Plasma and blood viscosity in metabolic syndrome

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KEYWORDS
Blood viscosity; Plasma viscosity; Metabolic syndrome

Abstract  Background and aim: The relationship between metabolic syndrome (MS) and blood and plasma viscosity has been scarcely investigated. In the present study we have evaluated the difference in blood and plasma viscosity between subjects with and without MS, in order to verify whether viscosity measurement can add more information on the overall cardiovascular risk connected with the presence of the MS.

Methods and Results: Two hundred and sixty nine women and 520 men have been enrolled. Blood and plasma viscosity have been measured with a cone-plate viscometer equipped with a cp-40 spindle. MS has been defined according to the third report of the National Cholesterol Education Program, Adult Treatment Panel III.

Eighty four women and 154 men fulfilled the criteria for MS. Hematocrit adjusted blood viscosity was higher in subjects with MS compared to those without the syndrome, both in males (shear rate 225 s⁻¹: 4.60 ± 0.38 vs. 4.52 ± 0.33 cP, p < 0.01) and females (4.57 ± 0.28 vs. 4.46 ± 0.31 cP, p < 0.01). Blood viscosity was correlated with all components of MS but glucose, and after adjustment for them the difference between subjects with or without MS was completely abolished. Plasma viscosity was significantly higher only in females with MS.

Conclusions: These data demonstrate that blood viscosity is increased in subjects with MS, but the increase seems to depend on the metabolic alterations of the syndrome. The independent contribution of the rise in blood viscosity to the cardiovascular risk connected with the presence of MS seems therefore negligible. The increased plasma viscosity in females with MS needs further clarification.

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Introduction

The metabolic syndrome (MS) is associated with increased risk for cardiovascular disease (CVD) and diabetes [1–3].

Insulin resistance, the hallmark of the syndrome, is associated with activation of hemostasis [4,5] and the excess CVD risk associated with MS may be mediated, in part, by hemorheological alterations.

Hemorheological alterations have been found associated with CVD, like stable and unstable angina pectoris, and myocardial infarction [6–10]. More specifically, blood viscosity has been reported associated to the severity of coronary atherosclerosis and infarct size [11,12]. We have
previously reported that hematocrit and blood viscosity are higher in male subjects with internal carotid atherosclerosis [13,14].

The relationship between MS and hemorheological variables has been scarcely investigated, and the results have been contrasting. For instance, Zhang et al. have demonstrated, in a Chinese population, that blood viscosity is strongly related to the severity of the MS, whereas Aloulou et al. found that the hyperviscosity syndrome of the MS was not proportional to its clinical scoring [15,16]. In a large population-based study, Wan-namethee et al. have demonstrated that MS is significantly associated with calculated blood viscosity and suggest this might be relevant for CVD risk [17]. Other reports have usually investigated very small number of subjects or patients with particular characteristics, like severe obesity [18].

The aim of the present study is to evaluate the difference in blood and plasma viscosity between subjects with and without MS, and to verify whether viscosity measurement can add more information on the overall cardiovascular risk connected with the presence of the MS.

Methods

Subjects

We used data on 269 women and 520 men who were participants in a regional Cardiovascular Disease Prevention Campaign. Subjects, who were all Caucasians, were examined according to a previously standardized protocol [19]. Briefly, participants were residents in the region and no exclusion criteria were adopted except age <30 years. For patients analyzed in the present study, the following exclusion criteria were adopted: females before menopause (menopause was defined as no menstrual periods for 12 consecutive months or bilateral oophorectomy), use of anticoagulant and/or diuretics. All participants were informed about the aim of the campaign and an informed consent was obtained before examination.

Cardiovascular risk factors assessment

All subjects were examined in the morning in a room at 22 °C, after overnight fasting. Well-trained personnel measured blood pressure, height and weight by routine methods. The mean of two sitting blood pressure readings was used. Body mass index (BMI) was computed as weight (in kilograms) divided by height (in squared meters). Waist circumference was measured midway between the lower rib margin and the iliac crest. A questionnaire was administered to evaluate smoking habit and drug use. Current smokers recorded the number of cigarettes smoked each day. Subjects were asked to record the age at which they started to smoke and those who stopped smoking also the age at which they gave up. Pack-years of cigarette consumption were calculated from these data assuming that smoking pattern indicated was stable throughout the life. A pack-year was defined as 20 cigarettes a day for a year.

Viscosity measurement

Venous blood for glucose, lipid, and viscosity analyses was collected after overnight fasting. Attention was paid to avoid venous stasis and the haemostatic loop, when used, was immediately removed after cannulation of the vein. Blood glucose and lipids were measured by routine methods. LDL-cholesterol was calculated according to Friedewald formula. Blood and plasma viscosity were measured within 2 h from blood withdrawal; the blood specimen was added with heparin (35 U.I./mL). Viscosity measurement was performed at 37 °C with a cone-plate viscometer (Wells-Brookfield DV-III, Stoughton, USA) equipped with a cp-40 spindle. Blood viscosity was evaluated at shear rates of 450 (11450), 225 (11225) and 90 (1190) s⁻¹. These values were chosen because, using our viscometer, these high shear rates warrant highly reliable measurement. For plasma viscosity the average of measurements at shear rates of 450 and 225 s⁻¹ was calculated. The coefficients of variation for blood and plasma viscosities were 2.8 and 2.1% respectively. Micro-hematocrit was measured without correction for plasma trapping. The coefficient of variation for micro-hematocrit was 1.2%.

Metabolic status classification

MS was defined as the presence of three or more of the following: 1. waist circumference >88 cm in women and >102 cm in men; 2. fasting triglycerides ≥150 mg/dl; 3. HDL cholesterol <50 mg/dl; 4. LDL cholesterol ≥3.5 mmol/L; 5. fasting glucose ≥6.5 mmol/L or use of antihypertensive drug therapy; and 6. smoking habit. All participants were classified as non-smoker, ex-smoker, or current smoker. Pack-years were calculated for smokers.

Statistical analysis

All statistical analyses were performed by SPSS 8.0 for Windows.

All data are expressed as mean and SD. Normal probability plots were examined to determine the skewness of variables. Data on triglycerides were log transformed. Unpaired two-sided t-test was used to compare continuous variables between males and females. ANOVA was used to compare variables between subjects with a different number of MS components. ANCOVA was used to adjust blood viscosity for hematocrit. Pearson correlation coefficients were calculated to examine the relationship between hemorheological variables and classical CHD risk factors.

Results

Clinical and biochemical characteristics of participating subjects, according to gender and MS, are reported in Table 1. Eighty four women (31.2%) and 154 men (29.6%) fulfilled the criteria for MS. In both sexes, subjects with MS were slightly older, had increased blood pressure, glucose, waist, BMI, triglycerides and had lower HDL.
cholesterol concentration. Total cholesterol was similar in those with and without MS. LDL cholesterol was slightly lower in males with MS compared to those without the syndrome. Cigarette smoking, as pack years, was similar in males and lower in females with MS. The prevalence of current smokers was 18.2% among females and 27.7% among males. Current smokers had higher levels of hematocrit ($47.28 \pm 4.59$ vs. $45.95 \pm 4.20$, $p < 0.0001$) and blood viscosity at all shear rates (shear rate $225/s$: $4.63 \pm 0.59$ vs. $4.53 \pm 0.53$ cP, $p < 0.05$).

Blood viscosity ($\eta$) was strongly correlated with hematocrit ($r$ between 0.611 and 0.793 at different shear rates; $p < 0.0001$), therefore hematocrit adjusted ($\eta^f$) values were calculated and used in all further analyses. After adjustment for hematocrit, no difference in $\eta$ between males and females was observed. Plasma viscosity was similar in both sexes as well.

Table 2 shows the hemorheological variables in the population studied, according to gender and MS. Adjusted blood viscosity was significantly higher both in males and females with MS, compared to subjects without the syndrome. Hematocrit was similar in both groups, whereas plasma viscosity was significantly higher only in females with MS.

In males, $\eta$ increased with increasing number of MS components ($p$ for trend $<0.005$; subjects with four and five components were grouped), whereas hematocrit and plasma viscosity did not. In females, both $\eta$ and plasma viscosity increased with increasing number of MS components ($p$ for trend $<0.001$ for $\eta$ and $=0.01$ for plasma viscosity) (Table 3).

Adjusted blood viscosity was significantly correlated with age and all MS components but glucose (Table 4). After adjustment for MS components, blood viscosity was no longer significantly different between subjects with and without MS ($\eta^f_{225}$ (cP); males: $4.51 \pm 0.35$ vs. $4.53 \pm 0.33$; females: $4.50 \pm 0.26$ vs. $4.51 \pm 0.31$, respectively).

Plasma viscosity was significantly correlated only with blood viscosity and blood pressure, and after adjustment for MS components it remained significantly higher in females with MS (data not shown).

## Discussion

The relationship between hemorheological variables, especially blood and plasma viscosity, and MS has not been extensively investigated, at least in population based studies. The technical problems related to viscosity measurement, for instance the necessity to make the measurement within a short lapse of time after blood withdrawal and the impossibility to freeze the blood sample to later perform the analysis, have probably contributed to the paucity of data. Nevertheless, the study of hemorheological variables in subjects with MS can be important to understand whether the pathogenetic mechanisms underlying the syndrome are also responsible for further alterations potentially able to aggravate the CVD risk burden. In our knowledge, this is the first report on the relationship between measured blood and plasma viscosity and MS in a quite large number of Caucasian subjects.

The findings of the present study demonstrate that blood viscosity is higher in subjects with MS, compared with those without MS, and increases with increasing number of components of MS, in both sexes and independently of hematocrit. However, blood viscosity is significantly correlated to components of the MS, and after adjustment for them, the difference between subjects with and without MS is completely abolished.

Smokers had higher levels of hematocrit. It is well known that smoking causes a rise in hematocrit and blood viscosity, probably a consequence of increased carbon monoxide concentration and hypoxia [21]. In the present study, the adjustment for hematocrit completely abolished the difference in blood viscosity between smokers and nonsmokers.

The association between blood viscosity and components of the MS has been previously reported [17,22]. However, in the study of Wannamethee et al. only older men (aged 60–79 years) have been investigated and blood viscosity has not been directly measured, but calculated from hematocrit and plasma viscosity. In the study of Fossum et al., blood viscosity has been directly measured but in healthy blood donors. In this latter study, though

### Table 1: Clinical and biochemical characteristics of subjects according to gender and MS.

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MS−</td>
<td>MS+</td>
<td>MS−</td>
<td>MS+</td>
</tr>
<tr>
<td>Number</td>
<td>366</td>
<td>154</td>
<td>185</td>
<td>84</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.8 ± 9.7</td>
<td>53.8 ± 9.1*</td>
<td>56.9 ± 5.9</td>
<td>59.0 ± 6.2**</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>128 ± 16</td>
<td>140 ± 16**</td>
<td>131 ± 18</td>
<td>144 ± 18**</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>80 ± 9</td>
<td>86 ± 9**</td>
<td>80 ± 8</td>
<td>86 ± 9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.8 ± 3.1</td>
<td>29.6 ± 4.1**</td>
<td>27.7 ± 4.0</td>
<td>30.3 ± 4.2**</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>92.3 ± 7.4</td>
<td>102.7 ± 11.6**</td>
<td>85.6 ± 10.4</td>
<td>96.2 ± 9.8**</td>
</tr>
<tr>
<td>T-cholesterol (mg/dL)</td>
<td>227 ± 48</td>
<td>221 ± 45</td>
<td>240 ± 48</td>
<td>248 ± 50</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>154 ± 46</td>
<td>145 ± 42*</td>
<td>162 ± 44</td>
<td>167 ± 45</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>46 ± 12</td>
<td>38 ± 10**</td>
<td>57 ± 14</td>
<td>46 ± 13**</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>136 ± 76</td>
<td>191 ± 77**</td>
<td>108 ± 46</td>
<td>178 ± 80**</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>96 ± 18</td>
<td>117 ± 42**</td>
<td>91 ± 12</td>
<td>114 ± 42**</td>
</tr>
<tr>
<td>Smoking (pack/years)</td>
<td>9.0 ± 10.5</td>
<td>10.1 ± 11.3</td>
<td>4.2 ± 8.3</td>
<td>2.0 ± 5.3*</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01.
performed in normal people, a strong correlation between
blood viscosity and blood pressure, waist–hip ratio and
blood lipids were found. Our findings confirm the associa-
tion between blood viscosity and components of the MS also
in women and younger subjects and show that it is inde-
pendent of hematocrit.

Insulin-resistance, consequence of abdominal adiposity,
probably plays a central role in the development of MS, and
the pathways leading from compensatory hyperinsulinemia
to blood lipid and blood pressure modification have been
clearly detailed. A direct effect of insulin-resistance and
hyperinsulinemia on hemorheological variables has also
been described [16,18]. Subjects with low insulin sensitivity
show higher plasma and blood viscosity that are further
increased by hyperinsulinemia, while hematocrit is not
modified. In these studies, the small number of subjects
investigated did not allow any type of correction for
components of the MS. Our findings strongly suggest that
hemorheological alterations observed in subjects with MS
are not independent but secondary to metabolic abnor-
malities. Indeed, the association between blood lipids and
blood viscosity has long been described [23]. Blood lipids
are in a dynamic equilibrium with cell membrane lipids, and
the structural and functional properties of erythrocytes are
strongly influenced by the percentage of cholesterol within
the double layer. Therefore, increasing cholesterol levels
causes a rise in red cell rigidity and, in turn, alteration of
the rheological properties of the blood [24]. Furthermore,
increased plasma lipids and low levels of HDL cholesterol
might favor erythrocyte membrane peroxidation, again
increasing red cell membrane rigidity and altering viscosity.

In some studies it has been suggested that increased
blood viscosity might contribute to insulin-resistance, sup-
porting the hypothesis that insulin resistance has a hemo-
dynamic basis [22,25]. This finding has not been confirmed
in further studies. Based on the results of the present study,
it is not possible to establish whether increased blood
viscosity is the cause or the consequence of metabolic
alterations. However, at least in clinical practice it seems
that the contribution of hemorheological alterations to the
picture of metabolic syndrome might be negligible.

Plasma viscosity, in our study, is increased only in
females with MS. Plasma viscosity has been even less
investigated than blood viscosity, with regard to metabolic
syndrome. Previous findings, in relatively small groups of
patients, have demonstrated increased plasma viscosity in
males and females with insulin resistance and metabolic
syndrome [26–28]. In the present study, plasma viscosity
remained significantly higher in females with MS even after
adjustment for age and all the components of MS. Unfortu-
nately, fibrinogen, which is a major protein affecting
plasma viscosity, has not been measured. Further studies
are needed to confirm this finding, and to investigate the
possible reasons of this increase.

### Table 2  Hemorheological variables according to gender and MS.

| Components | Males | Fema|les |
|------------|-------|------|
| PCV (%)    |       |      |
| MS–        | 47.74 ± 3.77 | 47.79 ± 3.69 | 47.26 ± 4.23 |
| MS+        | 47.81 ± 3.69 | 47.97 ± 3.69 | 48.07 ± 4.23 |
| a 0.05 (CP)| 4.10 ± 0.55  | 4.25 ± 0.32**| 4.05 ± 0.47  |
| a 0.25 (CP)| 4.52 ± 0.33  | 4.60 ± 0.38**| 4.46 ± 0.31  |
| a 0.15 (CP)| 5.23 ± 0.43  | 5.33 ± 0.50* | 5.17 ± 0.40  |
| PV (cP)    | 1.43 ± 0.14  | 1.43 ± 0.13  | 1.43 ± 0.13  |

*p < 0.05; **p < 0.01.

### Table 3  Hemorheological variables according to number of MS components.

<table>
<thead>
<tr>
<th>Components</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV (%)</td>
<td></td>
</tr>
<tr>
<td>MS–</td>
<td>47.48 ± 3.69</td>
</tr>
<tr>
<td>MS+</td>
<td>47.88 ± 4.00</td>
</tr>
<tr>
<td>a 0.05 (CP)</td>
<td>4.08 ± 0.38</td>
</tr>
<tr>
<td>a 0.25 (CP)</td>
<td>4.43 ± 0.44</td>
</tr>
<tr>
<td>a 0.15 (CP)</td>
<td>5.11 ± 0.56</td>
</tr>
<tr>
<td>PV (cP)</td>
<td>1.43 ± 0.13</td>
</tr>
</tbody>
</table>

*p for trend: * = 0.01; **< 0.005; *** < 0.001.
In conclusion, blood viscosity is increased in subjects with MS, but this rise seems to depend on the metabolic alterations of the MS. Plasma viscosity is significantly higher in females with MS, independently of the components of MS, and this aspect needs further clarification.

References


