Inhibition of Exercise-Induced Shortening of Bleeding Time by Fish Oil in Familial Hypercholesterolemia (Type IIa)

John-Bjarne Hansen, Vegard Lyngmo, Birgit Svensson, and Arne Nordøy

Fourteen patients suffering from familial hypercholesterolemia (type IIa) participated in a double-blind, placebo-controlled trial that evaluated the effects of fish oil ethyl ester (K-85, 5.7 g/day) or a hydroxymethylglutaryl coenzyme A reductase inhibitor (lovastatin, 40 mg/day) alone or in combination on lipid metabolism and bleeding time at rest and after standardized exercise. Lovastatin treatment reduced total cholesterol (-27%), low density lipoprotein cholesterol (-37%), and triglycerides (-18%), whereas high density lipoprotein cholesterol increased significantly (14%). K-85 affected total (-4%), low density lipoprotein (-9%), and high density lipoprotein (+7%) cholesterol insignificantly, whereas the triglyceride level decreased by 24% (p<0.001). The combined regimen caused an additive decrease in the triglyceride level (41%), which differed significantly (p<0.01) from that gained by lovastatin alone. Under basal conditions the bleeding time was not influenced by the different interventions. Standardized exercise shortened the bleeding time by 19% (p<0.001) and 16% (p<0.001) before intervention and after lovastatin treatment, respectively. After K-85 alone or in combination with lovastatin, the exercise-induced shortening of the bleeding time was totally inhibited, which may reflect a favorable influence of fish oil on the platelet-vessel wall interaction in these high-risk patients. (Arteriosclerosis and Thrombosis 1993;13:98–104)

KEY WORDS • n-3 fatty acids • lovastatin • hydroxymethylglutaryl coenzyme A reductase inhibitor • lipoproteins • bleeding time • physical exercise • familial hypercholesterolemia • fish oil

Familial hypercholesterolemia (FH) is associated with an increased risk of coronary heart disease (CHD). Hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors (i.e., lovastatin) are potent compounds that markedly reduce total and low density lipoprotein (LDL) cholesterol, moderately increase high density lipoprotein (HDL) cholesterol, and moderately decrease triglyceride levels. Several prospective clinical trials have shown that treatment with cholesterol-lowering drugs reduces the mortality of CHD and leads to regression of coronary atherosclerosis. Epidemiological studies suggest that populations with a high dietary intake of marine polyunsaturated fatty acids of the n-3 family are protected against CHD and leads to regression of coronary atherosclerosis. The principal protective effects of n-3 fatty acids have been related to a reduction in serum triglyceride and very low density lipoprotein (VLDL) levels and to their effects on platelet-vessel wall interactions that inhibit thrombogenesis.

Platelets and their interactions with the vessel wall are believed to be important in the atherosclerotic process and its complicating arterial thrombosis.

The bleeding time has been accepted as an in vivo test for platelet–vessel wall interaction. Traditionally, the bleeding time has been used to unveil a defect in the hemostatic mechanism. Recently, patients suffering from an acute myocardial infarction (MI) demonstrated a shortened bleeding time, a property probably related to the acute event itself. A shortening of the bleeding time has also been associated with short-term exercise. It may be suggested that the shortened bleeding time seen in MI patients and during exercise may reflect a prethrombotic situation that is caused by an enhanced blood–vessel wall reactivity.

The present study was designed to evaluate whether highly purified fish oils could have an additive effect to lovastatin therapy on serum lipid levels and bleeding time under basal conditions and after standardized exercise in patients with FH.

Methods

Subjects

Fifteen subjects who had been referred to the Lipid Clinic of the Department of Medicine, University Hospital of Tromsø, for hypercholesterolemia were recruited. All subjects were nonobese (within 15% of their ideal body weight) and had a total serum cholesterol level above 9.0 mmol/l and a triglyceride level below 2.0 mmol/l on two occasions after 8–20 weeks on a diet low in cholesterol and saturated fat (American Heart Association step 1 diet). The study group included seven men and eight women with an average age of 49 years.
(range, 29–59 years). Each subject had first-degree relatives who exhibited hypercholesterolemia without hypertriglyceridemia. Three patients demonstrated tendon xanthomas, and seven had a family history of premature cardiovascular diseases. All participants had normal thyroid, renal, and hepatic function, and none had diabetes, manifest cardiovascular disease, or other chronic illnesses. Patients with peptic ulcers, gastrointestinal disorders likely to influence drug absorption, alcoholism, drug abuse, or mental illness were excluded from participation. Seven of eight women were postmenopausal. None of the subjects used any drugs throughout the study. Two of the participants were smokers (50 g tobacco per week). The patients were asked to maintain their usual lifestyle and dietary restrictions throughout the study. One male patient was excluded from the study after his first intervention period because he did not adhere to the dietary restrictions. The study was approved by the regional board of research ethics, and informed, written consent was obtained from each patient.

**Experimental Design**

The study was carried out as a double-blind, placebo-controlled, crossover trial. The 15 patients were randomly allocated into three groups (A, B, and C; five each). The study included three intervention periods, each of which lasted 6 weeks, which were interrupted by washout periods of 6–8 weeks. Group A received 6 g fish oil ethyl ester (K-85) containing 94% n-3 fatty acids (K-85, Pronova A/S, Oslo, Norway) daily during the first intervention, 40 mg of an HMG-CoA reductase inhibitor (lovastatin [Mevacor], MSD Norway A/S, Drammen, Norway) daily during the second intervention period, and a combination of the regimens in the third period. Group B started with 40 mg lovastatin daily in the first period, continued with the combined regimen for 6 weeks during the second period, and ceased with 6 g K-85 daily for 6 weeks. Group C commenced with the combined regimen, continued with K-85, and finished with lovastatin. The patients were examined before and at the end of each intervention period, and a final test was carried out 12 weeks after the end of the last intervention period. The daily intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) was 3.3 and 1.8 g, respectively, in the K-85 groups. Placebo tablets for lovastatin and placebo capsules (olive oil) for K-85 as well as the active compounds were kindly provided by MSD Norway A/S and Pronova A/S. The fatty acid compositions of K-85 and the placebo are given in Table 1. Compliance was assessed by capsule/tablet counts and by measurements of total fatty acids in serum.

**Diet**

After clinical and biochemical examination at admission, the patients were referred to a diettian for advice. They were instructed to follow a stable American Heart Association step I diet.19 Adherence to the diet was recorded by using a 7-day self-administered questionnaire and a 30-minute interview by a diettian before the first intervention period and at the end of each regimen.

**Exercise Protocol**

The patients underwent a standardized exercise load before the first intervention, at the end of each intervention period, and 12 weeks after the end of the last intervention period. Bicycle ergometry was performed by a stepwise, 25-W increase from 75 to 150 W (each second minute) for 6 minutes, and this work load was then maintained for another 6 minutes. Each subject bicycled until exhaustion (at least 6 minutes) or until the test was finished after 12 minutes on the above regimen. Heart rate, blood pressure, and electrocardiographic (ECG) recordings were taken before (after 15 minutes of rest), each second minute during exercise, at the end, and at 2 and 5 minutes after cessation of the exercise. All subjects reached a maximal heart rate of at least 150 beats/min. None of the participants reported chest pain or showed pathological changes on the ECG in response to the exercise test.

**Blood Sampling**

Blood was drawn from an antecubital vein between 8 and 9 AM after 12 hours of overnight fasting by using a 16-gauge butterfly needle with minimal stasis. The blood was collected after 15 minutes of supine rest and immediately after cessation of the exercise test.

**Determination of Bleeding Time**

The bleeding time was determined by the method of Ivy et al,20 as modified by Mielke et al21 by the same

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**Table 1. Fatty Acid Composition of the Two Experimental Fats**

<table>
<thead>
<tr>
<th>Fatty acids (% of total fatty acids)</th>
<th>Fish oil (K-85)*</th>
<th>Olive oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>16:0</td>
<td>...</td>
<td>12</td>
</tr>
<tr>
<td>16:1 n-7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>18:0</td>
<td>...</td>
<td>3</td>
</tr>
<tr>
<td>18:1 n-9</td>
<td>...</td>
<td>77</td>
</tr>
<tr>
<td>18:2 n-6</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>18:3 n-3</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>18:4 n-3</td>
<td>3</td>
<td>...</td>
</tr>
<tr>
<td>20:1 n-9</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>20:4 n-6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>20:4 n-3</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>20:5 n-3 (EPA)</td>
<td>55</td>
<td>...</td>
</tr>
<tr>
<td>22:1 n-11</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>22:4 n-6</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>22:5 n-3</td>
<td>5</td>
<td>...</td>
</tr>
<tr>
<td>22:6 n-3 (DHA)</td>
<td>29</td>
<td>...</td>
</tr>
</tbody>
</table>

**EPA**, eicosapentaenoic acid; **DHA**, docosahexaenoic acid. *Contains 0.8 mg cholesterol per g, 3 mg vitamin A per kg, and 1.3 mg dl-α-tocopherol per g. The peroxide value is 5 meq/kg.
trained investigator (V.L.). Measurements were made after 15 minutes of rest in a supine position and exactly 5 minutes after cessation of exercise. Venostasis was achieved by a standard blood pressure cuff that was inflated to 40 mm Hg around the upper right arm for 30 seconds before the incisions were made and was maintained for the duration of the procedure. In an area with no visible veins on the volar surface of the forearm and approximately 5 cm below the cubital crease, two transverse incisions were made by the standardized Simplate II device from General Diagnostics. Every 30 seconds at the beginning and more often toward the end of the procedure, the blood from the skin incisions was taken up in a Whatman No. 1 filter paper disc, without touching the wounds, until no blood could be detected visually on the filter paper. The average of the bleeding times of the two incisions was recorded (to the nearest 5 seconds). Blood samples were taken from the contralateral cubital vein for hematological and lipid analyses.

**Hematological Analysis**

Blood was drawn before and immediately after exercise into EDTA-containing Vacutainer tubes, and hematological analysis, including hemoglobin concentration, red blood cell count, hematocrit, white blood cell count, platelet count, and mean platelet volume, was performed within 30 minutes on a Coulter Counter model S-plus III (Coulter Electronics Inc., Hialeah, Fla.).

**Total Fatty Acids in Serum**

Under resting conditions, blood was collected into glass tubes before and after each intervention period. Serum was prepared by clotting whole blood in a glass tube at room temperature for 1 hour and then centrifuged at 1,200g for 10 minutes. One-milliliter aliquots of serum were transferred into sterile plastic tubes, flushed with N₂, stored at −70°C until the study was completed, and analyzed before the randomization code was broken. Total lipids were extracted from 200 μl serum according to the method of Folch et al.²³ by using chloroform/methanol (2:1, vol/vol) as the solvent and butylated hydroxytoluene (75 mg/l) as the antioxidant. The extraction procedure was followed by transmethylation with boron trifluoride and a final extraction into hexane before gas-liquid chromatography analysis. The internal standard, heptadecaenoic acid (17:0), was added before the extraction procedure. The fatty acid methyl esters were dissolved in hexane and analyzed by gas-liquid chromatography on a Hewlett-Packard model 5830 A gas chromatograph that was fitted with a fused-silica capillary column (SP 2380, 30 m long, 0.32-mm i.d.) obtained from Supelco Inc., Bellefonte, Pa. Retention times and response factors for each fatty acid were determined with standards obtained from NU-Check Prep, Elysian, Minn. The fatty acid levels are reported as mole percents.

**Lipid and Lipoprotein Analyses**

Total cholesterol and triglyceride levels in serum were measured before and after each intervention on a GSA II selective "Greiner" analyzer with reagents from Boehringer Mannheim, Mannheim, FRG. HDL cholesterol was measured in the supernatant after precipitation of VLDL and LDL according to the procedure of Burstein et al.²⁴ LDL cholesterol was calculated by the formula of Friedewald et al²⁵:

\[
\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - \frac{\text{triglyceride}}{2.2}
\]

**Statistics**

Descriptive statistics on variables revealed a normal distribution of the data. Statistical significance of differences between means was estimated by Student's t test (paired t test for analysis before and after the exercise protocol and unpaired t test for evaluation of data between different intervention periods), and p<0.05 was considered statistically significant. Simple linear regression was performed to calculate regression lines and correlations. Analyses were performed on a personal computer with the STATGRAPHICS statistical software program (STSC, Rockville, Md.). Results are presented as mean±SD.

**Results**

Fourteen patients with FH completed the study protocol. Adherence to the prescribed diet, as evaluated by repeated self-administered questionnaires and interviews, was satisfactory among the participants. The body weight remained stable during the trial. Compliance was excellent, as assessed by pill counts of returned medications and by the distribution of total fatty acids in serum (data not shown), including the concentration of EPA (Figure 1). No adverse drug effects were reported during the intervention periods.

**Serum Lipids and Total Fatty Acids**

Baseline levels of serum lipids and percent changes that were induced by the different regimens are shown in Table 2. K-85 reduced serum triglyceride levels (p<0.01), whereas only nonsignificant changes were
observed in total, HDL, and LDL cholesterol fractions. A significant \((p<0.001)\) decrease in total and LDL cholesterol level was found after lovastatin treatment alone and in combination with K-85. Lovastatin also enhanced HDL cholesterol \((p<0.001)\) and decreased the triglyceride levels \((p<0.05)\). The combined medication had an additive suppressive influence on the triglyceride levels, which differed significantly \((p<0.01)\) from that achieved by lovastatin alone but not from that by K-85 alone. The participants had high basal levels of EPA in serum (Figure 1), which reflected the fact that their diets contained three to six main meals of fish each week. K-85 alone or in combination with lovastatin caused an equal increase in EPA, which differed significantly \((p<0.001)\) from that observed before intervention and after lovastatin treatment alone.

**Bleeding Time**

The average resting bleeding time in the hypercholesterolemic patients was \(5.9 \pm 2.0\) minutes \(\text{range, 3.0–10.2 minutes}\) before the first intervention and \(6.0 \pm 1.9\) minutes 12 weeks after the last intervention period \(\text{measurements were made 42–45 weeks apart}\). The bleeding times that were registered on these two occasions were strongly correlated \((r=0.76, p<0.001)\). When all preexercise measurements \(\text{four occasions}\) were considered in the same statistical analysis \(n=56)\, bleeding time was found to be negatively correlated with hemoglobin concentration \((r=-0.29, p<0.03)\) and hematocrit \((r=-0.34, p<0.02)\), whereas no statistical correlations were observed with the platelet count, mean platelet volume, or platelet mass \(\text{platelet count x mean platelet volume}\). Neither K-85 nor lovastatin treatment significantly changed the resting bleeding times (Figure 2).

With the standardized exercise load, each subject bicycled 6–12 minutes and reached a maximal heart rate and systolic blood pressure varying between \(150–180\) beats/min and \(180–240\) mm Hg, respectively. Five minutes after exercise, the heart rate and systolic blood pressure did not differ significantly from those observed before the exercise protocol \(\text{data not shown}\). Bicycle ergometry evoked a significant \((p<0.001)\) increase in the platelet and white blood cell count \(\text{Table 3}\), which overcame the hemoconcentration induced by plasma water exchange that was related to the short-term physical exercise. The enhancement in hematocrit reflected plasma water expulsion, as mean red blood cell volume was constant and the increase in red blood cell count disappeared after correcting for changes in plasma volume.\(^6\) The hemoconcentration and increase in platelets and white blood cells that were induced by exercise were not statistically different between the different treatment regimens.

The standardized bicycle exercise induced a marked reduction in the bleeding time \(\text{about 19±10\%}, p<0.001\) before the first intervention period \(\text{Figure 3}\). A similar effect \(\text{16±9\%}, p<0.001\) was observed after lovastatin treatment alone. The exercise-induced shortening of bleeding time was not significantly correlated with the changes in platelet count \((r=0.24, p=0.23)\), platelet mass \((r=0.28, p=0.16)\), white blood cell count \((r=0.11, p=0.58)\), or hematocrit \((r=0.00, p=0.98)\). However, K-85 alone or in combination with lovastatin was found to inhibit this exercise-induced shortening of the bleeding time. This response differed significantly \((p<0.05)\) from that observed before the trial and after lovastatin treatment.

**Discussion**

The present study confirmed that lovastatin is a potent cholesterol-lowering drug. It markedly reduced both total and LDL cholesterol levels, moderately increased HDL cholesterol levels, and moderately decreased the triglyceride levels in patients with FH. The principal effect of n-3 fatty acids on serum lipids has been related to a reduction in triglycerides and VLDL,\(^9\) a finding that has also been regularly observed in

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**Table 2.** Baseline Values and Percent Change in Serum Lipids in Fish Oil, Lovastatin, or Combined Treatment Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline (mmol/l)</th>
<th>K-85 (% change)</th>
<th>Lovastatin (% change)</th>
<th>K-85 + Lovastatin (% change)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>10.13±0.96</td>
<td>-4±9</td>
<td>-27±10†</td>
<td>-31±10‡</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.70±0.51</td>
<td>7±16</td>
<td>14±12†</td>
<td>6±18</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>7.69±1.06</td>
<td>-3±11</td>
<td>-37±11‡</td>
<td>-39±13‡</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.66±0.65</td>
<td>-24±32†</td>
<td>-18±23*</td>
<td>-41±18†</td>
</tr>
</tbody>
</table>

K-85, fish oil; HDL, high density lipoprotein; LDL, low density lipoprotein. Treatment regimens included 6 g/day K-85 and/or 40 mg/day lovastatin.

Significance of change: *\(p<0.05\), †\(p<0.01\), ‡\(p<0.001\).

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**Figure 2.** Bar graph of the bleeding time measured under basal conditions before the first intervention \(\text{BI}\) and at the end of each 6-week intervention period with fish oil \(\text{K-85}\), lovastatin \(40 \text{mg/day}\), or combined treatment. Values are mean±SD.
patients with FH\textsuperscript{27-30} and confirmed in the present study.

It has been reported that dietary supplementation with n-3 fatty acids may increase total and LDL cholesterol in subjects with hyperlipidemia.\textsuperscript{9} Such an effect would be most undesirable, as it is well documented that high levels of total cholesterol and LDL cholesterol in particular have been associated with a high risk for development of CHD. In our study, no significant changes in either total cholesterol or LDL cholesterol were observed in patients with FH who received 5.6 g n-3 fatty acids daily for 6 weeks. Most recent reports have demonstrated a similar response\textsuperscript{29-30} or a significant lowering of total cholesterol\textsuperscript{29} by n-3 fatty acids in subjects with FH. Combined lovastatin and fish oil treatment was for the first time shown to have an additive suppressive effect on the serum triglyceride levels, which differed significantly (\textit{p}<0.01) from those observed with lovastatin alone but not from fish oil treatment alone. It is not known whether this effect was caused by a combined suppressive effect on hepatic triglyceride synthesis and/or release or whether it reflected other mechanisms.

A recent investigation by Houwelingen et al\textsuperscript{11} in healthy volunteers demonstrated that the bleeding time was not influenced by a mackerel diet (1.4 g EPA and 2.4 g DHA daily) under basal conditions despite a significant decrease in thromboxane \textit{B}\textsubscript{2} formation, as measured in blood from the skin incisions. This observation indicated that an attenuated platelet thromboxane \textit{B}\textsubscript{2} synthesis caused by moderate amounts of n-3 fatty acids is insufficient to prolong the bleeding time under resting conditions. In our study, neither lovastatin treatment alone nor K-85 ingestion alone affected the bleeding time as measured under basal conditions.

The bleeding time in patients who have been admitted to hospital for acute MI has been reported to be significantly shortened compared with that of patients who were admitted to hospital for chest pain without a definite MI.\textsuperscript{14} In a 2-year follow-up study, the bleeding time was prolonged by about 24\% among those who had suffered an earlier MI and was not significantly different from that observed in those without a definite MI.\textsuperscript{15} Thus, it was suggested that the shortened bleeding time was related to the acute event. In another study that confirmed a shortened bleeding among MI patients, it was suggested that a prethrombotic tendency might be reflected by a shortened bleeding time.\textsuperscript{32} To evaluate whether the shortened bleeding time that occurred during the acute MI reflected increased platelet reactivity and/or enhanced platelet–vessel wall interactions, aspirin, which blocks the cyclooxygenase pathway and, thereby, thromboxane \textit{A}\textsubscript{2} production, was given to the MI patients. Aspirin prolonged the bleeding time, but it was still significantly shorter than in the control groups, thus indicating that mechanisms other than activation of the cyclooxygenase pathway in platelets were also involved.

The risk of cardiovascular complications has been reported to be several times higher during severe exercise than during other daily activities.\textsuperscript{33,34} During short-term exhaustive exercise among healthy volunteers, a 19–24\% shortening of the bleeding times has been reported.\textsuperscript{16-18} This mimics in magnitude the bleeding time shortening that has been observed in patients

\begin{table}[h]
\centering
\caption{Baseline Hematological Values and Percent Change Induced by Standardized Exercise After 6-Week Intervention With Fish Oil, Lovastatin, or Combined Regimen in 14 Patients With Familial Hypercholesterolemia}
\begin{tabular}{lccccc}
\hline
 & Baseline & K-85 & Lovastatin & K-85+lovastatin \\
 & (\%) & (\%) & (\%) & (\%) \\
\hline
RBC (10\textsuperscript{12}/l) & 4.69±0.45 & 4±3\dagger & 5±2\dagger & 8±4\dagger \\
Hct (ratio) & 42.5±3.4 & 4±3\dagger & 5±3\dagger & 7±3\dagger \\
MCV (fl) & 90.8±4.1 & 0±1 & 0±1 & 0±1 \\
WBC (10\textsuperscript{9}/l) & 6.4±2.5 & 45±32\ddagger & 50±31\ddagger & 49±29\ddagger \\
Pit (10\textsuperscript{12}/l) & 287±58 & 13±6\ddagger & 20±17\ddagger & 17±8\ddagger \\
MPV (fl) & 7.9±0.8 & 2±4 & 2±5 & 3±3 \dagger \\
\hline
\end{tabular}

K-85, fish oil; RBC, red blood cell count; Hct, hematocrit; MCV, mean corpuscular volume; WBC, white blood cell count; Pit, platelet count; MPV, mean platelet volume. Treatment regimens included 6 g/day K-85 and/or 40 mg/day lovastatin.

\textit{p}<0.05, \textit{f}p<0.001. Significance of difference with respect to preexercise observations: \textit{p}<0.05, \textit{\ddagger}p<0.01, \textit{\dagger}p<0.001.
\end{table}

\textbf{FIGURE 3.} Bar graph of the percent change in the bleeding time (percent change between preexercise and postexercise measurements) induced by standardized bicycle ergometry registered before the first intervention (BI) and at the end of each intervention period with fish oil (K-85, 6 g/day), lovastatin (40 mg/day), or combined treatment. Values are mean±SD. \textit{***}p<0.001 comparing preexercise and postexercise measurements; \textit{+}p<0.05 comparing the exercise-induced changes in bleeding time before the first intervention with those observed with fish oil alone or in combination with lovastatin.
suffering from an MI. Our study showed an exercise-induced shortening (19%) of the bleeding time among FH patients similar to that reported in healthy individuals. K-85 alone and in combination with lovastatin abolished the shortening of the bleeding time, whereas lovastatin alone was ineffective. It may be suggested that this inhibitory effect of n-3 fatty acids reflects an antithrombotic potential in this group of patients with a high risk for developing CHD.

The mechanisms by which n-3 fatty acids act are complex, and they involve the platelet plug formation, platelet–vessel wall interactions, and probably other cellular elements in the blood as well. Fatty acids of the n-3 type are known to inhibit platelet thromboxane B2 production in vitro and in blood from bleeding time incisions and to attenuate platelet aggregability in vitro. However, decreased vascular reactivity may play a more important role than decreased platelet plug formation in the delayed hemostasis that is caused by fish diets. Tissue factor–dependent activation of extrinsic coagulation in blood obtained from bleeding time wounds, local factors, and systemically produced factors in the vessel wall are known to influence vascular reactivity and to affect the bleeding time. It may be suggested that the effects of n-3 fatty acids are mediated partially by an attenuated procoagulant activity in the vessel wall, since serum enriched with n-3 fatty acids inhibits tissue factor activity in perturbed endothelial cells in vitro.

In conclusion, lovastatin treatment in FH patients showed a favorable effect on serum lipid levels but did not influence the bleeding time as measured under basal conditions and after short-term exercise. Fish oil (K-85) had an additive beneficial effect on serum triglyceride levels and abolished the exercise-induced shortening of bleeding time when used alone or in combination with lovastatin. The inhibitory effect of fish oils on possible prethrombotic blood–vessel wall interactions and their additive suppressive influence on serum triglycerides may imply a therapeutic potential in these patients who are at high risk for CHD.

References

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