n-3 Fatty acids do not enhance LDL susceptibility to oxidation in hypertriacylglycerolemic hemodialyzed subjects

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ABSTRACT Recent data suggest that treatment with n-3 fatty acids could enhance the susceptibility of plasma low-density-lipoprotein (LDL) to oxidation. Twelve hypertriacylglycerolemic, hemodialyzed patients were treated with 2.5 g n-3 fatty acids/d for 2 mo. Treatment was then withdrawn for 2 mo (washout phase). Plasma total cholesterol and LDL cholesterol increased significantly (9% and 28%) and plasma triacylglycerols decreased significantly after the n-3 phase compared with baseline and washout values. LDL susceptibility to oxidation was tested by oxidation of LDL particles with 2,2′-azobis (2-amidinopropane) dihydrochloride (AAPH). No significant changes were observed for the lag phase and the peroxidation rate. The vitamin E content of LDL also did not change significantly. The results thus suggest that a daily dosage of 2.5 g n-3 fatty acids does not enhance LDL susceptibility to oxidation, while retaining its hypertriacylglycerolemic effect.


KEY WORDS n-3 Fatty acids, oxidized low-density lipoprotein, hypertriacylglycerolemia, hemodialysis, fatty acid lipoprotein fraction have been observed in patients treated with n-3 fatty acids (6).

Whereas n-3 polyunsaturates certainly can be helpful for treating hypertriacylglycerolemia, it is questionable whether their effect on qualitative properties of lipoproteins could be as wanted as the quantitative effect (4, 5). Indeed, there is evidence showing that an increase in the LDL content of n-3 as well as n-6 fatty acids might render these lipoproteins more susceptible to oxidative modification (7–12). Oxidized LDLs are thought to be much more atherogenic than native ones, and consequently the antiatherogenic action of n-3 fatty acids could be partially quenched if these fatty acids were proven to effectively enhance LDL oxidation (13, 14). Furthermore, LDL oxidation might be even more relevant in hemodialyzed patients, because hemodialytic treatment itself has been reported to elicit oxidative processes (15–17).

In the present study, 12 hypertriacylglycerolemia hemodialyzed patients were treated with n-3 fatty acids with the aim of studying the effect on plasma lipid concentrations and on the susceptibility of LDL to oxidation.

SUBJECTS AND METHODS

Patients

Twelve patients (seven males, five females) with chronic renal failure who were currently undergoing hemodialytic treatment participated in the study. To be eligible, patients had to be free of diabetes mellitus, chronic liver disease, gastrointestinal disease, and autoimmune disease, and not to have suffered from a recent myocardial infarction (within 3 mo of the start of the study). Also, patients currently treated with lipid-lowering drugs or drugs known to affect plasma lipid


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concentrations, such as β-blockers and thiazide diuretics, were not eligible. Lastly, only subjects who had had a plasma triacylglycerol concentration > 2.82 mmol/L (250 mg/dL) for the last 3 mo were selected for the trial.

The mean (± SEM) age of the patients was 64 ± 2 y and their body mass index [BMI; weight (in kg)/height² (in m)] was 25.5 ± 0.8. Systolic blood pressure (average of three measurements obtained before three subsequent hemodialytic sessions) was 139 ± 6 mm Hg and diastolic blood pressure was 79 ± 2 mm Hg. The cause of chronic renal failure was chronic glomerulonephritis for six patients and chronic pyelonephritis for three patients; the cause of end-stage renal disease could not be determined in the remaining three patients. The mean (± SEM) concentration of serum creatinine was 1079 ± 43 μmol/L (12.2 ± 0.84 mg/dL), of blood urea nitrogen (BUN) was 63.2 ± 4.6 mmol/L, and of serum albumin was 42 ± 0.9 g/L. On admission, plasma cholesterol was 6.28 ± 0.31 mmol/L (243 ± 12 mg/dL), plasma triacylglycerols were 3.43 ± 0.33 mmol/L (304 ± 26 mg/dL), and plasma HDL cholesterol was 0.96 ± 0.05 mmol/L (37 ± 2 mg/dL). All patients consumed an isoenergetic diet in which protein intake ranged from 1.2 to 1.5 g/kg body wt (≈15% of total energy). Total fat supplied 30% of energy (equally divided among saturated, monounsaturated, and polyunsaturated fatty acids) and carbohydrates ≈65% of energy intake. The daily intake of cholesterol was 300 mg, of sodium 60–100 mmol, of potassium 40–60 mmol, of phosphate 19–39 mmol, and of calcium 25–50 mmol. Eight patients were currently treated with calcium-channel blocking drugs. All patients were taking calcium supplements plus a daily dosage of 0.5 μg calcitriol. None of the subjects consumed vitamin E or vitamin C supplements.

The mean duration of hemodialytic therapy was 4.9 ± 1.0 y (range: 2–12 y). All patients underwent a hemodialytic session lasting 3–4 h three times a week, using CUPROPHAN dialyzing membranes (Hospal SPA, Mirandola, Italy). The protocol was approved by the Institutional Review Board of the University of Padua. All patients gave informed consent to participate in the study.

Study protocol

The study consisted of two sequential phases, each one lasting 2 mo. During the first phase, patients were administered one capsule containing 85 mg ethyl esters of n−3 fatty acids three times per day for a total daily dose of 2.5 g eicosapentaenoic (20:5n−3) and docosahexaenoic (22:6n−3) acids. The ratio between 20:5 and 22:6 was 1.2. Each capsule contained 0.3 mg DL-α-tocopherol. In the second phase (washout phase), treatment with n−3 fatty acids was discontinued. No change in drug therapy or dietary habits was undertaken during either experimental phases. Also, patients did not consume vitamin E or any other vitamin supplements throughout the study. Compliance with the therapy was ascertained by interviewing patients frequently, supplying them the weekly dose of capsules, and having them return the empty capsule containers from the previous week. Further, each patient met with a dietitian every month and body weight was measured before and after each hemodialytic session. The fatty acid composition of LDL also served as a measure of compliance with treatment with n−3 fatty acids. Blood pressure was measured before and after hemodialytic treatments. Lastly, the following indexes were measured once a month: complete blood count and blood concentrations of glucose, creatinine, BUN, sodium, potassium, calcium, phosphorous, magnesium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatine phosphokinas (CPK), and albumin.

Biochemical analyses

Blood samples were drawn on days 0 (baseline), 30, and 60 of each phase, immediately before the dialytic treatment began. The mean of values obtained on days 30 and 60 was taken as representative of each phase. Plasma total cholesterol and triacylglycerols were measured by enzymatic methods (18, 19). Control sera for cholesterol and triacylglycerol analyses (PRE-CINORM L; Boehringer Mannheim, Mannheim, Germany) were included in each set of assays. The day-to-day CV was 1.1% for cholesterol and 1.3% for triacylglycerols. Plasma HDL cholesterol was determined in whole plasma after precipitation of apolipoprotein B–containing lipoproteins with phosphotungstic acid and magnesium chloride (20). Plasma VLDL (density < 1.006 kg/L) and LDL (density 1.006–1.063 kg/L) were separated by sequential ultracentrifugation (21). Plasma LDL and VLDL cholesterol were measured by enzymatic methods (18).

Oxidative modification of LDL

The susceptibility of plasma LDL to oxidative modification was measured in LDL samples obtained on days 0 (baseline), 30 (n−3 phase), and 120 (washout phase). Plasma LDL samples were dialyzed with a solution of 0.9% NaCl-EDTA (0.24 mmol/L), pH 7.4, for 24 h at 4 °C. The LDL protein concentration was determined according to Lowry’s procedure, as modified by Markwell et al (22). Dialyzed LDLs were then diluted with phosphate-buffered saline (pH 7.4) to obtain a final concentration of 0.1 g LDL protein/L. Lastly, LDLs were oxidized by adding to the sample 2,2′-azobis (2-aminopropane) dihydrochloride (AAPH) at a final concentration of 5 mmol/L (12, 23). The kinetics of peroxidative reactions were followed by measuring the formation of conjugated dienies by continuous monitoring of the absorbance at a wavelength of 234 nm with a DU 65 spectrophotometer (Beckman Instruments, Fullerton, CA) at 40 °C. The curve representing the progressive formation of conjugated dienies can be divided into two sections. The first one (lag phase), expressed in minutes, has a duration that is directly related to the content of antioxidants in the lipoprotein. The second part of the curve (peroxidation rate), expressed as absorbance × 1000/min, reflects the susceptibility of LDL to oxidation once antioxidants have been consumed.

Fatty acid composition of LDL

The fatty acid composition was determined by gas-liquid chromatography (24). LDL fatty acids were hydrolyzed and transesterified with methanol and sulfuric acid at 90 °C. Methylated fatty acids were then extracted with hexane and water. Samples were analyzed with a Perkin-Elmer 8500 gas chromatograph (Norwalk, CT) equipped with a CPM TM silica-gel capillary column, 30 m long. The gas-chromatographic procedure was conducted at a temperature of 150–250 °C. The fatty acid composition was also determined quantitatively by adding heptadecanoic acid (17:0) to the samples as an internal standard.
Vitamin E content of LDL

The concentration of vitamin E in LDL was determined by HPLC. One milliliter of hexane was added to a 0.5-mL aliquot of plasma LDL. After centrifugation at 1000 × g for 10 min at 4 °C, 0.6 mL of the organic phase was dried under a nitrogen stream. The pellet was redissolved in 0.1 mL ethyl ether and 0.5 mL methanol. Tocopherol acetate was used as an internal standard. HPLC analysis was carried out with a reversed-phase (C-18, 4.6 × 150 mm) column and a reversed-phase precolumn (C-18, 3.2 × 20 mm) (25).

Theoretic susceptibility of LDL to oxidation

The theoretic susceptibility of LDL to oxidation (Th-Ox), as influenced by the changes in the fatty acid composition of the lipoprotein, was estimated by using a modified version of an equation reported by Esterbauer and Jürgens (26). The equation consists of the sum of the figures obtained by multiplying the concentration of each polyunsaturated fatty acid detectable in LDL (expressed in mmol/L) by the number of double bonds of the fatty acid molecule minus 1:

\[ \text{Th-Ox} = (18:2 \times 1) + (18:3 \times 2) + (20:4) \times 3 + (20:5 \times 4) + (22:6 \times 5) \]

This equation allows an estimation of the number of oxidative sites in each fatty acid molecule, i.e., the number of methylenic groups enclosed between two double bonds.

Statistical analysis

All data are expressed as mean ± SEM. Analysis of variance was used to disclose significant differences between groups (27). The data were then compared by using a two-tailed paired t test, with Bonferroni’s adjustment to correct the overall α level (27). Analysis of variance with the Kruskall-Wallis test for nonparametric values was used to compare the fatty acid composition of LDLs (28). Linear regression was used to calculate the relation between the content of n-3 fatty acids in LDLs and the peroxidation rate, and between the content of linoleic acid (18:2) plus arachidonic acid (20:4) and the peroxidation rate itself (27).

RESULTS

Patients tolerated treatment with n-3 fatty acids and no side effects were observed. No significant change in body weight was observed throughout the study (baseline: 60.5 ± 3.5 kg; n-3 phase: 69.6 ± 3.4 kg; washout phase: 69.7 ± 3.4 kg).

Changes in plasma lipid and lipoprotein concentrations are shown in Table 1. After the n-3 phase, plasma total cholesterol increased by 9% (P < 0.001), plasma triacylglycerols decreased by 30% (P < 0.001), plasma LDL cholesterol increased by 28% (P < 0.001), HDL cholesterol increased by 5% (NS), and VLDL cholesterol decreased by 35% (P < 0.001). After the washout phase, plasma total cholesterol was 3% higher than at baseline, but 5% lower than that after the n-3 phase (NS). Plasma triacylglycerols were still 14% lower than at baseline (P < 0.05) but 22% higher than during the n-3 phase (P < 0.05); plasma LDL cholesterol was 15% higher than at baseline (P < 0.01) but 10% lower than during the n-3 phase (P < 0.01); plasma HDL cholesterol showed a 5% decrease as compared with baseline and a 10% decrease as compared with the n-3 phase (NS); and plasma VLDL cholesterol was 10% lower than at baseline (P < 0.01) and 25% higher than after the n-3 phase (P < 0.05).

Vitamin E concentrations were 4.2 ± 0.2 μmol/g LDL at baseline, 4.4 ± 0.2 μmol/g LDL after the n-3 phase, and 3.9 ± 0.3 μmol/g LDL after the washout phase. None of these differences was statistically significant.

The fatty acid composition of LDLs is shown in Table 2. A significant increase of 20.5 and 22.6 was observed during the n-3 phase (P < 0.01). After the washout phase, 20.5 and 22.6 were still higher than they were at baseline (P < 0.01); 18:2 and 20:4 were lower after the n-3 phase than at baseline, but this difference was not significant. Oleic acid (18:1) also decreased after the n-3 phase (NS). No significant changes were observed for the remaining fatty acids. No significant changes in the susceptibility of LDL to oxidation were observed after oxidation of the lipoproteins with AAPH. In particular, neither the lag phase (baseline: 22.7 ± 0.8 min; n-3 phase: 22.8 ± 0.7 min; washout phase: 22.4 ± 0.8) nor the peroxidation rate (baseline: 14.1 ± 1.1; n-3 phase: 12.6 ± 0.9; washout phase: 12.5 ± 0.4) showed any significant variation throughout the study. The peroxidation rate was significantly related to the content (mmol/LD fatty acid/L) of linoleic acid in LDLs (r = 0.362, P = 0.03) and a significant relation was found also for the sum of 18.2 + 20.4 (r = 0.369, P = 0.027). On the contrary, the relation between the content of n-3 fatty acids and peroxidation rate was not statistically significant (r = −0.146, P = 0.403).

| TABLE 1 |
| Changes in plasma lipid and lipoprotein concentrations* |

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>n-3 phase</th>
<th>Washout phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>6.28 ± 0.31(243 ± 12)</td>
<td>6.83 ± 0.36(264 ± 14)</td>
<td>6.49 ± 0.36 (251 ± 14)</td>
</tr>
<tr>
<td>Triacylglycerols</td>
<td>3.43 ± 0.33(304 ± 26)</td>
<td>2.39 ± 0.39(212 ± 30)</td>
<td>2.94 ± 0.34(260 ± 30)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>3.72 ± 0.26(144 ± 10)</td>
<td>4.78 ± 0.31(185 ± 12)</td>
<td>4.29 ± 0.36(166 ± 14)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.96 ± 0.05(37 ± 2)</td>
<td>1.01 ± 0.05(39 ± 2)</td>
<td>0.91 ± 0.03 (35 ± 1)</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>1.60 ± 0.18(62 ± 7)</td>
<td>1.03 ± 0.16(40 ± 6)</td>
<td>1.29 ± 0.18(50 ± 7)</td>
</tr>
</tbody>
</table>

* ± SEM.

1Significantly different from baseline; 2P < 0.01, 3P < 0.001, 4P < 0.05.

5Significantly different from n-3 phase; 5P < 0.05, 6P < 0.01.
TABLE 2
Fatty acid composition of LDL

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Baseline</th>
<th>n-3 phase</th>
<th>Washout phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:0</td>
<td>0.14 ± 0.03</td>
<td>0.10 ± 0.01</td>
<td>0.12 ± 0.03</td>
</tr>
<tr>
<td>14:0</td>
<td>0.87 ± 0.08</td>
<td>0.98 ± 0.16</td>
<td>0.88 ± 0.12</td>
</tr>
<tr>
<td>16:0</td>
<td>22.32 ± 0.69</td>
<td>24.01 ± 0.89</td>
<td>22.94 ± 0.58</td>
</tr>
<tr>
<td>16:1</td>
<td>1.87 ± 0.23</td>
<td>1.11 ± 0.24</td>
<td>1.19 ± 0.24</td>
</tr>
<tr>
<td>18:0</td>
<td>5.56 ± 0.27</td>
<td>5.75 ± 0.43</td>
<td>4.68 ± 0.49</td>
</tr>
<tr>
<td>18:1</td>
<td>20.57 ± 2.13</td>
<td>17.18 ± 0.99</td>
<td>19.79 ± 1.45</td>
</tr>
<tr>
<td>18:2</td>
<td>37.14 ± 1.91</td>
<td>34.08 ± 1.80</td>
<td>37.18 ± 2.07</td>
</tr>
<tr>
<td>18:3n-6</td>
<td>0.46 ± 0.04</td>
<td>0.19 ± 0.03</td>
<td>0.47 ± 0.04</td>
</tr>
<tr>
<td>18:3n-3</td>
<td>0.26 ± 0.05</td>
<td>0.11 ± 0.01</td>
<td>0.22 ± 0.04</td>
</tr>
<tr>
<td>20:4</td>
<td>8.56 ± 0.43</td>
<td>7.67 ± 0.26</td>
<td>8.40 ± 0.46</td>
</tr>
<tr>
<td>20:5</td>
<td>0.75 ± 0.15</td>
<td>4.35 ± 0.49</td>
<td>0.96 ± 0.12</td>
</tr>
<tr>
<td>22:6</td>
<td>1.55 ± 0.12</td>
<td>4.47 ± 0.32</td>
<td>3.25 ± 0.32</td>
</tr>
</tbody>
</table>

\( ^{1} \text{SEM} \)

\( ^{2} \) Significantly different from baseline, \( P < 0.01 \).

\( ^{3} \) Significantly different from n-3 phase, \( P < 0.01 \).

The total content of fatty acids in LDL, expressed as mmol LDL fatty acids/mL, was 6.83 ± 0.64 at baseline, 6.16 ± 0.37 after the n-3 phase, and 6.33 ± 0.48 after the washout phase. None of these differences was statistically significant. The content of polyunsaturated fatty acids in LDL (in mmol/L) and the Th-Ox are shown in Table 3. No significant changes in the Th-Ox were observed among the three phases of the study.

DISCUSSION

n-3 Fatty acids are known to lower plasma triacylglycerols by inhibiting VLDL synthesis in the liver, and indeed have been used successfully for treatment of patients with hypertria cylglycerolemia and end-stage renal disease (3–6). Moreover, n-3 fatty acids have been shown to raise plasma HDL cholesterol, an effect that is thought to be secondary to the lowering of plasma triacylglycerols (6). The changes induced by n-3 fatty acids on plasma lipids, however, may not be completely favorable because an increase of plasma LDL cholesterol has been observed in some patients (6, 29, 30). A rise in plasma LDL cholesterol also was seen in the present study. This unwanted effect, which resembles the increase in plasma cholesterol described in patients with non-insulin-dependent diabetes mellitus and hypertria cylglycerolemia, possibly reflects an insulin-resistant state in renal patients, and could somehow counterbalance the aforementioned positive changes that n-3 fatty acids induce on the plasma lipid profile (31).

Some additional concern about lipid-lowering treatment with n-3 fatty acids concerns the possible enhancement of the susceptibility of LDL to oxidative modification. Recent data suggest that enrichment of LDL molecules with polyunsaturated fatty acids, both of the n-6 and n-3 families, increases the proneness of these lipoproteins to oxidize (7–12, 26). The concern might be even greater in patients with kidney disease because oxidized LDLs, besides concurring in atherogenesis, are also thought to play a role in the development of nephrosclerosis and glomerulosclerosis (13, 32). Diseased glomeruli often have been found to be infiltrated by macrophages, which together with mesangial cells are able to oxidize LDL particles (32). Oxidized LDLs then might be avidly uptaken by macrophages and thereafter contribute to the formation of those lipid deposits that are thought to be involved in the genesis of glomerular damage (32). Furthermore, oxidative modification of LDL has been reported to be magnified in hemodialyzed patients, possibly ensuing from activation of neutrophils by the dialyzer membrane. Neutrophils then could produce free radicals and induce LDL oxidation (15–17). Consequently, it can be hypothesized that LDL particles with a fatty acid composition that would render them more susceptible to oxidation would be even more likely to undergo such modification in hemodialyzed patients.

In the present study, susceptibility of LDL to oxidation surprisingly did not increase after treatment with n-3 fatty acids. The reason why no change in the AAPH test was observed can be ascribed to two factors. First, the content of antioxidants, vitamin E in particular, in LDLs did not change throughout the study. Vitamin E, indeed, has been shown to be the major antioxidant present in LDLs, and dietary supplementation with \( \alpha \)-tocopherol has been proven to protect LDL from oxidative modification (33). The n-3 fatty acid capsules used in this study contained very small amounts of vitamin E, which did not affect the average concentration of \( \alpha \)-tocopherol in LDLs, and consequently did not influence the length of the lag phase measured in samples taken at the end of the n-3 phase. Second, the lack of enhancement of LDL oxidation was likely because the number of double bonds susceptible to peroxidative attack, belonging to polyunsaturates of LDL particles, did not increase enough to affect the peroxidation rate. Consistently, the Th-Ox was not significantly higher at the end of the n-3 phase. This data could be explained by the lower values of 18:2 and 20:4 in LDL after treatment with n-3 fatty acids, although this change was not significant. The increase in number of peroxidable sites, ensuing from incorporation of n-3 fatty acids into LDL molecules, then might have been mitigated by the lowering of n-6 polyunsaturates. For this reason, LDL particles might not have been as readily oxidizable as they should have been in patients treated with n-3 fatty acids. Consistent with these findings, a lowering of 18:2 and 20:4 in LDL after treatment with n-3 fatty acids was also observed by other authors (9, 34). Thus, an internal homeostasis between n-6 and n-3 fatty acids might be suggested by the present data, perhaps in analogy with the competition between these two classes of fatty acids, which is known to influence the synthesis of prostanoids (35).
Note that in the studies showing an increase in LDL oxidation in subjects treated with n-3 fatty acids, the mean dose was significantly higher than the one used in the present experiment (7–9). A greater intake of n-3 polyunsaturates certainly should overwhelm any other change in concentration of the n-6 polyunsaturates in LDLS, supplying the lipoprotein particle with many more double bonds susceptible to peroxidative attack, and therefore enhancing the proneness of LDL to oxidize.

Loughrey et al (36) did not observe a higher rate of LDL oxidation in hemodialyzed patients than in normal control subjects, when proneness of LDL to oxidize was studied by means of the AAPH test. These authors argued that in vitro tests may not reflect the effective modification of LDL occurring in vivo. The present study, however, differs from Loughrey et al’s in that each patient served as his own control, and because a significant change in the fatty acid composition of LDL was observed, a consistent modification of LDL susceptibility to oxidation should have occurred, independent of the hemodialytic therapy that patients were undergoing. Indeed, the AAPH test has proven to be quite sensitive in detecting changes in the susceptibility of LDL to oxidation due to variations in the fatty acid composition of these lipoproteins (12, 23, 37).

A last observation is that the content of 22:6 in LDL remained quite elevated after the washout phase, whereas 20:5 almost returned to the value at baseline. Several data indicate that 22:6 might have been metabolized more slowly than 20:5, which could explain the persistence of high concentrations of 22:6 in LDLS 2 mo after treatment with n-3 fatty acids was stopped (38).

In conclusion, the present data suggest that a daily dose of 2.5 g n-3 fatty acids is sufficient to induce a significant lowering of plasma triacylglycerols without causing any unwanted enhancement of LDL oxidation. These data thus should encourage the use of n-3 fatty acids, although the increase of plasma LDL cholesterol certainly raises some questions. The overall therapeutic usefulness of n-3 fatty acids, however, might not be completely jeopardized in patients in whom an increase of plasma LDL cholesterol is observed. n-3 Fatty acids are known to induce other effects that might contribute to lowering the cardiovascular risk, eg, changes in coagulation indexes and decreases in blood pressure (34, 38–41). Thus, a moderate rise in plasma LDL cholesterol might be acceptable in patients with pure hypertriglyceridemia, because of the other beneficial effects on the cardiovascular risk profile. Further, n-3 fatty acids could prove useful when used in association with hydroxymethylglutaryl-CoA inhibitors in patients with combined hyperlipidemia, in whom a single drug treatment is often insufficient to improve the plasma lipid profile. In this sense, case selection should help optimize the therapeutic indications of n-3 fatty acids.

REFERENCES


