Utility of Antiphosphatidylserine/Prothrombin and IgA Antiphospholipid Assays in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Currently, 3 antiphospholipid assays are widely used clinically [lupus anticoagulant (LAC), anticardiolipin (aCL), and anti-ß$_2$-glycoprotein I (anti-ß$_2$-GPI)]. LAC is the most specific assay, conferring the highest risk of thrombosis and pregnancy loss, but it cannot be validly performed in an anticoagulated patient. We investigated the usefulness of antiphosphatidylserine/prothrombin (anti-PS/PT) and its association with thrombosis. Anti-PS/PT is strongly associated with the presence of LAC. We also studied the association of IgA antiphospholipid isotypes and specific domains of ß$_2$-GPI with thrombosis in systemic lupus erythematosus (SLE).

Methods. Stored samples from patients with SLE, with and without past thrombosis, were assayed for antibodies to the whole ß$_2$-GPI protein (IgG/IgM/IgA), to ß$_2$-GPI domain 1 (IgG), to ß$_2$-GPI domain 4/5 (IgA), aCL (IgG/IgM/IgA), and anti-PS/PT (IgG, IgM, and IgG/M). LAC was detected using the dilute Russell's viper venom time (dRVVT) with confirmatory testing.

Results. Anti-PS/PT IgG and IgG/M and anti-ß$_2$-GPI IgG, IgM, and IgA were highly associated with a history of LAC by dRVVT ($p < 0.0001$). For all thrombosis, of the traditional ELISA assays, anti-ß$_2$-GPI IgA, IgG, and aCL IgA were most associated. Anti-PS/PT IgG and IgG/M had a similar magnitude of association to the traditional ELISA. For venous thrombosis, of the traditional ELISA, anti-ß$_2$-GPI (IgG and IgA), anti-PS/PT (IgG and IgG/M), and aCL IgA were associated. Again, anti-PS/PT (IgG and IgG/M) had the same magnitude of association as the traditional ELISA. For stroke, significant association was seen with anti-ß$_2$-GPI IgA D4/5.

Conclusion. In anticoagulated patients, where LAC testing is not valid, anti-PS/PT, either IgG or IgG/IgM, might serve as useful alternative tests to predict a higher risk of thrombosis. Anti-PS/PT antibodies were associated with all thrombosis and with venous thrombosis. IgA isotypes in secondary antiphospholipid syndrome are associated with thrombosis. Anti-ß$_2$-glycoprotein domain 1 was not shown to be associated with thrombosis in SLE. (First Release Feb 1 2013; J Rheumatol 2013;40:282–6; doi:10.3899/jrheum.120084)

Key Indexing Terms:
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DOMAIN 4/5 IgA
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The antiphospholipid syndrome (APS) is a hypercoagulable disorder defined by the association of arterial and venous thromboses and/or pregnancy morbidity (fetal loss, premature birth, or recurrent embryonic losses) occurring in the presence of antiphospholipid antibodies (aPL)[1]. The commonly used diagnostic tests are the lupus anticoagulant (LAC) functional coagulation assay, anticardiolipin (aCL), and anti-ß$_2$-glycoprotein I (anti-ß$_2$-GPI). Following a workshop in Sapporo, Japan, APS classification criteria were published in 1999[1] and updated in 2006 after another workshop in Sydney, Australia[2].

APL bind to phospholipid-binding proteins or phospholipid-protein complexes[3]. We first reported that the LAC was a better predictor of risk of venous thrombosis in SLE than was aCL[4]. In a review of 12 studies, Galli, *et al* found a significant association between thrombosis and LAC[5].

Prothrombin, another phospholipid-binding protein, was first proposed as a possible cofactor in LAC activity by Loeliger[6]. These antibodies are detected in complex with phosphatidylserine. Bertolaccini, *et al* found antiphosphatidylserine/prothrombin (anti-PS/PT) antibodies in 31% of patients with SLE in general and in 49% of patients with SLE who also had thrombosis[7]. Galli, *et al* found anti-PS/PT in 95% of patients with thrombosis[8].

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The LAC test cannot be validly performed in an anticoagulated patient. The first aim of our study was to investigate whether anti-PS/PT, which detects most LAC, is associated with thrombosis and with the diluted Russell's viper venom time (dRVVT) assay for the LAC. The second aim was to investigate the association of IgA assays with thrombosis in SLE. Finally, we investigated whether antibodies to specific domains of $ß_2$-GPI are important in patients with SLE who have APS.

MATERIALS AND METHODS

The Hopkins Lupus Cohort was approved by the Johns Hopkins University School of Medicine Institutional Review Board. All patients gave written informed consent. The study design was cross-sectional. Stored samples from 326 SLE patients with and without past thrombosis were included, of which 164 had a history of any thrombosis, 103 had a history of venous thrombosis, and 53 had a history of stroke. Samples were assayed for anti-$ß_2$-GPI (IgG/IgM/IgA), anti-$ß_2$-GPI domain 1 (IgG), anti-$ß_2$-GPI domain 4/5 (IgA), aCL (IgG/IgM/IgA), and anti-PS/PT (IgG, IgM, and IgG/M). Testing for aCL, anti-$ß_2$-GPI, and anti-PS/PT was done on 1 sample from each patient. All LAC results were confirmed (by mixing studies and confirmatory testing) using International Society on Thrombosis and Haemostasis guidelines[9].

Samples were tested for aCL and anti-$ß_2$-GPI using Quanta Lite ELISA kits (IgG, IgM, and IgA), approved by the US Food and Drug Administration. Antibodies to a complex of PS/PT of the IgG and IgM class were tested by the same kits, as well as by a prototype screening kit (investigational use only) that simultaneously detects both IgG and IgM antibodies to PS/PT. Researchers used only assays specifically detecting IgG antibodies to domain 1 of $ß_2$-GPI ($ß_2$-GPI D1) and another specifically detecting IgA antibodies to domains 4 and 5 of $ß_2$-GPI ($ß_2$-GPI D4/5).

All ELISA assays were manufactured by Inova Diagnostics Inc. These tests share a common procedure. Patient samples were diluted 1:100 and incubated in the microwell for 30 min. After washing each microwell 3 times, prediluted horseradish peroxidase-labeled conjugate was added and incubated for another 30 min. Wells were washed 3 times and liquid tetramethyl benzadine substrate was added and incubated for 30 min. Color change in microwells was read in a standard microplate reader.

Because no external, internationally recognized controls exist for PS/PT antibody, the results expressed are in arbitrary units, with a cutoff value of 30 units. Establishment of a cutoff for each assay was based on balancing sensitivity and specificity to achieve an optimal clinical utility. In the case of PS/PT, a total of 92 patients with APS, 247 healthy controls, and 43 disease controls were tested. The specificity for PS/PT was set to be high. The cutoff chosen resulted in a specificity of 99% for PS/PT IgG and 98.7% for PS/PT IgM. The determination of whether a test should be tilted toward higher sensitivity or specificity was based on the results of the clinical studies and input from clinical collaborators. In general, receiver-operating characteristics analysis provided a good estimation of an optimum cutoff. However, the final cutoff was adjusted to provide assay results with optimum usefulness for clinicians and their patients. Twenty-four LAC-positive samples were tested for the presence of PS/PT antibodies. All 24 patients were found to be positive for PS/PT IgG and/or PS/PT IgM antibodies. Similarly, the cutoff for anti-D1 IgG and anti-D4/5 IgA was 25 units. The units were derived from studies placing disease versus controls to determine what gave the best specificity and sensitivity. For D1 IgG, the calculations were based on in-house studies showing 97% specificity and 71% sensitivity, and for D4 IgA, specificity of 96%. The cutoffs for anti-$ß_2$-GPI domain 1 IgG and anti-$ß_2$-GPI D4/5 IgA were established in a similar manner. Based on clinical specimens, healthy controls, and disease control specimens, a cutoff was chosen to give a specificity of 97% for $ß_2$-GPI D1 IgG and 96% for $ß_2$-GPI D4/5 IgA. We did not test any samples with polyclonal B cell activation. The sensitivity of anti-D4/5 IgA antibodies was 21.3% for any thrombosis, 19.4% for venous thrombosis, and 30.2% for stroke.

Statistical analysis. The p values in all tables were calculated using chi-square tests for the binary variables (for those tests in which 25% had expected counts < 5, Fisher's exact test was used).

RESULTS

The clinical characteristics of 326 patients with SLE are shown in Table 1. Ninety percent of the patients were female, 50% were white, 40% were African American, and 10% were of other ethnicity. The mean age was 45 years. The mean SLE disease duration when the samples were taken was 11 years. The average time interval was 9 ± 8 years between sample collection and all thrombosis, 9 ± 8 years in patients with venous thrombosis, and 8 ± 7 years in patients with stroke. The mean SLE Disease Activity Index and Physician Global Assessment scores were 2.28 and 0.63, respectively. Seventy-eight percent of the patients were taking hydroxychloroquine.

These assays were highly associated with a history of LAC by dRVVT ($p < 0.0001$): anti-PS/PT IgG, IgM, and IgG/M, anti-$ß_2$-GPI IgG, IgM, and IgA. Anti-$ß_2$-GPI D1 was also highly associated with a history of LAC. IgG anti-$ß_2$-GPI and anti-PS/PT had the highest odds of being positive when LAC was present (IgG anti-$ß_2$-GPI, OR 20.3, 95% CI 5.7, 72.1; IgG anti-PS/PT, OR 14.7, 95% CI 6.3, 34.7; Table 2).

Thrombosis. For all thrombosis, anti-$ß_2$-GPI (IgA and IgG) and aCL IgA were the most highly associated (Table 3). Out of 164 patients, 134 had aPL positivity on the followup visit. Seventy-eight were positive for anticardiolipin and 66 were positive for LAC. Fifty-four patients had both aCL and LAC.

Table 1. Demographic characteristics (n = 326). Data are mean (SD) unless otherwise indicated.

Characteristics	
Age, yrs	45.7 (14.0)
Sex, n (%)	
Female	298 (91.4)
Male	28 (8.6)
Ethnicity, n (%)	
White	163 (50.0)
African-American	131 (40.2)
Other	32 (9.8)
Measures of disease activity	
Physician global assessment (0 to 3 VAS)	0.63 (0.66)
SELENA-SLEDAI	2.28 (3.12)
Serologies	
C3, mg/dl	115.7 (35.7)
C4, mg/dl	22.1 (10.6)
Anti-dsDNA ≥ 10, n (%)	67 (20.6)
Medications	
Prednisone, mg	4.17 (7.87)
Immunosuppressive, n (%)	117 (35.9)
Hydroxychloroquine, n (%)	254 (77.9)

VAS: visual analog scale; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index.

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For venous thrombosis, anti-ß$_2$-GPI IgG, IgA, anti-PS/PT (IgG and IgG/M), and aCL IgA were significantly associated (Table 4).

Stroke. For stroke, a significant association was seen with anti-ß$_2$-GPI IgA D4/5 (Table 5), but not with the presence of other aPL.

DISCUSSION

Our study shows evidence for an association of anti-PS/PT assays with LAC in SLE, as expected. Four previous studies found an association of anti-PS/PT and LAC[10,11,12,13]. One study failed to find a significant association[14]. The lack of correlation in the one study may exist because the APS patient population had experienced much pregnancy loss. Only 13 of the 62 patients with APS had thrombosis; the rest were patients with recurrent pregnancy loss[14].

In our study, we found that anti-PS/PT was significantly associated with all thrombosis and with venous thrombosis. A previous study found an association of anti-PS/PT (IgG and IgG/M) with all thrombosis in APS[11]. A study of 175 patients with SLE showed that the presence of anti-PS/PT antibodies conferred an OR of 9.6 for arterial thrombosis and 7.33 for venous thrombosis[13]. One study found an association (p = 0.009) with anti-PT (not anti-PS/PT) and venous thrombosis in SLE[15]. In contrast, another study of 22 patients with APS found no association of anti-PT antibodies with thrombosis[16]. A study of 175 patients with SLE failed to find a significant association with venous thrombosis[17]. Our results are in concordance with a similar study by Bertolaccini, *et al*[7]. However, we also found that anti-PS/PT IgG and IgG/M were significantly associated with a history of LAC. We could not find any significant association with stroke in our cohort.

Of particular note was the importance of IgA APS assays for both all thrombosis and venous thrombosis. Studies of IgA aCL in SLE have been conflicting. Two studies found

Table 2. Association of antiphospholipid assays with a history of lupus anticoagulant (LAC).

	Assay	LAC-positive, n = 71 No. (% positive)	LAC-negative n = 212 No. (% positive)	OR (95% CI)	p
Anti-PS/PT	IgM	35 (49)	16 (8)	11.9 (6.0, 23.7)	< 0.0001
	IgG	26 (37)	8 (4)	14.7 (6.3, 34.7)	< 0.0001
	IgG/M	34 (48)	16 (8)	11.3 (5.6, 22.4)	< 0.0001
Anticardiolipin	IgM	17 (24)	10 (5)	6.4 (2.8, 14.7)	< 0.0001
	IgG	20 (28)	9 (4)	8.8 (3.8, 20.6)	< 0.0001
	IgA	10 (14)	0 (0)		< 0.0001
Anti-ß$_2$-GPI	IgM	10 (14)	4 (2)	8.5 (2.6, 28.1)	< 0.0001
	IgG	16 (23)	3 (1)	20.3 (5.7, 72.1)	< 0.0001
	IgA	29 (41)	30 (14)	4.2 (2.3, 7.7)	< 0.0001
Anti-ß$_2$-GPI D1	IgG	9 (13)	5 (2)	6.0 (1.9, 18.6)	0.0005
Anti-ß$_2$-GPI D4/5	IgA	21 (30)	35 (17)	2.1 (1.1, 4.0)	0.0167

Anti-PS/PT: antiphosphatidylserine/prothrombin; anti-ß$_2$-GPI: anti-ß$_2$-glycoprotein I; anti-ß$_2$-GPI D1: anti-ß$_2$-glycoprotein I domain 1; anti-ß$_2$-GPI D4/5: anti-ß$_2$-glycoprotein I domain 4/5.

Table 3. Association of antiphospholipid assays with all thrombosis (venous or arterial).

	Assay	Thrombosis, n = 164 No. (% positive)	No Thrombosis, n = 162 No. (% positive)	OR 95% CI*	p (adjusted)*
IgG	Anti-ß$_2$-GPI	18 (11)	6 (4)	3.3 (1.2, 8.9)	0.021
	Anti-ß$_2$-GPI D1	11 (7)	9 (6)	1.1 (0.4, 2.9)	0.79
	aCL	22 (13)	16 (10)	1.4 (0.7, 2.9)	0.34
	Anti-PS/PT	26 (16)	14 (9)	2.2 (1.0, 4.8)	0.045
IgM	Anti-ß$_2$-GPI	8 (5)	9 (6)	0.8 (0.3, 2.3)	0.69
	aCL	19 (12)	14 (9)	1.3 (0.6, 2.8)	0.47
	Anti-PS/PT	43 (26)	25 (15)	1.9 (1.1, 3.3)	0.033
IgA	Anti-ß$_2$-GPI	48 (29)	24 (15)	2.4 (1.3, 4.2)	0.0028
	aCL	11 (7)	1 (1)	9.5 (1.2, 75.8)	0.034
	Anti-ß$_2$-GPI D4/5	35 (21)	28 (17)	1.3 (0.7, 2.3)	0.38
IgG/M	Anti-PS/PT	38 (23)	24 (15)	1.7 (0.9, 3.1)	0.087
LAC**	dRVVT	52 (37)	19 (13)	3.8 (2.0, 7.3)	< 0.0001

* Adjusted for age, sex, and ethnicity. ** Forty-three patients did not have dilute Russell viper venom test (dRVVT) results available. Thus, the total number of patients for the thrombosis group was 44, and the no-thrombosis group, 239. Anti-ß$_2$-GPI: anti-ß$_2$-glycoprotein I; anti-ß$_2$-GPI D1: anti-ß$_2$-glycoprotein I domain 1; aCL: anticardiolipin; anti-PS/PT: antiphosphatidylserine/prothrombin; LAC: lupus anticoagulant; anti-ß$_2$-GPI D4/5: anti-ß$_2$-glycoprotein I domain 4/5.

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Table 4. Association of antiphospholipid assays with venous thrombosis.

	Assay	Thrombosis, n = 103 No. (% positive)	No Thrombosis, n = 223 No. (% positive)	OR 95% CI*	p (adjusted)*
IgG	Anti-ß$_2$-GPI	15 (15)	9 (4)	3.7 (1.5, 9.1)	0.0048
	Anti-ß$_2$-GPI D1	9 (9)	11 (5)	1.7 (0.7, 4.2)	0.29
	aCL	17 (17)	21 (9)	1.7 (0.8, 3.5)	0.14
	Anti-PS/PT	21 (20)	19 (9)	2.7 (1.3, 5.8)	0.0082
IgM	Anti-ß$_2$-GPI	6 (6)	11 (5)	1.1 (0.4, 3.1)	0.88
	aCL	13 (13)	20 (9)	1.4 (0.7, 3.1)	0.36
	Anti-PS/PT	27 (26)	41 (18)	1.5 (0.8, 2.6)	0.19
IgA	Anti-ß$_2$-GPI	31 (30)	41 (18)	1.9 (1.1, 3.3)	0.024
	aCL	8 (8)	4 (2)	4.3 (1.2, 14.8)	0.023
	Anti-ß$_2$-GPI D4/5	20 (19)	43 (19)	1.0 (0.6, 1.9)	0.97
IgG/M	Anti-PS/PT	29 (28)	33 (15)	2.1 (1.2, 3.8)	0.015
LAC**	dRVVT	36 (41)	35 (18)	3.3 (1.8, 6.0)	< 0.0001

* Adjusted for age, sex, and ethnicity. ** Forty-three patients did not have dilute Russell viper venom test (dRVVT) results available. Thus, the total number of patients for the thrombosis group was 88, and the no-thrombosis group, 195. Anti-ß$_2$-GPI: anti-ß$_2$-glycoprotein I; anti-ß$_2$-GPI D1: anti-ß$_2$-glycoprotein I domain 1; aCL: anticardiolipin; anti-PS/PT: antiphosphatidylserine/prothrombin; LAC: lupus anticoagulant; anti-ß$_2$-GPI D4/5: anti-ß$_2$-glycoprotein I domain 4/5.

Table 5. Association of antiphospholipid assays with stroke.

	Assay	Stroke, n = 53 No. (% positive)	No Stroke, n = 273 No. (% positive)	OR 95% CI*	p (adjusted)*
IgG	Anti-ß$_2$-GPI	5 (9)	19 (7)	2.0 (0.7, 6.2)	0.21
	Anti-ß$_2$-GPI D1	3 (6)	17 (6)	1.1 (0.3, 4.1)	0.89
	aCL	7 (13)	31 (11)	1.6 (0.6, 4.1)	0.33
	Anti-PS/PT	8 (15)	32 (12)	2.5 (1.0, 6.3)	0.062
IgM	Anti-ß$_2$-GPI	2 (4)	15 (5)	0.7 (0.2, 3.3)	0.66
	aCL	8 (15)	25 (9)	1.6 (0.7, 4.1)	0.28
	Anti-PS/PT	14 (26)	54 (20)	1.6 (0.8, 3.2)	0.21
IgA	Anti-ß$_2$-GPI	17 (32)	55 (20)	1.9 (1.0, 3.7)	0.070
	aCL	4 (8)	8 (3)	2.0 (0.6, 7.4)	0.28
	Anti-ß$_2$-GPI D4/5	16 (30)	47 (17)	2.2 (1.1, 4.4)	0.033
IgG/M	Anti-PS/PT	11 (21)	51 (19)	1.5 (0.7, 3.2)	0.35
LAC**	dRVVT	17 (39)	54 (23)	2.3 (1.1, 4.8)	0.022

* Adjusted for age, sex, and ethnicity. ** Forty-three patients did not have dilute Russell viper venom test (dRVVT) results available. Thus, the total number of patients for the thrombosis group was 44, and the no-thrombosis group, 239. Anti-ß$_2$-GPI: anti-ß$_2$-glycoprotein I; anti-ß$_2$-GPI D1: anti-ß$_2$-glycoprotein I domain 1; aCL: anticardiolipin; anti-PS/PT: antiphosphatidylserine/prothrombin; LAC: lupus anticoagulant; anti-ß$_2$-GPI D4/5: anti-ß$_2$-glycoprotein I domain 4/5.

an association with all thrombosis[18,19], whereas 3 studies did not[20,21,22]. One study found a statistically significant association of IgA aCL with thrombosis and thrombocytopenia ($p = 0.02$)[19]. Similarly, no consensus has been reached about the association of IgA anti-ß$_2$-GPI and thrombosis in SLE. Several studies, including our own previous investigations[23,24,25], have found an association with venous thrombosis, but others have not[26,27]. In one study, a borderline association was seen in patients with arterial thrombosis ($p = 0.06$)[22].

To our knowledge, ours is the first study of stroke in SLE to show an association with D4/5 IgA. Two past non-SLE studies have suggested such an association[28,29]. IgA anti-ß$_2$-GPI targets D4 of the ß$_2$-GPI molecule in non-SLE patients and was associated with atherosclerosis (acute myocardial infarction, acute coronary syndrome, and peripheral artery disease)[28]. IgA anti-ß$_2$-GPI was present in 22% of non-SLE patients with ischemic stroke[29]. Interestingly, D4/5 IgA was not associated with venous thrombosis.

In contrast to a study by de Laat, *et al*[30], our study showed no association of IgG anti-ß$_2$-GPI D1 with thrombosis. In the de Laat study, anti-D1 IgG was significantly correlated with a history of thrombosis. However, that study did not differentiate between patients with APS and those with SLE (i.e., results were based on any thrombosis in either population). Our study specifically included only patients with SLE. Future studies will seek to clarify the differing results observed between these 2 studies.

Anti-PS/PT, either IgG or IgG/IgM, offers clinicians an

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alternative test to predict increased risk of thrombosis in anticoagulated patients where LAC measurement is not reliable. IgA isotype aPL antibodies are highly associated with thrombosis in SLE. For stroke, only D4/5 IgA was associated. These novel assays will require validation in additional cohorts.

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