Fasting lipids and anticoagulant antibodies as risk factors for vascular disease in systemic lupus erythematosus

A J MacGregor, V B Dhillon, A Binder, C A Forte, B C Knight, D J Betteridge, D A Isenberg

Abstract
Fasting cholesterol, triglyceride, low density lipoprotein cholesterol, high density lipoprotein cholesterol, apoprotein A1, and apoprotein B were measured in 64 patients with systemic lupus erythematosus to assess the risk factors for vascular disease. The relation between the lipid profile, steroid treatment, the presence of anticoagulant antibodies, and the prevalence of vascular disease was examined. Raised concentrations of triglyceride and apoprotein B were seen in those patients treated with more than the equivalent of 10 mg prednisolone a day in the six months before testing. An increase in vascular disease was found only in the subgroup of patients with increased triglycerides who also expressed anticoagulant antibodies. This study confirms the association between treatment with high doses of steroids in lupus and the development of an atherogenic plasma lipid profile. The presence of anticoagulant antibodies compounds the risk of developing vascular disease.

Patients with systemic lupus erythematosus have an increased incidence of atherosclerosis, thrombosis, and thromboembolic disease. Some studies have linked this increased incidence of vascular disease in lupus with the expression of antiphospholipid antibodies—notably, anticoagulant antibodies.

The close correlation between the presence of antiphospholipid antibodies and the lupus anticoagulant suggests that these antibodies may play a direct part in the pathogenesis of vascular disease. Antiphospholipid antibodies act at several sites in the coagulation cascade with an overall effect in vivo of promoting thrombosis. The enhancing effect of phospholipid on the endothelial cell factor thrombomodulin is neutralised by antiphospholipid antibodies. As a result, protein C activation on the surface of endothelial cells is inhibited, promoting thrombosis and suppressing fibrinolysis. IgG antiphospholipid antibodies interfere with cell surface prostacyclin formation and lead to platelet aggregation. Direct damage to endothelial cells is also recognised. Hyperlipidaemia is a recognised risk factor for vascular disease in lupus. The importance of hyperlipidaemia in the pathogenesis of atherosclerosis has been firmly established. Raised low density lipoprotein cholesterol and its major apoprotein (apoprotein B) are highly atherogenic. Increased concentrations of high density lipoprotein cholesterol and its major apoprotein (A1) afford protection from atherosclerosis. The role of triglyceride as an independent risk factor for atherosclerosis remains uncertain. Certain triglyceride-rich lipoproteins, such as remnant particles, are highly atherogenic.

Plasma lipids may predispose to vascular disease by mechanisms similar to those postulated for the action of antiphospholipid antibodies. There is an interaction with the clotting cascade, tending to promote thrombosis. Platelet aggregation is precipitated, and lipids may directly damage vascular endothelium.

This study examines the relation between fasting lipid concentrations, anticoagulant antibodies, and vascular disease in a group of 64 patients with systemic lupus erythematosus. It examines whether the risk of vascular disease is increased when anticoagulant antibodies and an abnormal lipid profile occur together.

Patients, materials, and methods
PATIENTS
The study group comprised carefully documented patients attending a specialist lupus clinic at the Bloomsbury Rheumatology Unit. All patients fulfilled the revised criteria of the American Rheumatism Association for the classification of SLE. In 64 sequentially assessed patients fasting cholesterol, triglyceride, low density lipoprotein cholesterol and high density lipoprotein cholesterol were measured. In 46 of these patients apoprotein A1 and apoprotein B were also measured. The control population consisted of 18 healthy controls matched for age and sex.

LIPID ASSAY
Total cholesterol, triglyceride, and high density lipoprotein cholesterol were measured using Boehringer diagnostic kits by an enzymatic colorimetric method. High density lipoprotein cholesterol was obtained after precipitation of very low density lipoprotein cholesterol and low...
density lipoprotein cholesterol by heparin manganous chloride. Low density lipoprotein cholesterol was derived by calculation using the Friedewald equation. Apolipoprotein AI and B were measured by an immunoturbidimetric method (Sigma).

**ANTICARDIOLIPIN ANTIBODY ASSAY**

Acaridiolipin antibodies were assayed on at least two occasions by an enzyme linked immunosorbent assay in 61 of the lupus patients. 29

**EFFECT OF TREATMENT**

The lupus patients were split into groups according to steroid treatment. Twenty two patients had not received steroids in the six months before testing; 28 patients had been treated with the equivalent of less than 10 mg/day of prednisolone for the previous six months; 14 had received larger doses. Student's t test was used to compare patient and control groups.

**Table 1** Geometric mean of lipid and apoprotein concentrations of the group with systemic lupus erythematosus (SLE) and of the control group.

<table>
<thead>
<tr>
<th>Lipid or Apoprotein</th>
<th>Prednisolone &gt;10 mg/day</th>
<th>Prednisolone &lt;10 mg/day</th>
<th>No steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (CI)</td>
<td>Mean (CI)</td>
<td>Mean (CI)</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.5 (4.5-6.5)</td>
<td>1.4 (1.3-1.5)</td>
<td>28 (27-29)</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>1.6 (1.5-1.7)</td>
<td>1.14 (1.1-1.2)</td>
<td>28 (27-29)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>1.23 (1.2-1.3)</td>
<td>2.49 (2.4-2.5)</td>
<td>28 (27-29)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.29 (1.2-1.3)</td>
<td>1.31 (1.2-1.3)</td>
<td>28 (27-29)</td>
</tr>
<tr>
<td>Apoprotein AI (mg/l)</td>
<td>15.3 (15.2-15.4)</td>
<td>14.0 (13.9-14.1)</td>
<td>28 (27-29)</td>
</tr>
<tr>
<td>Apoprotein B (mg/l)</td>
<td>713 (712-714)</td>
<td>713 (712-714)</td>
<td>28 (27-29)</td>
</tr>
</tbody>
</table>

Table 2 Mean of the logarithm (base 10) of the lipid and apoprotein concentrations of the group with systemic lupus erythematosus (SLE) and of the control group. The 95% confidence interval is shown in parentheses.

<table>
<thead>
<tr>
<th>Lipid or Apoprotein</th>
<th>Prednisolone &gt;10 mg/day</th>
<th>Prednisolone &lt;10 mg/day</th>
<th>No steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (CI)</td>
<td>Mean (CI)</td>
<td>Mean (CI)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.740 (0.686 to 0.794)</td>
<td>0.659 (0.605 to 0.702)</td>
<td>0.705 (0.658 to 0.752)</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>0.205 (0.188 to 0.222)</td>
<td>0.056 (-0.021 to 0.132)</td>
<td>0.021 (-0.065 to 0.107)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.109 (0.082 to 0.136)</td>
<td>0.116 (0.078 to 0.154)</td>
<td>0.159 (0.112 to 0.206)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.430 (0.375 to 0.487)</td>
<td>0.483 (0.430 to 0.536)</td>
<td>0.479 (0.410 to 0.548)</td>
</tr>
<tr>
<td>Apoprotein AI (mg/l)</td>
<td>3.165 (3.098 to 3.241)</td>
<td>3.147 (3.112 to 3.178)</td>
<td>3.181 (3.132 to 3.230)</td>
</tr>
<tr>
<td>Apoprotein B (mg/l)</td>
<td>2.961 (2.882 to 3.040)</td>
<td>2.853 (2.750 to 2.956)</td>
<td>2.792 (2.698 to 2.886)</td>
</tr>
</tbody>
</table>

*The group with SLE were divided according to the steroid treatment received in the previous six months.

The prevalence of vascular disease was reported in a major report. A clearly documented history of a major vascular event was present in 13 of the 64
triglyceride range (20 out of 61 patients), seven were anticoagulant antibody positive. Five of these seven patients had had a major vascular event. This compares with only eight patients who had had vascular events in the remaining 54 patients studied. The higher prevalence of vascular disease in this subgroup of anticoagulant positive patients with high triglyceride concentrations is significant ($\chi^2$ with Yates's correction) = 8.71, degree of freedom = 1, p < 0.01). Figure 3 illustrates this increased prevalence.

**Discussion**

Vascular complications contribute significantly to the morbidity and mortality of systemic lupus erythematosus. In this study the previous observation of an atherogenic plasma lipid profile in lupus patients was confirmed. Increased concentrations of triglyceride and apoprotein B were noted in patients who had been treated with doses of corticosteroids exceeding the equivalent of 10 mg/day prednisolone in the six months before testing. We were unable to detect lipid abnormalities in the lupus patients who had received no recent steroid treatment. In particular, the low concentrations of high density lipoprotein cholesterol that have been detected previously in untreated lupus patients were not found. The presence of normal concentrations of cholesterol and low density lipoprotein cholesterol in the group in whom apoprotein B was raised suggests that these patients may have abnormally dense particles of low density lipoprotein.

Vascular disease was a common complication in the group studied. We were unable to show a
direct relation between lipid concentrations and the prevalence of major vascular episodes. This is not surprising given the relatively small size of the group studied. Restricted patient numbers may also account for the lack of significant correlation between the expression of anticardiolipin antibodies and vascular disease. Previous studies have reported discordant results about this possible link. Some studies have described a strong positive association between anticardiolipin antibodies and thrombotic events. Others have not confirmed this. In this study vascular events were particularly common in those patients who had both an increased triglyceride concentration and who expressed anticardiolipin antibodies. This suggests that the two abnormalities compound the risk of vascular disease.

Multiple factors are likely to influence the risk of developing vascular complications in lupus. This study confirms the importance of anticardiolipin antibodies and steroid induced abnormalities in the fasting lipid profile in contributing to the pathogenesis of vascular disease in these patients. Possibly these two risk factors may be more intimately linked by similar participation in the mechanism of coagulation.

Fasting lipids and anticardiolipin antibodies as risk factors for vascular disease in systemic lupus erythematosus.

A J MacGregor, V B Dhillon, A Binder, C A Forte, B C Knight, D J Betteridge and D A Isenberg

doi: 10.1136/ard.51.2.152