Hemorrheologic Abnormalities in Defined Primary Dyslipoproteinemias With Both High and Low Atherosclerotic Risks

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Dyslipoproteinemias are associated with hemorrheologic abnormalities (elevated fibrinogen concentration, higher viscosity of plasma and blood). Epidemiologic data suggest that not only elevated lipoprotein concentrations (eg, low-density lipoprotein [LDL] cholesterol), but also hemorrheologic abnormalities could causally be involved in the atherosclerotic process. To elucidate potential effects of hemorrheological disturbances, we investigated patients suffering from primary hyperlipoproteinemias with both low (familial hypertriglyceridemia, n = 25) and high (type III hyperlipoproteinemia, n = 21; familial hypercholesterolemia, n = 19; mixed hyperlipoproteinemia, n = 19) atherosclerotic risk, as well as healthy controls (n = 49) in a cross-sectional design. Dyslipoproteinemias were classified by lipoprotein measurements (using ultracentrifugation), family history, and apolipoprotein E phenotype. Hemorrheology was characterized by the measurement of fibrinogen concentration, viscosity of plasma and blood at different shear rates, and red cell aggregation (RCA) at stasis and low shear. Fibrinogen concentration was lower in controls (2.38 ± 0.09 g/L) compared with familial hypercholesterolemia (3.19 ± 0.19 g/L), to type III hyperlipoproteinemia (3.02 ± 0.12 g/L), to familial hypertriglyceridemia (2.95 ± 0.21 g/L) and to mixed hyperlipoproteinemia (3.01 ± 0.12 g/L) (*P* < .05, respectively) without differences between dyslipoproteinemia groups. Plasma viscosity was higher in patients with type III hyperlipoproteinemia (1.42 ± 0.03 mPas), with familial hypertriglyceridemia (1.47 ± 0.04 mPas), and with mixed hyperlipoproteinemia (1.43 ± 0.02 mPas) compared with controls (1.29 ± 0.01 mPas) (*P* < .05, respectively). After including 6 lipoprotein parameters in a general linear model, plasma viscosity, blood viscosity, and RCA were higher in familial hypertriglyceridemia compared with healthy controls and familial hypercholesterolemia (*P* < .05, respectively). As most of the hemorrheologic abnormalities were still significant after adjusting for lipoprotein concentrations, they seem to be at least partly independent from direct lipoprotein effects. Hemorrheologic abnormalities in familial hypertriglyceridemia (low atherosclerotic risk) were at least as marked as in dyslipoproteinemias with high atherosclerotic risk, suggesting that it might be most important to determine lipoprotein concentrations and to define exactly the type of dyslipoproteinemia for estimating the individual cardiovascular risk in these patients.

LARGE EPIDEMIOLOGIC STUDIES have established dyslipoproteinemias as important risk factors for atherosclerotic diseases.[1,2] High concentrations of total and low-density lipoprotein (LDL) cholesterol,[1,2] as well as triglycerides,[3] were especially correlated with an increased risk of atherosclerosis. Additionally, the reduction of total cholesterol and LDL cholesterol concentrations was shown to substantially decrease cardiovascular and total mortality.[4,5]

Despite new insights in the pathogenesis of atherosclerosis within the last years, the pathophysiology of the atherosclerotic process has not yet been completely understood. Epidemiologic data suggest that hemorrheologic parameters could causally be involved in the formation of atherosclerotic plaques and thrombi, because fibrinogen concentration,[6,7] plasma viscosity,[8,9] and blood viscosity[10,11] were identified as independent atherosclerotic risk indicators.

In epidemiologic studies, lipoprotein concentrations were associated with hemorrheologic parameters. Koenig et al[12] found plasma viscosity to be linearly correlated with total cholesterol and apolipoprotein B and inversely correlated with high-density lipoprotein (HDL) cholesterol and apolipoprotein A-I. Other investigations show positive associations between plasma viscosity and triglycerides, as well as total cholesterol.[13,14] Leonhardt et al[15] investigated patients with the hyperlipoproteinemias type IIa, IIb, and IV. Mean plasma viscosity was highest in subjects with type IIb, followed in descending order by type IV, type IIa, and healthy controls. However, it is not known if beyond the effects of the lipoproteins themselves, these hemorrheologic disturbances have any additional effect on the course of the atherosclerotic process in patients with dyslipoproteinemias.

While some lipid disorders with elevated concentrations of cholesterol and/or triglycerides are at particular high risk for atherosclerosis complications, eg, type III hyperlipoproteinemia (type III HLP, familial dysbetalipoproteinemia)[16] and familial hypercholesterolemia (FH),[17] others do not seem to have a substantially elevated risk compared with healthy controls, eg, familial hypertriglyceridemia (FHTG)[18,19] and chylomicronemia.[18,19] Therefore, it is important not only to measure lipoprotein concentrations, but also to define the lipoprotein disorder to estimate cardiovascular risk.

To elucidate the potential effects of hemorrheologic abnormalities on atherosclerosis in patients with primary dyslipoproteinemias, we investigated dyslipidemic patients with both low FHTG and high (FH, type III HLP, primary mixed hyperlipoproteinemia [MHLP]) atherosclerotic risk, as well as control subjects with normal lipoprotein concentrations. In contrast to previous studies, we did not classify patients according to their dyslipoproteinemic phenotype, but according to criteria for defined, primary dyslipoproteinemias to investigate if patients suffering from dyslipoproteinemias with high atherosclerotic risk had more distinct, hemorrheologic abnormalities than patients suffering from dyslipoproteinemias with low atherosclerotic risk than controls.

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PATIENTS AND METHODS

We investigated 133 subjects (84 patients with primary dyslipoproteinemias and 49 healthy controls) in a cross-sectional design after informed consent was given according to the Declaration of Helsinki. Exclusion criteria were smoking, diabetes mellitus, chronic liver or renal disease, and hypothyroidism. Patients with unstable angina pectoris or a history of myocardial or cerebral infarction were not included. None of the patients was actually treated with any lipid-lowering drugs. The wash out phase after lipid-lowering therapy was at least 6 weeks.

Nineteen patients (6 women, 13 men; mean age, 42.9 ± 3.2 years; body-mass-index [BMI], 25.0 ± 0.6 kg/m^2) suffered from heterozygous FH. Diagnosis was established by markedly elevated LDL cholesterol concentration (>5.5 mmol/L) and normal triglycerides (<2.28 mmol/L), as well as at least 1 relative with markedly elevated LDL cholesterol or premature atherosclerosis.

Twenty-one patients (3 women, 18 men; mean age, 47.2 ± 2.4 years; BMI, 25.8 ± 0.6 kg/m^2) had type III HLP, which was diagnosed by determination of the apolipoprotein E phenotype (E2/E2) in patients with mixed hyperlipoproteinemia (total cholesterol concentration > 5.18 mmol/L and triglyceride concentration > 2.28 mmol/L).

Twenty-five patients (5 women, 20 men; mean age, 45.8 ± 2.1 years; BMI, 26.3 ± 0.9 kg/m^2) suffered from FHTG. Concentrations of triglycerides were greater than 3.20 mmol/L and LDL cholesterol less than 4.14 mmol/L in all patients. The diagnosis was established by obtaining the family history (at least 1 member of the family had hypertriglyceridemia) and by excluding type III HLP.

Nineteen patients (9 women, 10 men; mean age, 50.4 ± 3.1 years; BMI, 27.1 ± 1.0 kg/m^2) had MHLP, which was diagnosed by elevated LDL cholesterol concentrations (>4.14 mmol/L) and elevated triglyceride concentrations (>2.28 mmol/L) by excluding type III HLP. Forty-nine healthy subjects (22 women, 27 men; mean age, 38.9 ± 1.6 years; BMI, 23.9 ± 0.4 kg/m^2) served as controls. All of them had triglyceride concentrations less than 2.28 mmol/L and LDL cholesterol concentrations less than 4.14 mmol/L, as well as no family history for dyslipoproteinemias.

Blood was collected after an overnight fast from an antecubital vein in the sitting position in EDTA tubes (2.0 mg K_3 EDTA/mL blood; Greiner, Frickenhausen, Germany). Viscosity and red cell aggregation (RCA) measurements were conducted within 4 hours after blood collection. Hematocrit was determined after centrifugation using a capillary hematocrit centrifuge (Hettich, Tuttlingen, Germany). Platelet-poor plasma was obtained by centrifuging EDTA blood (3,000 rpm for 15 minutes).

Whole blood viscosity was measured at 37°C with a Contraves 30 low shear rotation viscosimeter (Contraves AG, Zurich, Switzerland) at shear rates continuously increasing from 5/s to 115/s, plasma viscosity was measured at 115/s.[20] Temperature was kept constant at 37°C with an automatic heating control unit, the actual shear rates were scanned by the viscosimeter. Rotation viscosimetry has been criticized recently because it may not reflect the 3-dimensional nature of a natural vessel (because blood is investigated as a thin film between 2 surfaces preventing the development of erythrocyte aggregates to their fullest extent).[21] However, rotation viscosimetry was used in most clinical studies evaluating cardiovascular risk and is therefore very well evaluated compared with lesser established methods (eg, capillary viscometry). In the results, whole blood viscosity at 3 representative shear rates (low shear, 5/s; medium shear, 26/s; and high shear, 93/s) is given. Blood viscosity and red blood cell aggregation were determined after standardization of the hematocrit to 0.45 with autologous plasma or autologous erythrocytes. RCA was determined at 0.45 hematocrit photometrically using the Myrenne erythrocyte aggregometer MA1 (Myrenne GmbH, Roetgen, Germany)[22] at stasis and low shear (3/s). When measured at low shear, RCA is enhanced compared with stasis because of an activation of erythrocytes by gravitation.

Fibrinogen concentration was measured nephelometrically (Behringwerke AG, Marburg, Germany) using the Behring Nephelometer (Behringwerke AG) with specific antibodies against human fibrinogen (OSCA 08/09, Behringwerke AG). The nephelometric assay not only detects fibrinogen, but also fragments of fibrin and fibrinogen. However, because the concentration of fragments in nonthromboembolic and noninflammatory conditions is very low (fragments < .001 g/L, D-dimer < .005 g/L), these fibrinogen-related components should have no significant influence on our determinations.

Very low-density lipoproteins (VLDL) were separated by ultracentrifugation (50,000 rpm, 20 hours, 4°C, Beckman rotor Ti 50, d = 1.006 g/mL). HDL cholesterol concentration was measured in the infranatant after heparin-manganese precipitation of LDL.[23] LDL cholesterol concentration was obtained by subtracting HDL cholesterol from total infranatant cholesterol. Triglycerides and cholesterol in plasma and lipoprotein fractions were measured enzymatically using an autoanalyzer (EPOS Autoanalyzer, Eppendorf, Hamburg, Germany). Apolipoprotein E phenotype was determined by isoelectric focusing.[24]

Determination of RCA was conducted in triplicate; all other laboratory measures in duplicate. The results are reported as mean values ± standard error of mean (SEM). In the statistical analysis, first anthropometric variables were compared between different dyslipoproteinemias with the Kruskal Wallis test using SPSS/PC+ (SPSS Software GmbH, Munich, Germany). Analysis of variance was then performed with SAS (SAS Institute Inc, Cary, NC) using a general linear model adjusted with the Scheffe's test. To test differences in hemorrheologic parameters between groups, covariates were included in the model: anthropometric variables in a first step, lipoprotein parameters in a second step. *P* values less than .05 were considered to indicate statistical significance.

RESULTS

Patients with type III HLP, FHTG, and MHLP were older than healthy controls ($P < .05$), and patients with MHLP had a greater BMI compared with control subjects ($P < .05$). Lipoprotein parameters in dyslipoproteinemic groups are presented in Table 1, hemorrheologic parameters in Table 2. In patients with FHTG, triglyceride concentration was well cor-

Table 1. Lipoprotein Parameters in Healthy Controls and Dyslipoproteinemias

	Controls (n = 49)	FH (n = 19)	Type III HLP (n = 21)	FHTG (n = 25)	MHLP (n = 19)
Total cholesterol (mmol/L)	5.14 ± 0.11	9.62 ± 0.37	9.09 ± 0.65	9.49 ± 1.27	9.18 ± 0.38
LDL cholesterol (mmol/L)	3.28 ± 0.12	7.72 ± 0.38	3.15 ± 0.28	2.24 ± 0.24	6.10 ± 0.27
HDL cholesterol (mmol/L)	1.34 ± 0.05	1.18 ± 0.08	1.03 ± 0.09	0.76 ± 0.05	1.06 ± 0.04
VLDL cholesterol (mmol/L)	0.50 ± 0.09	0.72 ± 0.11	5.44 ± 0.76	5.13 ± 0.68	2.16 ± 0.26
Total triglycerides (mmol/L)	1.11 ± 0.08	1.49 ± 0.16	5.51 ± 0.78	15.36 ± 4.46	3.69 ± 0.45
VLDL triglycerides (mmol/L)	0.87 ± 0.09	1.16 ± 0.18	4.73 ± 0.66	9.81 ± 1.45	3.39 ± 0.21

Table 2. Hemorrheologic Parameters in Healthy Controls and Dyslipoproteinemias

	Controls (n = 49)	FH (n = 19)	Type III HLP (n = 21)	FHTG (n = 25)	MHLP (n = 19)
Fibrinogen (g/L)	2.38 ± 0.09	3.19 ± 0.19*	3.02 ± 0.12*	2.95 ± 0.21*	3.01 ± 0.12*
Plasma viscosity (mPas)	1.29 ± 0.01	1.34 ± 0.03	1.42 ± 0.03*	1.47 ± 0.04*†	1.43 ± 0.02*
Hematocrit	0.42 ± 0.01	0.43 ± 0.01	0.43 ± 0.01	0.43 ± 0.01	0.44 ± 0.01
BV shear 5/s (mPas)	8.48 ± 0.13	8.11 ± 0.41	10.15 ± 0.61*†	10.54 ± 0.37*†	10.94 ± 0.58*†
BV shear 26/s (mPas)	5.90 ± 0.06	6.12 ± 0.13	6.55 ± 0.16*	6.48 ± 0.15*	6.48 ± 0.27
BV shear 93/s (mPas)	4.55 ± 0.05	4.72 ± 0.09	5.03 ± 0.09*	5.12 ± 0.10*	4.94 ± 0.16*
RCA (stasis) (U)	3.66 ± 0.14	4.04 ± 0.21	4.95 ± 0.30*	5.70 ± 0.28*†	4.73 ± 0.21*
RCA (3/s) (U)	9.05 ± 0.27	9.22 ± 0.40	10.39 ± 0.50	11.09 ± 0.34*†	10.48 ± 0.38*

Abbreviation: BV, whole blood viscosity.

* $P < .05$ compared with controls.

† $P < .05$ compared with FH, after adjustment for age, sex, and BMI.

related with fibrinogen concentration ($r = .63$, $P < .001$) and with plasma viscosity ($r = .81$, $P < .001$).

The general linear model including age, sex, and BMI showed lipoprotein differences between groups independent from these anthropometric variables with the exception of HDL cholesterol concentration, which was dependent on sex with higher concentrations in women (F value, 5.10; $P = .026$) and on BMI with higher concentrations in leaner subjects (F value, 6.73; $P = .011$). Hemorrheologic differences between groups were independent of age, sex, and BMI, except RCA at stasis, which depended on BMI with higher RCA in obese subjects (F value, 8.25; $P = .005$). The statistical comparisons of hemorrheologic parameters after adjustment for age, sex, and BMI are presented in Table 2. Hematocrit did not differ significantly between the dyslipoproteinemias and controls. However, type III HLP, FHTG, and MHLP had statistically significant abnormalities compared with healthy controls. Additionally, FHTG had a higher plasma viscosity and blood viscosity at low shear, as well as a higher RCA compared with FH ($P < .05$, respectively).

To assess the influence of lipoprotein concentrations on hemorrheologic differences between groups, subsequently, all lipoprotein parameters (concentration of total, LDL, HDL, and VLDL cholesterol, total and VLDL triglycerides) were additionally included in the general linear model. RCA at stasis depended on HDL cholesterol concentration (F value, 4.32; $P = .04$). The differences between groups concerning whole blood viscosity at higher shear rates (26/s and 93/s), as well as RCA at low shear (3/s) were no longer statistically significant. Fibrinogen concentration was significantly higher in patients with FH, type III HLP, and with MHLP compared with healthy subjects. Plasma viscosity was higher in patients with type III HLP, FHTG, and with MHLP in comparison with healthy subjects. In addition, plasma viscosity was increased in patients with FHTG and with type III HLP ($P < .05$, respectively) compared with FH patients. In patients with FHTG, RCA at stasis was enhanced compared with healthy controls, FH patients, and to patients with MHLP. Blood viscosity at low shear was lower in healthy subjects and in patients with FH in comparison with patients with type III HLP, FHTG, and with MHLP ($P < .05$, respectively).

DISCUSSION

In the present study, we found primary dyslipoproteinemias to be associated with hemorrheologic abnormalities, most of these abnormalities were independent of lipoprotein concentrations. In contrast to previous studies,[15] we did not classify patients according to the dyslipoproteinemic phenotype, but according to accepted criteria for defined primary dyslipoproteinemias. To our knowledge, this is the first study on hemorrheologic parameters in differently defined dyslipoproteinemias using this approach.

Epidemiologically, fibrinogen concentration was shown to weakly correlate with LDL cholesterol levels in postmenopausal women,[25] and in middle-aged men with[26] and without[27] coronary artery disease. In our study, dyslipoproteinemias with elevated LDL cholesterol concentrations (FH and MHLP) had higher fibrinogen levels compared with controls, which is in good agreement with a study from Jay et al,[28] who reported elevated fibrinogen concentrations in patients with familial hypercholesterolemia compared with controls. The reason for elevated fibrinogen concentration in these patients might be an incipient, subclinical atherosclerosis, which is known to be associated with elevated fibrinogen levels.[29,30] However, those dyslipoproteinemias with normal LDL cholesterol levels, but elevated triglyceride concentrations (type III HLP and FHTG), had higher fibrinogen concentrations than control subjects. The association of triglyceride and fibrinogen concentration is discussed controversially by other investigators. While some investigations found no association of triglycerides and fibrinogen,[31] others showed a weak positive correlation of both parameters[32] or even an inverse correlation between triglyceride and fibrinogen concentration.[33] The very strong positive correlation of triglyceride and fibrinogen concentration in FHTG in our study might be the result of a homogenous group with a defined, primary hypertriglyceridemia.

Compared with healthy controls, plasma viscosity was significantly increased in those dyslipoproteinemias with elevated triglyceride concentrations even after correction for triglyceride concentration. The direct effects of VLDL on plasma viscosity have been a matter of discussion. While in patients with marked hypertriglyceridemia (eg, chylomicronemia) plasma viscosity can be lowered by reducing plasma triglyceride concentration,[34] we did not observe a significant reduction in plasma

viscosity when moderately elevated triglycerides were lowered by 52% with gemfibrozil in patients with FHTG.[35] In contrast, Stein and Rosenson[36] showed a small, but statistically significant reduction not only in plasma viscosity (−5.2%), but also in serum viscosity (−6.1%) in moderately hypertriglyceridemic patients when triglycerides were lowered by 70%. However, recently we found plasma viscosity in patients with FHTG to be elevated due to concomitantly increased fibrinogen concentrations independent from triglycerides, because plasma viscosity became normal when fibrinogen was removed from hypertriglyceridemic samples in vitro.[37] Therefore, we are convinced that the "hypertriglyceridemia-associated effect" (eg, via concomitantly increased fibrinogen concentration) seems to be at least as pronounced as the direct effect of VLDL on plasma viscosity in patients with FHTG.

Despite an epidemiologic association of LDL cholesterol with plasma viscosity,[38] the direct effect of LDL cholesterol concentration on plasma viscosity seems to be even less than the effect of triglycerides. Physiologic concentrations of LDL had no effect on plasma viscosity in vitro,[14,15] only very high LDL cholesterol concentrations (>18 mmol/L) induced a marginal increase in plasma viscosity from 1.22 to 1.24 mm^2/s.[15] Therefore, the epidemiologic association between plasma viscosity and LDL cholesterol concentration seems to be at least partly independent from LDL cholesterol concentrations.

After correction for anthropometric data and lipoprotein concentrations, blood viscosity was elevated in patients suffering from the hypertriglyceridemic dyslipoproteinemias FHTG, type III HLP, and MHLP compared with controls and with patients with FH. Higher fibrinogen levels and higher plasma viscosity in type III HLP, FHTG, and MHLP might be partly responsible for these differences in blood viscosity between groups. However, it seems more probable that higher blood viscosity is mainly due to enhanced RCA in these patients, because differences in blood viscosity were statistically significant only at low shear (where RCA is the main determinant of blood viscosity) and not at high shear (where red cell deformability and plasma viscosity are the most important determinants of blood viscosity).

RCA was highest in patients with FHTG, but MHLP and type III HLP patients had also increased aggregability of red cells compared with controls. RCA has been supposed as a possible link between lipoprotein disorders and abnormal hemorrheology, because it is known to be inversely correlated with HDL cholesterol concentration. RCA decreased when HDL cholesterol concentration was raised in summer[39] or when HDL cholesterol increased after drug therapy with gemfibrozil[35] or with acipimox.[40] A possible explanation for this association was suggested by Sloop and Garber[21]: Large particles (>25 nm, eg, fibrinogen, LDL) simultaneously bind to receptors on the surface of 2 erythrocytes, and this bridging induces erythrocyte aggregation. HDL particles (5 to 12 nm), which are too small for bridging, might bind to these receptors resulting in a reduced binding of larger molecules and a decreased erythrocyte aggregation. According to this, the general linear model showed RCA at stasis to be dependent on HDL cholesterol concentration in our study. Patients suffering from dyslipoproteinemias with low HDL cholesterol concentrations (FHTG, type III HLP, MHLP) had higher RCA compared with controls. The impact of an isolated elevated red cell aggregability is not clear so far, but it seems to be a risk marker for the outcome in atherosclerotic diseases. It was shown to be higher in patients with unstable angina pectoris compared with patients with stable angina pectoris,[41] and it identified those patients with unstable angina pectoris who were at high risk for myocardial infarction.[42]

In summary, we found hemorrheologic parameters (plasma viscosity, blood viscosity, RCA) highest in those patients with elevated triglyceride concentrations, while in FH, these parameters did not differ from healthy controls. Fibrinogen concentration was the only hemorrheologic parameter, which was increased in FH patients. The present results suggest that fibrinogen concentration might be the best hemorrheologic risk marker, because after correcting for lipoprotein concentrations, it was elevated only in those dyslipoproteinemias with a substantial cardiovascular risk (FH, type III HLP, MHLP). The other hemorrheologic parameters were highest in patients with FHTG, a dyslipoproteinemia without a definitely increased risk for atherosclerosis.[18] Therefore, despite the epidemiologic association of these rheological parameters with atherosclerotic risk, it seems more reasonable to measure lipoprotein concentrations and to define exactly the type of dyslipoproteinemia to estimate cardiovascular risk. However, the routine measurement of additional rheological parameters (viscosity, RCA) seems to have no additional benefit in estimating the individual atherosclerotic risk in these patients.

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