Postprandial Hemorrheology and Apolipoprotein B Metabolism in Patients With Familial Hypertriglyceridemia

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Impaired postprandial lipoprotein metabolism has been found to be related to the extent of coronary artery disease. Moreover, since dyslipoproteinemias are associated with impaired hemorrheology, we investigated the effect of postprandial hypertriglyceridemia on hemorrheological parameters before and after triglyceride-lowering therapy. Triglyceride-rich lipoproteins (TRLs) separated by ultracentrifugation (d < 1.006 g/dL) and chylomicrons and chylomicron remnants (quantified by apolipoprotein [apo] B-48 determination) were determined after a fat load in 10 patients with familial hypertriglyceridemia before and after therapy with gemfibrozil (900 mg daily). Lipid and hemorrheological parameters (plasma and whole-blood viscosity [PV and BV], red cell aggregation [RCA], hematocrit, and fibrinogen) were determined at baseline and every hour up to 6 hours postprandially. Fasting total triglycerides and TRL triglycerides significantly decreased with gemfibrozil therapy ($P < .01$). Total triglycerides postprandially increased from 9.53 ± 1.72 to 14.47 ± 2.07 mmol/L (TRL triglycerides by 61%) before therapy ($P < .05$) and from 4.61 ± 1.28 to 7.17 ± 0.99 mmol/L (TRL triglycerides by 57%) after therapy ($P < .05$). The postprandial TRL apo B increase was reduced with gemfibrozil (from 11.6 ± 2.8 to 20.7 ± 5.0 mg/dL with therapy *v* 19.0 ± 7.6 to 33.0 ± 12.5 mg/dL before therapy, $P < .05$, respectively) with a proportionally greater increase in apo B-48 (119% and 169%, respectively) compared with apo B-100 (64% and 64%, respectively). Fasting RCA was improved with lipid-lowering therapy ($P < .05$), but PV, BV, RCA, and fibrinogen did not show any statistically significant postprandial changes either before or after lipid-lowering therapy. In summary, we did not find any statistically significant changes in hemorrheological parameters, despite a strong postprandial increase of triglycerides. In particular, these findings were independent of fasting triglyceride levels. We conclude that triglyceride-lowering therapy by gemfibrozil had no substantial beneficial effects with respect to hemorrheology in patients with familial hypertriglyceridemia.

HEMORRHEOLOGICAL PARAMETERS have been identified to be strongly related to the risk of atherosclerosis.[1-5] But it is still unclear whether there is a causal link between impaired hemorrheology and atherosclerosis or whether impaired hemorrheology is just a marker of atherosclerosis. Moreover, epidemiological investigations have shown an association of lipoproteins and hemorrheology in patients with coronary heart disease[5] and dyslipoproteinemias,[6] as well as in healthy subjects.[7,8]

Zilversmit[9] suggested that postprandial lipoproteins were important in atherogenesis. More recent investigations in patients with coronary heart disease found a substantial postprandial accumulation of chylomicron remnants,[10] a decreased postprandial clearance of chylomicrons and their remnants,[11] as well as a relation between the concentration of small chylomicron remnants and the progression of coronary lesions.[12] However, only little is known about the influence of postprandial triglyceride-rich lipoproteins (TRLs) on hemorrheological parameters[13,14] as a possible link between postprandial lipemia and atherogenesis. In severe hypertriglyceridemia, an increase in plasma viscosity (PV) is found,[15] which may result in severe complications (eg, acute pancreatitis or neurological disorders). Since these acute complications may occur at triglyceride concentrations greater than 11 mmol/L, we wondered whether in patients with familial hypertriglyceridemia the postprandial increase of triglycerides concomitantly elevates PV and whole-blood viscosity (BV) and whether triglyceride-lowering treatment can reduce these increases to avoid severe complications. Therefore, we investigated lipid and hemorrheological changes after a fat load before and after triglyceride-lowering treatment in patients with familial hypertriglyceridemia.

To investigate the effect of decreasing triglycerides on hemorrheology, the unwanted direct effects of the lipid-lowering drug on the hemorrheology have to be considered. Therefore, gemfibrozil was chosen as the lipid-lowering drug because it is the only fibric acid derivate that does not have direct beneficial effects on fasting hemorrheology by decreasing fibrinogen levels.[16] However, other fibric acid derivates are known to significantly decrease fibrinogen levels, especially bezafibrate (21%[17] to 44%[18]) and fenofibrate (up to 20%[19]).

In essence, two different methods have been used to investigate the postprandial metabolism of chylomicrons and chylomicron remnants. Retinyl esters have been shown to be transferred from chylomicrons to other lipoproteins, and the peak for retinyl esters did not correspond with the peak triglyceride concentration in some investigations.[20,21] The determination of apolipoprotein (apo) B-48 has been suggested to be the more reliable method to investigate the metabolism of chylomicrons and chylomicron remnants.[20] Therefore, we used apo B-48 quantification to examine postprandial TRLs and their impact on changes in hemorrheology.

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SUBJECTS AND METHODS

Study Design and Sample Collection

Ten patients (one woman and nine men; mean age, 42.3 ± 2.8 years; body mass index, 25.7 ± 0.9 kg/m^2) with familial hypertriglyceridemia were enrolled onto the study. The diagnosis of familial hypertriglyceridemia was established by family history, by measuring fasting plasma triglyceride (>2.85 mmol/L) and low-density lipoprotein (LDL) cholesterol (<3.85 mmol/L) levels, and by excluding familial combined hyperlipidemia (by determination of the ratio of apo B and triglycerides in plasma and TRLs[22]) and familial dysbetalipoproteinemia (by determination of apo E phenotype). Patients did not smoke or have chronic alcohol abuse, diabetes mellitus, or hypothyroidism, and all were free of cardiac symptoms and clinical signs of coronary heart disease.

Patients were admitted to the medical department in the morning after an overnight fast of at least 12 hours. A quantity of cream containing 50 g fat/m^2 body surface area was ingested within 5 minutes (100 g cream contains 31.7 g fat, including 1.0 g polyunsaturated and 9.2 g monounsaturated fatty acids, 110 mg cholesterol, and 3.6 g carbohydrates). Blood samples were collected at baseline and hourly after fat ingestion for 6 hours. Patients rested during the experiment to avoid the interference of physical activity.

After the experiment, patients were treated with gemfibrozil (900 mg daily orally; Parke-Davis, Berlin, Germany) for 6 weeks. The fat load test was performed again after this period.

Blood samples were obtained through an intravenous indwelling catheter positioned in an antecubital vein at the beginning of the experiment. Blood was collected in EDTA tubes (2.0 mg K_3EDTA/mL blood) for determination of hematological parameters and in granulate tubes for serum parameters (both Primavette S; Braun, Melsungen, Germany), in EDTA tubes for lipid and hemorrheological parameters (2.0 mg K_3EDTA/mL blood; Greiner, Frickenhausen, Germany), and in citrate tubes (0.1 mL citrate solution/mL blood, Primavette S; Braun) for determination of coagulation parameters.

BV, PV, and red cell aggregation (RCA) were determined immediately after blood sampling. Plasma was obtained by centrifugating EDTA blood (1,750 × *g*, 3,000 rpm at 4°C for 20 minutes). Coagulation parameters (with the exception of fibrinogen) and hematological and serum parameters were determined on the same day. Samples for lipoprotein isolation were stored in ice water until ultracentrifugation started the same day.

Lipoprotein Measurements

TRLs were separated in polyallomer tubes (Quick-Seal; Beckman, Palo Alto, CA) by ultracentrifugation (226,000 × *g*, 50,000 rpm for 20 hours at 4°C; Beckman rotor Ti 50) after the plasma had been adjusted to a density of 1.006 g/mL with sodium chloride (Svedberg flotation units [S_f] > 20). The supranatant was separated from the infranatant by a semiautomatic cutting unit. To quantify apo B-48 and B-100, TRLs were stored at −70°C until analyses were performed at the end of the study.

LDLs were precipitated from the infranatant by adding 20 µL (100 IE) heparin (Braun) and 20 µL 2-mol/L manganese chloride solution to 500 µL plasma.[23] High-density lipoprotein (HDL) cholesterol was determined in the supranatant after low-speed centrifugation (1,750 × *g*, 3,000 rpm at 25°C for 10 minutes. LDL cholesterol was calculated by subtracting HDL cholesterol from total infranatant cholesterol.

The HDL_3 cholesterol subfraction was determined from plasma after precipitation of other lipoproteins using reagents from Immuno (Quantolip; Immuno, Heidelberg, Germany). HDL_2 cholesterol was calculated by subtracting HDL_3 from total HDL cholesterol in plasma. Triglyceride and cholesterol levels in plasma and lipoprotein fractions were measured enzymatically (EPOS Autoanalyzer; Eppendorf, Hamburg, Germany) using reagents from Boehringer (Mannheim, Germany).

Total apo B in TRL was determined nephelometrically (Automatic Nephelometer 100; Behringwerke, Marburg, Germany) using specific antibodies for human apo B (Behringwerke).

Apo B-48 and B-100 were separated by sodium dodecyl sulfate (SDS) gel electrophoresis[24] using a 5% acrylamide gel (Serva, Heidelberg, Germany) that had been bonded to a sheet of GelBond PAG film (Pharmacia, Uppsala, Sweden) during polymerization.

TRLs were delipidated by adding 7 mL of a mixture of diethylether/ethanol 1:3 (both Merck, Darmstadt, Germany) to 1 mL TRL. After 20 hours of incubation at 4°C, the mixture was centrifugated (1,750 × *g*, 3,000 rpm at 25°C for 10 minutes and the infranatant was redissolved in diethylether/ethanol and centrifugated again. The infranatant was dried under a stream of nitrogen and dissolved in 100 µL sample buffer (4% SDS and 0.5% dithiothreitol, pH 8.0); 10 µL of this solution was applied to gels for electrophoresis.

After electrophoresis, gels were fixed with trichloroacetic acid (20%) and stained in Coomassie Brilliant blue R-250 (Serva, Heidelberg, Germany). After destaining with acetic acid (10%)/methanol (20%) for 72 hours, gels were scanned by the Image Master Desk Top Scanner 100 (Pharmacia Biotech, Freiburg, Germany; wavelength, 530 to 570 nm). Bands were quantified by calculating the product of optical density and band area (OD × mm^2).

Pure apo B-48 from chylous ascites and pure apo B-100 from LDL particles prepared by high-performance gel permeation chromatography[25] served as a reference for identification and quantification of apolipoproteins.

Apo E phenotype was determined by isoelectric focusing.[26] TRLs were delipidated and then dissolved in 30 µL sample buffer (containing 0.15% dithiothreitol, pH 8.6), and electrophoresis was performed using the acrylamide gel already described. Apolipoprotein bands were identified after staining using an apo E standard.

Hemorrheological Measurements

The hematocrit was determined after centrifugation with a capillary hematocrit centrifuge (Hettich, Tuttlingen, Germany). PV and BV were measured at 37°C with a Contraves 30 low-shear rotation viscosimeter (Contraves, Zurich, Switzerland) at shear rates continuously increasing from 5/s to 115/s.[27] Temperature was kept constant at 37°C with an automatic heat-control unit, and the actual shear rates were registered automatically by the viscosimeter. BV was determined at native hematocrit (native BV). Standard BV (standardized to a hematocrit of 0.45) was calculated as described previously.[28]

RCA was determined photometrically at native hematocrit using the Myrenne erythrocyte aggregometer (Myrenne, Roetgen, Germany).[29] Measurements were performed at stasis and low shear (3/s) and the temperature was kept constant at 25°C.

The fibrinogen level was measured nephelometrically with the Behring Laser Nephelometer using a specific antibody against human fibrinogen (OSCA 08/09; Behringwerke).

Immediately after centrifugation, plasma was stored at −70°C, and fibrinogen was determined at the end of the study in one assay to exclude assay drifts.

Statistical Analysis

Determination of RCA was conducted in triplicate, and all other laboratory measurements in duplicate. Results are reported as the mean ± SEM. The area under the curve (AUC) was calculated for lipid and hemorrheological parameters on the basis of fasting and six postprandial values (0 to 6 hours). Additionally, the AUC of values obtained by subtracting baseline values from postprandial values (D-AUC) is presented for total and TRL triglycerides. Statistical analyses were performed with the SPSS program (SPSS Software, Munich, Germany) using the paired-sample *t* test with Bonferroni correction. Pearson correlation coefficients were calculated to deter-

mine whether there was a correlation between lipid and hemorrheological parameters, and two-tailed probability is presented as a P value. P less than .05 was considered to indicate statistical significance.

The study was approved by the local ethics committee. Patients were included in the study after provision of written informed consent according to the Declaration of Helsinki.

RESULTS

Lipoprotein Parameters

Patients had familial hypertriglyceridemia as already defined, and six of them had apo E phenotype 3/3, three apo E 4/3, and one apo E 3/2. Lipoprotein parameters at baseline and with gemfibrozil therapy are listed in Table 1. Total and TRL triglycerides at baseline were strongly elevated, and total cholesterol was moderately increased over the normal range due to elevated TRL cholesterol. Baseline LDL and HDL cholesterol were low in these patients.

Total apo B in TRLs was strongly elevated at baseline. Due to the small total amount of apo B-48, it could not be quantified in three patients.

Under a 6-week treatment with gemfibrozil, total triglycerides decreased from 9.53 ± 1.72 to 4.61 ± 1.28 mmol/L ($P < .01$) and TRL triglycerides from 8.21 ± 1.53 to 4.07 ± 1.10 mmol/L ($P < .01$). In TRLs, the concentration of total apo B decreased from 19.0 ± 7.6 to 11.6 ± 2.8 mg/dL and the concentration of apo B-48 by 52% ($P < .05$, respectively).

HDL cholesterol significantly increased with therapy (from 0.67 ± 0.04 to 0.82 ± 0.06 mmol/L, $P < .05$), due to a significant elevation in HDL_3 cholesterol (from 0.55 ± 0.03 to 0.69 ± 0.06 mmol/L, $P < .05$).

Within the observation period of 6 hours, total triglycerides reached the highest concentration at 6 hours postprandially before treatment with gemfibrozil (+52%, $P < .05$) and at 5 hours with treatment (+62%, $P < .05$; Fig 1). The postprandial AUC was reduced from 72.37 ± 10.98 mmol · h/L before therapy to 37.07 ± 5.89 mmol · h/L with gemfibrozil ($P < .005$). However, the D-AUC did not decrease significantly with gemfibrozil therapy (15.20 ± 3.04 *v* 9.43 ± 3.75 mmol · h/L).

Postprandial TRL triglycerides increased 61% ($P < .01$) before and 57% ($P < .05$) after therapy. With gemfibrozil, the postprandial AUC was reduced from 64.13 ± 10.14 to 32.47 ± 5.34 mmol · h/L ($P < .005$); however, the decrease in D-AUC was not significant (14.88 ± 2.71 *v* 8.03 ± 3.02 mmol · h/L). The postprandial increase in TRL total apo B was comparable after (+78%, $P < .05$) and before (+73%, $P < .05$) gemfibrozil.

Table 1. Fasting Lipid Parameters After Decreasing Triglycerides (6 wk) Compared With Baseline

Parameter	Baseline	6 wk
Cholesterol (mmol/L)	6.71 ± 0.41	6.16 ± 0.33
HDL cholesterol (mmol/L)	0.67 ± 0.04	0.82 ± 0.06*
HDL_2 cholesterol (mmol/L)	0.13 ± 0.02	0.12 ± 0.01
HDL_3 cholesterol (mmol/L)	0.55 ± 0.03	0.69 ± 0.06*
LDL cholesterol (mmol/L)	2.34 ± 0.28	3.19 ± 0.25
TRL cholesterol (mmol/L)	3.69 ± 0.59	2.21 ± 0.52
Triglycerides (mmol/L)	9.53 ± 1.72	4.61 ± 1.28†
TRL triglycerides (mmol/L)	8.21 ± 1.53	4.07 ± 1.10†
Apo B in TRL (mg/dL)	19.0 ± 7.6	11.6 ± 2.8*
Apo B-100 in TRL (mg/dL)	15.6 ± 6.8	10.0 ± 2.5
Apo B-48 in TRL (mg/dL)	3.4 ± 1.0	1.6 ± 0.4*

*$P < .05$.
†$P < .01$.

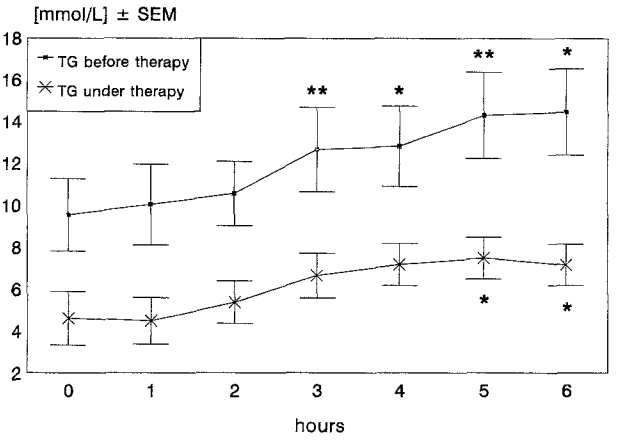

Fig 1. Postprandial plasma triglycerides (TG) after a fat load compared with fasting values (*$P < .05$, **$P < .01$).

At 6 hours, apo B-100 showed similar proportional increases before and after therapy (+64%, $P < .05$, respectively). Apo B-48 increased significantly from 3.4 ± 1.0 to 7.5 ± 2.8 mg/dL at 6 hours postprandially before therapy, and to a lesser extent from 1.6 ± 0.4 to 4.4 ± 1.4 mg/dL with therapy. No significant postprandial changes were found for total, HDL, HDL_2, HDL_3, LDL, and TRL cholesterol. Postprandial lipid parameters at baseline and with gemfibrozil therapy are summarized in Table 2.

Hemorrheological Parameters

Baseline fibrinogen was normal (normal range, 1.5 to 4.0 g/L) in these patients, and PV (normal range, 1.20 to 1.40 mPas) and BV (normal range, 3.5 to 5.0 mPas; shear rate, 93/s; hematocrit, 0.45) as well as RCA (normal range, 3.5 to 5.5 at stasis and 8.0 to 11.0 at shear rate 3/s) were in the upper-normal range.

Fasting hemorrheological parameters did not change significantly with lipid-lowering therapy, with the exception of RCA, which decreased at stasis ($P < .01$) and at a shear rate of 3/s ($P < .05$). Fasting hemorrheological parameters at baseline and after gemfibrozil treatment are shown in Table 3.

Plasma fibrinogen levels, PV, RCA, hematocrit, and native and standard BV did not show any statistically significant postprandial changes before or after the decrease in triglycerides. The postprandial AUC for PV (8.11 ± 0.12 before therapy *v* 7.87 ± 0.13 mPa · min^2 with therapy), for native BV (56.95 ± 1.80 before therapy *v* 53.72 ± 1.74 mPa · min^2 with therapy for shear rate 5/s, 33.73 ± 0.96 *v* 33.02 ± 0.87 mPa · min^2 for shear rate 26/s, and 26.61 ± 0.47 *v* 25.64 ± 0.48 mPa · min^2 for shear rate 93/s), and for standard BV (66.75 ± 1.96 before therapy *v* 65.80 ± 1.68 mPa · min^2 with therapy for shear rate 5/s, 37.96 ± 0.53 *v* 38.75 ± 0.90 mPa · min^2 for shear rate 26/s, and 29.58 ± 0.50 *v* 29.41 ± 0.54 mPa · min^2 for shear rate 93/s) also did not show any significant changes with gemfibrozil therapy. Postprandial hemorrheological parameters at baseline and after gemfibrozil for 0, 3, and 6 hours are summarized in Table 4.

Table 2. Postprandial Lipid Parameters After a Fat Load Before (Baseline) and After (6 wk) Decreasing Triglycerides Compared With Fasting Levels (0 h)

Parameter	Time (h)	Baseline	6 wk
Cholesterol (mmol/L)	0	6.71 ± 0.41	6.16 ± 0.33
	3	6.59 ± 0.42	5.96 ± 0.30
	6	6.72 ± 0.39	5.99 ± 0.31
HDL cholesterol (mmol/L)	0	0.67 ± 0.04	0.82 ± 0.06
	3	0.70 ± 0.08	0.76 ± 0.04
	6	0.65 ± 0.06	0.74 ± 0.03
HDL_2 cholesterol (mmol/L)	0	0.13 ± 0.02	0.12 ± 0.01
	3	0.18 ± 0.07	0.10 ± 0.01
	6	0.15 ± 0.04	0.10 ± 0.01
HDL_3 cholesterol (mmol/L)	0	0.55 ± 0.02	0.69 ± 0.06
	3	0.52 ± 0.03	0.64 ± 0.04
	6	0.51 ± 0.03	0.64 ± 0.04
LDL cholesterol (mmol/L)	0	2.34 ± 0.28	3.19 ± 0.25
	3	2.18 ± 0.26	2.99 ± 0.21
	6	2.12 ± 0.29	3.01 ± 0.19
TRL cholesterol (mmol/L)	0	3.69 ± 0.59	2.21 ± 0.52
	3	3.74 ± 0.64	2.21 ± 0.51
	6	4.05 ± 0.62	2.43 ± 0.49
Triglycerides (mmol/L)	0	9.53 ± 1.72	4.61 ± 1.28
	1	10.03 ± 1.92	4.49 ± 1.11
	2	10.56 ± 1.53	5.38 ± 1.01
	3	12.66 ± 2.02†	6.65 ± 1.06
	4	12.82 ± 1.92*	7.18 ± 1.01
	5	14.30 ± 2.07†	7.49 ± 1.00*
	6	14.47 ± 2.07*	7.17 ± 0.99*
TRL triglycerides (mmol/L)	0	8.21 ± 1.53	4.07 ± 1.10
	1	8.57 ± 1.56	4.07 ± 0.99
	2	9.72 ± 1.55†	4.76 ± 0.87
	3	10.79 ± 1.74†	5.76 ± 0.97
	4	11.75 ± 1.91†	6.28 ± 0.90*
	5	12.60 ± 2.00†	6.39 ± 0.88*
	6	13.20 ± 1.95†	6.35 ± 0.98*
Apo B in TRL (mg/dL)	0	19.0 ± 7.6	11.6 ± 2.8
	3	20.1 ± 6.9	18.6 ± 5.4
	6	33.0 ± 12.5*	20.7 ± 5.0*
Apo B-100 in TRL (mg/dL)	0	15.6 ± 6.8	10.0 ± 2.5
	3	14.9 ± 5.2	14.9 ± 4.5
	6	25.5 ± 9.8*	16.4 ± 4.0*
Apo B-48 in TRL (mg/dL)	0	3.4 ± 1.0	1.6 ± 0.4
	3	5.3 ± 1.8	3.8 ± 1.1
	6	7.5 ± 2.8*	4.4 ± 1.4*

*$P < .05$.
†$P < .01$.

Correlations

The increase in HDL cholesterol after gemfibrozil therapy was inversely correlated with the extent of the decrease in total triglycerides ($r = -.76$, $P = .012$) and in TRL triglycerides ($r = -.72$, $P = .02$). However, there were no statistically significant correlations between the improvement of lipid parameters and changes in hemorrheology.

No correlations were found between postprandial changes of lipid parameters and hemorrheology either before or after lipid-lowering therapy.

DISCUSSION

In the present study, the postprandial metabolism of lipids and its effect on hemorrheology was investigated in patients with familial hypertriglyceridemia before and after lipid-lowering therapy with gemfibrozil.

Table 3. Fasting Hemorrheological Parameters After Decreasing Triglycerides (6 wk) Compared With Baseline

Parameter	Baseline	6 wk	Normal Range
Hematocrit	0.43 ± 0.01	0.43 ± 0.01	0.37-0.50
PV (mPas)	1.39 ± 0.03	1.33 ± 0.03	1.20-1.40
Native BV (mPas)			
$5 \cdot s^{-1}$	10.05 ± 0.30	10.56 ± 1.37	7.0-12.0
$26 \cdot s^{-1}$	5.97 ± 0.18	6.27 ± 0.57	5.0-7.0
$93 \cdot s^{-1}$	4.67 ± 0.11	4.84 ± 0.43	3.5-5.0
Fibrinogen (g/L)	1.96 ± 0.19	1.89 ± 0.24	1.5-4.0
RCA			
M	5.52 ± 0.53	4.84 ± 0.39†	3.5-5.5
M1	11.07 ± 0.76	9.67 ± 0.68*	8.0-11.0

*$P < .05$.
†$P < .01$.

Triglycerides of ingested fat are hydrolyzed in the intestine and absorbed as free fatty acids or monoglycerides. After triglyceride resynthesis in mucosa cells, chylomicrons are secreted into the lymph within 1 hour postprandially.[30] Chylomicrons and chylomicron remnants can be quantified after the release into blood by measuring their main apolipoprotein component, apo B-48. In healthy subjects, the maximum concentration of apo B-48 is reached $3^{31,32}$ to 4^{33} hours postprandially, while no chylomicrons[30] or, at most, traces of chylomicrons[31] are present at 6^{31} and 8^{33} hours postprandially. However, in hypertriglyceridemic patients, clearance of chylomicrons and chylomicron remnants is delayed.[31] This is in good

Table 4. Postprandial Hemorrheological Parameters After a Fat Load Before (Baseline) and After (6 wk) Decreasing Triglycerides Compared With Fasting Level (0 h)

Parameter	Time (h)	Baseline	6 wk
Hematocrit	0	0.43 ± 0.01	0.43 ± 0.01
	3	0.42 ± 0.01	0.42 ± 0.01
	6	0.42 ± 0.01	0.41 ± 0.01
PV (mPas)	0	1.39 ± 0.03	1.33 ± 0.03
	3	1.35 ± 0.02	1.31 ± 0.02
	6	1.34 ± 0.02	1.31 ± 0.02
Native BV (mPas)			
$5 \cdot s^{-1}$	0	10.05 ± 0.30	10.56 ± 1.37
	3	9.42 ± 0.34	8.86 ± 0.33
	6	9.53 ± 0.43	8.10 ± 0.54
$26 \cdot s^{-1}$	0	5.97 ± 0.18	6.27 ± 0.57
	3	5.57 ± 0.18	5.40 ± 0.17
	6	5.51 ± 0.15	5.12 ± 0.29
$93 \cdot s^{-1}$	0	4.67 ± 0.11	4.84 ± 0.43
	3	4.41 ± 0.10	4.23 ± 0.08
	6	4.31 ± 0.13	4.08 ± 0.17
Fibrinogen (g/L)	0	1.96 ± 0.19	1.89 ± 0.24
	3	2.13 ± 0.22	1.93 ± 0.12
	6	2.05 ± 0.16	1.92 ± 0.15
RCA			
M	0	5.52 ± 0.53	4.84 ± 0.39
	3	5.37 ± 0.42	4.68 ± 0.45
	6	5.32 ± 0.38	4.52 ± 0.47
M1	0	11.07 ± 0.76	9.67 ± 0.68
	3	10.27 ± 0.80	8.95 ± 0.75
	6	10.31 ± 0.79	8.41 ± 0.69

agreement with our results, where apo B-48 levels increased until 6 hours postprandially. The greater proportional increase of apo B-48 versus apo B-100 in the first 3 hours was followed by an equal increase between 3 and 6 hours postprandially.

The effects of gemfibrozil on lipid metabolism resulting in reduced triglyceride and apo B concentrations in TRLs have been investigated by several groups.[32,34-36] Studies showed an increase in lipoprotein lipase (LPL) activity in postheparin plasma during therapy in moderate hypertriglyceridemics[36] and in healthy subjects.[34] One explanation for this might be a diminished hepatic production of the LPL inhibitor apo C-III, which is induced by fibrates through activation of the peroxisome proliferator–activated receptor.[37] Shepherd et al[38] found the apo B residence time in VLDL to be decreased under bezafibrate, concluding that the efficiency of delipidation was improved. However, other investigations did not show an elevation in LPL activity with gemfibrozil.[33,35] Simsolo et al[35] suggested that there was a decrease in hepatic VLDL secretion, because no changes in LPL activity were observed with gemfibrozil therapy despite a 46% reduction in triglycerides.

Our data support the latter hypothesis rather than a faster clearance of TRL with therapy, because TRL triglycerides and apo B showed comparable relative increases postprandially.

In our patients, the decrease in fasting triglycerides with therapy was inversely correlated with the increase in HDL cholesterol. An increase in HDL cholesterol has been a constant finding in hypertriglyceridemic patients treated with gemfibrozil due to an increasing synthesis of apo A-I and A-II.[36,39] The increase in HDL_3 cholesterol mainly contributes to this elevation in total HDL cholesterol in our study and previous reports.[40,41]

HDL cholesterol has been reported to be a possible link between dyslipoproteinemias and impaired flow properties. HDL cholesterol has been inversely correlated with fibrinogen levels[7,8] and with RCA,[6,42] although this relation has particularly been shown for HDL_2 cholesterol.[6] In our study, fasting RCA decreased under therapy, although the inverse correlation with increasing HDL cholesterol levels did not reach significance ($r = -.53$, $P = .14$).

Other hemorrheological parameters, especially fibrinogen and BV, did not significantly change with gemfibrozil therapy. This is interesting, because it has been a matter of discussion as to whether there is a correlation between fasting triglyceride levels and fibrinogen[43,44] or not.[45,46] According to a recent investigation in combined hyperlipoproteinemia,[16] we did not find a correlation between baseline or decreased triglycerides and fibrinogen despite high baseline levels of triglycerides and a marked reduction under therapy. Recently, we showed that there was no association between triglycerides and fibrinogen even in patients with chylomicronemia (triglycerides > 12 mmol/L).[15] However, hemorrheology is impaired in patients with chylomicronemia. We found PV and BV to be elevated in these patients and decreased when triglycerides were decreased by fish oil therapy.[15] Other investigations reported microcirculatory disturbances in patients with chylomicronemia.[47]

In the present study, neither before nor after lipid-lowering fibrinogen did PV or BV postprandially increase despite increasing triglycerides. Only a few and controversial results concerning postprandial rheological changes after a fat load have been reported. In one investigation of healthy volunteers, RCA and PV increased postprandially while fibrinogen remained unchanged.[14] Others did not find any changes in RCA but found a postprandial elevation of fibrinogen of 60% and of PV,[13] but these changes were not correlated with triglyceride levels.

Thus, in patients with strongly elevated triglycerides or chylomicronemia, enhanced PV and BV, probably responsible for microcirculatory disturbances, seem to be due to triglycerides and independent of fibrinogen levels. The PV and BV in the upper-normal range found in the present study may be due to the fact that a threshold for triglyceride concentration for which flow properties are impaired was not reached. This is in good agreement with a recent investigation in which we found normal hemorrheological parameters in patients with familial hypertriglyceridemia (mean triglyceride concentration, 7.44 mmol/L).[19]

In conclusion, we found an improved postprandial apo B metabolism in TRLs after decreasing fasting triglycerides. No changes in hemorrheology accompanying this improvement were observed, with the exception of a reduction in RCA. This decrease in RCA might be due to an elevation in HDL cholesterol. Since PV and BV showed no statistically significant postprandial changes, we suggest that the extent of the postprandial triglyceride increase in patients with familial hypertriglyceridemia is not great enough to have an adverse effect on hemorrheology. Therefore, gemfibrozil had no substantial advantages with respect to hemorrheology in these patients.

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