Association of IgA Anti-ß2 Glycoprotein I with Clinical and Laboratory Manifestations of Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** IgA isotypes of anticardiolipin and anti-ß$_2$ glycoprotein I (anti-ß$_2$-GPI) are omitted from the revised antiphospholipid syndrome (APS) classification criteria. Multiple studies have found a high prevalence of IgA anti-ß$_2$-GPI in systemic lupus erythematosus (SLE). We determined the frequency and associations of IgA anti-ß$_2$-GPI in a cohort of patients with SLE.

Methods. Anti-ß$_2$-GPI was measured in 796 patients with SLE (93% women, 53% white, 38% African American, mean age 45 yrs). IgA anti-ß$_2$-GPI (> 20 phospholipid units) was found in 20%. Using a cohort database, associations with cumulative thrombotic and other manifestations were determined.

Results. Of patients with SLE who demonstrated IgA anti-ß$_2$-GPI positivity, about 6% had transient ischemic attack (p = 0.070), 4% had superficial thrombophlebitis (p = 0.647), 20% had deep venous thrombosis (p = 0.003), 4% had other venous thrombosis (p = 0.827), 12% had stroke (p = 0.050), and 1% had myocardial infarction (p = 0.397).

Conclusion. IgG anti-ß$_2$-GPI has the strongest association with thrombosis in SLE. However, IgA anti-ß$_2$-GPI was more strongly associated with deep venous thrombosis and with stroke than was IgM. These results indicate that assessment of IgA anti-ß$_2$-GPI is associated with thrombosis in SLE, and that the classification criteria for APS should be revised to include IgA anti-ß$_2$-GPI in patients with SLE. (J Rheumatol First Release Oct 15 2010; doi:10.3899/jrheum.100568)

Key Indexing Terms:
ANTI-ß$_2$-GLYCOPROTEIN I SYSTEMIC LUPUS ERYTHEMATOSUS
ANTIPHOSPHOLIPID ANTIBODIES

Studies have recognized that the IgA isotype of anti-ß$_2$-glycoprotein I (anti-ß$_2$-GPI) is very frequent in patients with systemic lupus erythematosus (SLE)[1,2,3,4]. Fanopoulos, *et al* measured anticardiolipin antibodies (aCL) and anti-ß$_2$-GPI by ELISA in 48 patients with SLE and 100 control subjects, and found IgA anti-ß$_2$-GPI in 58% of patients with SLE versus in 2% of controls[1]. Moreover, compared to aCL and other isotypes of anti-ß$_2$-GPI, the highest antibody levels were seen in IgA anti-ß$_2$-GPI[1]. Tsutsumi and colleagues reported a 25% prevalence of IgA anti-ß$_2$-GPI in 124 Japanese patients with SLE[2]. The presence of IgA anti-ß$_2$-GPI was significantly associated with a history of thrombosis[2]. Lee, *et al* analyzed the isotypes of anti-ß$_2$-GPI in 270 patients with SLE[5]. The prevalence of IgG, IgM, and IgA anti-ß$_2$-GPI was 38.1%, 13.7%, and 34.8%, respectively[5]. Finally, Lakos, *et al* evaluated 70 patients [30 with antiphospholipid syndrome (APS) secondary to SLE, 3 with primary APS, 37 with SLE without APS] and found anti-ß$_2$-GPI antibodies of the IgA isotype present in 59.3% of patients with APS[6].

Studies have shown a high prevalence of IgA anti-ß$_2$-GPI in African Americans with SLE[3,7]. Cucurull, *et al* reported that IgA anti-ß$_2$-GPI was the most prevalent isotype (19%) among African American patients with SLE[3]. In another analysis of 418 consecutive patients with SLE or APS by our group, IgM (28.9%) and IgA (22.2%) were the most frequent isotypes of anti-ß$_2$-GPI[4]. IgA was the most prevalent isotype (8.9%) of anti-ß$_2$-GPI in African Americans[4].

Our aim was to determine the clinical significance of IgA anti-ß$_2$-GPI compared with the other isotypes in a large cohort of patients with SLE.

MATERIALS AND METHODS

Patients. A group of 796 patients with SLE (733 women; median age 45.0 yrs, range 19.1–85.7) were tested for all isotypes (IgG, IgM, and IgA) of anti-ß$_2$-GPI and aCL. There were 422 (53.5%) whites, 302 (38.3%) African Americans, 26 (3.3%) Hispanics, and 27 (3.4%) Asians. All the patients

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Supported by the National Institutes of Arthritis and Musculoskeletal and Skin Diseases (RO1 AR043727) and the Johns Hopkins University Institute for Clinical and Translational Research, Clinical Research Units.

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Accepted for publication August 17, 2010.

classified as having SLE met 4 or more of the 1982 revised American College of Rheumatology (ACR) criteria[8,9].

Protocol. The patients in the study were all part of the Johns Hopkins Hospital Lupus Cohort in Baltimore, which has been well described[10,11]. The study was approved by the Johns Hopkins University School of Medicine Institutional Review Board. All patients gave written informed consent. Patients were followed quarterly, or more often if required for disease activity or complications. Disease activity was measured with the Physician Global Assessment, Lupus Activity Index, and the Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index instrument score[12,13], and damage was recorded using the Systemic Lupus International Collaborating Clinics/ACR Damage Index[14].

Technique and statistics. Both aCL and anti-$ß_2$-GPI were measured by ELISA (Inova Diagnostics, San Diego, CA, USA). Statistical analyses were done using chi-squared and Fisher's exact tests (SAS Institute, Cary, NC, USA). A p value ≤ 0.05 was considered statistically significant. The strength of the association was measured by calculating the OR with its 95% CI.

RESULTS

Prevalence of anti-$ß_2$-GPI. Anti-$ß_2$-GPI of at least 1 isotype were present in 330 patients with SLE (41.5%). IgG, IgM, and IgA anti-$ß_2$-GPI were positive in 43 (5.4%), 126 (15.8%), and 161 (20.2%) patients, respectively (Table 1). The prevalence of isolated IgA anti-$ß_2$-GPI was 104 (13.1%). Anti-$ß_2$-GPI was more common in whites (57.6%) than in African Americans (37.2%). IgA anti-$ß_2$-GPI was the most frequent isotype detected in African Americans, whites, and Hispanics (Table 2).

Prevalence of aCL. A total of 480 out of 783 patients (61.3%) with SLE were positive for aCL. However, only 196 patients (25%) had both aCL and anti-$ß_2$-GPI, and 19 (2.4%) had isolated IgA aCL.

Table 1. Frequency of anti-$ß_2$ glycoprotein I and anticardiolipin, by isotype, in 796 patients with systemic lupus erythematosus.

	No. Patients (%)
Isotypes of anti-ß2-GPI	
IgG+ only	12 (1.5)
IgM+ only	74 (9.3)
IgA+ only	104 (13.1)
IgG, IgM+	5 (0.6)
IgG, IgA+	10 (1.3)
IgM, , IgA+	31 (3.9)
IgG, IgM, IgA+	16 (2.0)
Any IgG	43 (5.4)
Any IgM	126 (15.8)
Any IgA	161 (20.2)
Isotypes of anticardiolipin	
IgG+ only	114 (14.3)
IgM+ only	114 (14.3)
IgA+ only	19 (2.4)
IgG, IgM+	68 (8.5)
IgG, IgA+	11 (1.4)
IgM, , IgA+	9 (1.1)
IgG, IgM, IgA+	29 (3.6)
Any IgG	222 (27.9)
Any IgM	220 (27.6)
Any IgA	68 (8.5)

Thrombosis in anti-$ß_2$-GPI positives and negatives. A history of venous thrombosis (17.51% of total patients with SLE) was significantly associated with IgA anti-$ß_2$-GPI positivity (24.2%) as compared to the IgA anti-$ß_2$-GPI-negative (15.8%) isotype (OR 1.7, 95% CI 1.12–2.59; p = 0.0097). There was no statistical difference in IgA anti-$ß_2$-GPI with arterial thrombosis (p = 0.08). IgG anti-$ß_2$-GPI had a stronger association with venous thrombosis (OR 3.03, 95% CI 1.58–5.79; p = 0.0014) and arterial thrombosis (OR 2.18, 95% CI 1.04–4.60; p = 0.0553) than the IgA isotype. There was no significant association of IgM anti-$ß_2$-GPI with arterial or venous thrombosis in patients with SLE (Table 3).

Relationship of IgA anti-$ß_2$-GPI or aCL to pregnancy loss, livedo, and thrombocytopenia. Of patients with SLE in the cohort who had ever been pregnant (n = 569), 231 (40.6%) had a history of pregnancy loss. Neither aCL nor anti-$ß_2$-GPI were associated with pregnancy loss. There was a 27.5% prevalence of livedo reticularis in our cohort. No association was found between IgA anti-$ß_2$-GPI and a history of livedo reticularis. However, IgA anti-$ß_2$-GPI positivity was associated with a history of thrombocytopenia (OR 1.6, 95% CI 1.06–2.33, p = 0.0172).

Relationship of anti-$ß_2$-GPI IgG, IgM, and IgA with other serological markers. The lupus anticoagulant by dilute Russell viper venom time was associated with anti-$ß_2$-GPI of any isotype (p < 0.0001 for all isotypes). IgG and IgA anti-$ß_2$-GPI correlated significantly with anti-dsDNA, false-positive rapid plasma reagin, low C3, and low C4. Of the 3 isotypes of anti-$ß_2$-GPI, IgA had the strongest correlation with low C3 (p < 0.0001) and was the only isotype of anti-$ß_2$-GPI found to have a significant association with high erythrocyte sedimentation rate (ESR; p = 0.0001, OR 2.64, 95% CI 1.56–4.45) or anti-Sm (p = 0.0373, OR 1.58, 95% CI 1.04–2.41). No relationship was detected between C3, C4, anti-dsDNA, and the IgM anti-$ß_2$-GPI isotype (Table 4).

For the patients with IgA anti-$ß_2$-GPI alone (no IgG or IgM anti-$ß_2$-GPI), 22.1% had venous thrombosis and 11.9% had arterial thrombosis. For IgA aCL alone (IgG or IgM aCL), 11.1% had venous thrombosis and 5.3% had arterial thrombosis.

Other clinical associations with IgA anti-$ß_2$-GPI. A negative correlation was seen between the presence of IgA anti-$ß_2$-GPI and history of Sjögren's syndrome, dry eye, and dry mouth (OR 0.58, 95% CI 0.34–1.00, p = 0.0512; OR 0.56, 95% CI 0.35–0.90, p = 0.0142; and OR 0.56, 95% CI 0.32–1.00, p = 0.0566, respectively; Table 5). Significant associations were found between IgA anti-$ß_2$-GPI positivity and histories of pulmonary hypertension and pulmonary fibrosis (OR 2.26, 95% CI 1.15–4.56, p = 0.0240; and OR 1.89, 95% CI 1.06–3.35, p = 0.0445, respectively).

Table 2. Distribution of anti-ß$_2$ glycoprotein I (anti-ß$_2$-GPI) isotypes by ethnicity.

Ethnicity	Anti-ß$_2$-GPI, Total, n (%)	IgG Anti-ß$_2$-GPI, n (%)	IgM Anti-ß$_2$-GPI, n (%)	IgA Anti-ß$_2$-GPI, n (%)
Asian	7 (2.4)	2 (4.6)	1 (0.8)	4 (2.5)
African American	118 (37.2)	6 (14.0)	45 (36)	67 (41.9)
Hispanic	8 (2.8)	(0)	3 (2.4)	5 (3.1)
Caucasian	195 (57.6)	35 (81.4)	76 (60.8)	84 (52.5)

Table 3. Associations of anti-ß$_2$ glycoprotein I (anti-ß$_2$-GPI), by isotype, in systemic lupus erythematosus.

Factor	IgA Anti-ß$_2$-GPI Positive, %	IgA Anti-ß$_2$-GPI Negative, %	p for IgA Anti-ß$_2$-GPI	OR for IgA Anti-ß$_2$-GPI (95% CI)	OR for IgG Anti-ß$_2$-GPI (95% CI)	OR for IgM Anti-ß$_2$-GPI (95% CI)
Transient ischemic attack	5.7	2.6	0.070	2.30 (1.00–5.31)	3.69 (1.21–11.3)	2.64 (1.11–6.27)
Superficial thrombophlebitis	4.4	3.7	0.647	1.20 (0.51–2.85)	3.78 (1.37–10.4)	1.99 (0.86–4.57)
Deep venous thrombosis	19.9	10.7	0.003	2.08 (1.31–3.30)	3.33 (1.67–6.62)	0.94 (0.52–1.69)
Other venous thrombosis	4.4	4.2	0.827	1.06 (0.45–2.49)	3.36 (1.23–9.17)	1.18 (0.48–2.92)
Stroke	11.9	7	0.050	1.79 (1.01–3.15)	2.39 (1.02–5.61)	1.27 (0.66–2.46)
Myocardial infarction	1.2	2.9	0.397	0.43 (0.10–1.87)	0.91 (0.12–6.95)	0.27 (0.04–2.06)
Total arterial thrombosis (TIA, stroke, MI, and digital gangrene)	17.2	12.5	0.083	1.44 (0.9–2.34)	2.18 (1.04–4.60)	1.42 (0.84–2.39)
Total venous thrombosis (superficial, DVT, and other venous)	24.2	15.79	0.0097	1.70 (1.12–2.59)	3.03 (1.58–5.79)	1.22 (0.75–1.97)

TIA: transient ischemic attack; MI: myocardial infarction; DVT: deep venous thrombosis.

DISCUSSION

We found that 20% of our SLE cohort had IgA anti-ß$_2$-GPI, less than previous prevalence studies of 58%[1], 25%[2], 38.1%[5], and 59%[6]. IgA anti-ß$_2$-GPI was the most frequent anti-ß$_2$-GPI isotype detected in all ethnicities. Anti-ß$_2$-GPI was found more frequently in whites, yet the isotype with the highest prevalence in African Americans was IgA. There is evidence to support a high prevalence of IgA aCL and IgA anti-ß$_2$-GPI in African Americans with SLE as compared with other ethnic groups[3,7].

The association of the IgA isotype of antiphospholipid antibodies (aPL) with thrombosis and pregnancy morbidity has remained controversial[1,5,15,16,17]. In our study, IgA anti-ß$_2$-GPI was significantly ($p = 0.0097$) associated with venous thrombosis, but not arterial thrombosis. Similarly, Fanopoulos, *et al* concluded that there was a significantly higher frequency ($p < 0.01$) and level ($p < 0.05$) of IgA anti-ß$_2$-GPI in patients with SLE who have APS than in those without APS manifestations[1]. Lakos, *et al* demonstrated a strong relationship between increased IgA anti-ß$_2$-GPI antibody levels and a history of venous thrombosis ($p = 0.007$), thrombocytopenia ($p = 0.02$), heart valve disease ($p = 0.02$), livedo reticularis ($p = 0.01$), and epilepsy ($p = 0.01$)[6]. In the analysis of 270 patients with SLE by Lee, *et al*, stepwise multivariate logistic regression analysis was used to determine that IgA was the isotype of anti-ß$_2$-GPI most related to the occurrence of venous thrombosis[5].

Other studies, in contrast, have not found a significant association of IgA anti-ß$_2$-GPI with thrombosis in SLE[15,17]. The discrepancies between clinical findings in these other published results and ours may be attributable to the overall lower prevalence of IgA anti-ß$_2$-GPI found in their cohorts of patients with SLE, such as 8/134 (6%)[15] and 23/130 (17.7%)[17]. Further, lack of standardization of assays used for the measurement of aCL and anti-ß$_2$-GPI, as well as the ethnic composition of the populations studied, may contribute to the discrepancies seen in the frequency and isotype distribution of these aPL among studies[1,15,17].

Our study found, for the first time, that IgA anti-ß$_2$-GPI was associated with both pulmonary hypertension and pulmonary fibrosis. The Euro-Phospholipid Project found a 2.2% prevalence of pulmonary hypertension in its prospective multicenter study of 1000 consecutive patients with aPL associated with primary APS (53.1% of patients), SLE (36.2%), lupus-like syndrome (5%), or other diseases (5.9%)[18]. Asherson and Cervera found that aPL may activate and cause endothelial cell damage, leading to the vascular changes seen in patients with pulmonary hypertension[19]. The association with pulmonary fibrosis is not understood.

We found a negative association, for the first time, between IgA anti-ß$_2$-GPI and secondary Sjögren's syndrome. Anti-ß$_2$-GPI has not been measured in most studies of patients with Sjögren's syndrome[20,21,22]. However, when anti-ß$_2$-GPI was measured in primary Sjögren's syndrome, only 4% of 74 patients were positive in 1 study[21] and none of 80 patients was positive in another[22]. It has been reported that the frequency of aPL in secondary Sjögren's syn-

Table 4. Comparison of isotypes of anti-ß$_2$ glycoprotein I (anti-ß$_2$-GPI) with serologic tests in systemic lupus erythematosus.

Factor	IgG Anti-ß$_2$-GPI Present*, %	IgG Anti-ß$_2$-GPI Absent, %	p	OR (95% CI)
Coombs positivity	36.8	14.5	0.0010	3.37 (1.68–6.75)
Lupus anticoagulant (by RVVT)	86.1	26.2	< 0.0001	17.4 (7.22–41.8)
Anticardiolipin	97.6	59.2	< 0.0001	28.2 (3.85–206)
Anti-dsDNA	74.4	56.4	0.0254	2.25 (1.12–4.53)
Anti-Sm	14.3	18.5	0.6809	0.73 (0.30–1.77)
False-positive test for syphilis	51.3	13.2	< 0.0001	6.92 (3.55–13.5)
Low CH50	28.2	12.5	0.0122	2.75 (1.32–5.73)
Low C3	69.8	51.2	0.0187	2.20 (1.13–4.28)
Low C4	67.4	45.6	0.0069	2.48 (1.29–4.76)
Anti-Ro/SSa	21.4	30.0	0.2973	0.64 (0.30–1.35)
ESR	88.4	77.0	0.0913	2.27 (0.88–5.86)
	IgM Anti-ß$_2$-GPI Present	IgM Anti-ß$_2$-GPI Absent		
Coombs positivity	25.0	14.2	0.0070	2.01 (1.24–3.28)
Lupus anticoagulant (by RVVT)	52.4	25.2	< 0.0001	3.28 (2.21–4.86)
Anticardiolipin	84.0	57.0	< 0.0001	3.96 (2.40–6.55)
Anti-dsDNA	63.2	56.3	0.1677	1.33 (0.90–1.98)
Anti-Sm	13.1	19.3	0.1254	0.63 (0.36–1.11)
False positive test for syphilis	35.1	11.5	< 0.0001	4.15 (2.62–6.57)
Low CH50	17.7	12.5	0.1405	1.50 (0.88–2.55)
Low C3	58.4	51.1	0.1434	1.35 (0.91–1.96)
Low C4	52.8	45.6	0.1438	1.33 (0.91–1.96)
Anti-Ro/SSA	21.8	31.0	0.0414	0.62 (0.39–0.98)
ESR	78.4	77.5	0.9069	1.06 (0.66–1.68)
	IgA Anti-ß$_2$-GPI Present	IgA Anti-ß$_2$-GPI Absent		
Coombs positivity	20.7	14.7	0.0932	1.51 (0.94–2.42)
Lupus anticoagulant (by RVVT)	48.7	24.6	< 0.0001	2.91 (2.03–4.18)
Anticardiolipin	77.5	57.1	< 0.0001	2.58 (1.73–3.87)
Anti-dsDNA	76.9	52.4	< 0.0001	3.02 (2.03–4.50)
Anti-Sm	24.2	16.8	0.0373	1.58 (1.04–2.41)
False positive test for syphilis	28.6	11.8	< 0.0001	2.98 (1.92–4.62)
Low CH50	22.5	10.9	0.0004	2.37 (1.49–3.77)
Low C3	70.6	47.5	< 0.0001	2.66 (1.83–3.86)
Low C4	62.5	42.7	< 0.0001	2.23 (1.56–3.19)
Anti-Ro/SSA	32.9	28.7	0.3289	1.22 (0.84–1.77)
ESR	88.7	74.8	0.0001	2.64 (1.56–4.45)

* Positive value ≥ 20 phospholipid units. RVVT: Russell viper venom time; ESR: erythrocyte sedimentation rate.

Table 5. Relationship of IgA anti-ß$_2$ glycoprotein I (anti-ß$_2$-GPI) to some clinical manifestations.

Factor	IgA Anti-ß$_2$-GPI Present	IgA Anti-ß$_2$-GPI Absent	p	OR (95% CI)
Sjögren's syndrome, %	10.6	17.0	0.05	0.58 (0.34–1.00)
Dry eye, %	15.0	23.9	0.01	0.56 (0.35–0.90)
Dry mouth, %	9.4	15.5	0.06	0.56 (0.32–1.00)
SLICC/ACR Damage Index				
Pulmonary hypertension, %	8.9	4.1	0.02	2.26 (1.15–4.56)
Pulmonary fibrosis, %	12.0	6.8	0.04	1.89 (1.06–3.35)
Total pulmonary damage	0.27 ± 0.61	0.16 ± 0.45	0.007	

SLICC/ACR: Systemic Lupus International Collaborating Clinics/American College of Rheumatology.

drome is more linked to the underlying autoimmune disease, which appears to be the case in SLE[23].

Our study supports that IgA anti-ß$_2$-GPI is frequent in patients with SLE of all ethnicities. IgA anti-ß$_2$-GPI is associated with venous thrombosis. In contrast to the IgG or IgM isotypes, IgA anti-ß$_2$-GPI positivity was significantly associated with the presence of serological markers such as high ESR, low C3, and anti-Sm antibodies. IgA anti-ß$_2$-GPI also

differs from the other isotypes of anti-ß$_2$-GPI as it has significantly positive clinical correlations with pulmonary hypertension and pulmonary fibrosis, and is negatively associated with Sjögren's syndrome, dry eye, and dry mouth in patients with SLE. Given our results, we suggest that measuring IgA anti-ß$_2$-GPI may be important for assessing the risk of thrombosis and pulmonary disease in patients with SLE. Moreover, the classification criteria for the APS in patients with SLE should be revised to include IgA anti-ß$_2$-GPI.

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