Renal Biopsy in Lupus Patients with Low Levels of Proteinuria

LISA CHRISTOPHER-STINE, MARK SIEDNER, JANICE LIN, MARK HAAS, HEMAL PAREKH, MICHELLE PETRI, and DEREK M. FINE

ABSTRACT. ***Objective.*** Early and accurate detection of kidney involvement in systemic lupus erythematosus (SLE) improves outcomes. Renal biopsy is required for definitive diagnosis of lupus nephritis (LN). In the absence of acute renal failure (ARF), moderate levels of proteinuria (> 1000 mg/24 h) have been recommended by some to justify biopsy. We investigated whether patients with lower levels of proteinuria without ARF have significant renal disease and should be routinely biopsied.

Methods. We retrospectively evaluated 21 SLE patients with 24-h urine protein < 1000 mg who underwent kidney biopsies. Indications for biopsy included new-onset proteinuria, increasing proteinuria, or hematuria (> 5 red blood cells per high power field). No patient had ARF.

Results. Sixteen of 21 (77%) biopsies were diagnostic of LN: 3 class II, 10 class III (5 superimposed class V), 2 class IV (one superimposed class V), and one with class V. One patient had thrombotic microangiopathy. The remaining 4 (23%) patients had non-lupus renal disease. Thirteen patients with class III or greater LN required alterations in therapeutic regimen because of biopsy findings. Of 7 patients without hematuria at the time of biopsy, 4 (57%) had class III, IV, or V LN. One patient without hematuria and < 500 mg/24 h proteinuria had class III LN.

Conclusion. We found significant renal involvement (Class III, IV, or V LN) in SLE patients with < 1000 mg proteinuria with or without hematuria. Our findings suggest that biopsy be strongly considered in this patient population. (First Release Dec 15 2006; J Rheumatol 2007;34:332–5)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS RENAL LUPUS NEPHRITIS
PROTEINURIA BIOPSY

Lupus nephritis (LN) is a common complication of systemic lupus erythematosus (SLE), occurring in up to 60% of affected adults during the course of their disease[1]. Both the clinical presentation and histopathological forms of kidney involvement are highly variable. The focal and diffuse forms of LN (class III and IV, respectively) generally present with nephritic urine sediments and may have progressive renal failure. In contrast, membranous nephritis (class V) typically presents with nephrotic-range proteinuria. Several studies, however, have illustrated the poor reliability of diagnoses rendered on the basis of clinical features alone[2-5]. Thus, renal biopsy is an important tool in assessing patients with LN, and is often required for a definitive diagnosis of histopathological subtype and direction of proper treatment.

The decision to recommend renal biopsy can be complex. In the absence of acute renal failure, some physicians recommend biopsy in those with proteinuria > 500 mg/24 h[6]. Others have recommended biopsy only in patients with higher levels of proteinuria (> 1000 mg/24 h) and abnormal urine sediment[7]. However, several case series have suggested that significant kidney damage may occur in the setting of active proliferative LN without clinical signs of renal involvement[8,9]. Because early intervention is crucial to prevent poor outcomes[10,11], it is imperative that kidney biopsies be performed so that diagnoses can be made and appropriate treatment initiated.

We investigated whether SLE patients with levels of proteinuria < 1000 mg/24 h should be routinely biopsied to aid in achieving earlier diagnoses and treatment of LN.

MATERIALS AND METHODS

Patients with SLE who underwent kidney biopsy after 1995 were included if at the time of biopsy they had a 24-h urine protein < 1000 mg or spot protein:creatinine ratio < 1.0 (when 24-h collection had not been performed). Patients with a rise in creatinine > 0.2 mg/dl from baseline to biopsy date were excluded. The biopsies were classified according to the ISN/RPS guidelines[12] and were scored for activity and chronicity[11]. Significant renal disease was defined as any classification of class III, IV, or V lupus nephritis or thrombotic microangiopathy. These diagnoses were thought likely to prompt

From the Divisions of Nephrology and Rheumatology, Johns Hopkins University Department of Medicine, Baltimore, Maryland, USA.

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L. Christopher-Stine, MD, MPH, Assistant Professor of Medicine; M. Siedner, MPH; J. C. Lin, BS; M. Haas, MD, Professor of Pathology; H.J. Parekh, MD; M. Petri, MD, MPH, Professor of Medicine; D.M. Fine, MD, Assistant Professor of Medicine.

Address reprint requests to Dr. D.M. Fine, 1830 East Monument Street, Suite 416, Baltimore, MD 21205. E-mail: dfine1@jhmi.edu

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alterations in therapy. Clinical and laboratory features were obtained by review of the Johns Hopkins University Department of Medicine electronic patient record. A diagnosis of preexisting hypertension was met by evidence from chart records. New-onset hypertension was defined as systolic blood pressure > 140 mm Hg or diastolic > 90 mm Hg at the time of identification of kidney involvement in the absence of prior evidence of hypertension. Hematuria was classified as > 5 red blood cells per high power field on urine microscopy. Low C3 and C4 were classified as serum levels < 79 and < 12 mg/dl, respectively. Antiphospholipid antibody concentrations were considered positive if the patient had evidence of lupus anticoagulant by abnormal dilute Russell viper venom test (with abnormal confirmatory test) or 2 positive anticardiolipin antibody tests (IgG, IgM, or IgA) at least 6 weeks apart. This study was approved by the Johns Hopkins University Department of Medicine institutional review board.

Subjects with and without significant renal disease were compared using Student t tests and chi-square analysis. All data analyses were performed using Stata 9.0 (Stata Corp., College Station, TX, USA).

RESULTS

Twenty-one of the 235 biopsied patients in our database met the inclusion criteria. The indications for renal biopsy included new onset of proteinuria (n = 5), increasing levels of proteinuria (n = 2), hematuria in the absence of proteinuria (n = 4), or concurrent hematuria and proteinuria (n = 10). All patients had a stable serum creatinine between 0.5 and 1.5 mg/dl. The patient population comprised 15 Caucasians, 4 Asians, and 2 African Americans; 20 of 21 (95%) were female (Table 1). The mean age was 35.7 yrs (range 18–59). Of 21 patients, 17 (81%) had positive urine dipstick test (≥ 1+) for protein and 14 (67%) had hematuria. Of 7 patients without hematuria, dipstick test for heme pigment was insignificant (4 negative; 1 trace; 2 small). The mean proteinuria at the time of biopsy was 605 mg (± 290 SD), with a range at the time of biopsy of 80–980 mg/24 h. All but 3 patients had decreasing serum creatinine from baseline to biopsy date. One patient had a serum creatinine increase of 0.2 mg/dl [estimated glomerular filtration rate (GFR) decrease from 138 to 94 ml/min] and 2 others had an increase in creatinine of 0.1 mg/dl (estimated GFR decreases of 87 to 78 and 66 to 59 ml/min, respectively).

Sixteen of the 21 (77%) biopsies were diagnostic of LN: 3 class II, 10 class III (5 with superimposed class V), 2 with class IV (one superimposed with class V), and one with class V only (Table 2). The remaining 5 of 21 patients (24%) had focal segmental glomerulosclerosis (2 patients), thrombotic microangiopathy, mild hypertensive nephrosclerosis, and thin glomerular basement membrane disease. Of the 7 patients without hematuria at the time of biopsy, 4 (57%) had class III, IV, and/or V LN. Two of the 4 patients with hematuria and proteinuria < 500 mg had class III LN, and one of 4 patients without hematuria and < 500 mg proteinuria had class III LN. Based on these biopsy findings, the 13 patients with class III, IV, and V LN had their immunosuppressive regimens changed. The one with thrombotic microangiopathy was started on warfarin therapy.

Among these 21 patients with proteinuria < 1000 mg, we analyzed a number of secondary associations of significant renal disease. Patients with a diagnosis of significant renal disease (class III, IV, or V LN or thrombotic microangiopathy) had a nonsignificant lower mean age (30.1 vs 40.9 yrs; p = 0.11) and shorter mean duration of SLE (48 vs 174 mo; p = 0.06; Table 3). A higher proportion of patients with significant renal disease had low C3 (71% vs 14%; p = 0.03). Anti-dsDNA antibodies were also present in a higher proportion of patients (93% vs 57%; p = 0.05). There were no differences between those diagnosed with significant renal disease and those without it in terms of hematuria, presence of red blood cell casts, presence of antiphospholipid antibody, anemia, mean creatinine level, or current use of therapy with an angiotensin-converting enzyme inhibitor or corticosteroids. Those with significant renal disease were less likely to have a preexisting diagnosis of hypertension (21% vs 57%; p = 0.10) or diabetes mellitus (0% vs 14%; p = 0.16).

Table 1. Baseline demographic and laboratory findings in the study cohort.

Characteristic	N = 21
Age, yrs mean (SD), range	35.7 (10.5), 18–59
Ethnicity	
White (%)	15 (71)
Asian (%)	4 (19)
African American (%)	2 (10)
Female (%)	20 (95)
Positive urine dipstick (≥ 1+)	17 (81)
24 h urine protein, mg/dl, mean (SD), range	605 (290), 80–980
Hematuria (%)	14 (67)

DISCUSSION

Our findings demonstrate that in the absence of acute renal failure, the presence of proteinuria < 1000 mg (or urine protein:creatinine < 1.0 g protein/g creatinine) with or without hematuria may indicate significant renal involvement in patients with SLE. Half the patients in our cohort with hematuria and low-level proteinuria and one of 4 patients without hematuria or significant proteinuria had class III LN on biopsy. Our findings suggest that renal biopsy should be performed in these patients in the presence of new-onset or rising proteinuria to enable prompt diagnosis of LN and initiation of treatment earlier in the disease course. Those with low C3 and high dsDNA titers are more likely to have significant disease. Although limited by a small sample size, our study suggested that those with new proteinuria < 500 mg/24 h (protein:creatinine ratio < 0.5 mg protein/mg creatinine) may also have significant kidney disease.

Most of those diagnosed with significant kidney disease had low chronicity indices (< 2), and therefore most likely had recent onset of renal involvement. It is notable that 3 of the 4 patients with chronicity indices ≥ 2 had a normal serum creatinine and GFR, emphasizing that normal kidney function does not rule out underlying renal damage. This emphasizes the need for kidney biopsy in this population. Further, these 4 patients had mild activity (activity indices < 6), suggesting

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Table 2. Baseline demographic and clinical characteristics of the study cohort.

Patient	Age	Sex	Race	Protein, mg/24 h	Hematuria, RBC/HPF	Indication for Biopsy	Serum Cr, mg/dl	GFR*, ml/min	C3	C4	dsDNA Titer	aPL	Diagnosis	Activity Index	Chronicity Index
1	37	F	W	907	15–20	HAP	1.1	59	68	11	1:320	Yes	Class II	—	—
2	41	F	AA	196	10–15	H	0.7	119	94	15	ND	No	Class II	—	—
3	34	F	W	640	25–50	HAP	0.7	102	97	17	1:10	No	Class II	—	—
4	48	F	W	715	0	NP	0.9	71	160	21	ND	No	FSGS	—	—
5	38	F	W	445	0	NP	1.0	66	96	20	1:160	No	FSGS	—	—
6	51	F	W	240	0	NP	0.7	94	ND	ND	ND	No	Mild nephrosclerosis	—	—
7	37	F	W	80	25–50	H	0.8	86	88	17	ND	No	Thin basement membrane	—	—
8	28	F	W	522	20–25†	HAP	0.4	202	36	8	1:1190	Yes	Class III	4	2
9	21	F	A	200	5–10	H	1.0	74	22	4	1:20	No	Class III	2	0
10	39	F	W	900	0	RP	0.7	133	67	12	1:640	No	Class III	4	1
11	28	F	W	458	0–2	NP	1.5	44	83	16	1:40	No	Class III	5	5
12	47	F	A	177	5–10	H	1.0	63	36	11	1:640	No	Class III	2	0
13	33	F	W	547	0	NP	0.6	122	45	17	1:80	No	Class III, V	2	1
14	38	F	W	870	5–10	HAP	0.5	147	59	8	1:640	No	Class III, V	1	3
15	24	F	W	980	5–10	HAP	0.5	161	63	8	1:320	No	Class III, V	6	0
16	34	F	A	700	0–3	RP	0.7	102	93	18	1:10	No	Class III, V	1	3
17	22	F	W	860	5–10	HAP	0.7	111	64	8	1:640	No	Class III, V	6	0
18	18	F	W	680	5–8	HAP	0.5	171	48	7	ND	No	Class IV	7	0
19	29	F	A	806	5–10†	HAP	1.0	70	29	4	1:640	Yes	Class IV, V	6	1
20	43	M	W	972	10–15	HAP	1.1	78	112	23	1:40	No	Class V	—	—
21	59	F	AA	800	5–10	HAP	0.9	83	105	31	ND	Yes	Focal TMA	—	—

* GFR estimated using Modification of Diet in Renal Disease method. † RBC casts present. aPL: antiphospholipid antibody, FSGS: focal segmental glomerulosclerosis, TMA: thrombotic microangiopathy, H: hematuria, NP: new-onset proteinuria, RP: rising proteinuria, HAP: hematuria and proteinuria, ND: no data, W: white, AA: African American, A: Asian.

Table 3. Baseline demographics and clinical findings according to histologic classification of kidney biopsies.

	Class III, IV, V LN or TMA, n = 14	Class II or Non-lupus Lesions, n = 7	p
Age, yrs (SD)	33.1 (11.3)	40.9 (6.3)	0.11
Female (%)	13 (93)	7 (100)	0.40
Ethnicity			
White	9	6	
African American	1	1	—
Asian	4	0	
Preexisting hypertension (%)	3 (21)	4 (57)	0.10
New hypertension (%)	4 (29)	2 (29)	1.00
Diabetes mellitus (%)	0 (0)	1 (14)	0.16
SLE duration, mo, median (range)	48 (1–108)	177 (1–360)	0.06
Corticosteroid treatment (%)	11 (78)	6 (86)	0.69
ACE inhibitors (%)	6 (43)	3 (43)	1.00
Serum creatinine, mean (SD)	0.79 (0.30)	0.84 (0.16)	0.69
Low C3, mg/dl (%)	10 (71)	1/6 (20)	0.03
Low C4, mg/dl (%)	8 (57)	1/6 (20)	0.10
Anti-dsDNA (%)	13 (93)	4 (57)	0.05
Anemia, hematocrit < 33% (%)	4 (29)	2 (29)	1.00
Antiphospholipid antibody (%)	3 (21)	1 (14)	0.70
Hematuria (%)	10 (71)	4 (57)	0.55
Red blood cell casts (%)	2 (14)	0	0.29
Proteinuria < 0.5g/24h (%)	3 (21)	3 (43)	0.30

TMA: thrombotic microangiopathy, ACE: angiotensin-converting enzyme.

that even mild disease may lead to chronic changes. There were also 4 patients with moderate activity indexes of 6 or 7, but chronicity indices < 2 and serum creatinine of < 1.0, indicating there can also be significant activity in patients with normal creatinine and only mild proteinuria. All the activity in these biopsies was glomerular.

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Our study is limited by a small sample size, and therefore the power to make broad statements about subpopulations of patients with SLE and low-level proteinuria is also restricted. Despite this, we found a majority of SLE patients with 24-h proteinuria < 1000 mg had significant renal involvement defined by the need to alter therapy. Although a larger study would be useful in developing a clearer decision-making protocol for renal biopsy, our study argues for earlier biopsies in this group. A second limitation is the cross-sectional design of the study. Further, we were limited by the preexisting database collection guidelines, which did not include urine creatinine data on all patients. This prevented us using a more sensitive method for measuring hematuria or calculating a protein:creatinine ratio on all participants. A final limitation of the study is its generalizability to the population at large. In particular, nearly 3 out of 4 patients were Caucasian and only 2 (10%) were African American. In addition, the screening frequency for proteinuria in lupus patients done every 3 months at this institution may not be standard practice.

We present data from a cross-sectional study of 21 patients with SLE and stable renal function and proteinuria < 1000 mg/24 h that underwent renal biopsy to determine the etiology of their kidney involvement. A large majority of these patients were diagnosed with LN, and more than half had significant renal pathology requiring therapy alterations. These findings suggest the proteinuria threshold of 1000 mg/24 h may be inadequate, and should prompt longitudinal studies of longterm outcomes for such patients who receive early biopsy and treatment. To diagnose significant renal involvement promptly and improve longterm outcomes, lupus patients with low-level, new-onset, or rising proteinuria and normal renal function may require biopsy.

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