Screening for Proteinuria in Patients with Lupus: A Survey of Practice Preferences Among American Rheumatologists

MARK J. SIEDNER, LISA CHRISTOPHER-STINE, BRAD C. ASTOR, ALLAN C. GELBER, and DEREK M. FINE

ABSTRACT. ***Objective.*** Screening for proteinuria in patients with lupus requires a diagnostic method with adequate validity to detect early disease. Recent studies have called into question the validity of qualitative proteinuria measurements. We set out to assess if American rheumatologists have changed their practice preferences in response to these data.

Methods. Using an online survey tool, we questioned practicing physicians, who were members of the American College of Rheumatology in 2005, about their demographic characteristics and preferred method to detect proteinuria in patients with known lupus.

Results. In our survey, 64.6% of 473 respondents reported using qualitative urinalysis (dipstick) as the primary method of screening for proteinuria. The remaining 32.7% preferred quantitative measurements (spot protein to creatinine ratio 16.8%; 24-h protein 7.8%; microalbuminuria 4.1%; 24-h protein to creatinine ratio 4.1%). Rheumatologists in practice for more than 10 years were more likely than those in practice for less time to use a qualitative method. Although physicians using dipsticks were most likely to use 1+ as a cutoff for significant proteinuria, 28.5% report using a threshold of ≥ 2+.

Conclusion. Despite recent reports describing the inadequacy of urine dipstick as a measurement for low-grade proteinuria, the majority of practicing rheumatologists are utilizing that method for screening in patients with lupus. Because early detection of lupus nephritis has implications for prevention of renal associated morbidity and mortality, these findings should prompt further investigation of the adequacy and role of urine dipstick as a screening tool for lupus. (First Release April 15 2007; J Rheumatol 2007;34:973–7)

Key Indexing Terms:
LUPUS NEPHRITIS PROTEINURIA SCREENING PRACTICE GUIDELINES

It is estimated that 60% of patients with lupus experience renal involvement during the course of their disease[1]. Although renal involvement may be a poor prognostic indicator in patients with lupus[2], early detection and appropriate treatment can prevent significant morbidity and mortality. Conversely, a delay between diagnosis of renal disease and biopsy has been associated with a nearly 5-fold increase in risk of renal insufficiency and greater than 6-fold increase in risk of death[3]. Although multiple findings may indicate renal involvement in lupus, proteinuria is a cardinal feature and the most common index sign of disease[4]. Therefore, early and accurate detection of significant proteinuria is a crucial element of clinical care in patients with lupus[5].

There are no definitive guidelines for the screening of proteinuria in patients with lupus. Multiple recommendations suggest methods for detection of proteinuria, including the American College of Rheumatology (ACR) diagnostic criteria, and the British Isles Lupus Assessment Group (BILAG) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scoring systems[6-8]. Although all 3 include quantitative measurements, both BILAG scoring and ACR criteria also advocate the use of a qualitative urine dipstick as a satisfactory screening tool. The various recommendations suggest a wide range of viable options for detection of proteinuria in lupus nephritis.

However, the use of qualitative measurements as screening tools for proteinuria in lupus presents potential pitfalls. Recent evidence suggests that qualitative measurements for proteinuria may have inadequate validity[9-15]. Due to poor sensitivity, patients with false negative results may not be appropriately evaluated for renal biopsy or early treatment. Moreover, dipsticks can have imperfect specificity caused by concentrated or alkalinized urine, and the exclusive measurement of albumin[16]. False positive results require followup quantitative testing, necessitating a delay in diagnosis. There may also be confusion about when to evaluate further for renal disease

From Divisions of Nephrology and Rheumatology, Johns Hopkins University School of Medicine; and Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA.

Dr. Christopher-Stine was supported by an Arthritis Foundation Postdoctoral Fellowship Award and The Johns Hopkins Clinician Scientist Award.

M. Siedner, MPH, Johns Hopkins University School of Medicine; L. Christopher-Stine, MD, MPH, Assistant Professor of Medicine; A.C. Gelber, MD, MPH, PhD, Associate Professor of Medicine and Epidemiology, Division of Rheumatology; D.M. Fine, MD, Assistant Professor of Medicine, Division of Nephrology, Johns Hopkins University School of Medicine; B.C. Astor, MPH, PhD, Assistant Professor of Epidemiology and Medicine, Johns Hopkins School of Public Health.

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

Accepted for publication January 22, 2007.

when using qualitative methods, stemming from inconsistencies in published guidelines. In contrast, quantification of proteinuria provides definitive assessment of urine protein levels, and the use of random urine protein or albumin measurement (as a ratio to creatinine) is now widely accepted in nephrology practice[17].

The purpose of our study was to evaluate current practice methods by rheumatologists who care for patients with lupus. We aimed to determine the preferred methods of screening for proteinuria, and investigate if rheumatologists have responded to published accounts describing the poor validity of qualitative methods.

MATERIALS AND METHODS

Using the online survey tool, surveymonkey.com, we designed and sent a survey (Table 1) to physician members in the American College of Rheumatology directory who listed a working e-mail address and reported the United States as a home address. Assuming 2 subgroups of equal sample size, and a 10% difference in those responding to a specific question (qualitative versus quantitative method of detection), we set a target sample size of 450 to calculate statistically significant differences between groups. An initial pilot survey was sent to 867 members, selected in alphabetical order from the beginning of the ACR directory, to assess respondent participation rates. With an initial response rate of 17%, we sent an additional 1,800 surveys, also selected alphabetically, to meet our target sample size.

Sample size calculations and statistical analyses were conducted with Stata 9.0 (Stata Corporation, College Station, TX, USA). We first compiled demographic data about responders including geographic region, age, sex, years in practice, type of practice, and approximate number of patients with lupus seen per year. We then calculated the proportion of respondents who use various methods of screening for proteinuria. We performed chi-squared analysis of screening method (qualitative vs quantitative) by respondent characteristics, including years in practice (> or < 10 yrs), number of lupus patients seen per year (> or < 60 patients/yr), and type of practice (academic vs all others). Finally, we analyzed practice patterns of those using dipstick as a screening tool by assessing the dipstick threshold they use to consider further investigation.

RESULTS

Invitations to participate in the survey were e-mailed to 2,667 (50.7%) of the approximately 5,250 clinician members of the American College of Rheumatology. Surveys were returned by a total of 499 (18.7%). The demographic characteristics of respondents are summarized in Table 2. Respondents and nonrespondents were qualitatively similar in terms of geographic location and sex. Over half the respondents were in practice for more than 20 years (59.3%) and approximately two-thirds saw fewer than 60 lupus patients per year (67.9%). A plurality of respondents described themselves as academic (45.2%) versus in a group practice (24.7%), solo practice (17.4%), hospital-based practice (9.3%), or other practice (6.1%).

Of the 499 responders, 486 (97.4%) submitted a response to our question about preferred choice of screening known patients with lupus for proteinuria. Seven respondents (1.4%) reported using none of the above choices and 6 respondents (1.2%) denied screening patients for proteinuria. For the remaining 473 respondents, the most commonly used diagnostic tool was urine dipstick (n = 314; 64.6%), followed by spot protein to creatinine ratio (n = 81; 16.7%), 24-h protein (n = 38, 7.6%), microalbuminuria (n = 20; 4.1%), and 24-h protein to creatinine ratio (n = 20; 4.1%) (Table 3).

Respondents in practice for more than 10 years were significantly more likely to use dipstick than any of the quantitative methods (> 10 yrs in practice 70.4%, ≤ 10 yrs in practice 57.0%, $p < 0.01$) (Table 3). There was no significant difference in the proportion of respondents using dipstick as the primary diagnostic tool by type of practice (academic 66.9%, others 65.9%, $p = 0.78$) or number of lupus patients seen per year (≥ 60 lupus patients/yr 67.8%, < 60 lupus patients/yr 65.6%, $p = 0.65$).

Finally, we analyzed the preferences of these rheumatolo-

Table 1. Excerpts of survey sent to 2,667 rheumatologists listed in the American College of Rheumatology registry in 2004 and who supplied both a mailing address in the United States and a functional e-mail address. Possible responses are given in parentheses.

1. In which region of the country do you practice?
   (Northeast; Mid-Atlantic; West; Midwest; Southeast; Northwest)
2. What is your gender?
   (Male; Female)
3. In which type of practice do you work?
   (Academic; Hospital-based; Solo private practice; Group specialty practice)
4. Including fellowship, for how many years have you been practicing rheumatology?
   (< 5 years; 5–10 years; 10–15 years; 15–20 years; > 20 years)
5. Approximately how many patients do you see each year with a diagnosis of SLE?
   (I don't routinely see patients with lupus; < 20 patients per year; 20–40 patients per year; 40–60 patients per year; > 60 patients per year)
6. By which method do you SCREEN patients with known Lupus for proteinuria?
   (I don't screen patients routinely for renal disease; Urinalysis dipstick; 24-hour urine; Random protein: creatinine ratio; 24-hour urine protein:creatinine ratio)
7. When using urine dipstick as a screening tool, at what level of proteinuria do you suggest further testing and/or nephrology referral?
   (Trace; 1+; 2+; 3+; > 3+)

Table 2. Summary of demographic information compiled from responders and non-responders of a survey of American rheumatologists and comparative information about American College of Rheumatology members.

	Survey Respondents, n = 499, %	Survey Non-respondents, n = 2,168, %	ACR Members* %
Geographic region			
Southwest	19.8	22.8	South: 32.3
Northwest	6.4	4.0	West: 20.1
Midwest	21.0	21.3	Northeast: 25.0
Southeast	18.0	18.2	Midwest: 22.4
Mid-Atlantic	10.2	14.0	—
Northeast	21.8	19.1	—
Alaska/Hawaii	0.4	0.0	—
International	2.4	< 1.0	—
Sex			
Male	69.2	62.6	77.2
Female	30.8	37.4	22.8
Years in practice			
> 10	70.4	—	—
≤ 10	29.6	—	—
Practice type			
Academic	45.2	—	24.5
Hospital based	9.3	—	—
Solo Private	17.4	—	26.7
Group specialty	24.7	—	48.8
Other	6.1	—	—
Lupus patients seen per year			
≤ 60 patients	67.9	—	—
> 60 patients	32.9	—	—

* American College of Rheumatology Membership Directory, 2005.

Table 3. Survey responses about preferences for screening patients with lupus for proteinuria.*

	Dipstick (%)	Spot PrCr (%)	Quantitative Tests 24 h Pr (%)	24 h PrCr (%)	Urine Albumin (%)	p†
Respondents (n = 473)	314 (64.7)	81 (16.7)	38 (7.6)	20 (4.1)	20 (4.1)	NA
Subgroups						
No. of SLE patients seen/year						
< 60 (n = 320)	210 (65.6)		110 (34.4)			0.65
≥ 60 (n = 152)	103 (67.8)		49 (32.2)			
Type of practice						
Academic (n = 207)	136 (65.7)		71 (34.3)			0.78
All others (n = 266)	178 (66.9)		88 (33.0)			
Yrs in practice						
> 10 (n = 331)	233 (70.4)		98 (29.6)			< 0.01
≤ 10 (n = 142)	81 (57.0)		61 (43.0)			

* 24 h Pr: 24 h urine protein quantification; Spot PrCr: spot protein to creatinine ratio; 24 h PrCr: 24-h urine collection for protein to creatinine ratio. † p values shown are chi-squared analysis results for difference in proportion of respondents in sub-categories reporting use of urine dipstick versus quantitative testing as a primary screening method.

gists to recommend further diagnostic workup for their patients with suspected renal involvement. When asked at which dipstick level of proteinuria they consider secondary testing or nephrology consultation, 15.5% reported a threshold of trace, 56.0% reported a threshold of 1+, and 28.5% reported a threshold of ≥ 2+ proteinuria.

DISCUSSION

Our study estimates that a majority (64.6%) of practicing rheumatologists uses a qualitative test, the urine dipstick, as a preliminary screening tool for proteinuria in patients with known lupus. This finding may be of importance in light of recent reports that have called into question the adequacy of

qualitative urine diagnostic screening tests, and especially their ability to detect low levels of proteinuria. The National Kidney Foundation Kidney Disease Outcome Quality Initiative recommends against the use of urine dipstick due to its poor sensitivity for detection of proteinuria in early stages of renal disease[17]. Although few accounts in the rheumatology press have been published to date, a number of reports in the obstetrics literature corroborate this finding, specifically: a recent metaanalysis of urine dipstick for detection of low-level proteinuria, which resulted in a pooled likelihood ratio for urine dipstick of only 3.48, and a subsequent report describing a negative predictive value of 75% for a 1+ dipstick to detect subnephrotic range proteinuria[11,15]. Moreover, there is evidence that urine dipstick is a poor indicator of renal disease in patients with hypertension and diabetes mellitus, other conditions where detection of early renal involvement is critical[10,12]. In sum, despite growing data questioning the validity of qualitative tests to detect low range proteinuria, where lupus patients with early renal involvement may present, most rheumatologists continue to use dipstick as a screening test in this population.

Among those who implement urine dipstick as a screening tool, 28.5% reported a threshold of ≥ 2+ to consider further testing and/or nephrology referral. This threshold was not unexpected considering BILAG and ACR criteria for renal involvement, which suggest cutoffs of 2+ and 3+, respectively[6,7]. However, published reports estimating relationships between dipstick and quantified proteinuria equivalents suggest that a 2+ dipstick result corresponds to approximately 2-3 g proteinuria/24 h[18]. We have shown that low level proteinuria in patients with lupus is often associated with significant renal involvement, even in the absence of hematuria or renal failure[19]. Therefore, among the rheumatologists who do use dipstick to screen lupus patients, approximately one-quarter may be improperly selecting unnecessarily high thresholds to consider further workup of renal involvement.

Rheumatologists in practice for less than 10 years were less likely to use urine dipstick to detect proteinuria than those in practice longer (57.0% vs 70.4%, $p < 0.01$). We hypothesize that the relatively recent acceptance of spot protein to creatinine ratio testing may explain the significant difference in screening methods used by the 2 groups. As such, it is possible that rheumatologists in practice for less than 10 years and closer to training at academic institutions may be more familiar with this relatively novel diagnostic tool.

The major limitation of our study is the low response rate and resulting potential for responder bias. Out of 2,667 rheumatologists selected from the ACR registry, 499 responded to at least one question (18.7%). These respondents were self-selected among those receiving surveys and had working e-mail addresses and access to Internet use. They may not represent the true population of practicing rheumatologists in the United States. Another limitation is the specificity of the questionnaire. A small number of respondents commented that the diagnostic methodology used to detect renal involvement is more complicated than proteinuria screening alone. We attempted to address this issue by specifying that the method used was for patients with lupus and *no history of renal disease*. Although there are other factors to consider, such as the presence of hematuria or casts, our purpose was to focus on proteinuria in the absence of other signs.

Our study is important for the discovery that the majority of American rheumatologists may be using qualitative diagnostic methods to screen for proteinuria in patients with known lupus. We are concerned that, in light of recent data and recommendations outside the field of rheumatology, the urine dipstick assay may be insensitive for detection of renal disease and that published recommendations may be improperly guiding diagnostic practices. Future studies may help clarify the role of urine dipstick in screening of lupus patients and drive recommendations for rheumatologists. Ultimately, definitive guidelines will help ensure that patients with lupus are properly screened for proteinuria, a key step in the diagnosis of nephritis and a prerequisite for prevention of the increased morbidity and mortality associated with this condition.

REFERENCES

1. Cameron J. Lupus nephritis. J Am Soc Nephrol 1999;10:413-24.
2. Cervera RKM, Sebastiani F, Gil A, et al. European Working Party on Systemic Lupus Erythematosus: Morbidity and mortality in systemic lupus erythematosus during a 10-year period: A comparison study of early and late manifestations in a cohort of 1,000 patients. Medicine Baltimore 2003;82:299-308.
3. Esdaile JM, Joseph L, MacKenzie T, Kashgarian M, Hayslett JP. The benefit of early treatment with immunosuppressive agents in lupus nephritis. J Rheumatol 1994;21:2046-51.
4. Balow JE. Clinical presentation and monitoring of lupus nephritis. Lupus 2005;14:25-30.
5. Fine DM. Pharmacological therapy of lupus nephritis. JAMA 2005;293:3053-60.
6. Symmons DP, Coppock JS, Bacon PA, et al. Development and assessment of a computerized index of clinical disease activity in systemic lupus erythematosus. Members of the British Isles Lupus Assessment Group (BILAG). Q J Med 1988;69:927-37.
7. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
8. Liang MH, Socher SA, Roberts WN, Esdaile JM. Measurement of systemic lupus erythematosus activity in clinical research. Arthritis Rheum 1988;31:817-25.
9. Meyer NL, Mercer BM, Friedman SA, Sibai BM. Urinary dipstick protein: a poor predictor of absent or severe proteinuria. Am J Obstet Gynecol 1994;170:137-41.
10. Garcia C, Bordier L, Burnat P, et al. Urinary dipsticks must not be used to detect diabetes-induced incipient nephropathy [French]. Presse Med 2006;35:1117-21.
11. Gangaram R, Ojwang PJ, Moodley J, Maharaj D. The accuracy of urine dipsticks as a screening test for proteinuria in hypertensive disorders of pregnancy. Hypertens Pregnancy 2005;24:117-23.
12. Zeller A, Sigle JP, Battegay E, Martina B. Value of a standard urinary dipstick test for detecting microalbuminuria in patients with newly diagnosed hypertension. Swiss Med Wkly 2005;135:57-61.
13. Abitbol C, Zilleruelo G, Freundlich M, Strauss J. Quantitation of

proteinuria with urinary protein/creatinine ratios and random testing with dipsticks in nephrotic children. J Pediatr 1990;116:243-7.
14. Gai M, Motta D, Giunti S, et al. Comparison between 24-h proteinuria, urinary protein/creatinine ratio and dipstick test in patients with nephropathy: patterns of proteinuria in dipstick-negative patients. Scand J Clin Lab Invest 2006;66:299-307.
15. Waugh JJ, Clark TJ, Divakaran TG, Khan KS, Kilby MD. Accuracy of urinalysis dipstick techniques in predicting significant proteinuria in pregnancy. Obstet Gynecol 2004;103:769-77.
16. The American College of Rheumatology response criteria for proliferative and membranous renal disease in systemic lupus erythematosus clinical trials. Arthritis Rheum 2006;54:421-32.
17. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. 2002; Part 5. Evaluation of laboratory measurements for clinical assessment of kidney disease. [Internet. Accessed February 19, 2007] Available from: http://www.kidney.org/professionals/kdoqi/guidelines_ckd/toc.htm
18. Simerville J, Maxted W, Pahira J. Asymptomatic proteinuria is associated with significant renal disease in less than 1.5 percent of patients. Am Fam Physician 2005;71:1153-62.
19. Christopher-Stine L, Siedner M, Lin J, et al. Renal biopsy in lupus patients with low levels of proteinuria. J Rheumatol 2007;34:332-5.