Isotypes of Anti-ß$_2$-Glycoprotein I Antibodies: Association with Thrombosis in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To evaluate the association between isotypes of anti-ß$_2$-glycoprotein I antibodies (anti-ß$_2$-GPI) and thrombosis and to identify antiphospholipid antibodies (aPL) that are most associated with thrombosis in patients with systemic lupus erythematosus (SLE).

Methods. IgG anticardiolipin antibody (aCL) and isotypes of anti-ß$_2$-GPI were measured by ELISA, and clinical evidence of thrombosis was analyzed in 270 patients with SLE.

Results. IgG, IgM, and IgA anti-ß$_2$-GPI were positive in 38.1, 13.7, and 34.8% of patients, respectively. Patients with a history of thrombosis were significantly more likely to have lupus anticoagulant (LAC), IgG aCL, and the 3 anti-ß$_2$-GPI isotypes. Arterial thrombosis was associated with the presence of IgG aCL and the 3 anti-ß$_2$-GPI isotypes, whereas venous thrombosis was associated with LAC, IgG aCL, and IgA anti-ß$_2$-GPI. In stepwise multivariate logistic regression analysis, the variable that was associated with thrombosis was IgA anti-ß$_2$-GPI. The occurrence of arterial thrombosis was associated with IgG aCL and that of venous thrombosis was related to IgA anti-ß$_2$-GPI in stepwise multivariate analysis. The IgG, IgM, and IgA anti-ß$_2$-GPI titers were closely correlated with IgG aCL titers. The IgA anti-ß$_2$-GPI titers were also significantly correlated with those of IgG and IgM anti-ß$_2$-GPI.

Conclusion. The results suggest that anti-ß$_2$-GPI isotypes are related to the occurrence of thrombosis, and measurements of IgA anti-ß$_2$-GPI may be useful for predicting thrombotic episodes in patients with SLE. (J Rheumatol 2001;28:520–4)

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

The antiphospholipid syndrome (APS) is a symptom complex consisting of venous and arterial thrombosis, recurrent abortion, and thrombocytopenia in the presence of the lupus anticoagulant (LAC) or anticardiolipin antibody (aCL)[1-4]. A primary form, in patients without clinically or serologically evident autoimmune disease, and a secondary form, usually in patients with systemic lupus erythematosus (SLE), are both recognized. Assays for LAC and aCL have been shown to be useful for predicting thrombosis, in both cross sectional and prospective studies[5-7]. Research has shown that a large proportion of antiphospholipid antibodies (aPL) do not, in fact, recognize phospholipids, and that the antigenic targets of these antibodies are phospholipid-binding plasma proteins, most notably ß$_2$-glycoprotein I (ß$_2$-GPI) and prothrombin, or complexes of these proteins with phospholipids[8-12]. Moreover, it is reported that the presence of anti-ß$_2$-glycoprotein I antibodies (anti-ß$_2$-GPI) is more closely associated with manifestations of APS than the detection of aCL[13,14].

In several studies, the clinical manifestations of patients with IgA aCL differed from those of patients with IgG aCL, and determination of all 3 aCL isotypes was recommended to properly assess the specific clinical manifestations[15]. A recent study showed that IgA anti-ß$_2$-GPI is not uncommon in patients with SLE and that measuring anti-ß$_2$-GPI isotypes, as well as the aCL isotypes, is important for predicting the risk of thrombosis[16]. Although a number of studies have described the association between IgM or IgG anti-ß$_2$-GPI and thrombosis, there are few reports on the significance of IgA anti-ß$_2$-GPI[17-21].

To clarify the significance of the anti-ß$_2$-GPI isotypes, we analyzed the association between all 3 anti-ß$_2$-GPI isotypes and thrombosis in patients with SLE. In addition, we tried to identify which aPL was most associated with thrombosis.

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MATERIALS AND METHODS

Patients and samples. Serum samples were obtained from 270 Korean patients with SLE at the Department of Internal Medicine, Kangnam St. Mary's Hospital. All the patients classified as having SLE met at least 4 of the American College of Rheumatology (formerly American Rheumatism Association) criteria[22]. The mean age of the patients was 34 years (range 17–64 yrs) and the mean disease duration was 9 years (range 1–20 yrs); 13 patients were male (4.8%). The charts of the patients were reviewed retrospectively to look for thrombotic events between disease onset and the most recent followup, using our center's protocol. Of these patients, 16 had arterial thrombosis, and venous thrombosis occurred in 16 patients. Two patients had a history of both arterial and venous thrombosis. The patients with objectively verified thrombotic events were included in this study. Deep vein thrombosis was diagnosed by venography or Doppler ultrasonography; retinal thrombosis by ophthalmologic examination and fluorescent angiography; inferior vena cava, hepatic or splenic vein thrombosis by angiography; thrombosis in intracerebral vessels by computed tomographic scanning, magnetic resonance imaging or angiography; and peripheral or mesenteric artery thrombosis by arteriography or at surgery. A diagnosis of cerebral transient ischemic attack required neurologic symptoms or signs lasting less than 24 h in a patient who met the criteria for the classification of cerebrovascular disease of the National Institute of Neurological Disorders and Stroke[23]. Details are described in Table 1.

VDRL testing. The VDRL test was performed using a commercial kit. The presence of syphilis was confirmed by fluorescent treponemal antibody absorption or the *Treponema pallidum* immobilization test. When the screening VDRL test was positive and a confirmatory test was negative, the test was considered as a biologic false positive serologic test for syphilis (BFP-STS).

Detection of LAC. LAC was screened using the dilute Russell viper venom time (IL Test LAC Screen, Instrumentation Laboratory, Australia). If the test plasma clotting time was 20% longer than that of normal plasma, the presence of LAC was confirmed by the platelet neutralization test (IL Test LAC Confirm, Instrumentation Laboratory).

Detection of IgG aCL. IgG aCL was measured using a commercial ELISA kit (Mesacup Cardiolipin test, MBL Ltd., Nagoya, Japan). This assay was standardized against an internationally recognized sample obtained from the Anti-phospholipid Standardization Laboratory, University of Louisville, Kentucky, USA[24]. The cutoff value for IgG aCL was that given by the manufacturer. The IgG aCL levels in 80 healthy volunteers tested in our laboratory using these kits were below this cutoff value.

Measurement of anti-ß$_2$-GPI antibodies. To measure anti-ß$_2$-GPI isotypes, we used a method based on the technique described by Guerin, *et al*[25]. Briefly, microtiter plates (Nunc Maxisorp, Roskilde, Denmark) were coated with 2 µg/ml ß$_2$-GPI (Crystal Chem, Chicago, IL, USA). After a blocking procedure using 0.5% bovine serum albumin-phosphate buffered saline, the wells were incubated with serum samples diluted 1:50. Bound anti-ß$_2$-GPI in each sample was detected by peroxidase conjugated goat anti-human IgG/IgM/IgA antibody. Serial dilutions of a representative serum with high values of IgG/IgM/IgA anti-ß$_2$-GPI were included in every assay. The IgG/IgM/IgA anti-ß$_2$-GPI levels in the sample sera were calculated from the standard curve included with the assay. A reference range was established in a healthy control group (n = 80) using a mean value in arbitrary units (AU) ± 5 SD.

Table 1. Clinical features of thrombotic events.

Thrombosis		N
Arterial		
	Cerebral (stroke, transient ischemic attack)	5
	Mesenteric	5
	Peripheral	6
Venous		
	Deep vein thrombosis	12
	Retinal	1
	Inferior vena cava	1
	Hepatic (Budd-Chiari syndrome)	1
	Splenic	1
Arterial and venous		2

Statistical analysis. The association between aPL and thrombosis was tested using Fisher's exact test. A p value < 0.05 was considered statistically significant. The strength of the association was measured by calculating the odds ratio (OR). Multivariate logistic regression analysis and model selection by the stepwise method were used to identify the variables associated with a history of thrombosis. The regression coefficients, 95% confidence intervals (CI), and p values are given, and the results show the independent risk of each type of aPL for thrombosis. Spearman's correlation coefficient was used to analyze the relationships between anti-ß$_2$-GPI isotype titers and IgG aCL titers. Statistical analyses were performed using SPSS software (SPSS, Chicago, IL, USA).

RESULTS

Thrombosis and aPL. The presence of thrombosis was compared with the presence of aPL. In the univariate analysis, LAC, IgG aCL, and all 3 anti-ß$_2$-GPI isotypes were associated with a history of thrombosis. In the multivariate logistic regression analysis, 2 variables, IgG (OR 4.1, 95% CI 1.3~13.2; p = 0.018) and IgA anti-ß$_2$-GPI (OR 9.9, 95% CI 2.6~37.2; p = 0.001) were associated with thrombosis (Table 2). Stepwise multivariate logistic regression removed the variables in the following order: BFP-STS, IgM anti-ß$_2$-GPI, LAC, IgG aCL, and IgG anti-ß$_2$-GPI. Only IgA anti-ß$_2$-GPI (OR 12.2, 95% CI 3.3~44.9; p = 0.002) remained in this model.

With regard to arterial thrombosis, there was a significant association with IgG aCL and the 3 anti-ß$_2$-GPI isotypes in the univariate analysis. Multivariate analysis showed that the variable associated with the presence of arterial thrombosis was IgG aCL (OR 22.6, 95% CI 2.6~196.3; p = 0.005) (Table 3). In stepwise analysis, the variables were removed in the following order: IgA anti-ß$_2$-GPI, IgM anti-ß$_2$-GPI, BFP-STS, LAC, and IgG anti-ß$_2$-GPI. Finally, IgG aCL (OR 18.9, 95% CI 2.3~151.9; p = 0.006) remained in this model.

The presence of venous thrombosis was significantly associated with LAC, IgG aCL, and IgA anti-ß$_2$-GPI in the univariate analysis. In multivariate analysis, IgA anti-ß$_2$-GPI (OR 10.5, 95% CI 1.2~90.8; p = 0.033) was most associated with venous thrombosis (Table 4). In stepwise analysis, the variables were removed in the following order: IgM anti-ß$_2$-GPI, IgG aCL, BFP-STS, IgG anti-ß$_2$-GPI, and LAC. Finally, IgA anti-ß$_2$-GPI (OR 15.9, 95% CI 1.9~130.4; p = 0.010) remained in this model.

aPL levels in patients with SLE. The proportions of patients with SLE with abnormal values of BFP-STS, LAC, and IgG aCL were 11.2, 22.8, and 29.5%, respectively. For IgG, IgM, and IgA anti-ß$_2$-GPI, the respective proportions were 38.1, 13.7, and 34.8%.

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Table 2. Relationship between antiphospholipid antibodies and a history of thrombosis.

	Thrombosis (%)		Univariate Analysis		Multivariate Analysis	
	Yes	No	OR (95% CI)	p	OR (95% CI)	p
BFP-STS	6/28 (21.4)	21/213 (9.9)	2.5 (0.9–6.8)	0.102	1.3 (0.3–5.1)	0.725
LAC	12/27 (44.4)	40/201 (19.9)	3.2 (1.4–7.4)	0.007	0.7 (0.2–2.4)	0.539
IgG aCL	20/28 (71.4)	52/216 (24.1)	7.9 (3.3–19.0)	< 0.001	2.7 (0.5–14.4)	0.249
IgG anti-ß$_2$-GPI	17/24 (70.8)	42/131 (32.1)	5.1 (2.0–13.4)	< 0.001	4.1 (1.3–13.2)	0.018
IgM anti-ß$_2$-GPI	9/24 (37.5)	13/137 (9.5)	5.7 (2.1–15.6)	0.001	1.4 (0.4–5.2)	0.614
IgA anti-ß$_2$-GPI	18/24 (75.0)	38/137 (27.7)	7.8 (2.9–21.2)	< 0.001	9.9 (2.6–37.2)	0.001

BFP-STS: Biologic false-positive serologic test for syphilis.

Table 3. Relationship between antiphospholipid antibodies and a history of arterial thrombosis.

	Arterial Thrombosis (%)		Univariate Analysis		Multivariate Analysis	
	Yes	No	OR (95% CI)	p	OR (95% CI)	p
BFP-STS	4/15 (26.7)	23/226 (10.2)	3.2 (0.9–10.9)	0.072	3.6 (0.7–17.9)	0.115
LAC	5/15 (33.3)	47/213 (22.1)	1.8 (0.6–5.4)	0.342	0.2 (0.0–1.1)	0.058
IgG aCL	12/14 (85.7)	60/230 (26.1)	17.0 (3.7–78.2)	< 0.001	22.6 (2.6–196.3)	0.005
IgG anti-ß$_2$-GPI	10/14 (71.4)	49/141 (34.8)	4.7 (1.4–15.7)	0.010	3.6 (0.8–16.3)	0.097
IgM anti-ß$_2$-GPI	6/14 (42.9)	16/147 (10.9)	6.1 (1.9–20.0)	0.005	2.1 (0.4–10.9)	0.387
IgA anti-ß$_2$-GPI	11/14 (78.6)	45/147 (30.6)	8.3 (2.2–31.2)	0.001	2.3 (0.3–20.7)	0.442

BFP-STS: Biologic false-positive serologic test for syphilis.

Table 4. Relationship between antiphospholipid antibodies and a history of venous thrombosis.

	Venous Thrombosis (%)		Univariate Analysis		Multivariate Analysis	
	Yes	No	OR (95% CI)	p	OR (95% CI)	p
BFP-STS	4/15 (26.7)	23/226 (10.2)	3.2 (0.9–10.9)	0.072	1.4 (0.3–7.0)	0.676
LAC	8/14 (57.1)	44/214 (20.6)	5.2 (1.7–15.6)	0.004	3.8 (0.8–16.8)	0.081
IgG aCL	10/16 (62.5)	62/228 (27.2)	4.5 (1.6–12.8)	0.008	0.7 (0.1–7.1)	0.738
IgG anti-ß$_2$-GPI	8/12 (66.7)	51/143 (35.7)	3.6 (1.0–12.6)	0.059	1.7 (0.4–8.3)	0.482
IgM anti-ß$_2$-GPI	4/12 (33.3)	18/149 (12.1)	3.6 (1.0–13.3)	0.062	0.8 (0.2–3.9)	0.772
IgA anti-ß$_2$-GPI	9/12 (75.0)	47/149 (31.5)	6.5 (1.7–25.2)	0.004	10.5 (1.2–90.8)	0.033

BFP-STS: Biologic false-positive serologic test for syphilis.

Relationship between IgG aCL and anti-ß$_2$-GPI isotypes. Titers of IgG aCL in sera of patients with SLE were compared to the anti-ß$_2$-GPI isotype titers. The IgG aCL values were positively correlated with IgG, IgM, and IgA anti-ß$_2$-GPI ($\rho = 0.473$, $p < 0.001$; $\rho = 0.464$, $p < 0.001$; $\rho = 0.458$, $p < 0.001$).

Relationship between IgA and IgG or IgM anti-ß$_2$-GPI. Titers of IgA anti-ß$_2$-GPI were compared with those of IgG and IgM anti-ß$_2$-GPI. The IgA anti-ß$_2$-GPI titers correlated positively with the IgG and IgM anti-ß$_2$-GPI titers ($\rho = 0.367$, $p < 0.001$; $\rho = 0.677$, $p < 0.001$).

DISCUSSION

It is well known that SLE patients with moderate or high levels of IgG and IgM aCL are more susceptible to thrombotic events[5-7]. However, this does not rule out the possibility that IgA aCL isotypes play a role in thrombotic episodes. Kalunian, *et al*[26] found a specific association between a history of thrombosis and the presence of the IgA aCL isotype. Gharavi, *et al*[27] also reported that the presence of IgA aCL was significantly related to thrombosis. Although the concordance between IgA aCL and IgA anti-ß$_2$-GPI appears to be lower than the concordance between the IgG and IgM isotypes in SLE, the occurrence of IgA anti-ß$_2$-GPI was significantly associated with thrombosis in the study by Tsutsumi, *et al*[28]. Their results did not directly prove a relationship between the presence of IgA anti-ß$_2$-GPI and thrombosis, since most patients who had a history of thrombosis and positive IgA anti-ß$_2$-GPI were also positive for IgG or IgM anti-ß$_2$-GPI.

We used stepwise multivariate logistic regression analysis to determine which anti-ß$_2$-GPI isotype was most

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associated with thrombosis. Our results reveal that IgA anti-ß$_2$-GPI was most related to the occurrence of thrombosis. Racial differences were recently reported to play a role in the prevalence, isotype distribution, and clinical significance of aCL and anti-ß$_2$-GPI[29,30]. To confirm the role of IgA anti-ß$_2$-GPI in thrombosis, clinical studies of different races are needed.

We examined the association between aPL and the location of thrombosis. Stepwise multivariate logistic regression analysis revealed that a history of arterial thrombosis was associated with IgG aCL, whereas the occurrence of venous thrombosis was related to IgA anti-ß$_2$-GPI. Guglielmone and Fernandez[31] found no relationship between the site of thrombosis and aCL isotype. On the other hand, Tajima, *et al*[15] reported that thrombosis was frequently observed in patients with IgG aCL and LAC, while thrombocytopenia, skin ulcers, chilblain ulcers, and vasculitis were associated with IgA aCL. They suggested that patients with IgG aCL or LAC might develop thrombosis in larger vessels, while smaller vessels might be involved in patients with IgA aCL. In our study, the reason for the difference in the location of thrombosis is unknown and requires further investigation.

Of note, 28 (10.4%) of 270 patients with SLE were positive for anti-ß$_2$-GPI isotypes and negative for VDRL, LAC, and IgG aCL. One of these 28 patients, who was positive only for IgA anti-ß$_2$-GPI, had a thrombotic event. This finding is consistent with several studies in which the presence of clinical features of APS in rare cases is associated with a positive anti-ß$_2$-GPI assay, but a negative aCL assay[32,33]. Therefore, the determination of anti-ß$_2$-GPI is necessary in patients with SLE or signs of APS who test negative for aCL and LAC.

The IgG aCL titers were significantly correlated with the IgG, IgM, and IgA anti-ß$_2$-GPI titers to varying degrees. The IgA anti-ß$_2$-GPI titers were also correlated with the IgG and IgM anti-ß$_2$-GPI titers. These results are in good accordance with other reports[13,28].

This study had several limitations. We did not investigate other significant comorbidity factors for thrombosis, such as hyperlipidemia, diabetes, hypertension, and steroid usage. Therefore, we could not eliminate their contributions to the occurrence of thrombosis. Only IgG aCL was measured among 3 aCL isotypes; thus, IgG aCL was compared to 3 anti-ß$_2$-GPI isotypes in the multivariate analysis. In addition, the study had limited power to evaluate some variables that might be codependent, such as LAC and anti-ß$_2$-GPI. This introduced some biases into the results.

Our results suggest that anti-ß$_2$-GPI isotypes are related to the occurrence of thrombosis, and that measuring IgA anti-ß$_2$-GPI may be important for assessing the risk of thrombosis, especially venous thrombosis, in patients with SLE. Nevertheless, future prospective studies with larger numbers of patients are needed to clarify the significance of anti-ß$_2$-GPI.

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