IgM Anti-ß$_2$ Glycoprotein I Is Protective Against Lupus Nephritis and Renal Damage in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Antibodies to ß$_2$ glycoprotein I (IgG and IgM isotypes) have recently been added to the laboratory criteria of the revised antiphospholipid syndrome classification criteria. We investigated whether IgM anti-ß$_2$-glycoprotein I (anti-ß$_2$-GPI) is associated with clinical manifestations of systemic lupus erythematosus (SLE).

Methods. Anti-ß$_2$-GPI was measured in 796 patients with SLE (93% women, 53% white, 38% African American, mean age 45 yrs). IgM anti-ß$_2$-GPI (> 20 phospholipid units) was found in 16%. Associations were determined with clinical manifestations of SLE and with components of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Results. As expected, IgM anti-ß$_2$-GPI was highly associated with both the lupus anticoagulant and with anticardiolipin. It was associated with transient ischemic attack (OR 2.64, p = 0.04), but not significantly with venous or arterial thrombosis. IgM anti-ß$_2$-GPI was protective against lupus nephritis (OR 0.54, p = 0.049), renal damage (p = 0.019), and hypertension (OR 0.58, p = 0.008). This protective effect remained after adjustment for ethnicity.

Conclusion. In SLE, IgM anti-ß$_2$-GPI is not associated with thrombosis but is protective against lupus nephritis and renal damage. "Natural" autoantibodies of the IgM isotype may have a protective effect. (First Release Dec 1 2010; J Rheumatol 2011;38:450–3; doi:10.3899/jrheum.100650)

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

Elevated levels of antiphospholipid antibodies (aPL), including anticardiolipin antibodies (aCL), lupus anticoagulant (LAC), and anti-ß$_2$-glycoprotein I (anti-ß$_2$-GPI), are detected in about 10%–44% of patients with systemic lupus erythematosus (SLE)[1,2,3,4,5,6,7]. Evidence has shown that recurrent arterial or venous thromboses and pregnancy morbidity may develop in 30%–70% of patients with SLE who have aPL after 20 years of followup[3,5,8].

It is well known that in some patients with SLE, renal manifestations such as renal artery stenosis, renal infarction, intrarenal thromboses, systemic hypertension, proteinuria, thrombotic microangiopathy, and progressive renal failure have been associated with raised levels of aPL[9,10,11]. However, whether aPL play any role in the pathogenesis of lupus nephritis remains unknown. The few studies that have examined the relationship between aPL and lupus nephritis have had contradictory results[9,12,13,14,15].

The 2006 updated international classification criteria for the antiphospholipid syndrome (APS) have included the presence of antibodies to IgG and/or IgM anti-ß$_2$-GPI as part of the laboratory criteria[16]. Our aim was to investigate whether IgM anti-ß$_2$-GPI is associated with clinical manifestations of APS in patients with SLE.

MATERIALS AND METHODS

Patients. A total of 796 patients with SLE participated (733 women; median age 45.0 yrs, range 19.1–85.7). There were 422 whites (53.5%), 302 African Americans (38.3%), 26 Hispanics (3.3%), and 27 Asians (3.4%). All patients with SLE met 4 or more of the 1982 revised American College of Rheumatology criteria[17,18].

Protocol. The patients in the study were part of the Johns Hopkins Hospital Lupus Cohort, as described[19,20]. The study was approved by the Johns Hopkins University School of Medicine Institutional Review Board. All patients gave informed consent.

Patients were followed quarterly or more often if required by disease activity or complications. Disease activity was measured with the physician's global assessment, Lupus Activity Index, and the Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythe-

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

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Accepted for publication October 12, 2010.

matosus Disease Activity Index (SELENA SLEDAI)[21,22], and permanent organ damage recorded using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)[23]. Lupus nephritis was defined as 500–3000 mg/day of proteinuria. Nephrotic syndrome was defined as > 3000 mg/day of proteinuria.

Assays. Both anticardiolipin and anti-ß$_2$-GPI were measured by ELISA (Inova Diagnostics, San Diego, CA, USA). The LAC was measured by the dilute Russell's viper venom time with confirmatory testing[24].

Statistics. Statistical analyses were done using chi-squared and Fisher's exact tests (JMP v 5.0.1a, 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

IgM anti-ß$_2$-GPI was found in 15.8% of the patients with SLE, IgG anti-ß$_2$-GPI in 5.4%, and IgA anti-ß$_2$-GPI in 20.2%.

Relationship of IgM anti-ß$_2$-GPI to other aPL. IgM anti-ß$_2$-GPI was highly associated with the LAC (p = 0.0232) and with aCL (p < 0.0001).

Relationship of IgM anti-ß$_2$-GPI to thrombosis. IgM anti-ß$_2$-GPI was associated with transient ischemic attack (OR 2.64, p = 0.04), but not significantly with venous or arterial thrombosis (Table 1).

Relationship of IgM anti-ß$_2$-GPI to renal disease. IgM antibodies to ß$_2$-GPI had a significant negative correlation with renal damage (p = 0.019). The presence of IgM anti-ß$_2$-GPI was significantly less frequent in patients with SLE who had a history of proteinuria (OR 0.57, 95% CI 0.37–0.87; p = 0.009), nephrotic syndrome (OR 0.54, 95% CI 0.29–0.98; p = 0.049), and renal SLE (OR 0.58, 95% CI 0.39–0.87; p = 0.010; Table 2). In addition, IgM anti-ß$_2$-GPI was negatively associated with hypertension (OR 0.58, 95% CI 0.39–0.86; p = 0.008). After adjustment for ethnicity, all results remained statistically significant except for nephrotic syndrome. After adjustment for anti-dsDNA and low complement, IgM anti-ß$_2$-GPI remained protective against lupus nephritis (p = 0.0003) and against nephrotic syndrome (p = 0.0085).

IgM anti-ß$_2$-GPI was protective against renal damage (p = 0.042, adjusted for race), but not against other organ damage (damage score excluding renal damage 1.88 vs 1.75; p = 0.53).

DISCUSSION

As expected, we found that IgM anti-ß$_2$-GPI was highly associated with the LAC (p = 0.0232) and anticardiolipin (p < 0.0001). However, it was associated only with transient ischemic attack (OR 2.64, 95% CI 1.11–6.27; p = 0.04), and was not significantly associated with venous or arterial thrombosis. Similar to our results, Lakos and colleagues also described the correlation between IgM anti-ß$_2$-GPI antibodies and thrombotic manifestations of APS as weak[25]. They found that IgM anti-ß$_2$-GPI was associated only with thrombocytopenia and heart valve disease, with no significant relationship found between IgM anti-ß$_2$-GPI and thrombosis[25]. Amoroso, *et al* detected IgM anti-ß$_2$-GPI in 16% of 87 patients with SLE, with no association found with thrombosis (p = 0.08) or thrombocytopenia (p = 0.47)[26]. In contrast, Tsutsumi and colleagues found a significant relationship between the occurrence of IgM anti-ß$_2$-GPI and a history of deep vein thrombosis in their Japanese SLE cohort[15]. Our results, in the largest SLE sample to date, strongly suggest that IgM anti-ß$_2$-GPI should not be part of the thrombosis APS classification criterion for patients with SLE.

We found that IgM anti-ß$_2$-GPI protected against nephritis and renal damage in SLE. This negative association persisted when adjustment was made for ethnicity. The apparent protection, as well, against hypertension could reflect the lower frequency of nephritis. Antiphospholipid antibodies have been associated with thrombotic findings on renal biopsies. Indeed, several studies have found that aPL increase the risk of lupus nephropathy[27,28,29,30]. However, these studies did not include anti-ß$_2$-GPI.

Most studies found no relationship between aPL and lupus nephritis[9,13,14,15,31,32,33,34,35]. Two studies did find a negative association of aPL and lupus renal disease. In a study of 92 patients with SLE, Weidmann, *et al* found that 4 of 6 aPL were negatively associated with lupus nephritis[36]. Alarcon-Segovia, *et al* found that APS (rather than aPL) was protective against nephrotic syndrome[8]. Urinary loss of aPL did not completely explain the inverse relationship between nephrotic syndrome and aPL, especially of the IgM isotype[37].

IgM autoantibodies have been hypothesized to have a protective effect as "natural" autoantibodies[38]. The exact mechanism of the protective effect remains to be explored[39]. Our study proves, for the first time, the protective effect of IgM anti-ß$_2$-GPI in SLE.

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Table 1. Associations of antiphospholipid antibodies, by isotype, in systemic lupus erythematosus.

Factor	Antibody-negative, %	Antibody-positive, %	p	OR (95% CI)
IgM aCL				
Transient ischemic attack	2	6	0.0389	2.44 (1.09–5.42)
Superficial thrombophlebitis	4	5	0.5350	1.30 (0.60–2.83)
Deep venous thrombosis	12	14	0.5515	1.14 (0.72–1.81)
Other venous thrombosis	3	6	0.0738	1.95 (0.96–3.97)
Stroke	7	10	0.3102	1.32 (0.76–2.28)
Myocardial infarction	3	1	0.3110	0.45 (0.13–1.54)
IgG aCL				
Transient ischemic attack	2	6	0.0381	2.47 (1.11–5.50)
Superficial thrombophlebitis	3	5	0.1478	1.76 (0.83–3.71)
Deep venous thrombosis	10	20	0.0005	2.21 (1.43–3.40)
Other venous thrombosis	3	8	0.0045	2.89 (1.43–5.83)
Stroke	7	11	0.1423	1.54 (0.90–2.63)
Myocardial infarction	2	3	0.8044	1.11 (0.42–2.92)
IgA aCL				
Transient ischemic attack	3	4	0.4757	1.43 (0.42–4.92)
Superficial thrombophlebitis	4	4	0.7395	1.17 (0.35–3.97)
Deep venous thrombosis	12	21	0.0538	1.92 (1.02–3.61)
Other venous thrombosis	3	15	0.0002	5.26 (2.39–11.6)
Stroke	8	13	0.1047	1.86 (0.88–3.96)
Myocardial infarction	3	1	1.0000	0.55 (0.07–4.14)
IgM anti-ß$_2$-GPI				
Transient ischemic attack	3	7	0.0430	2.64 (1.11–6.27)
Superficial thrombophlebitis	3	6	0.1220	1.99 (0.86–4.57)
Deep venous thrombosis	13	12	1.0000	0.94 (0.52–1.69)
Other venous thrombosis	4	5	0.6335	1.18 (0.48–2.92)
Stroke	8	10	0.4729	1.27 (0.66–2.46)
Myocardial infarction	3	1	0.2286	0.27 (0.04–2.06)
IgG anti-ß$_2$-GPI				
Transient ischemic attack	3	10	0.0374	3.69 (1.21–11.3)
Superficial thrombophlebitis	3	12	0.0197	3.78 (1.37–10.4)
Deep venous thrombosis	12	30	0.0013	3.33 (1.67–6.62)
Other venous thrombosis	4	12	0.0293	3.36 (1.23–9.17)
Stroke	8	16	0.0730	2.39 (1.02–5.61)
Myocardial infarction	3	2	1.0000	0.91 (0.12–6.95)
IgA anti-ß$_2$-GPI				
Transient ischemic attack	3	6	0.0707	2.30 (1.00–5.31)
Superficial thrombophlebitis	4	4	0.6466	1.20 (0.51–2.85)
Deep venous thrombosis	11	20	0.0031	2.08 (1.31–3.30)
Other venous thrombosis	4	4	0.8273	1.06 (0.45–2.49)
Stroke	7	12	0.0502	1.79 (1.01–3.15)
Myocardial infarction	3	1	0.3968	0.43 (0.10–1.87)
Lupus anticoagulant				
Transient ischemic attack	2	7	0.0004	4.55 (1.98–10.4)
Superficial thrombophlebitis	3	5	0.2212	1.63 (0.77–3.43)
Deep venous thrombosis	6	27	< 0.0001	5.91 (3.75–9.32)
Other venous thrombosis	2	10	< 0.0001	5.20 (2.48–10.9)
Stroke	5	14	< 0.0001	2.90 (1.72–4.89)
Myocardial infarction	2	3	0.3228	1.61 (0.65–4.01)

aCL: anticardiolipin antibodies; anti-ß$_2$-GPI: anti-ß$_2$ glycoprotein I.

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Table 2. Relationship of IgM anti-ß$_2$ glycoprotein I to systemic lupus erythematosus renal disease.

Clinical Manifestation	IgM Anti-ß$_2$-GPI-positive	IgM Anti-ß$_2$-GPI-negative	p	OR (95% CI)	Adjusted p (for race)
Proteinuria, %	28	41	0.009	0.57 (0.37–0.87)	0.035
Nephrotic syndrome, %	10	18	0.049	0.54 (0.29–0.98)	0.108
Renal SLE, %	33	46	0.010	0.58 (0.39–0.87)	0.022
Hypertension, %	35	48	0.008	0.58 (0.39–0.86)	0.003
SLICC/ACR Damage Index					
Persistent proteinuria, %	2	8	0.007	0.19 (0.05–0.79)	0.043
Total renal damage score	0.05 ± 0.34	0.19 ± 0.64	0.019		0.042

Anti-ß$_2$-GPI: anti-ß$_2$ glycoprotein I; SLE: systemic lupus erythematosus; SLICC/ACR: Systemic Lupus International Collaborating Clinics/American College of Rheumatology.

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