Antiphospholipid, anti-β2-glycoprotein-I and anti-oxidized-low-density-lipoprotein antibodies in antiphospholipid syndrome

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Summary

Antiphospholipid antibodies (aPL), anti-β2-glycoprotein I (anti-β2-GPI) and anti-oxidized-low-density lipoprotein (LDL) antibodies are all implicated in the pathogenesis of antiphospholipid syndrome. To investigate whether different autoantibodies or combinations thereof produced distinct effects related to their antigenic specificities, we examined the frequencies of antiphospholipid syndrome (APS)-related features in the presence of different antibodies [aPL, β2-GPI, anti-oxidized low density lipoprotein (LDL)] in 125 patients with APS. Median follow-up was 72 months: 58 patients were diagnosed as primary APS and 67 as APS plus systemic lupus erythematosus (SLE). Anticardiolipin antibodies (aCL), anti-β2-GPI and anti-oxidized LDL antibodies were determined by ELISA; lupus anticoagulant (LA) by standard coagulometric methods. Univariate analysis showed that patients positive for anti-β2-GPI had a higher risk of recurrent thrombotic events (OR = 3.64, 95%CI, p = 0.01) and pregnancy loss (OR = 2.99, 95%CI, p = 0.004). Patients positive for anti-oxidized LDL antibodies had a 2.24-fold increase in the risk of arterial thrombosis (2.24, 95%CI, p = 0.03) and lower risk of thrombocytopenia (OR = 0.41 95%CI, p = 0.04). Patients positive for aCL antibodies had a higher risk of pregnancy loss (OR = 4.62 95%CI, p = 0.001). When these data were tested by multivariate logistic regression, the association between anti-β2-GPI and pregnancy loss and the negative association between anti-oxidized LDL antibodies and thrombocytopenia disappeared.

Introduction

Antiphospholipid syndrome (APS) has been defined as the occurrence of thrombosis (arterial or venous), fetal loss and/or thrombocytopenia, in the presence of antiphospholipid antibodies (aPL). Since the initial report,¹² numerous studies have confirmed the strong link between aPL, mainly anticardiolipin (aCL) and lupus anticoagulant (LA), and such symptoms, in patients with both primary and secondary APS.³⁴ Recent data indicate that the antigenic targets of antibodies detected in conventional aCL and LA assays are phospholipid-binding plasma proteins or complexes of these proteins with phospholipid. These proteins have been identified as β2-glycoprotein I (β2-GPI) for aCL⁵–⁷ and prothrombin for LA.⁸⁹ These autoantibodies seem to be not only markers of disease, but also direct contributors to the development of thrombosis, fetal loss and thrombocytopenia.¹⁰–¹³ Antibodies binding to oxidized low-density
lipoprotein (LDL) might also be considered aPL because LDL contains both phospholipid and a lipid-binding protein—apolipoprotein B. Antibodies to oxidized LDL are associated with atherosclerosis and arterial thrombosis.

Since these autoantibodies play a role in the pathogenesis, and they and their targets are extremely heterogeneous, it is reasonable to assume that different autoantibodies or combination of autoantibodies will display distinct effects directly related to their antigenic specificities, which might explain the observed clinical spectrum of APS.

In the present study, we sought to assess the association of these autoantibodies (aPL, anti-β2-GPI and anti-oxidized LDL) with APS symptoms, in an attempt to classify patients with APS into low- or high-risk groups.

**Methods**

**Patients**

Serum samples were obtained from 125 patients (102 female, 23 male) with APS attending the Lupus Clinic at St Thomas’ Hospital, London. All patients satisfied criteria for the diagnosis of APS. Fifty-eight were diagnosed as primary APS, while the others (67 patients) fulfilled criteria for the classification of SLE. Thrombotic events were diagnosed by image techniques (deep venous thrombosis by venography or ultrasonography; pulmonary embolism by radionuclide lung scanning or angiography; thrombosis in intracerebral vessels by computed tomographic scanning, magnetic resonance imaging, or angiography; peripheral or mesenteric artery thrombosis by arteriography or at surgery). Retinal thrombosis was diagnosed by ophthalmological examination. The diagnosis of myocardial infarction required an acute clinical presentation with typical electrocardiographic features and an elevated creatine kinase MB fraction. A diagnosis of cerebral transient ischaemic attack required neurologic symptoms or signs lasting <24 h in a patient who met the criteria for the classification of cerebrovascular disease of the National Institute of Neurological Disorders and Stroke. The diagnosis of amaurosis fugax was established when sudden monocular blindness lasted <24 h.

For data analysis, we considered all symptoms suffered by the patients since the diagnosis of the APS until serum samples were obtained. Clinical data were taken from the patient’s file.

Control sera for the anti-β2-GPI and anti-oxidized LDL antibodies were taken from 70 sex-matched young healthy donors.

**Anticardiolipin antibodies**

aCL antibodies were determined by enzyme-linked immunosorbent assay (ELISA).

**Lupus anticoagulant (LA)**

Because many patients were on Warfarin at the time of the study, data regarding LA were taken from the patient’s files if available. A LA was present when prolonged dilute Russell’s viper venom time was corrected after platelet neutralization.

**Purification of β2-GPI**

Human β2-GPI was purified by perchloric acid treatment of normal plasma. Perchloric acid (2.5 ml) was added to 100 ml plasma, dropwise under constant stirring. It was left to stand for 30 min at 4 °C with constant stirring and followed by centrifugation for 30 min (10,000 rpm, 4 °C). The supernatant was neutralized with 1M sodium hydroxide and dialysed against 20 mM Tris/HCl buffer (pH 7.4). This was further purified by ion-exchange chromatography on QAE-Sephadex A–50 (Pharmacia Biotech) with 20 mM Tris and increasing molarity of NaCl (20–500 mM), and characterized by sodium dodecyl sulphate-polyacrilamide gel electrophoresis and immunoblotting with the reference β2-GPI and rabbit antiserum (Boehringer).

**Anti β2-GPI bodies (ELISA)**

Irradiated microtitre plates (Dynatech) were coated with 100 ml/well of 10 mg/ml purified β2-GPI in 0.1M carbonate buffer (pH 9.5, coating buffer) overnight at 4 °C. After washing three times with phosphate-buffered saline (PBS, 100 ml/well), plates were blocked with 1% BSA/PBS (100 ml/well) for 2 h at room temperature. Test serum samples diluted 1:100 in 1% BSA/PBS were then added to block plates (50 ml/well). After 3 h incubation at room temperature, plates were washed with PBS and 50 ml/well of conjugated alkaline phosphatase. Affinity-purified goat anti-human IgG (Sigma), diluted 1:500 in 1% BSA/PBS, was added to each well and incubated for 1 h. Plates were then washed three times and 50 ml of 1 mg/ml p-nitrophenyl phosphate (Sigma) in diethanolamine buffer (pH 9.8) was added. After 70 min., the absorbance was read at 405 nm. Rabbit anti-β2-GPI (Boehringer), was used as a positive control of antigen coating.

Values higher than the mean +3SD of healthy donors were considered positive.

**LDL isolation**

LDL was isolated from pooled plasma of healthy fasting human donors by density gradient ultracentri-
fugation at 65 000 rpm (Beckman L8–70, rotor VTI 65) for 35 min at 4 °C and subsequently further purified in a second density gradient ultracentrifugation (49 000 rpm, 18 h, 4 °C). The LDL was then dialysed against PBS (4 °C for 30 h) (0.14 M NaCl/0.01 M phosphate buffer).

**Oxidation of LDL**

Oxidized LDL was prepared by incubating the LDL for 3 h at 37 °C with 0.5 M malondialdehyde (MDA) at a constant ratio of 100 ml/mg of LDL. MDA was freshly generated from MDA-bis-dimethylacetal by acid hydrolysis: MDA-bis-dimethylacetal (88 ml) was incubated with 12 ml 4M HCl and 400 ml of water at 37 °C for 10 min. The reaction was stopped by adjusting the pH to 7.4 with 1M NaOH, subsequently adjusting the volume to 1 ml with distilled water. After conjugation, MDA-LDL was extensively dialysed against PBS to remove any unreacted MDA.

**Anti-oxidized LDL antibodies**

Microtitre plates for determination of anti-oxidized LDL antibodies were coated with either native or with MDA-LDL, both at 10 mg/ml in PBS. The plates were incubated for 2 h at 37 °C and overnight at 4 °C. After washing four times with PBS, plates were blocked with 1% BSA/PBS for 2 h at room temperature. Serum samples were diluted 1:100 in 1% BSA/PBS and incubated for 3 h at room temperature. After washing, an alkaline phosphatase-conjugated anti-human IgG (Sigma) was diluted 1:1000 in 1% BSA/PBS and added. It was left then for 3 h at room temperature. 1mg/ml p-nitrophenyl-phosphate (Sigma) in 500 mM carbonate buffer containing 1mM MgCl₂ (pH 9.8) was used as substrate. The reaction was stopped with 1M NaOH after 60 min. The absorbance was read at 405 nm, and results were expressed as optical densities. Binding of antibodies to oxidized LDL was calculated by subtracting the binding of native LDL from binding to MDA-LDL.

Values higher than the mean + 3SD of healthy donors were considered positive.

**Statistical analysis**

Data was analysed using SPSS on IBM PCs. The differences regarding the various clinical parameters, between aCL, LA, anti-β2-GPI and anti-oxidized LDL-positive and -negative patients, were evaluated using the $\chi^2$ test or Fisher’s exact test where applicable. $p<0.05$ was regarded as statistically significant.

The risk for the development of APS-related symptoms for patients with different autoantibodies (aCL, LA, anti-β2-GPI and anti-oxidized LDL) was estimated from odds ratios (OR) with a 95% confidence interval (95% CI).

For a more precise analysis, we distributed the values of anti-β2-GPI and anti-oxidized LDL antibodies in quartiles. The risk for the development of APS-related disorders into the four categories defined for anti-β2-GPI and anti-oxidized LDL antibodies was calculated by Likelihood Ratio (LR) in each quartile.

Multivariate logistic regression analysis assessed the independent effects of the factors which showed statistically significant association in the univariate analysis. A logistic regression model was used (inclusion $p<0.10$ and exclusion $p>0.15$). For this analysis, aCL and LA were categorized as positive or negative. Anti-β2-GPI and anti-oxidized LDL antibodies were also divided into two categories: higher or lower than the mean value of patients. The autoantibodies were considered as independent variables and the APS-related symptoms as dependent variables.

**Results**

Table 1 shows the characteristics of patients. The high number of female patients in this study is probably due to referral bias to our SLE and APS pregnancy clinic. Of 102 women in the study, 79 became pregnant at some time during follow-up, and 49 had one or more fetal losses. No LA test was performed in 23 patients who were receiving oral anticoagulant treatment. The mean (SD) for anti-β2-GPI antibodies was 0.23 (0.04) and that for anti-oxidized LDL antibodies was 0.24 (0.18).

There were no statistically significant differences

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>125 (100)</td>
</tr>
<tr>
<td>Female</td>
<td>102 (81.6)</td>
</tr>
<tr>
<td>Male</td>
<td>23 (28.4)</td>
</tr>
<tr>
<td>Median age (years) (range)</td>
<td>38 (20–66)</td>
</tr>
<tr>
<td>Median duration of APS (range)</td>
<td>81 (21–120)</td>
</tr>
<tr>
<td>Primary APS</td>
<td>58 (46.4)</td>
</tr>
<tr>
<td>APS plus SLE</td>
<td>67 (53.6)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>111 (88.8)</td>
</tr>
<tr>
<td>Arterial</td>
<td>62 (53.8)</td>
</tr>
<tr>
<td>Venous</td>
<td>44 (39.6)</td>
</tr>
<tr>
<td>Both</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>Recurrent thrombotic events</td>
<td>83 (66.7)</td>
</tr>
<tr>
<td>Pregnancy loss</td>
<td>49/79 (62)</td>
</tr>
<tr>
<td>Thrombocytopenia (platelets &lt;150 000)</td>
<td>33 (26.4)</td>
</tr>
<tr>
<td>Positive anticardiolipin antibody test (IgG and/or IgM)</td>
<td>90 (72)</td>
</tr>
<tr>
<td>Positive lupus anticoagulant test</td>
<td>71/102 (69.5)</td>
</tr>
</tbody>
</table>
between patients with primary APS and patients with APS plus SLE, regarding APS-related symptoms or antibody profiles.

Univariate analysis (Table 2) showed that patients positive for anti-β2-GPI antibodies have a higher risk of suffering recurrent thrombotic events (OR = 3.64, \(p = 0.01\)) and pregnancy loss (OR = 2.99, \(p = 0.004\)) than those negative for such antibodies. This analysis also showed that those patients positive for anti-oxidized LDL antibodies had a 2.24-fold increase in the risk (\(p = 0.03\)) of arterial thrombosis and a lower risk of thrombocytopenia (OR = 0.41, \(p = 0.04\)). Finally, patients positive for aCL antibodies showed a higher risk of pregnancy loss (OR = 4.62, \(p = 0.001\)).

We divided the values of anti-β2-GPI and anti-oxidized LDL antibodies into four quartiles, to determine more precisely which values of these antibodies were associated with a higher risk of developing the clinical associations found in the univariate analysis. A high level of anti-β2-GPI (highest quartile of distribution) showed the strongest association with the presence of recurrent thrombosis (OR = 3.17) (Table 3). Anti-oxidized LDL antibodies levels above the p50 showed the highest risk for developing arterial thrombosis (OR = 4.66). Levels above the p75 did not show statistical significance, probably because of the small number of patients in this group (3 patients) (Table 3).

Statistically significant associations found in the univariate analysis were tested in multivariate logistic regression model that also included all potentially confounding variables such as age, length of follow-up, smoking, diagnosis (primary APS or APS plus SLE), treatment and the presence of other antibodies.

When the association between the value of anti-oxidized LDL antibodies and arterial thrombosis was tested in a regression logistic model, age, smoking, treatment with aspirin, aCL and anti-β2-GPI antibodies were included as potentially confounding factors (Table 4). The analysis showed an increase in the OR between positive values of anti-oxidized LDL antibodies and the presence of arterial thrombosis (OR = 5.2, \(p = 0.0024\)).

The association between anti-β2-GPI and aCL antibodies and a history of pregnancy loss was also tested in a logistic regression model. This model included aCL and LA antibodies, smoking and treatment with Warfarin (Table 5). The statistically significant association between positive anti-β2-GPI antibodies levels and pregnancy loss disappeared. Positive aCL antibodies test appeared as an independent risk factor for pregnancy loss (OR = 5.63, \(p = 0.0043\)).

When the association between positive values of anti-β2-GPI antibodies and recurrent thrombotic events were tested, no possible confounding factors appeared in the logistic regression model. Therefore, the OR value found in the univariate analysis was not modified.

The negative association between positive levels of anti-oxidized LDL antibodies and thrombocyto-

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**Table 2** Associations between the different antibodies and APS-related features (univariate analysis)

<table>
<thead>
<tr>
<th></th>
<th>Anti-β2-GPI</th>
<th>Anti-oxidized LDL</th>
<th>aCL</th>
<th>LA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR  95% CI</td>
<td>OR  95% CI</td>
<td>OR  95% CI</td>
<td>OR  95% CI</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>0.55 (0.27–1.13)</td>
<td>2.24 (1.08–4.64)</td>
<td>1.97 (0.88–4.39)</td>
<td>0.77 (0.32–1.87)</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>0.94 (0.45–1.97)</td>
<td>0.64 (0.30–1.36)</td>
<td>1.90 (0.85–4.28)</td>
<td>0.92 (0.36–2.38)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.86 (0.32–2.26)</td>
<td>0.52 (0.19–1.48)</td>
<td>1.50 (0.54–4.14)</td>
<td>1.43 (0.40–5.08)</td>
</tr>
<tr>
<td>Recurrent thrombosis</td>
<td>3.64 (1.40–9.48)</td>
<td>1.20 (0.52–2.75)</td>
<td>0.43 (0.17–1.03)</td>
<td>0.46 (0.17–1.22)</td>
</tr>
<tr>
<td>Fetal loss</td>
<td>2.99 (1.12–7.98)</td>
<td>0.67 (0.27–1.68)</td>
<td>4.62 (1.68–12.7)</td>
<td>2.43 (0.75–7.80)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.96 (0.43–2.14)</td>
<td>0.41 (0.17–0.97)</td>
<td>1.61 (0.63–4.18)</td>
<td>1.42 (0.51–3.96)</td>
</tr>
</tbody>
</table>

**Table 3** Likelihood ratio for the development of recurrent thrombotic events and abortions for patients in the four percentiles defined for anti-β2GPI and anti-oxidized LDL antibodies

<table>
<thead>
<tr>
<th>Anti-β2-GPI antibodies</th>
<th>Anti-oxidized LDL antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent thrombosis</td>
<td>Arterial thrombosis</td>
</tr>
<tr>
<td>Fetal loss</td>
<td>Arterial thrombosis</td>
</tr>
<tr>
<td>0–p25</td>
<td>0.94 (0.49–1.91)</td>
</tr>
<tr>
<td>p25–p50</td>
<td>0.71 (0.39–1.32)</td>
</tr>
<tr>
<td>p50–p75</td>
<td>0.75 (0.39–1.50)</td>
</tr>
<tr>
<td>p75–p100</td>
<td>3.17 (1.12–9.67)</td>
</tr>
</tbody>
</table>

Data are likelihood ratios (95% CIs).
Table 4 Multifactorial logistic regression analysis of arterial thrombosis

| Regression coefficient (SE) | p   |
|----------------------------|--|---|
| Anti-oxidized LDL (positive/negative) | 1.41 (0.47) | 0.0030 |
| Age (>45 yrs) | 1.35 (0.56) | 0.0162 |
| Smoking (yes/no) | 1.31 (0.49) | 0.0078 |
| Treatment with Aspirin (yes/no) | 1.35 (0.47) | 0.0043 |
| aCL (positive/negative) | 1.42 (0.56) | 0.0104 |
| anti-β2GPI (positive/negative) | -1.78 (0.54) | 0.0011 |
| Whole model | | 0.0000 |

Table 5 Multifactorial logistic regression analysis of fetal loss

| Regression coefficient (SE) | p   |
|----------------------------|--|---|
| aCL (positive/negative) | 1.94 (0.62) | 0.0018 |
| LA (positive/negative) | 1.34 (0.70) | 0.0551 |
| Smoking (yes/no) | -1.27 (0.60) | 0.0338 |
| Treatment with Warfarin (yes/no) | -0.92 (0.56) | 0.099 |
| Whole model | | 0.0001 |

penia disappeared when tested in a logistic regression model which included treatment with aspirin and patients with primary APS or APS plus SLE. (OR = 0.4191, p = 0.075).

**Discussion**

Despite a decade of clinical studies, our present knowledge about APS is derived from retrospective case series, case-control studies, prospective follow-up studies and very few therapeutic clinical trials. Thus, we have still to identify the risk factors that might stratify patients at different likelihoods of developing clinical complications.

In contrast to previous studies, no correlation was found between the presence of aCL, anti-β2-GPI and LA with the first thrombotic event. This could possibly be due to either fluctuation in antibody levels or the retrospective nature of our study.

Our results show that positive values of anti-oxidized LDL antibodies were associated with arterial thrombosis. These results agree with a recent study which showed a prevalence of anti-oxidized LDL antibodies of 23.4% in APS patients and higher levels of these antibodies in patients with arterial thrombosis compared to those without arterial thrombosis. In our study, the risk for arterial thrombosis in patients with anti-oxidized LDL antibodies was 2.24 compared with patients without these antibodies. The association of confounding factors (aCL and anti-β2-GPI antibodies) increased the risk to 5.2

Although Vaarala et al. showed that patients with high levels of aCL antibodies had a higher risk of myocardial infarction, and that this risk was independent of any other factors, they also showed a correlation between the levels of aCL antibodies and antibodies to oxidized LDL. Their joint effect was additive for the risk of myocardial infarction. All these results suggest that anti-oxidized LDL antibodies may play a role in the development of arterial thrombosis. The mechanisms which can lead to arterial thrombotic events in APS remains unknown.

Recent data have shown that antibodies binding to a complex of cardiolipin and β2-GPI crossreact with anti-oxidized LDL antibodies in patients with SLE. Therefore, anti-oxidized LDL antibodies might be involved, due to shared common epitopes with aCL antibodies. Also, the presence of these antibodies may be an indirect measure of serum high levels of oxidized LDL. Several mechanisms can explain the contribution of oxidized LDL to arterial thrombotic events. First, it has been reported that persistent exposure of endothelium to oxidized LDL can activate these cells and eventually lead to cell injury. Activated endothelial cells acquire characteristics on their luminal surface leading to thrombin generation and fibrin production. Second, oxidized LDL can activate circulating monocytes and they can also acquire procoagulant properties. Third, oxidized LDL has been reported to stimulate aggregation of platelets. These hyperaggregable platelets adhere to activated endothelial cells which express von Willebrand factor on their surface and to subendothelial proteins exposed in the gaps that open between injured endothelial cells.

We did not find a higher risk for venous thrombosis in patients with raised levels of anti-oxidized LDL antibodies. It is known that when recurrent thrombosis was analysed in the same patient, an arterial thrombosis was followed by an arterial thrombosis in more than 90% of cases and a venous thrombosis was followed by a venous thrombosis in more than 70%. Our data showed the same trend. These results suggest that arterial and venous thrombosis might have different pathogenic mechanisms in APS as in other thrombophilic disorders. Anti-oxidized LDL antibodies would be markers for arterial but not for venous thrombosis. No relationship between anti-oxidized LDL and fetal loss was found.

In our study, a high level of anti-β2-GPI antibodies (highest quartile of distribution) was associated with
a 3.6-fold increase in the risk of recurrent thrombotic events. The presence of anti-β2-GPI and the IgG isotype of aCL antibodies have been widely associated with primary thrombosis in APS. As far as we know, no risk factors for recurrent thrombotic events have been previously identified. Although this finding must be confirmed in prospective studies, it might have important therapeutic implications, since prophylactic treatment for recurrence of thrombosis in APS patients is still controversial. The most recent and largest retrospective studies suggest that these patients should receive high-intensity Warfarin [International Normalized Ratio (INR) > 3] on a long-term basis, to avoid recurrences. Only one prospective study has analysed the issue of prophylactic anticoagulant therapy in APS. In this study, the recurrent thrombotic events in 11 APS patients with venous thrombosis and a control group of 34 patients with venous thrombosis but without APS were analysed. The follow-up time was 6 months. All were treated with Warfarin targeted to an INR between 2.0 and 3.0. Results showed a similar incidence of recurrences in both groups following discontinuation of Warfarin. As this study had a small number of patients and a short follow-up, it is uncertain whether these observations will be applicable to a larger series of APS patients over a longer follow-up.

Forty-nine out of 79 (62%) pregnant women had miscarriages during the follow-up period. The results showed that the risk of fetal loss was associated only with the presence of aCL antibodies. The apparent association with anti-β2-GPI antibodies found in the univariate analysis disappeared in the multifactorial logistic regression model. The association between miscarriages and aCL antibodies has been widely described in numerous retrospective studies and in some prospective studies. The consensus is that high levels of aPL are predictive of pregnancy loss, but few studies have examined the risk for adverse fetal outcome associated with aPL. Lockwood et al. reported that the relative risk of fetal mortality was increased over sevenfold in their aPL-positive group. Similar results were obtained by Pattison et al. (RR = 7.62). Lynch et al. reported that the relative risk of an adverse fetal outcome was increased for all measures of aPL except IgM and IgA aCL. Following adjustment for confounding variables (maternal age, race, cigarette smoking and gestational age at the first prenatal visit), an abnormality of the aPL profile or an elevated IgG aCL remained independent risk factors for an adverse fetal outcome. In our study, only the presence of aCL antibodies was a risk factor for recurrent fetal loss. LA did not appear as a risk for a poor fetal outcome. Triplett et al. suggested that LA and aCL antibodies have independent effects on the risk of pregnancy loss and thrombosis, and that it is difficult to quantify the associated risk with the different aPL. Finally, a study from Rix et al. reported that the highest prevalence of fetal loss occurred in the subset of their cohort who had the highest levels of IgG aCL. Recent studies suggest that anti-β2-GPI or anti-prothrombin antibodies are more closely associated with fetal loss and thrombosis than aPL. In our study, although anti-β2-GPI antibodies appeared as a risk factor for pregnancy loss in univariate analysis, the logistic regression model containing aCL and LA, showed that anti-β2-GPI antibody was only a confounding factor. The disparity between the literature and our own results might be the consequence of different factors as the definition for recurrent pregnancy loss, the variability of the techniques to determine the different antibodies and the spontaneous fluctuations of these antibodies.

In summary, in an attempt to identify subgroups of APS patients with different risks to develop APS related symptoms, we found that the risk for arterial thrombosis was increased in patients with levels of anti-oxidized LDL antibodies over the third quartile of distribution. Patients with the highest levels of anti-β2-GPI antibodies had a 3.1-fold increased risk of recurrent thrombotic events and patients with aCL antibodies had a higher risk of pregnancy loss. Although these results must be confirmed by prospective studies, they might have important therapeutic consequences.

Acknowledgements

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