Effects of n-3 Fatty Acids and Fenofibrate on Lipid and Hemorrheological Parameters in Familial Dysbetalipoproteinemia and Familial Hypertriglyceridemia

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There is increasing evidence that hemorrheological abnormalities are associated with an enhanced risk of atherosclerosis. The n-3 fatty acids (n-3-FA) have been shown to have beneficial effects on atherosclerosis in patients with dyslipoproteinemias. We studied 23 patients with elevated plasma triglycerides to evaluate the influence of fish oil and fenofibrate therapy on hemorrheological parameters (15 patients with familial hypertriglyceridemia [FHTG] and eight with familial dysbetalipoproteinemia [FDL]). The patients (one woman and 22 men aged 45.7 ± 2.0 years) were treated with increasing doses of n-3-FA (1.8 to 3.6 g/d: 0.9 to 1.8 g eicosapentaenoic acid and 0.6 to 1.2 g docosahexaenoic acid) for 8 weeks. Lipid parameters, whole-blood viscosity at different shear rates, plasma viscosity, fibrinogen concentration, and red blood cell aggregation (RCA) were measured at baseline and at weeks 2, 4, 8 (end of n-3-FA therapy), and 12. Compliance was ensured by measuring plasma concentrations of eicosapentaenoic acid and docosahexaenoic acid. After 12 weeks, patients began treatment with fenofibrate (250 mg daily); investigations were performed again at week 20. Total triglycerides (from 6.90 ± 1.70 to 3.61 ± 0.78 mmol/L in FDL and 7.44 ± 1.50 to 4.15 ± 0.55 in FHTG), very–low-density lipoprotein (VLDL) triglycerides, and VLDL cholesterol were significantly decreased with n-3-FA therapy in both groups ($P < .05$). In FHTG, low-density lipoprotein (LDL) cholesterol increased significantly (from 2.75 ± 0.28 to 3.97 ± 0.35 mmol/L, $P < .01$); in FDL, total cholesterol decreased (from 9.76 ± 1.32 to 7.34 ± 1.07 mmol/L, $P < .05$). No significant changes were observed in hemorrheological parameters, except for reduced RCA with 3.6 g n-3-FA in FHTG. However, with fenofibrate therapy, in addition to comparable lipoprotein changes seen with fish oil, fibrinogen levels and plasma and blood viscosity decreased in patients with FDL. We conclude that n-3-FA and fenofibrate have comparable effects on lipid parameters in patients with FDL and FHTG. Because of additional beneficial effects on hemorrheological parameters, fenofibrate may be preferred for the treatment of FDL.

EPIDEMIOLOGICAL studies have shown an association between hemorrheological abnormalities and increased risk of atherosclerosis.[1-6] n-3 fatty acids (n-3-FA) either supplemented or included in the diet decrease serum triglycerides in patients with hypertriglyceridemia[7-11] and have beneficial effects on atherosclerosis.[12,13] Until now, no consistent significant association between plasma triglyceride concentration and coronary heart disease has been found. Therefore, the beneficial effect of n-3-FA on atherosclerosis may be mediated by improving hemorrheology. However, the influence of n-3-FA on hemorrheological parameters has been the subject of controversy. Some investigations, including a randomized double-blind clinical trial,[14] showed a reduction in fibrinogen with n-3-FA, whereas others found a temporary reduction in fibrinogen only,[15] no effect,[16] or even an increase in fibrinogen.[17] These nonconclusive results for therapy with n-3-FA may have been due to different therapeutic dosages and/or poorly defined patient cohorts.

We therefore investigated the effects of supplementation with n-3-FA in a lipid-lowering diet in well-defined dyslipoproteinemias—familial dysbetalipoproteinemia ([FDL] type III hyperlipoproteinemia) and familial hypertriglyceridemia (FHTG)—on plasma lipoproteins and hemorrheology. In both disorders, plasma triglycerides are elevated, but only in FDL atherosclerotic risk is strongly enhanced.

SUBJECTS AND METHODS

Patients and Study Design

Twenty-five patients with primary hypertriglyceridemia (plasma triglycerides > 2.85 mmol/L) were included in the study after providing written informed consent. The study was approved by the local ethics committee. Exclusion criteria were smoking, diabetes mellitus, obesity (body mass index > 28.5 kg/m^2), arterial hypertension (systolic blood pressure > 180 mm Hg and diastolic blood pressure > 100 mm Hg), chronic liver disease (γ-glutamyl transpeptidase > 70 U/L) or renal disease (creatinine > 2 mg/dL), and hypothyroidism (thyrotropin > 4.0 μU/mL or total thyroxine < 5 μg/dL). Patients with chronic alcohol abuse, unstable angina pectoris, or a history of myocardial or cerebral infarction were not included. Besides the study medication, no antilipidemic or lipid-affecting (β-blockers, thiazides, corticoides, or estrogens) drugs were allowed. Two patients had to be excluded after entering the study (one patient became pregnant, and another had to withdraw from therapy because of gastrointestinal side effects with n-3-FA 3.6 g/d); 23 patients (one woman and 22 men; mean age, 45.7 ± 2.0 years) finished the study.

Fifteen patients had FHTG, and 8 had FDL. The diagnosis of FDL was established by determination of apolipoprotein E phenotype (2/2); familial combined hyperlipidemia was excluded by measuring the ratio of triglyceride and apolipoprotein B in very–low-density lipoprotein (VLDL) according to the criteria of Brunzell et al.[18] The diagnosis of FHTG was established by obtaining the family history (at least one member of the family suffered from hypertriglyceridemia) and excluding FDL and familial combined hyperlipidemia.

All lipid-lowering drugs were withdrawn for at least 6 weeks. After starting a lipid-lowering diet for 4 weeks, the patients began treatment with fish oil capsules (3 g/d) containing 1.8 g n-3-FA

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ethyl esters (50% eicosapentaenoic acid and 33% docosahexaenoic acid) for 2 weeks to acclimate them to the intake of fish oil. This was followed by a regimen of fish oil 6 g/d containing 3.6 g ethyl esters (Feniko; Fournier Pharma, Sulzbach, Germany) for 6 weeks. Investigations were performed at baseline and at weeks 2, 4, 8 (end of n-3-FA therapy), and 12. At week 12, the patients were started on slow-release fenofibrate 250 mg (Fournier Pharma) daily for 8 weeks; a final investigation was performed at week 20.

Methods

After an overnight fast, venous blood samples were drawn from an antecubital vein into EDTA-containing tubes between 8 and 9 AM with patients in the sitting position without venostasis. The hematocrit was determined after centrifugation with a capillary hematocrit centrifuge. All viscosity and red blood cell aggregation (RCA) measurements were made within 4 hours after blood sampling. Lipoprotein analyses from plasma and ultracentrifugation were performed or started on the same day. Plasma was obtained by centrifuging EDTA blood (3,000 rpm for 15 minutes).

Plasma viscosity and blood viscosity were measured at 37°C with a Contraves 30 low-shear–rotation viscosimeter (Contraves, Zurich, Switzerland) at shear rates continuously increasing from 1/s to 115/s.[19] Temperature was kept constant at 37°C with an automatic heating-control unit; the actual shear rates were scanned automatically by the viscosimeter. Blood viscosity was determined after standardization to a hematocrit of 0.45 with autologous plasma. RCA was determined photometrically at hematocrit 0.45 using an erythrocyte aggregometer (Myrenne, Roetgen, Germany).[20] Measurements were performed at stasis and low shear (3/s). Transit time and clogging rate were determined with the St. George's blood filtrometer (Carri-Med, Dorking, UK) to assess red blood cell filterability as described previously.[21]

Fibrinogen level was measured nephelometrically using the Behring Laser Nephelometer (Behringwerke, Marburg, Germany) with a specific antibody against human fibrinogen (OSCA 08/09; Behringwerke). Free eicosapentaenoic and docosahexaenoic acid in plasma were determined by high-performance liquid chromatography,[22] because changes in free fatty acids and phospholipid fatty acids have been reported to be similar after supplementation of the diet with n-3-FA.[23] Apolipoprotein E phenotype was determined by isoelectric focusing as described previously.[24] Creatinine, blood glucose, and γ-glutamyl transpeptidase levels were measured by standard laboratory techniques (EPOS Autoanalyzer; Eppendorf, Hamburg, Germany). All measurements were performed with fresh plasma on the same day (with the exception of eicosapentaenoic and docosahexaenoic acid, which were determined from deep-frozen plasma, −70°C).

VLDLs were separated by ultracentrifugation (50,000 rpm for 20 hours at 4°C; Beckman 50-Ti rotor, d = 1.006 g/mL). HDL cholesterol was determined in the infranatant after heparin-manganese precipitation of low-density lipoproteins (LDL).[25] LDL cholesterol content was calculated by subtracting HDL cholesterol from total infranatant cholesterol. Triglyceride and cholesterol levels in plasma and lipoprotein fractions were measured enzymatically by an autoanalyzer (EPOS Autoanalyzer; Eppendorf) using reagents from Boehringer (Mannheim, Germany).

Apolipoprotein levels were measured with the Behring Laser Nephelometer (reagents from Behringwerke). Determination of RCA was made in triplicate, and all other laboratory measurements are in duplicate. The results are reported as the mean ± SEM. Statistical analyses were performed with SPSS (SPSS Software, Munich, Germany) using the Wilcoxon matched-pairs signed-rank test to assess differences within groups under therapy. Blood values during fish oil therapy were compared with baseline levels (week 0); values during fenofibrate therapy (week 20) were compared with values after the fish oil washout (week 12). No differences in statistically significant changes were seen when values obtained with fenofibrate therapy were compared with baseline levels (week 0) instead of fish oil washout levels (week 12). The only exception was the fibrinogen decrease, which did not reach significance in comparison to baseline ($P = .14$), whereas the decrease was significant in comparison to the fish oil washout ($P < .05$).

The Mann-Whitney U test was used to assess differences between groups (FDL *v* FHTG). P values less than .05 were considered to indicate statistical significance.

RESULTS

Body weight and safety parameters did not differ significantly during therapy with fish oil or fenofibrate, with the exception of a slight increase in creatinine during fenofibrate therapy (from 1.03 ± 0.05 at baseline to 1.10 ± 0.05 mg/dL, $P < .05$) in FHTG patients (Table 1).

Abdominal discomfort in one patient under therapy with n-3-FA 3.6 g/d led to exclusion from the study. Compliance of patients was ensured by measuring plasma concentrations of eicosapentaenoic and docosahexaenoic acid. Plasma concentrations of n-3-FA markedly increased in all patients under treatment. Eicosapentaenoic acid concentration increased from 1.23 ± 0.18 to 3.50 ± 0.47 ($P < .005$) and 4.77 ± 0.74 ($P < .001$) μmol/L under n-3-FA therapy with 1.8 g and 3.6 g/d, respectively. The corresponding levels of docosahexapentaenoic acid were 1.09 ± 0.14 μmol/L at baseline and 1.96 ± 0.38 ($P < .05$) and 1.88 ± 0.20 ($P < .005$) μmol/L under fish oil therapy.

Lipid Parameters

Lipid parameters at baseline showed no statistically significant differences between FDL and FHTG. In patients with FHTG, total triglycerides decreased by 44% ($P < .05$; Fig 1), LDL cholesterol increased by 44% ($P < .01$; Fig 2), and VLDL cholesterol significantly declined by 33% ($P < .01$) and VLDL triglycerides by 39% ($P < .05$; Table 2) under therapy with n-3-FA. Comparable results were observed under fenofibrate therapy (significant reduction in total and VLDL triglycerides and VLDL

Table 1. Safety Parameters Under Fish Oil and Fenofibrate Therapy Compared with Baseline (week 0) in Patients With FHTG (n = 15) and FDL (n = 8)

Parameter	Baseline (week 0)	n-3-FA 3.6 g/d (week 8)	Fenofibrate 250 mg/d (week 20)
FHTG			
Creatinine (mg/dL)	1.03 ± 0.05	1.02 ± 0.05	1.10 ± 0.05*
Prothrombin index	0.97 ± 0.02	0.98 ± 0.02	0.97 ± 0.02
Blood glucose (mmol/L)	4.69 ± 0.19	4.79 ± 0.18	4.91 ± 0.23
γ-Glutamyl transpeptidase (μkat/L)	0.27 ± 0.08	0.28 ± 0.07	0.35 ± 0.10
FDL			
Creatinine (mg/dL)	1.12 ± 0.08	1.15 ± 0.02	1.18 ± 0.06
Prothrombin index	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Blood glucose (mmol/L)	4.77 ± 0.20	4.91 ± 0.22	4.92 ± 0.19
γ-Glutamyl transpeptidase (μkat/L)	0.23 ± 0.03	0.27 ± 0.08	0.36 ± 0.17

*$P < .05$.

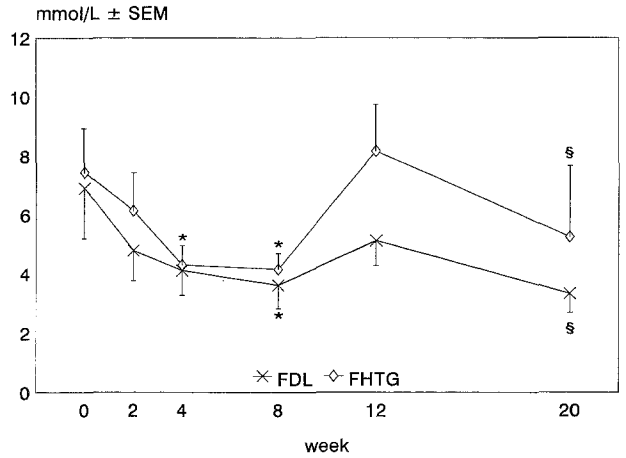

Fig 1. Total plasma triglycerides under fish oil therapy (week 0 to week 8) *v* baseline (week 0, **P* < .05) and under fenofibrate therapy (week 12 to week 20) *v* fish oil washout (week 12, §*P* < .05) in patients with FDL and FHTG.

cholesterol and significant increase in LDL cholesterol). Additionally, total cholesterol and apolipoprotein B decreased while HDL_3 cholesterol increased significantly (Table 2). Under both n-3-FA and fenofibrate therapy, total triglycerides decreased in 12 of 15 patients; LDL cholesterol increased in 13 patients with fish oil and in 12 with fenofibrate therapy.

In FDL, significant decreases in VLDL cholesterol of 54% ($P < .05$) and in VLDL triglycerides of 61% ($P < .05$) were observed under therapy with n-3-FA; additionally, total cholesterol (−25%, $P < .05$) and apolipoprotein B (−34%, $P < .05$) were reduced significantly (Table 3). Comparable results were observed during fenofibrate therapy: significant reductions were seen in total (−22%) and VLDL (−28%) cholesterol, total (−35%) and VLDL (−31%) triglycerides, and apolipoprotein B (−26%) (Table 3). Total triglycerides decreased in seven of eight patients under fish oil and in all patients under fenofibrate therapy.

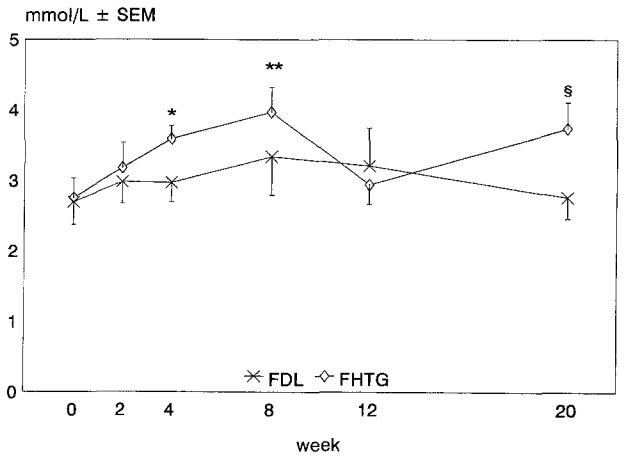

Fig 2. LDL cholesterol under fish oil therapy (week 0 to week 8) *v* baseline (week 0, **P* < .05 and ***P* < .01) and under fenofibrate therapy (week 12 to week 20) *v* fish oil washout (week 12, §*P* < .05) in patients with FDL and FHTG.

Hemorrheological Parameters

Plasma viscosity was higher for FDL compared with FHTG ($P < .005$); whole-blood viscosity showed a trend to higher values in FDL compared with FHTG, which did not reach significance ($P = .11$). In FHTG, no significant changes were observed in fibrinogen concentration, plasma viscosity, standard blood viscosity, or parameters of red blood cell filterability under therapy with fish oil or fenofibrate. However, RCA was significantly decreased under therapy with fish oil for stasis (from 5.47 ± 0.34 to 4.81 ± 0.29 U) and for a shear rate of 3/s (from 10.50 ± 0.43 to 9.47 ± 0.45 U; Table 4). Decreasing RCA was observed in 13 of 15 patients.

Since the erythrocyte aggregometer was not available at the beginning of the study, RCA was not determined in patients with FDL.

Therapy with n-3-FA did not alter hemorrheological parameters in patients with FDL. However, under fenofibrate, fibrinogen concentration (−20%, $P < .05$), plasma viscosity (−6%, $P < .05$), and standard blood viscosity for all shear rates ($P < .05$) were significantly reduced; no statistical significant changes were observed for red blood cell filterability (Table 5).

DISCUSSION

There is a different purpose in the treatment of patients with FDL versus FHTG. Patients with FHTG and elevated triglycerides are in danger of developing acutely severe complications (eg, pancreatitis) as part of the chylomicronemia syndrome, whereas the atherosclerotic risk is not definitely elevated in these patients.[26] In contrast, patients with FDL are known to have a strongly enhanced risk for atherosclerosis.[27] Therefore, therapy in FHTG is intended to avoid chylomicronemia and in FDL to reduce the development or progression of atherosclerosis.

In our study, n-3-FA reduced VLDL cholesterol and VLDL triglycerides without changing their ratio in subjects with FDL. These data confirm the results of the two previous reports on fish oil therapy in patients with type III hyperlipoproteinemia (FDL). In nine patients with homozygosity of the apolipoprotein E2 isoform treated with 15 g fish oil (containing 2.7 g eicosapentaenoic acid and 1.8 g docosahexaenoic acid) daily for 16 weeks, VLDL cholesterol and VLDL triglycerides decreased by 45% and 62%, respectively, whereas the abnormal VLDL cholesterol to VLDL triglyceride ratio remained unchanged.[28] Dallongeville et al[29] observed a reduction of 54% in VLDL cholesterol and 62% in VLDL triglycerides with n-3-FA 6 g/d over a period of 12 weeks in type III hyperlipoproteneinemia (FDL). They concluded from these results that VLDL and chylomicron remnants decreased in type III hyperlipoproteinemia under fish oil therapy.

Total cholesterol and total plasma triglycerides also decreased significantly in our study (−25% and −48%, respectively) and in previous reports (−19% and −53%, respectively,[28] and 26% and 57%, respectively[29]). These results indicate that ethyl esters are well absorbed in the intestine and highly effective in reducing triglycerides. The main advantage of ethyl ester preparations is the higher

Table 2. Lipid Parameters Under Fish Oil Therapy Compared With Baseline (week 0) and Under Fenofibrate Therapy Compared With Washout (week 12) in Patients With FHTG (n = 15)

Parameter	Baseline (week 0)	n-3-FA 1.8 g/d (week 2)	n-3-FA 3.6 g/d (week 4)	n-3-FA 3.6 g/d (week 8)	Washout (week 12)	Fenofibrate 250 mg/d (week 20)
Age (yr)	44.07 ± 2.51					
Height (cm)	177.40 ± 1.95					
Body weight (kg)	78.0 ± 2.6	78.0 ± 2.6	78.3 ± 2.6	78.5 ± 2.7	79.0 ± 2.7	78.3 ± 2.8
Total cholesterol (mmol/L)	6.67 ± 0.41	6.69 ± 0.35	6.43 ± 0.24	6.77 ± 0.33	7.31 ± 0.44	6.46 ± 0.26‡
HDL cholesterol (mmol/L)	0.92 ± 0.05	0.84 ± 0.04	0.84 ± 0.05	0.83 ± 0.03	0.85 ± 0.04	0.96 ± 0.05
HDL_2 cholesterol (mmol/L)	0.23 ± 0.05	0.15 ± 0.02	0.12 ± 0.01	0.12 ± 0.01*	0.14 ± 0.01	0.14 ± 0.01
HDL_3 cholesterol (mmol/L)	0.68 ± 0.04	0.72 ± 0.04	0.72 ± 0.04	0.71 ± 0.03	0.71 ± 0.03	0.82 ± 0.04‡
LDL cholesterol (mmol/L)	2.75 ± 0.28	3.18 ± 0.36	3.59 ± 0.19*	3.97 ± 0.35†	2.94 ± 0.28	3.74 ± 0.37‡
Total triglycerides (mmol/L)	7.44 ± 1.50	6.13 ± 1.30	4.30 ± 0.65*	4.15 ± 0.55*	8.16 ± 1.58	5.25 ± 2.42‡
VLDL cholesterol (mmol/L)	3.00 ± 0.40	2.69 ± 0.35	2.07 ± 0.27	2.00 ± 0.23†	3.53 ± 0.51	1.78 ± 0.38§
VLDL triglycerides (mmol/L)	5.82 ± 1.13	5.54 ± 1.19	4.01 ± 0.67	3.57 ± 0.50*	7.31 ± 1.39	4.56 ± 2.06‡
VLDL-C:VLDL-T	0.25 ± 0.02	0.26 ± 0.02	0.29 ± 0.05	0.27 ± 0.02	0.25 ± 0.02	0.25 ± 0.02
Apo A-I (mg/dL)	141.0 ± 9.7	141.7 ± 9.1	130.9 ± 5.4	134.6 ± 7.8	143.0 ± 9.4	147.9 ± 13.6
Apo B (mg/dL)	176.2 ± 19.9	187.1 ± 15.5	165.4 ± 9.6	159.6 ± 7.0	190.9 ± 23.0	163.7 ± 14.5‡

*$P < .05$, †$P < .01$: *v* baseline.
‡$P < .05$, §$P < .01$: *v* washout period.

content of n-3-FA (60% of the total fat content), resulting in a smaller total amount of ingested fish oil and therefore possibly an improved compliance of patients. In addition, the amount of calories is smaller (3.6 g n-3-FA corresponds to 266 kJ, *v* 680 kJ in other preparations[30]), so the weight gain due to n-3-FA may be avoided.

In type III hyperlipoproteinemia (FDL), plasma viscosity, whole-blood viscosity, and RCA are increased.[31] In our study, enhancement of plasma viscosity was statistically significant in FDL compared with FHTG. Hemorrheological abnormalities have been shown to be associated with an increased risk of atherosclerosis.[1-6] Therefore, an elevated risk of atherosclerosis in patients with FDL seems to be at least partly due to impaired hemorrheology. In our study, no significant effects of fish oil on hemorrheological parameters, including fibrinogen, were observed. The reason for the lack of effect, particularly on fibrinogen, might be the relatively short observation period (6 weeks on the highest dosage). It is true that Radack et al[14] showed a 14% reduction in fibrinogen after 8 weeks, but the effect was much more pronounced after 20 weeks (23% reduction). In contrast, Hostmark et al[15] found the greatest fibrinogen reduction after 3 weeks of treatment, whereas significance was lost after 9 weeks. Haglund et al[16] found an 11% reduction of fibrinogen under treatment with vitamin E–supplemented fish oil, but no reduction under normal fish oil. One study even showed an increase in fibrinogen under fish oil.[17] A lack of control of compliance by measuring plasma n-3-FA concentrations (except for the investigations by Radack et al and Dallongeville et al) may be a reason for these conflicting results.

In FHTG, VLDL cholesterol and VLDL triglycerides decreased concomitantly (−33% and −39%, respectively) and total triglycerides decreased 44%. This is in good agreement with data from previous trials.[7,9,11,32] Fish oil therapy has also been shown to reduce chylomicrons in type V hyperlipoproteinemia[7] and in primary chylomicronemia.[30,32]

Table 3. Lipid Parameters Under Fish Oil Therapy Compared With Baseline (week 0) and Under Fenofibrate Therapy Compared With Washout (week 12) in Patients With FDL (n = 8)

Parameter	Baseline (week 0)	n-3-FA 1.8 g/d (week 2)	n-3-FA 3.6 g/d (week 4)	n-3-FA 3.6 g/d (week 8)	Washout (week 12)	Fenofibrate 250 mg/d (week 20)
Age (yr)	48.63 ± 3.33					
Height (cm)	175.25 ± 1.45					
Body weight (kg)	74.9 ± 2.2	74.0 ± 2.8	74.4 ± 2.5	74.1 ± 2.7	73.8 ± 2.9	73.8 ± 3.2
Total cholesterol (mmol/L)	9.76 ± 1.32	8.00 ± 1.01*	7.52 ± 0.92*	7.34 ± 1.07*	8.65 ± 1.07	6.77 ± 0.76†
HDL cholesterol (mmol/L)	1.00 ± 0.06	1.07 ± 0.12	1.03 ± 0.11	1.05 ± 0.12	1.04 ± 0.14	1.11 ± 0.14
HDL_2 cholesterol (mmol/L)	0.19 ± 0.02	0.21 ± 0.02	0.18 ± 0.02	0.23 ± 0.04	0.22 ± 0.03	0.24 ± 0.03
HDL_3 cholesterol (mmol/L)	0.80 ± 0.07	0.88 ± 0.13	0.85 ± 0.10	0.83 ± 0.10	0.83 ± 0.13	0.88 ± 0.13
LDL cholesterol (mmol/L)	2.69 ± 0.32	2.98 ± 0.31	2.97 ± 0.28	3.34 ± 0.55	3.21 ± 0.53	2.76 ± 0.30
Total triglycerides (mmol/L)	6.90 ± 1.70	4.79 ± 1.03	4.11 ± 0.84	3.61 ± 0.78*	5.12 ± 0.85	3.33 ± 0.65†
VLDL cholesterol (mmol/L)	5.88 ± 1.22	3.37 ± 0.68*	3.31 ± 0.70*	2.69 ± 0.50*	4.13 ± 0.93	2.99 ± 0.65†
VLDL triglycerides (mmol/L)	5.89 ± 1.52	3.54 ± 0.76*	3.22 ± 0.78*	2.32 ± 0.37*	3.72 ± 0.76	2.58 ± 0.44†
VLDL-C:VLDL-T	0.48 ± 0.04	0.43 ± 0.03	0.49 ± 0.04	0.51 ± 0.05	0.47 ± 0.03	0.48 ± 0.04
Apo A-I (mg/dL)	146.0 ± 10.5	147.2 ± 12.4	141.6 ± 8.6	135.8 ± 9.2	146.9 ± 12.7	146.6 ± 12.1
Apo B (mg/dL)	172.3 ± 31.6	133.3 ± 28.8*	130.8 ± 21.5*	114.7 ± 25.1*	137.0 ± 27.2	102.8 ± 14.9†

*$P < .05$ *v* baseline.
†$P < .05$ *v* washout period.

Table 4. Hemorrheological Parameters Under Fish Oil Therapy Compared with Baseline (week 0) and Under Fenofibrate Therapy Compared With Washout (week 12) in Patients With FHTG (n = 15)

Parameter	Baseline (week 0)	n-3-FA 1.8 g/d (week 2)	n-3-FA 3.6 g/d (week 4)	n-3-FA 3.6 g/d (week 8)	Washout (week 12)	Fenofibrate 250 mg/d (week 20)
Fibrinogen (g/L)	2.69 ± 0.12	2.74 ± 0.15	2.72 ± 0.14	2.63 ± 0.14	2.89 ± 0.18	2.79 ± 0.20
Plasma viscosity (mPa · s)	1.36 ± 0.02	1.44 ± 0.04	1.37 ± 0.02	1.37 ± 0.02	1.42 ± 0.03	1.38 ± 0.02
Standard blood viscosity (mPa · s)						
Shear rate 5/s	11.40 ± 0.42	10.91 ± 0.30	10.52 ± 0.27	11.05 ± 0.40	11.37 ± 0.51	10.74 ± 0.25
Shear rate 9/s	8.15 ± 0.32	7.92 ± 0.29	7.71 ± 0.30	7.85 ± 0.31	8.52 ± 0.46	8.37 ± 0.15
Shear rate 37/s	5.81 ± 0.11	5.73 ± 0.08	5.68 ± 0.12	5.74 ± 0.12	6.06 ± 0.19	5.91 ± 0.09
Shear rate 78/s	5.03 ± 0.08	4.99 ± 0.07	4.93 ± 0.10	4.95 ± 0.09	5.19 ± 0.14	5.06 ± 0.08
Shear rate 118/s	4.67 ± 0.07	4.66 ± 0.06	4.56 ± 0.08	4.60 ± 0.08	4.82 ± 0.13	4.70 ± 0.08
RCA (U)						
Stasis	5.47 ± 0.34	5.17 ± 0.28	4.97 ± 0.28*	4.81 ± .029†	4.97 ± 0.27*	4.77 ± 0.30
Shear rate 3/s	10.50 ± 0.43	9.96 ± 0.48	9.41 ± 0.46*	9.47 ± .045*	10.01 ± 0.35	9.35 ± 0.55
Clogging rate (U)	1.10 ± 0.18	0.96 ± 0.13	1.18 ± 0.23	1.06 ± 0.18	0.97 ± 0.15	1.05 ± 0.14
Transit time (s)	7.90 ± 0.39	7.95 ± 0.39	8.27 ± 0.40	8.82 ± 0.79	9.46 ± 0.77	9.05 ± 0.36

*$P < .5$ *v* baseline.

†$P < .01$ *v* baseline.

The mechanisms leading to decreased triglycerides under fish oil therapy have been a matter of controversy. One possible mechanism is an enhanced clearance of VLDL particles under fish oil, but it seems more likely that VLDL production in liver is depressed.[33-35]

LDL cholesterol significantly increased under fish oil therapy by 44%. Because of low baseline levels in hypertriglyceridemic patients, LDL cholesterol under fish oil therapy remains within an acceptable range (mean, 3.97 ± 0.35 mmol/L). Several studies demonstrated increases in LDL cholesterol.[9,35] Although the mechanisms leading to an increase in LDL cholesterol are still unknown, it is unlikely that LDL cholesterol is generated by an enhanced catabolism of VLDL particles in FHTG.[9,35]

The only significant changes in hemorrheological parameters were beneficial effects on erythrocyte aggregation. RCA decreased under fish oil at stasis and at a shear rate of 3/s. This reduction is probably due to a change in the composition of erythrocyte membrane phospholipids under n-3-FA therapy.[36] Elevated RCA has been shown to identify patients with unstable angina pectoris who are at high risk for myocardial infarction.[37] Patients with stable angina pectoris had lower RCA values than patients with unstable angina[38,39] and higher RCA values than healthy controls.[39] Thus, RCA is correlated with the clinical severity of coronary heart disease, and therefore, RCA reduction under n-3-FA therapy may contribute to the beneficial effects of fish oil on atherosclerosis.

In patients with FDL, fenofibrate therapy significantly reduced VLDL cholesterol (28%), VLDL triglycerides (31%), total triglycerides (−35%), and total cholesterol (−22%) to a comparable extent as obtained with fish oil therapy. A slight nonsignificant increase in HDL was observed (+7%). Under immediate-release fenofibrate 300 mg/d, triglycerides decreased by 51% and HDL cholesterol increased by 21% in six patients with FDL.[40] In nine patients with FDL, triglycerides were reduced by 56%.[41] The lesser extent of triglyceride reduction in our study may be due to the lower triglyceride levels after the fish oil washout period as compared with the beginning of the study (5.12 *v* 6.90 mmol/L).

Less is known about the influence of fenofibrate on hemorrheological parameters. In one study, significant beneficial effects on hemostatic variables (fibrinogen, plasma viscosity, and RCA) were observed.[42] Fibrinogen decreased 18% in patients with coronary heart disease and hyperlipidemia[42] and 16% in hypercholesterolemics[43] under fenofibrate. This is in good agreement with our results, wherein

Table 5. Hemorrheological Parameters Under Fish Oil Therapy Compared With Baseline (week 0) and Under Fenofibrate Therapy Compared With Washout (week 12) in Patients With FDL (n = 8)

Parameter	Baseline (week 0)	n-3-FA 1.8 g/d (week 2)	n-3-FA 3.6 g/d (week 4)	n-3-FA 3.6 g/d (week 8)	Washout (week 12)	Fenofibrate 250 mg/d (week 20)
Fibrinogen (g/L)	2.53 ± 0.06	2.60 ± 0.19	2.51 ± 0.12	2.54 ± 0.10	2.77 ± 0.09	2.22 ± 0.20*
Plasma viscosity (mPa · s)	1.51 ± 0.02	1.49 ± 0.04	1.52 ± 0.05	1.46 ± 0.03	1.49 ± 0.02	1.40 ± 0.02*
Standard blood viscosity (mPa · s)						
Shear rate 5/s	12.57 ± 0.76	11.77 ± 0.52	12.81 ± 1.17	13.33 ± 0.71	12.94 ± 0.64	10.34 ± 0.46*
Shear rate 9/s	9.48 ± 0.66	8.77 ± 0.72	9.82 ± 1.08	10.02 ± 0.75	9.50 ± 0.60	6.89 ± 0.35*
Shear rate 37/s	6.42 ± 0.29	6.14 ± 0.23	6.41 ± 0.48	6.70 ± 0.42	6.45 ± 0.28	5.30 ± 0.15*
Shear rate 78/s	5.44 ± 0.22	5.25 ± 0.15	5.45 ± 0.40	5.68 ± 0.35	5.38 ± 0.18	4.57 ± 0.13*
Shear rate 118/s	5.06 ± 0.20	4.88 ± 0.15	5.07 ± 0.36	5.27 ± 0.32	4.99 ± 0.17	4.28 ± 0.12*
Clogging rate (U)	0.57 ± 0.10	0.80 ± 0.20	1.13 ± 0.30	1.70 ± 0.70	0.68 ± 0.12	0.50 ± 0.10
Transit time (s)	7.89 ± 0.27	7.80 ± 0.36	7.62 ± 0.26	7.73 ± 0.19	7.66 ± 0.28	7.78 ± 0.31

*$P < .05$ *v* washout period.

fibrinogen concentration (−20%) and plasma viscosity (−6%) decreased under fenofibrate in FDL. Whole-blood viscosity concomitantly decreased for all shear rates (reductions between −14% and −27%).

In patients with FHTG, VLDL cholesterol (−50%), VLDL triglycerides (−38%), total triglycerides (−36%), and total cholesterol (−12%) significantly decreased under fenofibrate. Analogous to fish oil therapy, LDL cholesterol increased (+27%), whereas the mechanisms might be the same as discussed earlier. In several previous studies (summarized in a review[44]), triglycerides decreased by 28% to 60% and LDL cholesterol increased by 2% to 29%. Fibrinogen, plasma viscosity, blood viscosity, and RCA showed slight but nonsignificant decreases under therapy with fenofibrate. We cannot explain why these reductions in FHTG did not reach significance. One possible explanation is the increase in LDL cholesterol (which correlates with fibrinogen levels[45]) in FHTG, whereas LDL cholesterol tended to decrease in FDL.

We conclude that n-3-FA and fenofibrate had comparable effects on lipid parameters in patients with FDL and FHTG. Because of additional beneficial effects on hemorrheological parameters, fenofibrate may be preferable in FDL.

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