Lipid profile is associated with risk of thrombotic complications

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Dear Sirs,

Venous thromboembolism (VTE) is a leading cause of morbidity and mortality worldwide (1). The most common complications of the disease are thrombotic recurrence, post-thrombotic syndrome (PTS) and pulmonary embolism (PE). Risk of recurrence of VTE depends on the persistence of thrombotic risk factors. For patients with thrombosis associated with a trigger factor, the risk of recurrence is nearly 3%, whereas in patients with a persistent risk factor or idiopathic thrombosis, the risk increases to 10% (2). PTS is associated with a high rate of sick leave, and despite proper anticoagulation it has an incidence of 17-50% (3, 4).

The association between venous and arterial thrombosis has been studied in the recent years and has been based on the hypothesis that the two entities share a number of risk factors. A relationship between lipids and thrombotic events has been analysed, especially in cardiovascular disease. Lipids and lipoproteins modulate the expression and/or function of thrombotic, fibrinolytic and rheological factors and can therefore influence the homeostasis of the haemostatic system (5, 6).

In a recent issue of Thrombosis and Haemostasis, van Schouwenburg et al. (7) found no association between venous thrombosis, apolipoproteins and the classical lipoproteins. In this context, we have analysed a possible association between the lipid profile, recurrence of thrombotic events and post-thrombotic syndrome.

In total, we studied 313 consecutive patients referred to the Hematology Department between January, 2008 and June, 2012 who were diagnosed with VTE (deep venous thrombosis [DVT], PE or both). These patients were referred for thrombophilia testing and/or control of anticoagulant therapy. We have excluded patients undergoing statin therapy:

The diagnosis of VTE and recurrent thrombotic events was performed by physical examination (colour, skin condition, lesions and temperature, edema, asymmetry, peripheral pulses etc.) and was confirmed by objective tests (Eco-Doppler). PE was diagnosed based on ventilation/perfusion lung scanning or spiral computed tomography, following the protocol currently used in our hospital. PTS was defined according to the CEAP clinical scale. Diagnosis of PTS and the presence of residual thrombus were confirmed by objective testing (Eco-Doppler) at three, six and twelve months after the acute event.

Demographic variables, age and sex as well as classic cardiovascular risk factors (dyslipidaemia, smoking, hypertension and diabetes mellitus) were collected from each patient. Cardiovascular risk factors were defined as follows: dyslipidaemia (total cholesterol >220 mg/dl, high-density lipoprotein [HDL] <35 mg/dl, total cholesterol/HDL cholesterol >4.5 or triglycerides >200 mg/dl, in at least three successive determinations; or use of hypolipidaemic drugs), hypertension (HTA) (diastolic blood pressure >90 mmHg and/or systolic blood pressure >140 mmHg detected 24 hours after admission on several measurements, or use of antihypertensive drugs preadmission), diabetes mellitus (DM) (fasting glucose >126 mg/dl or prior use of oral hypoglycaemic medications or insulin), smoking (regular consumption of more than 10 cigarettes per day at the time of enrolling or two years prior).

Lipid profile including total cholesterol, HDL, low-density lipoprotein (LDL) and triglycerides was tested for all patients. From each patient we obtained fasting venous blood samples in tubes of 5 ml without anticoagulant and separator gel, which were processed immediately by centrifugation at 1,500 rpm for 15 minutes, separating the plasma and freezing the samples at -70°C in aliquots of 0.5 ml. All determinations were performed in an autoanalyzer ADVIA Centaur XP Immunoassay System (Siemens, Germany).

We conducted a descriptive study of the discrete variables (age and sex) and calculated the frequency of each category (dyslipidaemia, HTA, DM and smoking status). For continuous variables we calculated the descriptive statistics (mean, median, standard deviation, standard error, minimum and maximum). The comparison of percentages was performed using Fisher’s exact test. We calculated the p-value by univariate logistic regression models. All comparisons were made with a significance level of 0.05. The magnitude of the associations was estimated by odds ratio (OR) and confidence intervals at 95% (CI95%). Statistical analysis of the data was performed using Stata v.10 (StataCorp LP, College Station, TX, USA). In order to avoid the influence of age and sex, as well as cardiovascular risk factors in the results, we performed the analysis adjusted for the different categories.

The mean age of patients was 57.4 ± 17.3 years (range 18-95), 54.6% of whom were men. The distribution of cardiovascular risk factors is shown in Table 1A. Of the 313 cases included in the study, 64.9% (n = 203) had DVT, 26.8% (n = 84) had PE, whereas 8.3% (n = 26) had both PE and DVT at diagnosis. After the adjustment for age and sex, when we compared the patient group with a control group of 347 patients with no history of thrombosis, the multivariable analysis showed that dyslipidaemia

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is a risk factor for VTE (OR: 3.87, 95% CI: 2.72-5.56, p <0.0001) (Table 1A).

In the group, 97 patients had experienced a recurrent thrombotic event, 76 had presented with DVT, 13 had experienced PE and 8 had both DVT and PE at diagnosis. After adjustment for age and sex, low levels of HDL and high levels of LDL were associated with risk of recurrence. The findings of these analyses demonstrated an association between HDL <35 mg/dl (2.76 (1.12-6.94), p = 0.026) and LDL levels >180 mg/dl (2.22 (1.15-4.29), p = 0.017) and the risk of developing PTS (OR: 5.29, 95% CI: 2.63-10.83, p <0.0001) and the risk of developing PTS and recurrence (15). On the other hand, HDL cholesterol has antiatherogenic properties resulting from the inhibition of platelet and erythrocyte aggregation, reducing blood viscosity and attenuating the expression of tissue factor and selectins (8, 9). Also, there is a positive correlation between the levels of Apo AI and the response of anticoagulant protein C/protein S system (10).

Alterations in the lipid profile are a well-established risk factor for arterial thrombosis (11), but their involvement in venous thrombosis is debated and is being studied further (6, 7, 12-14). Even though the atherosclerotic process does not take place in the venous system, there seems to be an association between dyslipidaemia, risk of thrombosis, and possibly with the development of PTS and recurrence (15). On the other hand, some studies support the involvement of lipid abnormalities in venous thrombosis from another perspective, and they described that venous thrombosis is less common in patients undergoing statin treatment (16). Furthermore, in patients with idiopathic first thrombotic event who are treated with low-dose aspirin following anticoagulant therapy, a reduction is seen in the ratio of major vascular events (myocardial infarction, stroke or death from cardiovascular accident) (17).

The results obtained by Deguchi et al. in a group of men under 55 years indicated an almost three-fold risk of thrombosis in patients with HDL levels <40 mg/dl, and a 3.5-fold increase in individuals with LDL levels > 160 mg/dl (12). Similarly, results published by Doggen et al. showed a decreased thrombotic risk in patients with elevated HDL levels (> 66.1 mg/dl) (6). Recently, van Schouwenburg et al. have published a slight association in the univariate analysis between venous thromboembolism and total cholesterol levels (p=0.045), LDL (p=0.003), triglycerides (p=0.01), non-HDL cholesterol (p=0.02) and Chl/HDL ratio (p=0.03) (7) reporting that this association was lost after adjustment for sex and age (7). The results of the authors’ study are consistent with those found by our group in a previous study which supports an association between VTE and dyslipidaemia (OR: 3.2, 95%CI: 1.83-5.86, p = 0.0001). Nevertheless, in our group of patients the relationship was maintained even after adjusting for sex and age. We think that the study design and the group size may account for the disparate results. Studies on a possible link between lipid levels and thrombotic complications are

Table 1A: Characteristic of the study population.

<table>
<thead>
<tr>
<th>Lipid levels (mg/dl)</th>
<th>Patients</th>
<th>Controls</th>
<th>P-value</th>
<th>OR (CI95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>57.4 ± 17.3</td>
<td>57.4 ± 17.3</td>
<td>&lt;0.0001</td>
<td>1.03 (1.02-1.04)</td>
</tr>
<tr>
<td>Sex (women/men) (%)</td>
<td>171/142 (45.4/54.6)</td>
<td>187/195 (48.1/51.1)</td>
<td>0.14</td>
<td>1.35 (0.91-2.02)</td>
</tr>
<tr>
<td>Dyslipidaemia n (%)</td>
<td>44 (46.2)</td>
<td>66 (19.1)</td>
<td>&lt;0.0001</td>
<td>3.87 (2.72-5.56)</td>
</tr>
<tr>
<td>Hypertension n (%)</td>
<td>117 (37.4)</td>
<td>113 (32.7)</td>
<td>&lt;0.0001</td>
<td>2.96 (1.93-4.56)</td>
</tr>
<tr>
<td>Diabetes mellitus n (%)</td>
<td>25 (8.0)</td>
<td>32 (9.3)</td>
<td>0.002</td>
<td>3.71 (1.67-8.81)</td>
</tr>
<tr>
<td>Smoking n (%)</td>
<td>77 (24.6)</td>
<td>61 (17.7)</td>
<td>0.4087</td>
<td>1.21 (0.77-1.88)</td>
</tr>
</tbody>
</table>

Table 1B: Risk of recurrence and post-thrombotic syndrome related to HDL and LDL levels, and their ratios.

<table>
<thead>
<tr>
<th>Lipid levels (mg/dl)</th>
<th>Recurrence</th>
<th>Post-thrombotic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted OR (a)</td>
<td>P-value</td>
</tr>
<tr>
<td>HDL &lt;35 mg/dl</td>
<td>2.76 (1.12-6.94)</td>
<td>0.026</td>
</tr>
<tr>
<td>LDL &gt;180 mg/dl</td>
<td>2.22 (1.15-4.29)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

(a) Adjustment was made by age and sex. (b) Adjustment was made by cardiovascular risk factors (smoking, HTA and DM).
rare. According to the results obtained by our group which examined 772 patients with a first spontaneous thrombotic event, those patients who developed a recurrent event had HDL levels which were significantly lower (p = 0.04) than those seen in patients without recurrence (13). However, no studies have yet investigated the correlation between PTS and lipid profile.

In summary, patients with low levels of HDL and patients with high levels of LDL have an increased risk of developing a recurrent thrombotic event or PTS. Future investigations are needed to confirm these results and to clarify the impact of lipid profile in the outcome of patients with VTE. These studies may shed light on the relationship between arterial and venous thrombosis.

References