Association Between Rheology and Components of Lipoproteins in Human Blood
Results From the MONICA Project

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Background. Recent studies have suggested that several hemostatic factors, leukocyte count, and plasma viscosity are predictive of coronary heart disease. Detailed analyses on lifestyle correlates, in particular plasma lipids and lipoproteins, of determinants of blood rheology have not been reported from epidemiological studies.

Methods and Results. We studied the relation between determinants of blood rheology and components of lipoproteins in a large sample of a population aged 25–64 years. The rheological parameters investigated were plasma viscosity, hemoglobin, and total serum protein; the lipoprotein variables included total cholesterol, high density lipoprotein (HDL) cholesterol, and the apoproteins A-I, A-II, and B. Covariates considered for possible confounding effects were age, body mass index, smoking behavior, alcohol consumption, and hypertension. Plasma viscosity was found to have a positive linear association with total cholesterol and apoprotein B (partial correlations after adjustment for all covariables including total serum protein for men and women were r=0.23/0.19 and 0.24/0.25, respectively) and a small negative linear association with HDL cholesterol (r=-0.14/-0.10) and with apoprotein A-I (r=-0.08/-0.06). Polynomial regression showed a strong quadratic relation with HDL cholesterol in men, whereas no other variable revealed an appreciable deviation from linearity. The covariables had only a small, if any, confounding effect. Total serum protein, after control for the covariables, appeared to be associated only with total cholesterol. No association was found with hemoglobin.

Conclusions. We conclude that rheological mechanisms may be involved in the pathogenesis of ischemic syndromes in hyperlipidemias. However, the finding that in particular men with very low HDL cholesterol exhibit increased plasma viscosity cannot be explained in pure rheological terms but may be, at least in part, the result of concomitant hypertriglyceridemia. This was not assessed in this study. (Circulation 1992;85:2197–2204)

Key Words • viscosity, plasma • hemoglobin • cholesterol • apolipoproteins • serum protein, total

Total cholesterol is a well-established primary risk factor for coronary heart disease (CHD) in asymptomatic persons as well as in patients after a first myocardial infarction.1–3 There is increasing evidence that low density lipoprotein (LDL) cholesterol and possibly also its apoprotein B moiety predict coronary events more accurately than total cholesterol.4–6 Increased high density lipoprotein (HDL) cholesterol (HDL C) is associated with improved prognosis in CHD and may exert a protective role.7,8

Data from the Northwick Park study,9 the Gothenburg study,10 and also from the Framingham cohort11 demonstrated a significant association between total cholesterol and fibrinogen. Moreover, according to results from these cohorts, elevated plasma fibrinogen levels may be regarded as an independent cardiovascular risk factor.9–11

Recently published data from the Caerphilly and Speedwell Collaborative Heart Disease Studies12 suggest that increased plasma viscosity also carries an independent risk for subsequent manifestations of CHD.

It is widely accepted that plasma viscosity (which is closely related to fibrinogen levels) can determine volume flow in a given vascular bed, in particular on the microcirculatory level. Increased plasma viscosity (or blood viscosity) may further enhance the risk of thrombus formation.

It is, therefore, of interest to investigate the interaction between hemorheological/hemostatic variables and established cardiovascular risk factors. However, de-
talled analyses on the relation between determinants of blood rheology (e.g., plasma viscosity) on one hand and components of plasma lipoproteins on the other hand have not yet been reported from epidemiological studies. The present study, therefore, analyzes the associations of total cholesterol, HDL C, and the apoproteins A-I, A-II, and B with hemorheological variables (in particular, plasma viscosity) in a large sample of a population.

Methods

Study Design and Subjects

The MONICA project (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) is a World Health Organization (WHO)–coordinated, observational long-term study. Its main objective is to measure trends in cardiovascular mortality and morbidity and to assess the extent to which these trends are related to changes in risk factor levels and/or medical care, measured at the same time in different communities in different countries. The present analysis was performed on data from the first cross-sectional study of the MONICA (Augsburg, FRG) center in 1984 and 1985. The study population, sampling frame, and data collection have been reported previously. Briefly, 4,022 of the 5,312 potentially eligible individuals, aged 25–64 years, initially sampled at random (two-stage, age/sex-stratified cluster sampling) from a study population of 282,279 inhabitants of a mixed urban/rural area participated in the study.

In 79% (n = 3,175) of participants, all three rheological variables could be measured. Further exclusion criteria for the present analysis were history of stroke, myocardial infarction, or angina pectoris (n=239); chronic obstructive pulmonary disease (n=42); diabetes mellitus (n=82); rheumatoid disorders; or other acute or chronic inflammatory disorders and malignant diseases as determined by questionnaire (n=380). Use of lipid-lowering drugs or other medication influencing blood rheology (n=32) was not allowed. A total of 642 participants were thus excluded (multiple mentioning possible). Finally, individuals with incomplete laboratory studies (n=322) were not considered, leaving 2,211 participants (1,123 men and 1,088 women) to form the study population of this report.

Blood Sampling

Nonfasting blood samples were drawn according to the recommendations of the International Committee for Standardization in Haematology. Only short-term venous occlusion and minimal suction were applied. In a subsample of 1,047 persons, the venous occlusion time was recorded and related to the hemorheological variables. No significant correlations were found.

Experimental Procedures

Blood was taken in EDTA to measure hemoglobin by the cyanate method (TOA hemoglobin meter and diluter, Colora Inc., Munich, FRG). An aliquot of the sample was centrifuged at 3,000g for 15 minutes. A Harkness Coulter viscometer (Coulter Electronics, Luton, UK), adjusted to 37°C, was used to measure plasma viscosity. The measurement procedure and the sample preparation met the criteria of the International Committee for Standardization in Haematology. Total serum protein (in grams per liter) was quantified by a standard biuret technique using an SMAC autoanalyzer (Technicon Co., Ardsley, N.Y.). Hemoglobin (in grams per deciliter) measurements were performed in duplicate and plasma viscosity (in millipascal · seconds) tests in triplicate. For quality control, hemoglobin and plasma viscosity measurements were compared daily with standard solutions. The coefficients of variation were 1.4% for hemoglobin and 1.0% for plasma viscosity. There was no baseline shift during the 8-month data collection period. At irregular intervals, duplicates were measured in a single-blind fashion. Their coefficients of variation were 3.8% for hemoglobin, 2.0% for plasma viscosity, and 1.3% for total serum protein. Eighty-four percent of the hemoglobin duplicates agreed better than 5%. The corresponding values were 93% for plasma viscosity and 97% for total serum protein.

Total serum cholesterol was analyzed by a routine enzymatic method (CHOD-PAP method, Boehringer, Mannheim, FRG). The coefficient of variation for repeatedly measured duplicates was 1.1%. Ninety-eight percent of the cholesterol duplicates agreed better than 5%. HDL C was also measured enzymatically after precipitation of the apoprotein B–containing lipoproteins with phosphotungstate/Mg2+ (Boehringer).

The apoproteins A-I, A-II, and B were analyzed by kinetic immunoturbidimetry on a Hitachi autoanalyzer, model 705. The method is described in more detail elsewhere. The intra-assay coefficients of variation for apoprotein B (range, 400–3,000 mg/l) were between 2.5% and 1.5%. The corresponding values for the interassay coefficients of variation were between 5.7% and 3.2%. Similar coefficients of variation were found for apoprotein A-I and A-II. The comparison with radial immunodiffusion (IMMUNO Co., Heidelberg, FRG) showed excellent agreement (r = 0.95).

Regular internal and external quality control procedures were carried out according to the recommendations of the WHO center for lipid standardization in Prague.

After an interview of 30-minute duration, blood pressure (BP; Hawksley Zero Sphygmomanometer) was measured according to the recommendations of the American Heart Association. Body height (in meters), body weight (in kilograms), body mass index (BMI; weight divided by the square of height), smoking behavior, and alcohol consumption were determined as described elsewhere.

Statistical Methods

The associations between the hemorheological variables and the lipoprotein variables were analyzed with simple and multiple linear regression techniques. The hemorheological variables plasma viscosity, hemoglobin, and total serum protein were used as continuous dependent variables. The lipid/lipoprotein variables total cholesterol and HDL C and the apoprotein variables A-I, A-II, and B were used as continuous independent variables of interest. Continuous independent variables were also used as sex-specific quintiles. In
addition, total cholesterol was categorized according to cut points recommended at the National Heart, Lung, and Blood Institute (NHLBI) Consensus Conference. The covariates considered were taken to represent groups: age (the four 10-year groups the sampling design was based on), BMI (according to Bray), smoking behavior (nonsmoker, actual smoker), alcohol consumption (men: 0, <40, ≥40 g/day; women: 0, <20, ≥20 g/day), and hypertension (using the 140/90 mm Hg cutoff).

For ease of interpretation, we first assessed linear relations by computing separate regressions for each of the hemorheological variables with each of the lipoprotein variables. Various subsets of covariates were included as independent variables. The categorical variables were turned into 0–1 dummy variables in the usual way, and the continuous variables were centered around the mean. All regressions were run separately for each sex.

Possible curvature was then examined by including in these regressions second- and third-order polynomial terms for the continuous variables of interest. Nonsignificant polynomial terms were eliminated in a hierarchical backward-stepping manner, starting from the third-degree terms and retaining for a significant term all its lower-order terms. Testing was carried out at the 5% significance level.

To take into account the wide age range present in the study group, we investigated these regression curves further for parallelism in the four age groups of the sampling design. To this end, we included, in each of the third-degree polynomial models described above, the interaction between the variable of interest and age. We then tested the significance of the global interaction effect. For a significant interaction, the interaction terms comparing any two of the polynomials were eliminated in a backward-stepping manner. The remaining terms were then individually eliminated in a hierarchical backward-stepping fashion, i.e., first considering interaction terms that contained the third-degree polynomial terms. When a term remained in the model, all lower-order terms were retained as well. All tests used the 5% significance level throughout.

The possible need for transformations of original continuous variables was judged from distribution statistics (skewness, percentiles).

Adjusted means and regression lines displayed in graphic representations were obtained by setting covariates to their sex-specific mean values.

All computations and the graphic work were done by use of version 6.06 SAS software on an IBM VM/CMS mainframe.

Results

Table 1 presents descriptive statistics of the hemorheological variables and different components of lipoprotein variables for both men and women. The mean of plasma viscosity was marginally higher in men than in women, hemoglobin showed the well-known sex difference, and total serum protein was somewhat higher in men than in women. Means of total cholesterol and of apoproteins A-II and B were lower in women than in men, whereas HDL C and apoprotein A-I showed the opposite behavior.

For all variables, the percentiles in our subsample were nearly identical to those of the original random sample.

Effects of Lipids and Lipoproteins on Plasma Viscosity

Table 2 summarizes separate linear regressions of plasma viscosity on total cholesterol and on HDL C.

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**Table 1. Sample Means, Standard Deviations, Skewnesses, and Percentiles of Hemorheological Variables by Sex**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Skewness</th>
<th>5</th>
<th>10</th>
<th>50</th>
<th>90</th>
<th>95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n=1,123)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV (mPa·sec)</td>
<td>1.255</td>
<td>0.064</td>
<td>0.8</td>
<td>1.16</td>
<td>1.18</td>
<td>1.25</td>
<td>1.34</td>
<td>1.37</td>
</tr>
<tr>
<td>HB (g/dl)</td>
<td>15.02</td>
<td>1.49</td>
<td>1.0</td>
<td>12.9</td>
<td>13.4</td>
<td>14.9</td>
<td>16.7</td>
<td>17.4</td>
</tr>
<tr>
<td>TSP (g/l)</td>
<td>72.77</td>
<td>3.84</td>
<td>0.1</td>
<td>66.9</td>
<td>68.1</td>
<td>72.5</td>
<td>77.8</td>
<td>79.2</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>233.3</td>
<td>45.9</td>
<td>0.7</td>
<td>165</td>
<td>180</td>
<td>230</td>
<td>293</td>
<td>310</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>51.5</td>
<td>14.5</td>
<td>0.8</td>
<td>31</td>
<td>35</td>
<td>50</td>
<td>69</td>
<td>77</td>
</tr>
<tr>
<td>AA-I (mg/dl)</td>
<td>136.3</td>
<td>21.4</td>
<td>0.6</td>
<td>105</td>
<td>111</td>
<td>134</td>
<td>163</td>
<td>176</td>
</tr>
<tr>
<td>AA-II (mg/dl)</td>
<td>41.9</td>
<td>9.8</td>
<td>1.4</td>
<td>30</td>
<td>32</td>
<td>40</td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>AB (mg/dl)</td>
<td>85.4</td>
<td>20.9</td>
<td>0.3</td>
<td>52</td>
<td>59</td>
<td>85</td>
<td>113</td>
<td>123</td>
</tr>
<tr>
<td>Women (n=1,088)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PV (mPa·sec)</td>
<td>1.242</td>
<td>0.065</td>
<td>0.7</td>
<td>1.15</td>
<td>1.17</td>
<td>1.24</td>
<td>1.33</td>
<td>1.36</td>
</tr>
<tr>
<td>HB (g/dl)</td>
<td>13.53</td>
<td>1.33</td>
<td>1.3</td>
<td>11.7</td>
<td>12.1</td>
<td>13.4</td>
<td>14.9</td>
<td>15.8</td>
</tr>
<tr>
<td>TSP (g/l)</td>
<td>71.35</td>
<td>3.94</td>
<td>0.1</td>
<td>65.1</td>
<td>66.6</td>
<td>71.2</td>
<td>76.4</td>
<td>77.7</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>226.4</td>
<td>44.9</td>
<td>0.6</td>
<td>160</td>
<td>173</td>
<td>222</td>
<td>286</td>
<td>308</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>64.1</td>
<td>16.4</td>
<td>0.6</td>
<td>39</td>
<td>45</td>
<td>62</td>
<td>86</td>
<td>94</td>
</tr>
<tr>
<td>AA-I (mg/dl)</td>
<td>153.8</td>
<td>27.5</td>
<td>1.8</td>
<td>116</td>
<td>123</td>
<td>152</td>
<td>187</td>
<td>199</td>
</tr>
<tr>
<td>AA-II (mg/dl)</td>
<td>38.6</td>
<td>7.7</td>
<td>1.4</td>
<td>29</td>
<td>31</td>
<td>37</td>
<td>48</td>
<td>53</td>
</tr>
<tr>
<td>AB (mg/dl)</td>
<td>76.6</td>
<td>19.9</td>
<td>0.8</td>
<td>49</td>
<td>54</td>
<td>73</td>
<td>104</td>
<td>114</td>
</tr>
</tbody>
</table>

PV, plasma viscosity; HB, hemoglobin; TSP, total serum protein; TC, total cholesterol; HDL, high density lipoprotein cholesterol; AA-I, apoprotein A-I; AA-II, apoprotein A-II; AB, apoprotein B.
TABLE 2. Multiple Linear Regressions of Plasma Viscosity (Dependent Variable) on Each of the Cholesterol Variables (Unadjusted and Adjusted for Covariables by Sex)

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Total cholesterol</th>
<th>HDL cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$b$</td>
<td>$r$</td>
</tr>
<tr>
<td>Men $(n=1,123)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.00049</td>
<td>0.35</td>
</tr>
<tr>
<td>Age</td>
<td>0.00045</td>
<td>0.31</td>
</tr>
<tr>
<td>Age, BMI, smk, alc, hyp</td>
<td>0.00040</td>
<td>0.28</td>
</tr>
<tr>
<td>Age, BMI, smk, alc, hyp, TSP</td>
<td>0.00026</td>
<td>0.23</td>
</tr>
<tr>
<td>Women $(n=1,088)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.00053</td>
<td>0.36</td>
</tr>
<tr>
<td>Age</td>
<td>0.00045</td>
<td>0.28</td>
</tr>
<tr>
<td>Age, BMI, smk, alc, hyp</td>
<td>0.00043</td>
<td>0.28</td>
</tr>
<tr>
<td>Age, BMI, smk, alc, hyp, TSP</td>
<td>0.00023</td>
<td>0.19</td>
</tr>
</tbody>
</table>

HDL, high density lipoprotein; $b$, expected change in plasma viscosity (in mPa · sec) per unit change in the corresponding cholesterol variable (mg/dl); BMI, body mass index; smk, smoking behavior; alc, alcohol consumption; hyp, hypertension (140/90 mm Hg cutoff); TSP, total serum protein.

Each line contains the regression coefficient ($b$), the partial correlation coefficient ($r$), and the corresponding probability value ($p$) of the lipid/lipoprotein variable in the regression of plasma viscosity on that lipid/lipoprotein variable and on covariables.

In both men and women, a positive linear relation was found between plasma viscosity and total cholesterol. In men, the unadjusted regression coefficient was 0.00049, meaning that an increase in total cholesterol of 100 mg/dl yields an expected increase in plasma viscosity of approximately 0.05 mPa · sec. In women, the corresponding increase was similar. Adjustment for all covariables (age, BMI, smoking behavior, alcohol consumption, hypertension) and total serum protein still left a substantial association ($p<0.005$ in both sexes). The expected adjusted increase in plasma viscosity corresponding to an increase in total cholesterol of 100 mg/dl is 0.026 mPa · sec in men and 0.023 mPa · sec in women.

For HDL C, a weak negative linear relation to plasma viscosity was found. After adjustment for all covariables, this association became even smaller in men and was almost zero in women. Further adjustment for total serum protein resulted in an appreciable negative association in both sexes ($r=-0.14$ for men and $r=-0.10$ for women).

Association of Lipids and Lipoproteins With Total Serum Protein and Hemoglobin

For total serum protein, too, a positive linear relation to total cholesterol was found for men ($r=0.18$) and for women ($r=0.21$) after adjustment for the covariables. In contrast to plasma viscosity, total serum protein showed a small positive association with HDL C ($r=0.09$ in men and $r=0.07$ in women, adjusted for the covariables). Total serum protein levels correlated positively with plasma viscosity ($r=0.56$ for men and $r=0.67$ for women).

The same regression analyses were carried out for hemoglobin. No substantial relation was seen in either sex.

Effects of Apoproteins on Hemorheological Variables

Table 3 summarizes separate linear regressions of plasma viscosity on the apoproteins A-I, A-II, and B.

TABLE 3. Multiple Linear Regressions of Plasma Viscosity (Dependent Variable) on Each of the Apoprotein Variables (Unadjusted and Adjusted for Covariables by Sex)

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Apoprotein A-I</th>
<th>Apoprotein A-II</th>
<th>Apoprotein B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$b$</td>
<td>$r$</td>
<td>$p$</td>
</tr>
<tr>
<td>Men $(n=1,123)$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.00016</td>
<td>0.05</td>
<td>0.070</td>
</tr>
<tr>
<td>Age</td>
<td>0.00011</td>
<td>0.04</td>
<td>0.196</td>
</tr>
<tr>
<td>Age, BMI, smk, alc, hyp</td>
<td>0.00011</td>
<td>0.04</td>
<td>0.226</td>
</tr>
<tr>
<td>Age, BMI, smk, alc, hyp, TSP</td>
<td>-0.00020</td>
<td>-0.08</td>
<td>0.007</td>
</tr>
<tr>
<td>Women $(n=1,088)$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.00003</td>
<td>0.01</td>
<td>0.642</td>
</tr>
<tr>
<td>Age</td>
<td>-0.00002</td>
<td>-0.01</td>
<td>0.785</td>
</tr>
<tr>
<td>Age, BMI, smk, alc, hyp</td>
<td>0.00005</td>
<td>0.02</td>
<td>0.516</td>
</tr>
<tr>
<td>Age, BMI, smk, alc, hyp, TSP</td>
<td>-0.00010</td>
<td>-0.06</td>
<td>0.052</td>
</tr>
</tbody>
</table>

$b$, Expected change in plasma viscosity (in mPa · sec) per unit change in the corresponding apoprotein variable (mg/dl); BMI, body mass index; smk, smoking behavior; alc, alcohol consumption; hyp, hypertension (140/90 mm Hg cutoff); TSP, total serum protein.
In both sexes, a substantial positive unadjusted association with apoprotein B was found that was only moderately lowered after adjustment for the covariates, including total serum protein (p<0.005). Total cholesterol and apoprotein B were highly correlated (r=0.86 for both sexes).

There was practically no relation between apoprotein A-I and plasma viscosity (r=0.05 in men and r=0.01 in women). After further control for total serum protein, however, a weak negative relation was found in men (r=-0.08) and in women (r=-0.06). HDL C and apoprotein A-I were highly correlated (r=0.79 for men and r=0.78 for women).

For hemoglobin, again, no relation to apoproteins was seen, whereas total serum protein was positively associated with apoprotein A-I and B. This relation was of the same magnitude as with HDL C or total cholesterol.

**Modified Analyses**

All of these regressions have also been run with logarithmic transformations of the continuous variables where suggested by the skewness statistic in Table 1, but no substantially different results were obtained.

Figures 1 and 2 present results of the polynomial regressions for plasma viscosity in graphic form. Shown are polynomials of the degree determined in the way specified in the “Statistical Methods” section, after adjustment for all covariates (dashed line) and for all covariates plus total serum protein (solid line). In these plots, the range of the x values is limited to the sex-specific fifth to 95th percentile of each variable. In Figure 1, plots of similarly adjusted means in categories corresponding to the NHLBI Consensus Conference for total cholesterol and in sex-specific quintiles for HDL C are added for comparison.

From these plots it can be seen that the linear statistics presented in Tables 2 and 3 may be regarded as adequate descriptions of the relations in question for all variables except for HDL C in men. Here, a substantial quadratic effect shows in both adjustments, with a clear tendency to increased plasma viscosity at low HDL C levels. The regression coefficients (and their standard errors) are given in Table 4.

**Figure 1.** Graphs showing relation of total cholesterol and high density lipoprotein (HDL) cholesterol to plasma viscosity (PV). Polynomials of significant degree ≤3 and means, adjusted for age, body mass index, smoking behavior, alcohol consumption, and hypertension (---) and for the additional effect of total serum protein (--).

**Figure 2.** Graphs showing relation of apoproteins A-I, A-II, and B to plasma viscosity (PV). Polynomials of significant degree ≤3 adjusted for age, body mass index, smoking behavior, alcohol consumption, and hypertension (---) and for the additional effect of total serum protein (--).
errors) for the linear and the quadratic term are 
\[-0.00071 (0.00012)\) and \[0.0000173 (0.0000038),\]
respectively, when adjusting for the covariables and total serum protein (solid line). In women, the quadratic effect is not as striking as in men. Neither are those for total cholesterol and for apoprotein A-I in men. The slightly S-shaped (third-degree polynomial) dashed curve for apoprotein B in men, too, does not indicate a serious deviation from linearity.

When we investigated the question of whether third-degree polynomials, after adjustment for the covariables and total serum protein, could be considered parallel in the four age groups, only the regression of plasma viscosity on apoprotein A-I in women turned out to have a statistically significant interaction with age \((p=0.0002)\).

**Relation Between Lipids, Lipoproteins, and Plasma Viscosity in Participants Excluded From the Analysis**

There was no marked change in the results (only the linear relation was analyzed) for total cholesterol and apoprotein B in both sexes and for HDL C in men. Partial correlation coefficients adjusted for all covariables including total serum protein were 0.19 and 0.25 in men and 0.20 and 0.26 in women for total cholesterol and apoprotein B, respectively, and \[-0.16\] for HDL C in men.

For apoprotein A-II in men and apoprotein A-I and A-II in women, no significant correlations with plasma viscosity were seen, as found in the subsample. Whereas in the subsample there was an appreciable correlation between HDL C and plasma viscosity in women, there was no such relation in those excluded.

For apoprotein A-I, a stronger relation with plasma viscosity was found in men \((r=-0.14; \ p=0.018)\) compared with the subsample \((r=-0.08)\).

**Discussion**

Our results show a substantial positive independent association between total cholesterol and plasma viscosity in both men and women. The correlation coefficients found in our subsample after adjustment for the covariables were of the same magnitude as reported by Seplowitz et al\(^{28}\) \((r=0.29)\), although their data were obtained in the clinical setting in patients with hyperlipoproteinemia type IIa. In all of the relations studied between the various lipoprotein variables and plasma viscosity, the confounding effect of age was small (see Tables 2 and 3).

There was an interaction with age for the relation between apoprotein A-I and plasma viscosity in women, which, however, was not considered meaningful because it could not be demonstrated similarly for the relation between HDL C and plasma viscosity. In particular, no different forms of the relation were obtained in premenopausal and postmenopausal women for other lipid/lipoprotein variables.

When the relation between the apoproteins and plasma viscosity was analyzed, a positive association of the same magnitude as with total cholesterol was found with apoprotein B. Apoprotein A-II was also positively associated with plasma viscosity.

Introducing total serum protein as an additional control variable in our analyses led to a further moderate attenuation in the relation of plasma viscosity with total cholesterol and apoprotein B. This may reflect the rheological impact of plasmatic molecules other than lipoprotein particles. Even after this adjustment, however, a substantial association was seen, the only exception being apoprotein A-II. Its association with plasma viscosity vanished after control for total serum protein. For HDL C and apoprotein A-I, a stronger negative linear relation with plasma viscosity was found after adjustment for total serum protein. This correlation has been nonsignificant before adjustment and significant after total serum protein had been introduced as a control variable, although the resulting association was rather small \((r\) ranging from \[-0.14\) to \[-0.06\); see Tables 2 and 3). Figures 1 and 2 show that the relations of plasma viscosity with HDL C and apoprotein A-I are somewhat U-shaped before adjustment for total serum protein, resulting in a linear correlation of nearly zero. After adjustment for total serum protein as well, these U shapes are bent downward on the right-hand side, exhibiting a relation more appropriately described by the linear correlations.

Studies in patients with various forms of hyperlipoproteinemias found a lipoprotein concentration-dependent increase of plasma viscosity. This could be shown for the LDL, for the very low density lipoprotein (VLDL),\(^{28,30}\) and in particular for chylomicrons,\(^{28}\) and hence for total triglycerides. The magnitude of the correlation proved to be dependent on the size of the lipoprotein particles. Schuff-Werner et al\(^{30}\) reported a stronger dependency of plasma viscosity on LDL C levels than on fibrinogen, which supports these observations.

Solerte et al\(^{31}\) recently showed a positive association between the apoprotein B concentration, reflecting the blood LDL concentration, and plasma as well as whole-blood viscosity in non-insulin-dependent diabetics. Other authors demonstrated complex hemorheological abnormalities in patients with hyperlipoproteinemias.\(^{32-34}\)

Whereas the positive association between total cholesterol and apoprotein A-II and B on one hand and plasma viscosity on the other hand may be explained by the rheological effect of the "high-molecular-weight" lipoprotein particles suspended in plasma, the negative linear relation between HDL C and plasma viscosity is not interpretable on a purely mechanistic basis. Plasma concentrations of HDL C are relatively low, however, and HDL particles are smaller than LDL and, especially, VLDL and chylomicrons.

In two recent studies, inverse linear relations between HDL C and whole-blood viscosity\(^{35}\) and between HDL C and erythrocyte aggregation\(^{36}\) were found. Both rheological parameters are strongly correlated with plasma viscosity and fibrinogen.\(^{37}\)

In our analyses, a quadratic effect was seen in addition (Figure 1). Only men with low HDL C \((<40\ mg/dl)\) exhibited an increased plasma viscosity. The relation between HDL C and plasma viscosity demonstrated here is in accordance with the protective function of this lipoprotein in CHD. Individuals with extremely low HDL C levels carry an excessive coronary risk.\(^{3}\) As triglycerides were not determined in our study, elevated plasma levels of this lipid fraction, which have been shown to correspond with low HDL C,\(^{38,39}\) may offer at least a partial explanation for our findings. However, because a similar relation has recently been reported
between fibrinogen and HDL C,40,41 other mechanisms may be involved as well. To date, attempts to explain this association remain speculative.

Further research during recent years focused on the relation between a variety of hemostatic and fibrinolytic variables and hyperlipidemia.42–46

Hyperlipidemias present with a disturbed hemorheological profile that on one hand may be regarded as an epiphenomenon. On the other hand, under certain conditions (in particular, in patients with manifest atherosclerosis of different organs and limited tissue perfusion) it may be clinically relevant. It is widely accepted that plasma viscosity can determine volume flow in a given vascular bed. This notion is supported by interventional studies: Lipid-lowering therapy by either diet or drug treatment reduces pathologically altered hemostatic parameters and/or ameliorates blood fluidity46–51 and may even lead to increased myocardial perfusion and to clinical improvement in patients with angina pectoris caused by severe CHD.52

In conclusion, we found a substantial association between components of several lipoproteins and plasma viscosity. Our results support the view that rheological mechanisms may be involved in the pathogenesis of ischemic syndromes in hyperlipidemias.

Acknowledgments

The authors wish to thank Gerardo Heiss, MD, PhD, for helpful comments on an earlier draft of the manuscript and Jirina Koenig for preparing the manuscript.

References

39. Patsch JR, Prasad S, Gotto AM, Patsch W: High density lipoproteins: Relationship of the plasma levels of this lipoprotein species to its composition, to the magnitude of postprandial lipemia and to the activities of lipoprotein lipase and hepatic lipase. J Clin Invest 1987;80:341–349
Association between rheology and components of lipoproteins in human blood. Results from the MONICA project.
W Koenig, M Sund, E Ernst, W Mraz, V Hombach and U Keil

*Circulation*. 1992;85:2197-2204
doi: 10.1161/01.CIR.85.6.2197

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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