The Effect of Supplementation With Omega-3 Fatty Acids on Soluble Markers of Endothelial Function in Patients With Coronary Heart Disease

Odd Johansen, Ingebjørg Seljeflot, Arne T. Høstmark, Harald Arnesen

Abstract—During progression of atherosclerosis the overlying endothelial cells alter their expression of some surface molecules. Circulating levels of such molecules may be quantified. We investigated the effect of omega-3 fatty acids (n-3 FA) on the levels of tissue plasminogen activator antigen, von Willebrand factor, and the soluble forms of thrombomodulin, P-selectin, E-selectin, and vascular cell adhesion molecule-1 in 54 patients with coronary heart disease. Twenty-three of the patients had taken 5.1 g/d n-3 FA for 6 months (group I) and 31 were given corn oil as placebo (group II). For another 4 weeks (“the study period”) they all got 5.1 g/d of n-3 FA. Compliance was confirmed by demonstration of changes in relevant fatty acids in serum phospholipids. At baseline, significant differences between the groups were found with lower median values of von Willebrand factor (128% versus 147%) and soluble thrombomodulin (24.9 versus 32.5 ng/mL) and higher median values of soluble E-selectin (41.4 versus 35.5 ng/mL) and soluble vascular cell adhesion molecule-1 (573 versus 473 ng/mL) in group I. During the study period differences in changes between the groups were found; tissue plasminogen activator antigen and soluble thrombomodulin decreased ($P$ for difference between the groups 0.001 and 0.015, respectively), whereas soluble E-selectin and soluble vascular cell adhesion molecule-1 increased ($P$ for difference between the groups <0.01 for both) in group II relative to group I. Our results indicate that n-3 FA supplementation decreases hemostatic markers of atherosclerosis, whereas markers of inflammation may be increased. The latter may be the result of lipid peroxidation as a simultaneous decrease of vitamin E and increase in thiobarbituric acid–reactive substances were observed. (Arterioscler Thromb Vasc Biol. 1999;19:1681-1686.)

Key Words: omega-3 fatty acids ■ endothelial cell markers ■ atherogenesis ■ adhesion molecules

The process of atherosclerosis is looked on as a chronic inflammation in the vessel wall. An altered function of the overlying endothelium is an early feature of atherosclerosis. This endothelial activation or dysfunction is considered to be indicative of atherosclerosis, and may even be a contributing factor to the progression of the process.

In humans, oxidized LDL cholesterol plays a key role in the development of atherosclerosis. The development of vascular lumen narrowing is mainly a consequence of accumulation of subendothelial oxidized LDL cholesterol and the extra vascular migration of monocytes being transformed into foam cells. The initial step in atherosclerosis is supposed to be the targeting of monocytes to the sites of inflammation and endothelial injury.

During progression of atherosclerosis, activation of the overlying endothelial cells includes altered expression of some surface molecules. Sensitive methods have made it possible to quantitate the soluble forms of such molecules in the circulation.

Increased concentrations of hemostatic endothelial surface molecules such as thrombomodulin (TM), von Willebrand factor (vWF) and tissue plasminogen activator antigen (t-PAag) have been demonstrated in plasma from patients with atherosclerotic disease.

In addition, vascular cell adhesion molecule-1 (VCAM-1) and the adhesion molecules E-selectin (E-sel) and P-selectin (P-sel), which play an important role in the inflammatory process, have recently been shown to circulate in increased amounts in patients with activated endothelium, also along with atherosclerosis. The soluble forms of these surface molecules may thus be looked on as markers of atherothrombotic activity.

Based on epidemiological evidence and clinical studies, dietary intake of n-3 fatty acids (n-3 FA) has been suggested to counteract atherosclerosis. In addition, animal models have shown a retarded experimentally induced atherosclerosis after supplementation with n-3 FA although the regulatory mechanisms are poorly understood.
Incubation of endothelial cell cultures with the n-3 FA docosahexaenoic acid (DHA) has been shown to reduce the expression of VCAM-1 and E-sel on the cell surface.13

The aim of the present study was to investigate whether highly concentrated n-3 FA supplementation would influence the circulating levels of some endothelial surface molecules indicative of vascular endothelial function and atherosclerotic activity.

Thus, we measured the circulating levels of t-PAag, vWF, soluble TM (sTM), soluble P-sel (sP-sel), soluble E-sel (sE-sel), and soluble VCAM-1 (sVCAM-1) during supplementation with highly concentrated n-3 FA or placebo to patients with atherosclerotic coronary heart disease (CHD). As polyunsaturated fatty acids are prone to peroxidation, we also measured the levels of vitamin E and thiobarbituric acid–reactive substances (TBARS) as markers of the oxidative state.

**Methods**

**Study Design, Patient Population, and Fatty Acid Supplementation**

The study was performed as a continuum of patients with CHD who took part in a larger randomized study on restenosis after percutaneous transluminal coronary angioplasty, the Coronary Angioplasty Restenosis Trial study.14 All 388 patients had advanced coronary artery disease, and had been successfully treated with percutaneous transluminal coronary angioplasty 6 months earlier. The study population was initially randomly assigned to receive a daily supplementation of 3×1 g gelatin capsules twice daily, each capsule containing either 84% ethyl esters of n-3 polyunsaturated fatty acids (0.45 g of eicosapentaenoic acid [EPA] and 0.39 g of DHA, with the addition of 4 mg α-tocopherol) (Omacor, Pronova AS) or an equal amount of ethyl ester of corn oil as placebo. The limited amount of α-tocopherol was added for stabilization of the capsule content.

All of the consecutively recruited 54 patients in the present study were asymptomatic with respect to myocardial ischemia at the start of the study. Twenty-three of the patients took the n-3 FA supplementation for 6 months (group I) and 31 took the placebo (group II). All patients were then given n-3 FA supplementation in the same dose as for group I, for another 4 weeks.

Study design of the consecutively recruited 54 patients for the present study who were asymptomatic with respect to myocardial ischemia at the start of the study. Twenty-three of the patients took the n-3 FA supplementation for 6 months (group I) and 31 took the placebo (group II). All patients were then given n-3 FA supplementation in the same dose as for group I, for another 4 weeks.

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo (corn oil)</th>
<th>n-3 FA</th>
<th>n-3 FA</th>
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<tr>
<td>Baseline</td>
<td></td>
<td></td>
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<td>4 weeks</td>
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**Laboratory Methods**

Blood samples were drawn with minimal stasis from an antecubital vein in the overnight fasting state at 7:30 AM to 8 AM (samples at baseline) or 9 AM to 10 AM (samples after 4 weeks) (Vacutainer System, Becton Dickinson). Serum was prepared by centrifugation (2000g for 10 minutes) within 1 hour, frozen, and stored at −70°C for batch analyses of serum phospholipid fatty acids, vitamin E, and TBARS. In addition, serum was prepared for determinations of serum lipoproteins.

Total cholesterol, HDL cholesterol, and triglycerides were determined by conventional enzymatic methods (Boehringer Mannheim GmbH).

The fatty acids in serum phospholipids were quantified by gas-liquid chromatography. Serum lipids were extracted with n-butanol after addition of an internal standard (phosphatidyliccholine diheptadecanoyl, Sigma). An antioxidant (2,6-di-tert-butyl-p-creosol; Fluka AG) was added to the n-butanol before extraction. Phospholipids were isolated from the total lipid extracts by solid-phase extraction on aminopropyl columns (Varian) and transmethylated. The phospholipid fatty acids were quantified by gas chromatography. Fatty acid methyl ester mixture Me-81- added C17:0 methyl ester (Larodan) was used as an external standard. A human serum pool sample was included as a control to monitor the analytic performance. The results were quantified as milligrams of phospholipid fatty acid per liter of serum.

Vitamin E concentration in serum was analyzed by a Shimadzu/Waters high performance liquid chromatography system.15 TBARS were determined by a colorimetric method, as described previously.16

Citrated blood (Becton Dickinson Vacutainer tubes containing 0.129 mol/L trisodium citrate in dilution, 1:10) was collected and stored on ice until platelet-poor plasma was obtained within 30 minutes by centrifugation at 4°C and 2500g for 20 minutes for determination of t-PAag, vWF, sTM, sP-sel, sE-sel, and sVCAM-1. Enzyme immunoassays with the following commercially available kits were used throughout: TintElize tPA antigen (Biopool AB), Asserachrom vWF (Stago Diagnostica), Asserachrom TM (Stago Diagnostica), GMP-140 (Takara Biochemicals), human soluble E-selectin Parameter (R&D Systems Europe), and human soluble VCAM-1 Parameter (R&D Systems), respectively.

**Statistical Analysis**

Variables in the categorical data were evaluated by the Mantel-Haenszel test and differences between continuous variables by the Mann-Whitney test. A 2-sided P value of ≤0.05 was considered statistically significant. The EPI Info software program was used throughout.

**Results**

All 54 patients followed the study protocol and were evaluable after 4 weeks. There were no differences between the
Fatty Acids in Serum Phospholipids

Regarding the values of serum phospholipid fatty acids (Table 2) before the start of the 4-week study period, EPA, DHA, and total n-3 FA were significantly higher in the group that had been taking Omacor for 6 months, compared with the placebo group, whereas linoleic acid, arachidonic acid, and total n-6 fatty acids were significantly higher in the latter group. After the 4-week treatment period, the group differences were abolished except for arachidonic acid. The group differences in relative changes from baseline were statistically significant for all fatty acid measurements given.

Serum Lipoproteins

Regarding the values of serum lipids at baseline, no statistically significant group differences were found, although the triglycerides were 21% lower in group I compared with group II (Table 2). After the 4-week treatment period, HDL cholesterol was significantly higher in group II, and a highly significant reduction in triglycerides was found in group II compared with group I.

Endothelial Cell Markers

At baseline, significantly lower values of vWF (median, 128% versus 147%; P = 0.05) and sTM (median, 24.9 versus 32.5 ng/mL; P = 0.01) because of the lowering of the values in group II, (Table 3). Significant differences between the study groups in relative changes from baseline were obtained for t-PAag (P < 0.01) and sTM (P = 0.02) (reduced in group II), and sE-sel (P < 0.01) and sVCAM-1 (P < 0.01) (increased in group II).

Markers of Oxidative State

Serum concentrations of vitamin E were significantly lower in group I at baseline (median, 36 versus 48 μmol/L; P < 0.01). At end of the study period this difference was abolished, and the difference in relative changes from baseline between the study groups was highly significant (P < 0.01) because of the lowering of the values in group II (Table 4).

At baseline, higher values of TBARS were encountered in group I (median, 1.60 versus 1.12 μmol/L; P = 0.05). At end of the study, this difference was reversed, although not statistically significant. The group difference in relative changes from baseline did not attain statistical significance (P = 0.08). The values in both groups were higher at the end of the study.

Discussion

The present clinical study was undertaken in a somewhat unusual design at the end of a larger prospective randomized trial, taking advantage of a previous 6-month intervention period with n-3 FA or placebo. Thereby, the problem of groups in baseline characteristics or use of relevant drugs (Table 1).

| TABLE 2. Serum Phospholipid Fatty Acids (mg/L) and Serum Lipids (mmol/L) at Baseline and After 4 Weeks in the Two Treatment Groups [Median (25, 75 Quartiles)] |
|---------------------------------|----------|----------|----------|----------|----------|----------|----------|----------|
|                                | Group I  | Group II | P1       | Group I  | Group II | P2       | PD       |
| Linoleic (18:2n-6)              | 259 (232,298) | 341 (301,407) | <0.01    | 256 (205,310) | 268 (214,302) | 0.78     | <0.01    |
| Arachidonic (20:4n-6)           | 98 (80,114) | 122 (102,149) | <0.01    | 94 (82,115) | 113 (103,133) | 0.02     | 0.02     |
| Eicosapentanoic (20:5n-3)       | 98 (71,130) | 21 (17,35) | <0.01    | 103 (85,127) | 102 (90,124) | 0.85     | <0.01    |
| Docosahexaenoic (22:6n-3)       | 139 (116,157) | 103 (78,115) | <0.01    | 131 (118,155) | 134 (116,154) | 0.92     | <0.01    |
| Total n-3 FA                    | 279 (195,324) | 151 (115,178) | <0.01    | 263 (236,316) | 273 (236,308) | 0.90     | <0.01    |
| Total n-6 FA                    | 378 (344,465) | 499 (462,555) | <0.01    | 380 (314,442) | 420 (355,450) | 0.47     | <0.01    |
| Total cholesterol               | 6.3 (5.5,6.7) | 6.5 (5.7,7.1) | 0.33     | 6.2 (5.9,7.8) | 6.5 (5.7,7.3) | 0.90     | 0.57     |
| HDL cholesterol                 | 1.12 (0.90,1.24) | 1.25 (1.07,1.43) | 0.10     | 1.17 (0.98,1.36) | 1.36 (1.15,1.65) | 0.03     | 0.27     |
| Triglycerides                   | 1.33 (0.98,1.95) | 1.69 (1.27,2.03) | 0.10     | 1.40 (1.06,2.32) | 1.18 (0.99,1.70) | 0.14     | <0.01    |

Baseline, after 6 months’ supplementation with n-3 FA in group I and placebo (corn oil) in group II; P1, group differences at baseline; P2, group differences after 4 weeks’ treatment; PD, group differences in relative changes from baseline.

| TABLE 3. Endothelial Cell Markers at Baseline and After 4 Weeks in the Two Treatment Groups [Median (25, 75 Quartiles)] |
|---------------------------------|----------|----------|----------|----------|----------|----------|----------|
|                                | Group I  | Group II | P1       | Group I  | Group II | P2       | PD       |
| tPAag (ng/mL)                   | 10.5 (9.0,12.8) | 12.1 (9.5,15.4) | 0.10     | 11.0 (9.2,12.1) | 9.9 (6.7,11.7) | 0.23     | <0.01    |
| vWF (%)                         | 128 (116,150) | 147 (131,163) | 0.05     | 122 (111,142) | 129 (114,153) | 0.31     | 0.10     |
| sTM (ng/mL)                     | 24.9 (18.4,29.9) | 32.5 (26.4,41.3) | <0.01    | 24.5 (19.1,32.3) | 28.0 (20.6,36.7) | 0.22     | 0.02     |
| sP-sel (ng/mL)                  | 45.5 (37.2,48.0) | 46.9 (40.7,54.8) | 0.24     | 44.4 (36.5,51.5) | 41.3 (34.0,47.0) | 0.34     | 0.10     |
| sE-sel (ng/mL)                  | 41.4 (36.1,51.7) | 35.5 (27.3,44.5) | 0.02     | 45.6 (33.1,53.4) | 42.9 (30.6,51.6) | 0.50     | <0.01    |
| sVCAM-1 (ng/mL)                 | 573 (505,692) | 473 (382,590) | 0.04     | 616 (486,732) | 591 (440,693) | 0.58     | <0.01    |

P1, group differences at baseline; P2, group differences after 4 weeks’ treatment; PD, group differences in relative changes from baseline.
long-lasting washout mechanisms for these fatty acids\(^\text{18,19}\) was avoided.

The 54 patients were consecutively recruited at the end of a larger randomized trial on restenosis after percutaneous transluminal coronary angioplasty. Nevertheless, the number of patients from the 2 treatment groups differed (23 versus 31) and some baseline characteristics varied somewhat, although not statistically significant.

We could demonstrate compliance with the n-3 FA supplementation regimens by the differences between the groups in the most relevant fatty acids in serum phospholipids at baseline, this being largely reduced after another 4 weeks of n-3 FA supplementation to both groups. The difference in changes in triglycerides between the groups over 4 weeks was also statistically significant (\(P<0.001\)), whereas no differences at baseline or in changes between the groups during the study period could be shown for total cholesterol or HDL cholesterol. These findings are in accordance with previous studies for both short-term and long-term interventions with n-3 FA.\(^\text{20,21}\)

Our hypothesis was that n-3 FA supplementation might improve the endothelial dysfunctional state in the present population with advanced CHD, and this might be evaluated by the presently measured soluble markers. The finding of lower values of the hemostatic markers vWF, and sTM in group I at baseline, and the significant reductions in sTM and t-Paag in group II during the study period would fit this hypothesis. However, the finding of higher values of the inflammatory markers sE-sel and sVCAM-1 in group I at baseline, and the significant increasing change in these markers in group II during the study period, was unexpected. All over, the findings seem to indicate that supplementation with highly concentrated n-3 FA to patients with coronary atherosclerotic disease decreases the hemostatic activity of the endothelium, whereas the inflammatory activity might be increased. Concerning the changes in t-Paag, this may possibly be linked to the simultaneous changes in triglycerides. Triglycerides have been demonstrated to stimulate cultured endothelial cells to release plasminogen activator inhibitor-1 (PAI-1).\(^\text{22}\) Thus, a reduction in triglycerides may lead to reduced PAI-1 secretion. It is also suggested that in steady-state conditions t-Paag mainly reflects the level of PAI-1,\(^\text{23}\) as the t-Paag method used determines both t-PA and PAI-1. Accordingly, the t-Paag reductions obtained during n-3 FA supplementation might reflect reduced endothelial secretion of PAI-1 along with the reduction in triglycerides.

As vWF is well known as a platelet-related risk factor for CHD, the presently found reduction in this variable would be easily explained as a beneficially reduced potential to platelet activation during supplementation with n-3 FA. Although TM is mainly known as an antithrombotic variable,\(^\text{24}\) the reduction of sTM could also be discussed along with the antifibrinolytic property of TM, which has recently been demonstrated. In complex with thrombin, TM is able to activate the plasma protein TAFI (thrombin activatable fibrinolysis inhibitor) to TAFIa, which inhibits the conversion of plasminogen to plasmin.\(^\text{25}\) The reduced levels of sTM during n-3 FA supplementation might thus be looked on as a beneficial consequence of reduced atherosclerotic activity.

Concerning the markers of inflammation, our results are not in accordance with some previously published studies. However, it should be emphasized that our study was performed as a clinical trial in patients with atherosclerotic disease and not in isolated cells. We are not aware of previous studies on soluble inflammatory factors that have been performed in a population readily comparable with ours. However, similar results, that is, an increase in sE-sel and sVCAM-1 after supplementation with n-3 FA, were recently described by Seljeflot et al\(^\text{26}\) in a population of healthy individuals at high risk for atherosclerotic disease states. De Caterina et al\(^\text{13}\) found in their study on cultured human endothelial cells that exposure to DHA led to reduced expression of cytokine-induced adhesion molecules. The same response, however, was not obtained with EPA, the fatty acid showing the highest increase during oral supplementation with n-3 FA. Furthermore, Endres et al\(^\text{27}\) reported on reduced levels of interleukin-1 and tumor necrosis factor in isolated monocytes from healthy volunteers after supplementation with 4.6 g/d of EPA and DHA for 6 weeks.

In a recent study by Abe et al\(^\text{28}\) a similar design was used. After 6 weeks, sE-sel was significantly increased in the Omacor group compared with the placebo group, whereas VCAM-1 was largely unchanged in both groups. After continuous supplementation with the same amount of Omacor to some of the individuals for another 7 to 12 months, sE-sel was significantly reduced, whereas VCAM-1 was still unchanged. There are, however, several differences in populations that can explain the apparent differences in results compared with ours. The study by Abe et al\(^\text{28}\) included severe hypertriglyceridemic individuals, with \(\approx 30\%\) of them diabetics. The long-term reduction in sE-sel was most prominent in diabetics who also showed a long-term reduction in VCAM-1, whereas this variable was virtually increased in nondiabetics.

Finally, moderate beneficial effects with n-3 FA have been demonstrated in different inflammatory diseases such as rheumatoid arthritis,\(^\text{29,30}\) and clinical benefit of n-3 FA has also been reported in patients with psoriasis.\(^\text{31}\)

On the other hand, Blok et al\(^\text{32}\) reported in a prospective trial that fish oil supplementation did not affect the concentrations of circulating cytokines. Furthermore, they found the ex vivo production of cytokines (interleukin-1β, tumor necro-

### TABLE 4. Serum Levels of Vitamin E and TBARS at Baseline and After 4 Weeks in the Two Treatment Groups [Median (25, 75 Quartiles)]

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>P1</th>
<th>Group I</th>
<th>Group II</th>
<th>P2</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E (μmol/L)</td>
<td>36 (33, 41)</td>
<td>48 (37, 49)</td>
<td>&lt;0.01</td>
<td>35.5 (32, 40)</td>
<td>39 (31, 40)</td>
<td>0.63</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TBARS (μmol/L)</td>
<td>1.60 (1.12, 2.08)</td>
<td>1.12 (0.88, 1.44)</td>
<td>0.05</td>
<td>2.44 (1.60, 3.69)</td>
<td>3.45 (1.76, 7.05)</td>
<td>0.16</td>
<td>0.08</td>
</tr>
</tbody>
</table>
sialic acid, and interleukin-Ra), after endotoxin stimulation of whole blood, to be significantly increased during fish oil supplementation. However, the observed increase was not significantly different from that in the placebo group.

The reason for the apparent discrepancy is not clear. However, it is well known that polyunsaturated fatty acids are prone to peroxidation and that generated free radicals and oxidized LDL may both be cytotoxic. Various authors have suggested the possible deleterious effects of n-3 FA supplementation because of their increased susceptibility to oxidation, although contradictory results have been reported. This could also be discussed along with the decreased levels of vitamin E after n-3 FA supplementation encountered in the present study. This finding is in accordance with what we have recently reported in another study and also with the results from Hau et al., suggesting a consumption of antioxidants caused by an increased level of oxidation after n-3 FA supplementation.

Increased TBARS values after long-term supplementation with n-3 FA, as evidenced by the differences between the groups at baseline and the differences in changes between the groups during the study period, further supports the hypothesis of increased peroxidation. It is noteworthy that the values obtained after 4 weeks were >2-fold the values at baseline in both study groups. This could possibly be explained by diurnal variations, as the latest measurements for practical reasons were undertaken systematically ~2½ hours later in the day, and Børsheim et al. have recently reported on increasing values during the morning hours as part of diurnal variations.

It should be pointed out that the present study was undertaken with a highly concentrated n-3 FA preparation that might induce oxidation far more easily than when n-3 FA are supplemented as part of the diet. Halvorsen et al. showed an increase in bacterial adherence to monocytes after supplementation with EPA concentrate in an ex vivo model of humans, and they found a tendency to increased generation of hydrogen peroxides after EPA ingestion. These findings could also be of relevance to our results, suggesting a proinflammatory response with an increased oxidative stress after ingestion of highly concentrated n-3 FA, in a situation with a suboptimal supply of vitamin E.

The regulation of adhesion molecule expression has been shown to be influenced by oxidative processes in cell culture, and it has been described to vary in response to different oxidation pathways. Our findings could thus be speculated to result from an effect of n-3 FA on some of the regulatory mechanisms. Nuclear factor-kB, which is an important transcription factor in chronic inflammatory diseases because it acts on different genes that encode for proinflammatory substances (among others, E-selectin and VCAM-1), has been shown to be activated by oxidants. As discussed, the ingestion of n-3 FA could have resulted in an increased amount of oxidants, thus explaining the increased levels of E-selectin and VCAM-1 via the nuclear factor-kB pathway.

In conclusion, we could demonstrate that high-dosage n-3 FA supplementation decreases circulating t-PAAg and sTM and increases sE-sel and sVCAM-1 in blood from patients with CHD. In addition to reduced levels of hemostatic markers of atherosclerosis, these results might indicate a proinflammatory response that could be adverse, possibly brought about by an increased peroxidation as demonstrated by a consumption of vitamin E and increased TBARS. The results suggest the question of whether vitamin E should be supplied in high doses when n-3 FA concentrates are given. In view of the beneficial results obtained with increased intake of n-3 FA in the diet, the clinical implications of the present results should be further clarified.

Acknowledgments

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