceridemic patients (19). In addition, favorable changes were noted, including reduced blood pressure, in patients with insulin resistance (20). A controlled study using the hyperglycemic-clamp technique failed to detect any abnormalities in glucose handling after 16 wk of 4 g n-3 ethyl esters/d in hypertensive subjects (18); with a similar protocol, the same authors saw no changes in diabetic control (as assessed by five criteria) after 6 mo of fish-oil feeding in a small group of NIDDM patients (40).

For the first time, the present study allows the evaluation of a very large sample of patients, 21% of whom met the definition of syndrome X, ie, hypertriglyceridemia, arterial hypertension, low HDL-cholesterol concentrations, and impaired glucose tolerance (41). The study thus had the proper size and patient selection to clarify some of the questions that have emerged from the smaller, frequently uncontrolled studies of patients with combined alterations of lipid and glucose metabolism; in addition, a relatively low daily dose of n-3 ethyl esters was chosen. Earlier data from one of the participating centers had shown that even with a low intake of n-3 fatty acids, their incorporation into plasma membranes may be long lasting (33), thus providing the cellular mechanism for the proposed alterations of insulin binding and glucose handling. It can be assumed and confirmed by monitoring plasma and RBC fatty acid composition in treated patients that exposure to n-3 ethyl esters under the present conditions does result in significant changes in tissue homeostasis, as typically induced by fish-oil intake (42).

Administration of n-3 ethyl esters resulted in a significant lowering of plasma triacylglycerol concentrations, in a range similar to that reported by most investigators in the field (4) using higher doses of either n-3 ethyl esters or fish-oil triacylglycerols, and in modest changes of LDL-cholesterol concentrations. It is generally maintained that administration of n-3 fatty acids or of fish oil results in increased LDL-cholesterol in normolipidemic or hypertriglyceridemic patients (4). There was also a contention that some forms of fish oil derived from sources rich in DHA (eg, pollock oil) might be effective in reducing cholesterol (43). A comparative study with the three major dietary oils, ie, those rich in n-9 monounsaturates, n-6 polyunsaturates, and n-3 fatty acids, in patients with moderate type II hyperlipoproteinemia, indicated that n-3 fatty acids gave the best hypcholesterolemic response (44). n-3 Fatty acids may thus act in a way similar to that of fibrates, ie, by lowering cholesterol only in hypercholesterolemic patients, with an LDL cholesterol–raising effect in hypertriglyceridemia (40, 44–46).

The present study offered an insight into the effects of n-3 ethyl esters on lipid and lipoprotein variables in patients with normal glycemic control and in those with impaired glucose tolerance or NIDDM. There were minimal changes in indexes of glycemic control, and patients with impaired glucose tolerance or NIDDM had a hypotriglyceridemic response to n-3 ethyl esters similar to that of normoglycemic subjects. There appeared to be an HDL cholesterol–raising effect in men with impaired glucose tolerance and NIDDM, pointing to a possible selective activity on HDL metabolism in diabetic individuals. The effects of n-3 fatty acids on total and HDL-cholesterol concentrations are generally small (4), with few exceptions (17, 43). The HDL-subfraction distribution, instead, is significantly altered, with a selective alteration in the HDL2 subfraction, which increases ~30% after treatment (47). The mechanism is unclear, although it may be an adaptive response to the differential activity of n-3 fatty acids on lipoprotein and hepatic lipases (48). The present study did not evaluate changes in the HDL subfractions. The HDL composition in NIDDM typically shows a decrease of the large HDL2 and lipoprotein(A-I) fraction with a shift to smaller particles (49). These findings are likely related to the triacylglycerol enrichment in the HDL of diabetics (50, 51), making them more sensitive to the HDL2 cholesterol–raising properties of n-3 ethyl esters and, in some cases, leading to a higher cholesterol content in the whole HDL fraction (17).

The lack of effect on glucose metabolism of n-3 ethyl esters in patients with impaired glycemic control is noteworthy and rules out concern about the prescription of these products to diabetics. Prior investigations suggested that insulin secretion might be reduced after n-3 fatty acid intake because of changes in membrane fluidity and responsiveness of islet cells to normal stimuli (10), possibly because of impaired calcium flux across cell types exposed to marine lipids (52). The present study failed to provide any evidence of impaired insulin secretion, whereas the recent hyperglycemic-clamp study ruled out an effect on peripheral sensitivity (18).

Although the diabetic patients did experience a significant improvement in lipoprotein metabolism, there was no evidence for a correction of other typical traits of syndrome X, particularly blood pressure. Meta-analyses of blood pressure changes after treatment with n-3 fatty acids have not yielded a uniform conclusion (53). A better response seems to take place after high doses of n-3 fatty acids in nondrug-treated hypertensive subjects.
subjects with arterial disease (54). In the present study, most of the hypertensive patients were already taking some form of medication and n-3 fatty acid intake did not cause a significant blood pressure reduction.

The reported multicenter study meets a growing demand (55) and indicated that a large group of patients with hypertriglyceridemia and abnormal glucose metabolism responded well to a moderate daily dose of n-3 ethyl esters without consequent impairment of glycemic control. This population was representative of what is generally seen in the clinical treatment of diabetes and hyperlipidemia, also providing a significant number of cases with the risk factor constellation (syndrome X) for myocardial infarction (56). This study therefore indicates that n-3 ethyl esters can provide a suitable option for the management of a growing segment of the middle-aged population, including postmenopausal women, in whom hypertriglyceridemia may be a major risk for cardiovascular death (57).

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