Effect of ω-3 Fatty Acids and Simvastatin on Hemostatic Risk Factors and Postprandial Hyperlipemia in Patients With Combined Hyperlipemia

Arne Nordøy, Kaare H. Bønaa, Per Morten Sandset, John-Bjarne Hansen, Hugo Nilsen

Abstract—Patients with combined hyperlipemia have lipid abnormalities associated with an increased tendency to develop atherosclerosis and thrombosis. This tendency may be accelerated during postprandial hyperlipemia. In the present double-blind parallel study, 41 patients with combined hyperlipemia and serum triacylglycerols between 2.0 and 15.0 mmol/L and serum total cholesterol >5.3 mmol/L at the end of a 3-month dietary run-in period were treated with simvastatin at 20 mg/d for at least 10 weeks; patients were then randomized into 2 groups receiving simvastatin+ω-3 fatty acids at 3.36 g/d or placebo (corn oil) for an additional 5 weeks. Hemostatic variables that have been associated with increased thrombotic tendency were evaluated with subjects in the fasting state and during postprandial hyperlipemia before and after combined treatment. Supplementation of ω-3 fatty acid reduced tissue factor pathway inhibitor antigen (P<0.05) in the fasting state, reduced the degree of postprandial hyperlipemia (P<0.005), and reduced activated factor VII concentration appearing during postprandial hyperlipemia. In conclusion, ω-3 fatty acids given in addition to simvastatin to patients with combined hyperlipemia reduced the free tissue factor pathway inhibitor fraction in the fasting state and inhibited the activation of factor VII occurring during postprandial lipemia, thus representing a potential beneficial effect on the hemostatic risk profile in this patient group. (Arterioscler Thromb Vasc Biol. 2000;20:259-265.)

Key Words: combined hyperlipemia • postprandial hyperlipemia • hemostatic risk factors

Rupture of an atherosclerotic plaque with subsequent formation of an occlusive thrombus is the major cause of myocardial infarction. The extrinsic coagulation system has been suggested to play a crucial role in the initiation of blood coagulation in atherosclerotic disease. Tissue factor (TF) is an integral membrane protein that functions as a cofactor to enhance the proteolytic activity of activated factor VII (FVIIa) toward factor IX and factor X, which leads to the formation of a fibrin clot. TF is synthesized in perturbed endothelial cells, which may render them thrombogenic, and is also present in the cores of atherosclerotic plaques. Thus, transient exposure of TF at the surface of atherosclerotic plaque or perturbed endothelial cells may cause low-grade triggering of blood coagulation. TF pathway inhibitor (TFPI) is a potent inhibitor of TF-induced coagulation, which exerts its function by neutralizing the catalytic activity of factor Xa and by feedback inhibition of the TF-FVIIa complex.

Factor VII (FVII) is the first enzyme involved in the extrinsic pathway of blood coagulation. The major proportion of FVII circulates in plasma in the zymogen form, whereas low but significant levels appear in an activated form (FVIIa), which serves as the primer for triggering the clotting cascade. In epidemiological studies, the coagulation activity of factor VII (FVIIa) is positively correlated to serum triglycerides (less consistently to serum cholesterol) and is found to predict coronary heart disease (CHD). Reliable assays for determination of FVIIa have been developed recently, and measurement of FVIIa has been found to be highly relevant for understanding the role of FVII in CHD. FVIIa has been found to be elevated in acute coronary syndromes but unchanged in a follow-up study of patients suffering from myocardial infarction at a young age.

Familial combined hyperlipemia is the most common form of hyperlipemia in young survivors of myocardial infarction. These lipid abnormalities are caused by a heterogeneous combination of predisposing and environmental factors. Affected individuals have elevated concentrations of LDL, VLDL, or both. Such lipid profiles are frequently associated with an unfavorable decrease in HDL concentration, an elevated apolipoprotein B concentration, and increased prevalence of atherogenic small dense LDL particles.

Subjects with combined hyperlipemia commonly show changes in hemostatic variables associated with increased risk for developing thrombotic events. These changes have been associated with increased procoagulant activity and with inhibition of the fibrinolytic potential. The patients also commonly show insulin resistance that is probably related to...
TABLE 1. Characteristics, Including Main Serum Lipid Concentrations, of the 2 Groups Given Simvastatin With the Addition of ω-3 FAs or Corn Oil  

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Simvastatin + ω-3 FAs</th>
<th>Simvastatin + Corn Oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n/n</td>
<td>15/6</td>
<td>14/6</td>
</tr>
<tr>
<td>Age, y</td>
<td>46.8 ± 9.2</td>
<td>46.7 ± 7.8</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171.7 ± 8.5</td>
<td>175.8 ± 10.3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>81.2 ± 10.8</td>
<td>88.9 ± 13.5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.6 ± 4.0</td>
<td>28.8 ± 3.7</td>
</tr>
<tr>
<td>Waist-hip ratio</td>
<td>0.90 ± 0.06</td>
<td>0.90 ± 0.06</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>21.4 ± 9.4</td>
<td>23.0 ± 8.1</td>
</tr>
<tr>
<td>Cholesterol, mmol·L⁻¹</td>
<td>7.75 ± 1.57</td>
<td>8.51 ± 2.51</td>
</tr>
<tr>
<td>TAGs, mmol·L⁻¹</td>
<td>4.42 ± 2.29</td>
<td>5.08 ± 4.29</td>
</tr>
<tr>
<td>HDL cholesterol, mmol·L⁻¹</td>
<td>0.96 ± 0.27</td>
<td>0.92 ± 0.2</td>
</tr>
<tr>
<td>Glucose intoller/diabetes, n/n</td>
<td>5/1</td>
<td>1/2</td>
</tr>
</tbody>
</table>

Values are mean ± SD or number of patients (n).

an excessive postprandial release of free fatty acids (FFAs) caused by impaired suppression of hormone-sensitive lipase; however, other mechanisms are also involved. Characteristically, the postprandial hyperlipemia in patients with combined hyperlipemia is usually excessive with regard to extent and duration.

We have recently investigated the effects of simvastatin and ω-3 fatty acids (ω-3 FAs) on lipids, lipoproteins, and antioxidant capacity in a heterogeneous group of patients with combined or mixed hyperlipemia. The combination of these 2 treatments efficiently reduced serum LDL and VLDL cholesterol and triglycerides with an increase in HDL cholesterol. These 2 patients also had well-regulated diabetes mellitus.

**Methods**

**Patients**

Forty-one patients (12 women and 29 men) aged 25 to 60 years referred to The Lipid Clinic at the Department of Medicine, University Hospital of Tromsø, for combined hyperlipemia were recruited for the study. All subjects had been consuming habitual diets, and none were taking lipid-lowering medication, antioxidants, or fish oil concentrates at the time when they were recruited for the study. Seventeen were regular smokers. Before entry into the drug-intervention phase of the study, a mean fasting serum triacylglycerol (TAG) concentration (after a 16-week dietary run-in period) between 2.0 and 15.0 mmol/L and serum total cholesterol >5.3 mmol/L were required. The subjects’ characteristics, including body weight, body mass index, and serum lipid levels, are given in Table 1. Two of the participants had experienced acute myocardial infarction 2 and 3 years before, respectively, but were now without symptoms. These 2 patients also had well-regulated diabetes mellitus that was treated with diet only. The others had no cardiovascular, liver, or renal diseases, bleeding disorders, alcoholism, or other diseases that might influence lipid metabolism or hemostasis. In addition, none used drugs affecting lipid metabolism or hemostasis.

The study was approved by the Regional Board of Research Ethics, and each subject gave written informed consent. The study was conducted at the Clinical Research Center at the University Hospital.

**Study Design**

This double-blind placebo-controlled trial with patients randomized for age and sex was initiated with a 16-week dietary run-in period during which the participants were following guidelines aiming at a dietary composition in which the energy supplied from carbohydrates, fats, and proteins was 55/35/10, respectively. At a maximum of 6-day intervals at the end of the dietary run-in period, 2 blood samples were collected from all patients after 12 hours of fasting. The means of the results obtained by lipid analysis after the diet were used as baseline values. Physical examination, a dietary interview, and a fat tolerance test were performed. The patients were then treated with simvastatin (Zocor, MSD Norge A/S) at 20 mg/d (evening) for 5 to 10 weeks. The patients were finally again randomized (by age and sex) into 2 groups, each including an equal number of participants that had used simvastatin for 5 or 10 weeks, respectively. All patients were then, for the last 5 weeks, given simvastatin 20 mg/d. In addition, one of the 2 groups (n=21) was given a supplement of highly purified ω-3 FAs given as 4 g/d of ethyl esters of eicosapentaenoic acid (45%) and docosahexaenoic acid 39%, (Omacor Pharmacia and Upjohn AS), and the other group (n=20) was given placebo (4 g corn oil/d) in indistinguishable soft gelatin capsules, each containing 1 g of oil. Further details of the Omacor and the placebo capsules have been reported previously.

**Blood Collection**

With patients in the fasting state, blood samples were collected twice before any intervention with drugs and twice at the end of the last intervention period, 15 weeks later. In addition, blood samples were collected 5 times during the fat-load tests, which were also carried out before any drug intervention and at the end of the study. Lipids, lipoproteins, glucose, and insulin were measured in all blood samples. Blood for preparation of plasma for measurement of FFAs was collected into Vacutainers containing disodium EDTA as anticoagulant (0.12 mL EDTA K₂, 0.34 mol/L per tube) and kept on melting ice until centrifugation at 2000g for 15 minutes at 4°C. Plasma was transferred into sterile cryovials in aliquots of 1 mL, flushed with nitrogen, and stored at −70°C until analysis. Separate blood samples were collected by antecubital vein puncture in the other arm for coagulation and fibrinolytic assays with patients in the fasting state and at 4 hours and 8 hours after the fat-load test. Blood samples were collected into Vacutainer tubes containing either 1.7 mg/mL disodium EDTA or 1/10 vol of 0.129 mmol/L sodium citrate for lipid analysis or for coagulation and fibrinolysis assays, respectively. Samples for measurement of tissue plasminogen activator (tPA) activity were collected into Biopool Stabilite blood collection tubes (Biopool AB). Plasma was prepared by centrifugation at 2000g for 15 minutes at 22°C, and aliquots were transferred into sterile cryovials of 1 mL, flushed with N₂, and stored at −70°C.

**Oral Fat-Load Test**

The oral fat-load test was carried out at the end of the dietary run-in period and after the final intervention period in each subject. Between 7 and 8 AM after an overnight fast, a needle was inserted into the patient’s antecubital vein, and fasting blood samples were drawn. A fatty meal consisting of 200 mL cream (36% fat), 1 egg yolk, and 2 waffles containing a total of 78 g fat, 490 mg cholesterol, and 760 kcal energy was given. The meal was ingested over a 15-minute period and was well tolerated by all participants. Apart from the test meal, only no-caloric mineral water and an apple were allowed between the test meal and the 8-hour blood sample drawing. The extent of postprandial hypertriglyceridemia was assessed by the response areas under the curve (AUCs: integrated, absolute, and incremental [iAUC]) of plasma TAG measured every second hour over the 8-hour study period and by the triglyceridemic response defined as average of the 2 highest postprandial TAG concentrations minus the baseline concentration according to Patch et al.
serum cholesterol was measured in parallel with TAG, whereas serum FFAs were measured at baseline and at 4 and 6 hours after intake of the meal. Serum insulin, glucose, and the hemostatic variables included (see below) were measured in the fasting state and at 4 and 8 hours after intake of the meal.

Clinical and Laboratory Measurements

All methods used for lipid, glucose, and insulin analyses have recently been described, except for the following modifications: serum FFAs and total phospholipid FAs were, after separation, transmethylated with 1% and 2% sulfuric acid, respectively, in methanol, extracted into hexane, and evaporated into dryness. The following hemostatic variables were investigated by routine methods and included the following coagulation variables, all related to the extrinsic coagulation system: total FVIIc, activated 2-chain form of FVII (FVIIa), total amount of FVII antigen (FVIIag), lipoprotein-bound TFPI activity (TFPIag), and lipoprotein-free TFPI antigen (TFPIag). In addition, von Willebrand factor activity, clottable fibrinogen and the fibrinolytic modulators, plasminogen activator inhibitor 1 (PAI-1), and tPA antigen (tPAag) were included. Routine hematology, including red and white blood cell counts, and platelet parameters were followed throughout.

Statistical Analysis

Independent relations between fasting lipid levels, hemostatic variables, and glucose/insulin levels and postprandial hyperlipemia were investigated by multiple linear regression. Spearman correlation coefficients were used to examine correlations between changes in hemostatic variables and lipid values. Differences in coagulation factors and fibrinolytic activity before and after a standardized fat meal were tested by 1-sample t test. Two-sided probability values of P<0.05 were considered to indicate statistical significance. ANOVA was used to assess differences between groups in the fasting levels and in AUCs and iAUCs. The SAS software package was used.

Results

Patients

All patients remained in the study throughout the entire study period. The compliance based on capsules consumed and increase of ω-3 FA in serum phospholipids was excellent.

The group characteristics given in Table 1 showed no significant differences between the 2 groups. Simvastatin and ω-3 FA compared with simvastatin and placebo reduced serum concentrations of total cholesterol (P=0.05), TAGs (P<0.01), and apolipoprotein E (P<0.05) as recently described.

Effects on Hemostatic Variables

As shown in Table 2, only TFPIag concentrations were significantly more reduced (P<0.05) by the combination of simvastatin and ω-3 FA than they were in the control group. When the hemostatic parameters were compared within the 2 groups, a similar trend was seen in both groups, with increased concentrations of fibrinogen, FVIIa, and PAI-1ag, and a reduction in the concentrations of FVIIag, TFPIag, and TFPIag. However, only in the group given supplementation of ω-3 FA did these deviations become significant. Blood platelet count and mean platelet volume were not significantly influenced by treatment (results not shown).

Postprandial Hyperlipemia and Glucose Metabolism

A highly significant reduction in postprandial hyperlipemia measured both as incremental TAG concentrations (iAUC) and as triglyceridemic response was observed (Table 3, Figure 1) after combined treatment with simvastatin and ω-3 FA compared with simvastatin alone. As shown in Figure 2, the concentration of total FFAs showed a decline at 4 hours and only a moderate but significant (P<0.05) increase at 6 hours after the fat load in these patients with combined hyperlipemia. After intervention, both groups showed significant reductions in fasting concentrations of FFA, an increase of ≈200% after 4 hours, and a final decline at 6 hours. No effect attributable to the supplement of ω-3 FA was seen. No significant differences in the concentrations of total cholesterol during postprandial hyperlipemia were observed between the 2 groups before or after intervention (results not shown).

A moderate nonsignificant increase in glucose and insulin concentrations occurred during postprandial hyperlipemia in both groups before and after treatment (Table 3). A significant increase (P<0.05) in the insulin/glucose ratio was
observed in the group given simvastatin plus omega-3 FA (Table 3).

**Postprandial Hyperlipemia and Hemostatic Variables**

As shown in Figure 3, a trend toward increased concentrations of FVIIc and FVIIa was observed during postprandial hyperlipemia. This increase of FVIIa during postprandial hyperlipemia was significantly reduced \( (P<0.05) \) after treatment with simvastatin and \( \omega-3 \) FA. None of the other coagulation variables measured during postprandial hyperlipemia showed significant changes after treatment with simvastatin and \( \omega-3 \) FA (results not shown). Both tPAag and PAI-1a showed a decline 8 hours after intake of the standardized meal without significant differences between the 2 groups after intervention (Figure 4).

**Discussion**

Epidemiological, clinical, and experimental studies have shown that dyslipidemia associated with insulin resistance and hypertension also may include a procoagulant state with activation of the coagulation system and inhibition of the fibrinolytic activities.11,24,25 In the early prospective epidemiological studies, it was shown that FVIIc, fibrinogen, PAI-1a, and tPAag may represent independent risk factors for development of CHD.11,24,25 In a recent study of patients with combined hyperlipemia, we have confirmed that FVIIa and FVIIc are correlated with the triglyceride-rich lipoproteins, particularly with the concentration of intermediate density lipoproteins (IDL) TAGs.21 TFPIa showed a significant correlation with the concentration of LDL, a lipoprotein fraction also associated with increased risk for CHD.

In human plasma, 80% of TFPI is bound to lipoproteins, especially LDL, whereas 10% to 20% circulates in a free form.26 A positive correlation between the total plasma TFPI activity and LDL cholesterol/apolipoprotein B has been reported in normal individuals27 and in hypercholesterolemic patients.28,29 In the present study, we found that treatment with simvastatin alone induced a significant reduction of triglyceride-rich lipoproteins and LDL that was paralleled by

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**TABLE 3. Serum TAGs Measured as AUC and iAUC and Triglyceridemic Response, Glucose, Insulin, and Insulin/Glucose Ratio in Subjects With Combined Hyperlipemia During Postprandial Hyperlipemia Before and After Treatment With Simvastatin and \( \omega-3 \) FAs or Placebo (Corn Oil)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Simvastatin + ( \omega-3 ) FAs (n=19)*</th>
<th>Simvastatin + Corn Oil (n=17)*</th>
<th>Effect Attributable to ( \omega-3 ) FAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAG iAUC, mmol \cdot h \cdot L ^{-1}</td>
<td>14.6±11.7</td>
<td>8.8±4.7\dagger</td>
<td>10.7±7.9</td>
</tr>
<tr>
<td>TAG AUC, mmol \cdot h \cdot L ^{-1}</td>
<td>46.9±18.9</td>
<td>23.9±9.1\dagger</td>
<td>45.8±33.5</td>
</tr>
<tr>
<td>Triglyceridemic response, mmol/L</td>
<td>3.14±2.12</td>
<td>1.77±0.80§</td>
<td>2.20±1.41</td>
</tr>
<tr>
<td>Glucose AUC, mmol \cdot h \cdot L ^{-1}</td>
<td>41.2±3.9</td>
<td>42.3±5.0</td>
<td>44.0±15.4</td>
</tr>
<tr>
<td>Insulin AUC, pmol \cdot h \cdot L ^{-1}</td>
<td>69.9±28.5</td>
<td>92.6±43.8§</td>
<td>85.5±29.3</td>
</tr>
<tr>
<td>Insulin/glucose ratio</td>
<td>13.5±5.2</td>
<td>17.1±4.9\dagger</td>
<td>16.1±6.4</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*\( n=15 \) for glucose and insulin measurements.\dagger \( P<0.05 \), ‡ \( P<0.01 \), and § \( P<0.001 \) for significance of change within group.

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Figure 1. Line plot of plasma TAG concentration after ingestion of the oral fat load in patients with combined hyperlipemia before (○) and after (●) treatment with simvastatin plus \( \omega-3 \) FA and before (□) and after (▲) treatment with simvastatin plus corn oil. Values are mean±SD.
a reduction of TFPI. As previously shown, this reduction was directly correlated to the reduction of LDL, which was due to a specific decrease in LDL-TFPI complexes in plasma. No further decrease in the total inhibitory capacity of TFPI, reflected by the TFPI method, was seen after adding ω-3 FA as a supplement to simvastatin. The free form of plasma TFPI, reflected by the TFPI method, was unchanged by statins alone but showed a modest decrease by adding ω-3 FA to statin treatment. The mechanism beyond this observation is unknown. However, it has been reported recently that the free form of TFPI showed a weak, but positive, correlation to the concentrations of both triglycerides and cholesterol in human plasma. Thus, if this relation is causal, it would be expected that a decrease in these serum lipids would be accompanied by a decrease in TFPI. In the present study, we actually observed that combined treatment with simvastatin and ω-3 FA suppressed serum cholesterol and triglycerides more efficiently than simvastatin alone. The clinical significance of the reduced TFPI activity seen by simvastatin and ω-3 FA treatment is unknown.

A significant reduction in total FVIIag was followed by a 30% increase in the amount of FVIIa in those patients taking simvastatin and ω-3 FA. The mechanism(s) for this apparent unfavorable shift in the FVII status is unknown. It may be speculated that the decreased plasma TFPI would attenuate its ability to inhibit low-grade triggering of the coagulation cascade. However, precautions should be taken. First, these results were not significantly different from those observed in the corn oil group, and even though a similar trend was observed in the corn oil group, the changes did not reach statistical significance. Second, the surprising findings should be confirmed in other studies.

Previously, it has been shown that subjects with combined hyperlipemia have a lower concentration of FVIIa than control subjects with normal plasma lipid levels. This observation has been associated with a low activity of lipoprotein lipase, an important factor in the metabolic defects present in many patients with combined hyperlipemia. Lipoprotein lipase activity was not evaluated in the present study. However, it is known that ω-3 FA may stimulate lipolysis. Thus, lipoprotein lipase may represent a common link for the reduction of triglycerides and activation of FVII by supplementation of ω-3 FA. The significance of the increase of FVIIa is not known; however, increased FVIIa has been associated with increased thrombotic tendency. Thus, statins and ω-3 FAs have complex effects on the
extrinsic clotting system. Whether the total thrombotic risk profile is increased or not is substance for further investigation.

Postprandial Hyperlipemia

Postprandial hypertriglyceridemia may represent an independent predictor for CHD.35,36 It has been shown that the level of fasting triglycerides predicts the degree of postprandial lipemia, an association confirmed in our patients with combined hyperlipemia.37 By treatment with simvastatin, the degree of postprandial hyperlipemia was reduced; however, it was reduced significantly more when ω-3 FAs were added. This confirms that ω-3 FA in the diet reduces both the degree and the extent of postprandial hypertriglyceridemia.38,39 In healthy subjects, it has been shown that resistance to insulin-mediated glucose disposal or compensatory hyperinsulinemia are predictors of postprandial lipemic response to meals.40 In the present study, glucose and insulin concentrations were followed during the postprandial hyperlipemia both before and after treatment. The insulin/glucose ratio increased significantly in the group given ω-3 FAs. The physiological effect of this is not known. However, previous studies in healthy subjects, in patients with non—insulin-dependent diabetes mellitus, and in patients with insulin resistance have shown that long-term treatment with similar amounts of ω-3 FA did not induce any deterioration of glycemic control.41-43

Subgroup analysis in the present study did not reveal any special group that reacted with an increased ratio. Furthermore, there was no relation between the effect on postprandial hyperlipemia and the increased insulin/glucose ratio.

During postprandial hyperlipemia, there was a trend toward increased concentrations of FVII, unaffected by treatment with simvastatin or ω-3 FA. A similar increase in the concentration of FVII, was seen, but this increase was abolished after intervention with simvastatin and ω-3 FA, indicating an association with the reduction of chylomicron and chylomicron remnants. Contrary to the observations by Silveira et al.,32 we observed no positive correlations between the concentration of FFAs and FVII during postprandial hyperlipemia. This was also the situation when the concentrations of the individual FAs of the FFA fraction were evaluated (results not shown). FVII, showed no changes or even a reduction during postprandial hyperlipemia, confirming previous observations.32,44 In summary, both the total coagulant and activated forms of FVII increased during postprandial hyperlipemia, both suggesting increased thrombotic tendency. This tendency could be inhibited by simvastatin and ω-3 FA.

It has previously been reported that PAI-1 has a strong diurnal variation.42 In the study by Salomaa et al.,45 a marked decline in PAI-1 was observed during the 8 hours after the intake of both fat-free meals and meals containing cream or sunflower oil, adding a fat load of 1 g per kilogram of body weight. A similar reduction was seen in the concentration of tPA. Also, in the present study, a decline of PAI-1 concentration was observed at both 4 and 8 hours after intake of the meals without relation to treatment or TAG levels, indicating that the plasma concentrations of triglycerides have minor effects on the diurnal variation in PAI-1. As in previous studies, tPA was also reduced during postprandial hyperlipemia,8 indicating that the total fibrinolytic potential was mainly unaffected by triglyceride concentrations or treatment.

The present study has shown that when patients with combined hyperlipemia are treated with diet and simvastatin with or without supplementation of ω-3 FA, only minor changes occurred in the concentrations of coagulation factors and fibrinolytic variables usually associated with increased thrombotic tendency. However, during postprandial hyperlipemia, which was reduced by both treatments (significantly more so after ω-3 FA), the activation of FVII was significantly reduced, indicating that such treatment may reduce the thrombotic potential associated with intake of fat-rich meals in these patients. In addition, such treatment reduces the concentration of atherogenic lipoproteins.

References


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