Anti-ß$_2$-Glycoprotein I: Prevalence, Clinical Correlations, and Importance of Persistent Positivity in Patients with Antiphospholipid Syndrome and Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Antibodies to ß$_2$-glycoprotein I (anti-ß$_2$-GPI) are found in a large percentage of patients with primary or secondary antiphospholipid syndrome (APS). Our aim was to identify the prevalence and clinical correlation of these antibodies in patients with APS and systemic lupus erythematosus (SLE), in comparison to anticardiolipin (aCL) and the lupus anticoagulant (LAC). We investigated whether serial samples improve clinical utility.

Methods. Serum samples for anti–ß$_2$-GPI (IgG, IgM, IgA), aCL (IgG, IgM, IgA), and LAC (by dilute Russell viper venom time; RVVT) were collected from 418 consecutive patients with SLE or APS between October 2002 and March 2003. Clinical and serologic data of these patients were analyzed.

Results. A total of 185 (44.5%) patients were positive for anti–ß$_2$-GPI, 55.3% were positive for aCL, and 31.1% for LAC. Anti-ß$_2$-GPI was more common in Caucasians than in African Americans ($p = 0.098$). IgM and IgA were the most frequent isotypes of anti-ß$_2$-GPI. aCL and anti-ß$_2$-GPI were highly associated ($p < 0.0001$ to $p = 0.0177$, depending on isotype). A positive association was found between the presence of the LAC by dilute RVVT and anti-ß$_2$-GPI IgG ($p < 0.0001$), IgM ($p < 0.0001$), and IgA ($p = 0.0002$) antibodies. Persistent positivity increased the association of venous and arterial thrombosis with anti-ß$_2$-GPI (IgG and IgM isotypes). Pregnancy loss, seizures, and migraines were not associated with anti-ß$_2$-GPI. IgA anti-ß$_2$-GPI was not significantly associated with any manifestation of APS.

Conclusion. The prevalence of anti-ß$_2$-GPI IgM and IgA was very high in our population. Measurement of anti-ß$_2$-GPI IgG is clinically useful in identifying patients with SLE at higher risk for venous and arterial thrombosis. Persistent positivity increased the association of IgG anti-ß$_2$-GPI with venous thrombosis and anti-ß$_2$-GPI IgM with arterial thrombosis. IgA anti-ß$_2$-GPI was not significantly associated with APS manifestations. (J Rheumatol 2006;33:1775–9)

Key Indexing Terms:
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Antiphospholipid antibodies (aPL) bind to plasma proteins with an affinity for phospholipid surfaces. Many of the identified antigens (ß$_2$-glycoprotein and prothrombin) are involved in blood coagulation. Anticardiolipin antibodies (aCL) and the lupus anticoagulant (LAC) are included in classification criteria, but the importance of other aPL, including anti-ß$_2$-glycoprotein I (anti-ß$_2$-GPI), is not yet accepted. LAC and aCL IgG and IgM antibodies are associated with the clinical features of the antiphospholipid syndrome (APS): venous and arterial thrombosis and pregnancy morbidity. In addition, aCL and LAC have been associated with a spectrum of other clinical manifestations, such as thrombocytopenia, livedo reticularis, and seizures. The syndrome can occur as a primary disorder or may be secondary to a connective tissue disease, especially systemic lupus erythematosus (SLE).

The major target antigen of aCL and many lupus anticoagulants is ß$_2$-GPI. ß$_2$-GPI is a 50 kDa lipophilic plasma protein (formerly called apolipoprotein H) that is composed of 5 fingerlike domains. In 1990 several groups[1-3] described ß$_2$-GPI as the cofactor required for antiphospholipid antibody-phospholipid interaction. The lipid-binding site resides in domain 5 but aPL bind to domain 1. *In vivo*, ß$_2$-GPI binds to negatively charged phospholipids (phosphatidylserine) on activated or apoptotic cell membranes. There is currently no consensus on the clinical utility of anti-ß$_2$-GPI in comparison to LAC or aCL testing[4-11].

In this study, anti-ß$_2$-GPI (IgG, IgM, and IgA) was measured in patients with SLE and APS in order to clarify the prevalence of the antibodies, their association with the clinical features of the APS syndrome, and the importance of persistent positivity.

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MATERIALS AND METHODS

Serum samples were obtained from 418 consecutive and unselected patients (396 women, 24 men) from the Lupus Center at the Johns Hopkins Hospital, Baltimore, between October 2002 and March 2003. Both aCL and anti-$ß_2$-GPI were measured using Inova assays (Inova Diagnostics, San Diego, CA, USA). The dilute Russell viper venom time (dRVVT) test was performed as described[12], with mixing and confirmatory studies.

Interassay precision for the anti-$ß_2$-GPI assay was assessed at 4 levels of antibody activity using 4 standards supplied by the manufacturer. These were run with each run and the mean, standard deviation, and coefficient of variation percentage calculated for cumulative runs. These data are summarized for 10 runs in Table 1.

Patients were classified as having primary APS (1.2%), APS secondary to SLE (17%), SLE with any aPL (54.3%), and SLE without aPL (27.5%). All the patients classified as having SLE fulfilled at least 4 of the 1982 revised criteria of the American College of Rheumatology[13]. To be classified as APS, patients had to meet the Sapporo criteria proposed by the international consensus committee[14]. There were 237 Caucasians (56.7%), 157 African Americans (37.5%), and 24 other ethnicity, including Hispanic and Asian (5.7%).

Medical records of each patient were reviewed to ascertain the clinical manifestations of APS, including: venous thrombosis, arterial thrombosis, pregnancy loss, thrombocytopenia, and livedo reticularis. Migraines and seizures were also recorded. Venous thrombosis was confirmed by venogram or ultrasound. Arterial thrombosis was confirmed by computerized tomography, magnetic resonance imaging, or arteriogram.

Statistical analysis. Statistical analyses were done using chi-square and Fisher's exact tests (JMP v 5.0.1a, SAS Institute Inc., Cary, NC, USA). A p value of 0.05 was taken as statistically significant. All analyses were prespecified, and Bonferroni corrections were not applied.

RESULTS

Prevalence of aCL, LAC, and anti-$ß_2$-GPI. Of the 418 patients, 186 tested positive for anti-$ß_2$-GPI of at least one isotype, representing 44.5% of the entire population (Table 2). Among the patients who tested positive for any anti-$ß_2$-GPI (186 patients), 29.6% were IgG, 65% IgM, and 50% IgA; 137 (73.7%) patients were positive for both anti-$ß_2$-GPI and aCL antibodies; 77 (41.4%) were positive for both anti-$ß_2$-GPI and the LAC (dRVVT). The prevalence of LAC (by dRVVT) in our population was 31.1% (130 patients). Only 5 patients with primary APS were included: 4 were positive for anti-$ß_2$-GPI, 3 were positive for aCL, and all 5 were positive for LAC.

Table 3 shows the distribution of anti-$ß_2$-GPI isotypes by ethnicity. There was a striking difference in IgM anti-$ß_2$-GPI, which was more common in Caucasians.

Thirty-seven of 418 (9%) were positive for anti-$ß_2$-GPI, but negative for both aCL and LAC. Of 187 patients negative for aCL, 49 (26%) had anti-$ß_2$-GPI (7 IgG, 24 IgM, and 27 IgA) and 44 (23.5%) had LAC.

Table 1. Precision of the anti-$ß_2$-GPI assay.

	Anti-$ß_2$-GPI Concentration			
	18.75	37.5	75	150
IgG	18.7, 37, 2.1	37, 3.2, 6.5	78, 3.9, 7.6	144, 1.1, 3.2
IgM	18.5, 98, 5.5	39.1, 1.0, 2.7	79, 3.2, 5.8	141, 1.8, 3.3
IgA	17.8, 0.94, 5.3	39, 0.82, 2.1	79.9, 0.77, 4.2	147, 1.0, 3.4

The mean, standard deviation, and coefficient of variation percentage for 10 cumulative runs for each antibody concentration.

Table 2. Prevalence of anti-$ß_2$-GPI. Comparison of anti-$ß_2$-GPI titers, by isotype, in 418 patients.

	IgG+	IgM+	IgA+	Any +
Anti-$ß_2$-GPI-positive	55 (13.2%)	121 (28.9%)	93 (22.2%)	186 (44.5%)

Prevalence of clinical features in anti-$ß_2$-GPI-positive patients. Table 4 shows the prevalence of clinical features by anti-$ß_2$-GPI status.

Importance of persistent positivity for anti-$ß_2$-GPI. Patients with SLE were seen routinely at 3-month intervals; at the second visit, repeat samples were collected for anti-$ß_2$-GPI. Thirty-four out of 138 tested twice were persistently positive for anti-$ß_2$-GPI. Table 5 shows that persistent positivity for anti-$ß_2$-GPI was more strongly associated with arterial and venous thrombosis for the IgG isotype and with arterial thrombosis for the IgM isotype. Pregnancy loss was not associated with anti-$ß_2$-GPI of any isotype. Livedo reticularis was only associated with IgG and IgA isotypes.

In data not shown, no assay was associated with seizures or migraines.

Thrombosis. In those with a history of thrombosis (93 patients), anti-$ß_2$-GPI was detected in 44 patients (47.3%), aCL in 52 (55.9%), and LAC in 53 (57%). In 21 patients with a history of thrombosis negative for both LAC and aCL, 4 had anti-$ß_2$-GPI (0 IgG, 2 IgM, 3 IgA). In 41 patients with a history of thrombosis who were negative for aCL antibodies, 20 had the LAC and 9 had anti-$ß_2$-GPI (1 IgG, 2 IgM, and 8 IgA). In 40 patients with a history of thrombosis who were negative for LAC, 10 had anti-$ß_2$-GPI and 19 had aCL (6 IgG, 17 IgM, and 1 IgA).

DISCUSSION

Anti-$ß_2$-glycoprotein I was highly prevalent in our series. Strikingly, it was more prevalent in Caucasians than in African Americans. IgM and IgA anti-$ß_2$-GPI were the most prevalent isotypes. The high prevalence of IgA over other isotypes has been found in SLE[15], APS[16], and cancer[17]. Anti-$ß_2$-GPI was found rarely in our patients who were negative for both aCL and LAC, but was found more often in those negative for just aCL, in agreement with previous studies[16,18,19].

Anti-$ß_2$-GPI is associated with arterial and venous thrombosis. These associations are greater when anti-$ß_2$-GPI is persistently positive. Thus, the requirement of the Sapporo classification criteria that aCL and LAC assays be positive twice (6 weeks apart) should now be extended to anti-$ß_2$-GPI. Several groups[20-23] have found no association of anti-$ß_2$-GPI with thrombosis, but many have[5-9,11,24-30], as reviewed in Galli, *et al*[31].

Livedo reticularis was associated with IgG and IgA anti-

Table 3. Distribution of anti-ß$_2$-glycoprotein I, by ethnicity. Number positive for each anti-ß$_2$-GPI isotype (percentage of total, N = 418).

Race	Total no.	Anti-ß$_2$-GPI, IgG+	Anti-ß$_2$-GPI, IgM+	Anti-ß$_2$-GPI, IgA+	Anti-ß$_2$-GPI, Any +
Caucasian	238 (60.3)	35 (8.9)	86 (21.8)	52 (13.2)	113 (27.1)
African American	157 (39.7)	17 (4.3)	32 (8.1)	35 (8.9)	61 (14.6)
p		0.29	0.0008	1.0	0.0982

Table 4. Comparison of clinical features in anti-ß$_2$-GPI positives and negatives.

	No Anti-ß$_2$-GPI, n = 233 (%)	Any Anti-ß$_2$-GPI, n = 185 (%)	Anti-ß$_2$-GPI, IgG, n = 45 (%)	Anti-ß$_2$-GPI, IgM, n = 123 (%)	Anti-ß$_2$-GPI, IgA, n = 98 (%)
Arterial thrombosis	26 (11.1)	23 (12.4)	4 (8.8)	12 (9.7)	16 (16.3)
Venous thrombosis	22 (9.4)	29 (15.7)	8 (17.7)	20 (16.2)	17 (17.3)
Pregnancy loss	61 (26)	42 (22.7)	8 (17.7)	28 (22.8)	22 (22.4)
Thrombocytopenia	45 (19.3)	35 (18.9)	12 (26.6)	20 (16.2)	22 (22.4)
Seizures	16 (6.8)	11 (5.9)	3 (6.6)	5 (4)	7 (7.1)
Migraine	31 (13.3)	31 (16.7)	8 (17.7)	21 (17)	13 (13.2)
Livedo reticularis	38 (16.3)	56 (30)	13 (28.8)	38 (30.8)	30 (30.6)

Table 5. Association of anti-ß$_2$-GPI with clinical features of APS, based on persistent positivity versus intermittent positivity.

	Persistently Positive vs Intermittently Positive or Negative			Ever Positive vs Negative		
	OR	95% CI	p	OR	95% CI	p
			Anti-ß$_2$-Glycoprotein I IgG			
Arterial thrombosis	5.32	1.33, 21.2	0.0497	3.44	1.14, 10.38	0.0392
Venous thrombosis	6.37	1.82, 22.31	0.0125	2.02	0.78, 5.23	NS
Pregnancy loss	0.38	0.05, 2.92	NS	0.47	0.15, 1.43	NS
Livedo reticularis	1.80	0.43, 7.54	NS	2.91	1.21, 7.00	0.0231
			Anti-ß$_2$-Glycoprotein I IgM			
Arterial thrombosis	5.63	1.40, 22.6	0.0455	1.93	0.52, 7.19	NS
Venous thrombosis	1.73	0.43, 6.98	NS	2.04	0.79, 5.23	NS
Pregnancy loss	1.19	0.30, 4.82	NS	1.25	0.50, 3.10	NS
Livedo reticularis	0.82	0.17, 4.06	NS	1.30	0.50, 3.35	NS
			Anti-ß$_2$-Glycoprotein I IgA			
Arterial thrombosis	3.30	0.90, 12.1	NS	3.04	0.86, 10.7	NS
Venous thrombosis	2.30	0.83, 6.36	NS	1.60	0.61, 4.20	NS
Pregnancy loss	0.61	0.19, 1.93	NS	0.62	0.23, 1.68	NS
Livedo reticularis	1.89	0.69, 5.17	NS	1.30	0.50, 3.35	NS

NS: nonsignificant.

ß$_2$-GPI. Previous studies have been inconsistent, with one finding an association with IgA[26], one with anti-ß$_2$-GPI, unspecified isotype[32], and one finding no correlation[33].

Pregnancy loss was not associated with any isotype of anti-ß$_2$-GPI, confirming previous negative studies[25,34,35]. Others have found an association with pregnancy loss[7,36,37] or preeclampsia[38].

This series found a high prevalence of the IgA isotype in anti-ß$_2$-GPI. Persistent positivity of the IgA isotype was not associated with thrombosis, pregnancy loss, or livedo reticularis. Other studies of IgA anti-ß$_2$-GPI did not address the issue of persistent positivity[4,26,39]. These results suggest that the IgA isotype of anti-ß$_2$-GPI should not be added to classification criteria.

In the Sydney revision of the Sapporo APS classification criteria, both IgG and IgM anti-ß$_2$-GPI have been added to the laboratory requirement. Our data do not support the addition of IgM anti-ß$_2$-GPI in the SLE population. The Sydney revision uses the "3-month" rule of persistent positivity, in contrast to the Sapporo 6-week rule. Ours is the first series to use the 3-month persistent positivity rule.

Comparison of our results with past studies is limited by differences in assays, ethnicity, and selection of patients. We could not address the issue of low versus high affinity anti-ß$_2$-

GPI. However, the results strongly support the association of persistently positive anti-ß$_2$-GPI (IgG) with venous and arterial thromboses, and suggest that the addition of anti-ß$_2$-GPI (IgG) to the classification criteria for APS is valid[40].

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