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Original article

High incidence of proliferative and membranous nephritis in SLE patients with low proteinuria in the Accelerating Medicines Partnership

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Abstract

Objective. Delayed detection of LN associates with worse outcomes. There are conflicting recommendations regarding a threshold level of proteinuria at which biopsy will likely yield actionable management. This study addressed the association of urine protein:creatinine ratios (UPCR) with clinical characteristics and investigated the incidence of proliferative and membranous histology in patients with a UPCR between 0.5 and 1.

Methods. A total of 275 SLE patients (113 first biopsy, 162 repeat) were enrolled in the multicentre multi-ethnic/racial Accelerating Medicines Partnership across 15 US sites at the time of a clinically indicated renal biopsy. Patients were followed for 1 year.

Results. At biopsy, 54 patients had UPCR <1 and 221 had UPCR ≥ 1. Independent of UPCR or biopsy number, a majority (92%) of patients had class III, IV, V or mixed histology. Moreover, patients with UPCR <1 and class III, IV, V, or mixed had a median activity index of 4.5 and chronicity index of 3, yet 39% of these patients had an inactive sediment. Neither anti-dsDNA nor low complement distinguished class I or II from III, IV, V or mixed in patients with UPCR <1. Of 29 patients with baseline UPCR <1 and class III, IV, V or mixed, 23 (79%) had a UPCR <0.5 at 1 year.

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CLINICAL SCIENCE

Conclusion. In this prospective study, three-quarters of patients with UPCR <1 had histology showing class III, IV, V or mixed with accompanying activity and chronicity despite an inactive sediment or normal serologies. These data support renal biopsy at thresholds lower than a UPCR of 1.

Key words: systemic lupus erythematosus, lupus nephritis, diagnosis

Rheumatology key messages

- Renal biopsy is likely warranted in SLE patients with UPCR between 0.5 and 1.
- Clinical trials have excluded LN patients with low proteinuria despite proliferative/membranous disease.

Introduction

SLE is an autoimmune disease characterized by heterogeneous clinical manifestations primarily targeting women of child-bearing age [1]. In nearly 60% of patients the kidney is affected, which in turn associates with the highest standardized mortality ratio in SLE [2, 3]. Therefore, determining inflammation and fibrosis in the kidneys represents a critical aspect of management since early recognition and treatment associate with better outcomes [2, 4]. A biopsy of the kidney is considered the gold standard to assess the presence and severity of LN and clinicians traditionally rely on proteinuria, often measured by random urine protein:creatinine ratios (UPCR), to drive decisions regarding when to retrieve renal tissue [5].

The most recent EULAR and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) guidelines recommend performing a biopsy to investigate any sign of kidney involvement including an active urinary sediment, an unexplained decrease in glomerular filtration rate and/or a UPCR >0.5 [6]. This is in contrast to ACR guidelines which state that a kidney biopsy is indicated when serum creatinine increases in the absence of an alternative cause, UPCR >1, or UPCR >0.5 in the presence of haematuria or cellular casts [5]. Prior studies have characterized patients with significant pathology including International Society of Nephrology and the Renal Pathology Society (ISN/RPS) class III, IV, V or mixed LN in patients with little to no proteinuria [7–22]. A number of these studies have described so called 'silent' LN, which refers to patients with renal disease in the absence of any urinary abnormalities and/or proteinuria [7–19]. Other retrospective studies that specifically included patients with UPCR 0.5–1 found that most patients with this degree of proteinuria had treatment 'actionable' classes, supporting that a lower UPCR threshold for biopsy (as per EULAR/ERA-EDTA guidelines) may lead to earlier detection of patients at risk of progressive renal damage [21–23]. However, clinical application of the EULAR/ERA-EDTA guidelines has not been confirmed in a prospective study.

While the EULAR/ERA-EDTA guidelines recommend a biopsy at UPCR >0.5, clinical trials investigating LN therapies have excluded patients with UPCR <1. For example, the recent LN trials evaluating the efficacy of abatacept, voclosporin and belimumab required at least a baseline UPCR >1 with definitions of complete renal response related to reduction in proteinuria below 0.5, which may be too readily achievable for patients with UPCR <1 compared with higher baseline levels [24–26]. Because clinical trials do not capture patients with low baseline proteinuria and little is known about the natural history of this group, there is no standardized approach to assessing renal responses in these patients. As a result, novel therapies that are efficacious for those with a lower UPCR may be overlooked and treatments that are approved may not be appropriate for this population.

The Accelerating Medicines Partnership (AMP) LN study is a public–private partnership initiated in 2014 to deconstruct the heterogeneity of disease and to develop new ways of identifying and validating promising biological targets for diagnostics and drug development. Phases 0 and 1 focused on technical development with optimization of kidney tissue dissociation, cryopreservation and single cell RNA sequencing, with Phase 2 applying these technical advances to patients longitudinally followed for 1 year after undergoing a clinically indicated percutaneous renal biopsy [27]. Accordingly, the resulting multicentre prospective cohort represents the opportunity to leverage a large well-characterized population of racially and ethnically diverse patients to address associations between baseline proteinuria and renal histologic findings in a real-world setting across many clinical sites. Specifically, in consideration of current conflicting recommendations regarding renal biopsy indications and the value of proteinuria *per se* to inform management, baseline UPCR between 0.5 and 1 were compared with ratios ≥1 with regard to patient demographics, histologic class, activity index (AI) and chronicity index (CI), and serology.

Methods

Study design and patient population

Patients undergoing a clinically indicated renal biopsy to evaluate proteinuria (defined for inclusion in AMP as a UPCR >0.5) at the direction of the treating rheumatologist or nephrologist were approached and recruited for this study if they were over the age of 16 years and

fulfilled the revised ACR or the SLICC classification criteria for SLE [28, 29]. The definition of clinically indicated was not prespecified but included suspected LN *de novo*, ongoing activity and dissatisfaction with treatment, or new relapse. Patients with a history of kidney transplant, recent use of rituximab within 6 months of biopsy or who were pregnant were excluded. In compliance with the Helsinki Declaration, all SLE patients provided written informed consent approved by the respective institutional review boards and ethics committees of the participating sites (Cedars-Sinai; University of Cincinnati; Albert Einstein College of Medicine; Johns Hopkins; University of Michigan; Medical University of South Carolina; Northwell Health; NYU Grossman School of Medicine; University of Rochester; Texas Tech; University of California sites including San Francisco, Los Angeles and San Diego; University of North Carolina; and University of Texas Health) for obtaining an extra renal core or leftover tissue and participation in follow-up visits. For this study, patients were included from Phase I and Phase 2 of AMP during which patients were followed longitudinally.

UPCR was measured on a 24-h urine collection or from a random spot urine. At baseline only 23% of patients had a 24-h urine collection in addition to a random measurement. Consistent with prior reports, it was found that there was a strong correlation between the 24 h and random UPCR in this cohort ($r = 0.891$, $P < 0.0001$, $n = 63$) [30, 31]. As such, only random UPCR measurements were included for consistency and to reflect the measure commonly obtained by providers in a real-world setting. Biopsies were reviewed by board certified pathologists at the institution where the biopsy took place and assigned histological classes and AI and CI according to the ISN/RPS classification [32, 33].

In total, 317 patients were consecutively enrolled at any of 15 clinical sites in the US between January 2016 and March 2020, of whom 275 were included in this analysis. Those excluded included 22 patients with a kidney biopsy that did not show LN, 13 with advanced sclerosing pathology and 7 with no random UPCR recorded. At the time of biopsy and at each visit thereafter (12, 26 and 52 weeks), demographics, clinical characteristics and laboratory measures were recorded. Participants were treated for LN according to standard of care determined by their treating physician. Laboratory measurements were carried out in local laboratories with abnormal results defined as per the cutoffs of the laboratory.

Statistical analysis

Descriptive statistics are presented as mean (S.D.) or median and interquartile range (IQR) for continuous variables and frequencies for categorical variables. A two-tailed Student's *t*-test or Wilcoxon's test were used to compare continuous variables, and Pearson's chi-squared or Fisher's exact were used to compare categorical variables where appropriate. Pearson's correlation was used to associate 24 h and random UPCR measures. Missing data is reflected in the sample size, which is reported where it differs from the overall sample size.

Results

Of the 275 SLE patients included in the analysis, the baseline random UPCR was <1 in 54 (20%) and ≥1 in 221 (80%). Patients at their first kidney biopsy were more likely to have UPCR <1 (Table 1). Patients with a UPCR <1 at their first biopsy were slightly older (Tables 1 and 2). Overall, there was an increased frequency of Black patients with UPCR <1. While not significant, a higher percentage of Hispanic patients had a UPCR ≥1 and this trend was predominantly driven by those undergoing a repeat biopsy (Tables 1 and 2).

Only 8% of patients had class I or II histology, although those classes were more frequent in patients with UPCR <1 independent of biopsy number (Tables 1 and 2). National Institutes of Health AI and CI did not significantly differ by UPCR (Tables 1 and 2). Haematuria and pyuria more often associated with higher UPCR regardless of biopsy number (Tables 1 and 2). No patients with baseline UPCR 0.5–1, for whom estimated glomerular filtration rate measures were recorded ($n = 44$ at 6 months and $n = 46$ at 12 months), developed stage 5 chronic kidney disease (estimated glomerular filtration rate <15 ml/min/1.73 m^2) during the 12-month follow-up period. For patients with UPCR ≥1, 6 of 152 patients with available data had stage 5 chronic kidney disease at 6 months and 7 of 147 patients had stage 5 chronic kidney disease at 12 months. Similarly, 0 of 38 patients with available data having a baseline UPCR 0.5–1 had a 2-fold increase in serum creatinine at 12 months, but 8 of 168 patients with a baseline UPCR ≥1 did have a doubling of serum creatinine at 12 months (Tables 1 and 2).

Given that lower levels of proteinuria were associated with a spectrum from benign to more advanced findings on kidney biopsy, further evaluation focused only on those patients with a baseline UPCR <1 to identify whether any clinical or laboratory characteristics might be useful in differentiating patients likely to have more aggressive disease requiring immunosuppression. Only 8% of males compared with 27% of females with UPCR <1 had class I or II (supplementary Table S1, available at *Rheumatology* online). Class V was more common among Black patients (supplementary Table S1, available at *Rheumatology* online). An increased frequency of patients with class III or IV had a low C3 (72%) at the time of biopsy than those with class V (36%) or class II (25%) (supplementary Table S1, available at *Rheumatology* online). Seven of 46 patients with UPCR <1 and recorded anti-dsDNA and complement levels had negative anti-dsDNA antibodies and normal C3 and C4 levels. Of these, one was class II, one was class IV, four were class V and one was mixed class III/V, illustrating that normal serology did not rule out disease likely requiring treatment (supplementary Table S1,

Table 1 Baseline characteristics by UPCR classification

Baseline characteristics	UPCR <1 ($n = 54$)	UPCR ≥1 ($n = 221$)	*P*-value
Sex: female	41 (75.9)	190 (86)	0.071
Age, years, mean (S.D.)	38.5 (13.1)	34.6 (11.2)	**0.0271**
Ethnicity: Hispanic ($n = 274$)	10 (18.9)	70 (31.7)	0.0655
Race			0.1297
Asian	6 (11.1)	40 (18.1)	
Black	30 (55.6)	84 (38)	
White	13 (24.1)	69 (31.2)	
Other/unknown	5 (9.3)	28 (12.7)	
Race: Black	30 (55.6)	84 (38)	**0.0190**
First biopsy	29 (53.7)	84 (38)	**0.0356**
Serum creatinine, mg/dl, median (IQR) ($n = 273$)	0.82 (0.72–1.06)	0.9 (0.7–1.39)	0.4078
High serum creatinine ($n = 273$)[a]	10 (18.9)	72 (32.7)	**0.0482**
Doubling of serum creatinine at 12 months ($n = 204$)	0 (0.0)	8 (4.8)	0.3561
Activity index, median (IQR) ($n = 202$)	4 (2–7)	4.5 (1–8)	0.4106
Chronicity index, median (IQR) ($n = 202$)	3 (1–3)	3 (1–5)	0.707
Low C3 ($n = 267$)[a]	28 (57.1)	139 (63.8)	0.3871
Low C4 ($n = 266$)[a]	22 (44.9)	121 (55.8)	0.1684
Positive anti-dsDNA ($n = 262$)	40 (81.6)	150 (70.4)	0.113
High urine sediment WBC ($n = 271$)	18 (34)	114 (52.3)	**0.0166**
High urine sediment RBC ($n = 271$)	19 (35.8)	112 (51.4)	**0.0425**
Immunologic combination ($n = 259$)			0.1629
Anti-dsDNA-NL, complement-NL	7 (15.2)	34 (16)	
Anti-dsDNA-NL, complement-LO	1 (2.2)	29 (13.6)	
Anti-dsDNA-HI, complement-NL	8 (17.4)	29 (13.6)	
Anti-dsDNA-HI, complement-LO	30 (65.2	121 (56.8)	
Biopsy class			
I	1 (1.9)	3 (1.4)	0.5851
II	11 (20.4)	8 (3.6)	**0.0001**
III	15 (27.8)	35 (15.8)	**0.0496**
IV	4 (7.4)	43 (19.5)	**0.0424**
III, IV	0 (0)	3 (1.4)	1.0000
V	11 (20.4)	61 (27.6)	0.3057
III, V	10 (18.5)	41 (18.5)	1.0000
IV, V	2 (3.7)	27 (12.2)	0.0832
Medications			
HCQ	49 (90.7)	178 (80.5)	0.1078
Prednisone/methylprednisolone	32 (59.3)	159 (71.9)	0.0984
Mycophenolate	26 (48.1)	113 (51.1)	0.7621
AZA	4 (7.4)	23 (10.4)	0.6173
Belimumab	2 (3.7)	8 (3.6)	1.0000
Tacrolimus	1 (1.9)	15 (6.8)	0.2104
CYC	0 (0)	5 (2.3)	0.5867
ACE or ARB	25 (46.3)	97 (43.9)	0.7621

Data are presented as n (%) unless otherwise specified. [a]Classified by local laboratory cutoffs. Bold text highlights significant *P*-values. UPCR: urine protein creatinine ratio; anti-dsDNA: anti-dsDNA autoantibodies; WBC: white blood cells; RBC: red blood cells; NL: normal level; LO: low; HI: high; ACE: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers.

available at *Rheumatology* online). Three of these seven patients with UPCR <1 and normal serology had no haematuria or pyuria, including one patient with class II and two patients with class V histology.

For patients with UPCR <1, compared with patients with class I or II, those with class III, IV, V or mixed trended towards having increased haematuria (42% *vs* 17%) and had more pyuria (44% *vs* 0%). However, 58% of patients with III, IV, V or mixed histology had no haematuria, 56% had no pyuria and 39% had neither pyuria nor haematuria, indicating that the urine sediment may be misleading with regard to prediction of renal pathology. The National Institutes of Health AI and CI were available for 30 patients with UPCR <1 and class III, IV, V or mixed histology. The median AI for these patients was 4.5 and the median chronicity index was 3. Looking more closely, 23 (77%) had an AI ≥2 and 17 (57%) had a CI ≥3. In addition, in these patients, activity did not significantly differ based on the presence of an active sediment [median (IQR), no haematuria or pyuria:

TABLE 2 Baseline characteristics by UPCR classification stratified by biopsy number at AMP enrolment

Baseline characteristics	First biopsy ($n = 113$)				Repeat biopsy ($n = 162$)			
	n	UPCR <1 ($n = 29$)	UPCR ≥1 ($n = 84$)	*P*-value	*n*	UPCR <1 ($n = 25$)	UPCR ≥1 ($n = 137$)	*P*-value
Sex: female	113	22 (75.9)	75 (89.3)	0.1181	162	19 (76)	115 (83.9)	0.3875
Age, years, median (IQR)	113	35 (30–43)	30 (26–39)	0.0763	162	33 (31–55)	35 (26–42)	0.2762
Ethnicity: Hispanic	112	6 (21.4)	25 (29.8)	0.3934	162	4 (16)	45 (32.8)	0.0917
Race	113			0.4394	162			0.3083
Asian		3 (10.3)	13 (15.5)			3 (12)	27 (19.7)	
Black		15 (51.7)	29 (34.5)			15 (60)	55 (40.1)	
White		9 (31)	30 (35.7)			4 (16)	39 (28.5)	
Other/unknown		2 (6.9)	12 (14.3)			3 (12)	16 (11.7)	
Race: Black	113	15 (51.7)	29 (34.5)	0.1015	162	15 (60)	55 (40.1)	0.0653
Biopsy class	113			0.0704	162			**0.0006**
Class I or II		4 (13.8)	3 (3.6)			8 (32)	8 (5.8)	
Class III, IV, V or mixed		25 (86.2)	81 (96.4)			17 (68)	129 (94.2)	
Serum creatinine, mg/dl, median (IQR)	113	0.82 (0.7–1)	0.8 (0.7–1.2)	0.8903	160	0.9 (0.7–1.1)	0.95 (0.7–1.6)	0.3751
High serum creatinine[a]	113	4 (13.8)	17 (20.2)	0.4417	160	6 (25)	55 (40.4)	0.151
Doubling of serum creatinine at 12 months	70	0 (0.0)	1 (1.9)	1.000	134	0 (0.0)	7 (6.1)	0.5936
Activity index, median (IQR)	83	4 (3–7)	4 (1–8)	0.6834	119	3.5 (0–5)	5 (1–9)	0.1085
Chronicity index, median (IQR)	83	2 (1–3)	1 (0–3)	0.1502	119	3 (1.5–4)	4 (2–6)	0.2474
Low C3[a]	109	19 (70.4)	56 (68.3)	0.8398	158	9 (40.9)	83 (61)	0.0758
Low C4[a]	108	15 (55.6)	58 (71.6)	0.1228	158	7 (31.8)	63 (46.3)	0.2038
Positive anti-dsDNA	108	23 (82.1)	63 (78.8)	0.7012	154	17 (81)	87 (65.4)	0.1576
High urine sediment WBC	110	11 (39.3)	49 (59.8)	0.0604	161	7 (28)	65 (47.8)	0.0673
High urine sediment RBC	110	13 (46.4)	53 (64.6)	0.0895	161	6 (24)	59 (43.4)	0.0695
Immunologic combination	106			0.547	153			0.1721
Anti-dsDNA-NL, complement-NL		4 (15.4)	7 (8.8)			3 (15)	27 (20.3)	
Anti-dsDNA-NL, complement-LO		1 (3.8)	10 (12.5)			0 (0)	19 (14.3)	
Anti-dsDNA-HI, complement-NL		3 (11.5)	10 (12.5)			5 (25)	19 (14.3)	
Anti-dsDNA-HI, complement-LO		18 (69.2)	53 (66.3)			12 (60)	68 (51.1)	

Data are presented as n (%) unless otherwise specified. [a]Classified by local laboratory cutoffs. Bold text highlights significant *P*-values. UPCR: urine protein:creatinine ratio; anti-dsDNA: anti-dsDNA autoantibodies; WBC: white blood cells; RBC: red blood cells; NL: normal level; LO: low; HI: high.

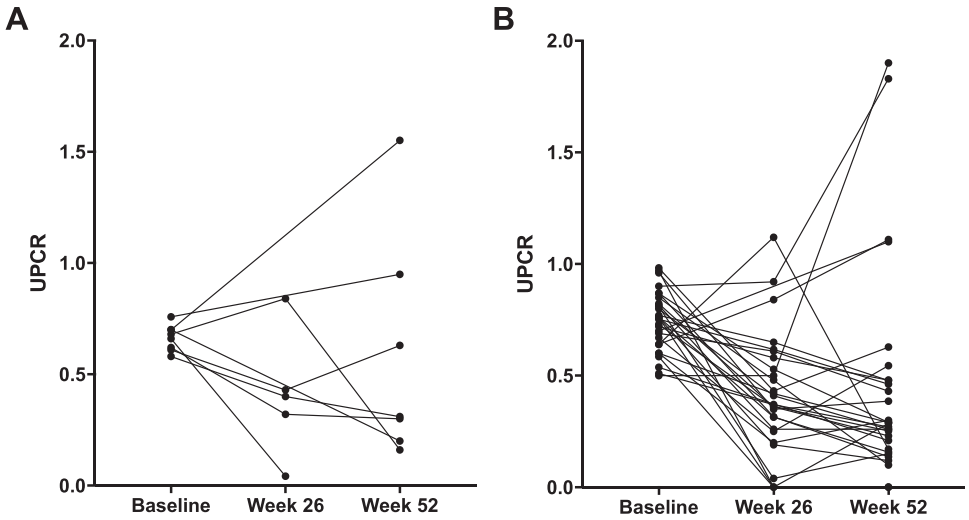
AI 4 (0–5), $n = 14$, *vs* haematuria or pyuria present: AI 5 (3–8), $n = 14$, $P = 0.18$] or a serum creatinine ≥1 mg/dl [normal creatinine: AI 5 (2.5–7.5), $n = 21$, *vs* creatinine ≥1 mg/dl: AI 4 (0–5.5), $n = 9$, $P = 0.22$]. Chronicity also did not differ based on the presence of an active sediment [no haematuria or pyuria: CI 3 (1–4), $n = 14$, *vs* haematuria or pyuria present: CI 2.5 (1–3), $n = 14$, $P = 0.73$] or a serum creatinine ≥1 mg/dl [normal creatinine: CI 3 (1–3), $n = 21$, *vs* creatinine ≥1 mg/dl: CI 2 (0.5–4), $n = 9$, $P = 0.94$].

Follow-up data at 1 year were available for seven patients with a baseline UPCR <1 and renal histology indicating class II. One (14%) of these patients had an increase in UPCR to above 1 at 1 year follow-up (Fig. 1A). Follow-up data at 1 year were available for 29 patients with a baseline UPCR <1 and renal histology indicating either class III, IV, V or mixed. One year after the biopsy, 23 (79%) had a UPCR <0.5 [median (IQR): 0.26 (0.15–0.3)], 2 (7%) remained at UPCR 0.5–1 [0.59 (0.55–0.63)] and 4 (14%) increased UPCR to >1 [1.5 (1.10–1.87)] (Fig. 1B).

Discussion

In addressing the clinical relevance of baseline proteinuria there were very few differences observed between patients biopsied with UPCR 0.5–1 compared with those with a UPCR ≥1. Although class II was most often accompanied by a UPCR <1, nearly 80% of patients with minimal proteinuria did have class III, IV, V or mixed. AI and CI did not significantly associate with UPCR whether the biopsy was *de novo* or a repeat and the CI was >3 in 57% of biopsies from patients with low levels of proteinuria and class III, IV, V or mixed histology. Serologic variables could not reliably distinguish between histological classes in patients with UPCR <1, although there was a trend for low C3 to associate with more advanced classes, and nearly half of patients with UPCR <1 and proliferative or membranous histology had no active sediment. At 1 year follow-up, three-quarters of patients with UPCR 0.5–1 and proliferative, membranous or mixed biopsy class had a reduction in UPCR to <0.5.

FIG. 1 Change in UPCR over 1 year for patients with baseline UPCR <1



(**A**) UPCR at baseline ($n = 8$), 6 months ($n = 5$) and 1 year ($n = 7$) for patients with baseline UPCR <1 and class II renal histology. (**B**) UPCR at baseline ($n = 29$), 6 months ($n = 28$) and 1 year ($n = 29$) for patients with baseline UPCR <1 and class III, IV, V or mixed renal histology. UPCR: urine protein:creatinine ratio.

Both EULAR/ERA-EDTA and ACR recommend treating patients with immunosuppressive agents for proliferative, membranous or mixed disease [5, 6]. That over half the patients with UPCR <1 had already accrued chronic damage at the time of first biopsy and a majority associated with treatable histologic classes suggests that an aggressive approach to renal biopsy may be warranted. These observations are consistent with and extend two retrospective analyses. Chedid *et al.* found that of 31 LN patients undergoing their first biopsy with UPCR 0.5–1 in the absence of an active sediment, 71% were class III, IV, V or mixed, with a mean chronicity of 2.1 [23]. In the same study, six of nine patients with UPCR <0.5 and no active sediment had class III, IV, V or mixed histology, with a mean chronicity of 2.3 [23]. In an older, more limited retrospective study, Christopher-Stine and colleagues reported that 13 of 21 patients with proteinuria <1 g/day had class III, IV, V or mixed LN, including 4 patients in the absence of haematuria [21]. Similarly, the absence of an active sediment did not reassure mild disease in this study. The ACR guidelines recommend a renal biopsy at UPCR <1 only in the presence of an active sediment [5]. In the AMP study an active sediment did associate with proliferative and membranous pathology, but nearly half of patients with those histological findings and UPCR <1 still did not have any haematuria or pyuria, illustrating that the absence of sediment is not reliable in assuring that histology is sufficiently so mild as to not warrant treatment. Together, these observations support the updated EULAR/ERA-EDTA recommendations, which favor a lower threshold for renal biopsy at UPCR >0.5 independent of an active urinary sediment and suggest that a biopsy may be beneficial at even lower proteinuria levels [6].

The consideration of *de novo* or relapsed disease often influences the decision to biopsy and current clinical guidelines do not provide a detailed algorithm for when repeat biopsy is warranted [5, 6]. Herein, we stratified analyses based on first *vs* repeat biopsy because clinicians may have a different propensity to biopsy when a patient presents with a history of known LN and relapsed disease which may clinically differ from the initial insult [34]. With the inference that repeat biopsy was indicative of a relapse, biopsies from patients with UPCR <1 had chronicity and proliferative or membranous histology similar to that seen in patients with higher UPCR independent of biopsy number. This is consistent with studies showing that repeat biopsies harbour chronic damage regardless of the level of proteinuria [35–37]. In addition, Fava and colleagues recently reported that 82% of patients with previous class I/II converted to a higher ISN class on repeat biopsy and that class changes overall were very common and can occur at any point in the natural history of LN [38]. Any prior biopsy showing proliferative disease was a poor prognostic factor irrespective of the class identified on a subsequent biopsy, reinforcing the clinical importance of not missing proliferative histology for UPCR <1 [38]. While these findings together support a biopsy threshold of a UPCR at 0.5 rather than 1 in patients with relapse, it may be that the threshold for this population should be decreased as several studies have demonstrated persistent histologic findings even in the presence of a complete clinical response [35–37, 39, 40]. Most recently, two prospective observational studies have shown that protocolized biopsies taken prior to the withdrawal of maintenance therapy regardless of proteinuria levels may improve outcomes [35, 36]. Future studies which

involve harvesting tissue from serial biopsies should seek to identify noninvasive biomarkers of persistent subclinical disease to simplify the indication for repeat biopsy.

Evaluating renal response to induction therapy is highly informative in the therapeutic management of LN. Patients described herein with UPCR <1 had histology that would be an indication for pharmacologic intervention [6]. Given that treatment response is generally determined using changes in UPCR from baseline, there is currently no standard for evaluating therapeutic responses in patients with baseline UPCR <1. Most of these patients had improvement in UPCR at 1 year in the longitudinal analysis. While these patients may have been identified early in their disease, and immediate treatment was sufficient to induce remission, the presence of chronicity even in patients at first biopsy indicates that nephritis may have been smouldering for some time. In the absence of a reliable marker or repeat biopsy it is harder to gauge whether a reduction in proteinuria in this population translates to disease remission and reduction in the progression of disease. This highlights the crucial need for studies like AMP that will assess renal response in relation to molecular analyses with the goal of finding biomarkers of therapeutic responses. A novel biological surrogate of response would make it more feasible for investigators to include these patients in clinical trials and it would give clinicians and their patients a reliable tool to assess treatment efficacy.

Several limitations are acknowledged. This was a cross-sectional evaluation of biopsy characteristics and longitudinal assessment of clinical outcome measured by UPCR. Repeat biopsies were not performed as part of the longitudinal assessment, and therefore this study cannot assess whether UPCR improvements associated with treatment were accompanied by histological changes. There was no standard treatment prescribed as part of this study and as such the longitudinal assessment cannot address whether reductions in UPCR to below 0.5 associate with any specific regimen. Thus, in this study actionable management implies a biopsy class of membranous or proliferative which would warrant immunosuppressive therapy. For uniformity, a random spot urine was used to measure UPCR in this study because most patients did not have a 24-h urine collection completed. While this may have introduced some inaccuracy, a random UPCR significantly associated with 24-h measures in this cohort, has been shown to reliably measure proteinuria in LN and likely is more reflective of the measure obtained by clinicians in real-world clinical practice [30, 31]. Reliability of the urine sediment was based on reports from the local site clinical laboratories and not done centrally. It is acknowledged that red blood cells could be the consequence of menstruation. The comparison of patients with class II histology to patients with proliferative, membranous or mixed histology for those with UPCR <1 was limited by a small sample size and underpowered to perform tests of significance. Biopsies were performed at the discretion of treating physicians and entry criteria required the biopsy to be 'clinically indicated' but no further specifics were provided. It is not known whether all patients at each site with UPCR <1 underwent a biopsy and therefore, this study did not include all consecutive patients with UPCR between 0.5 and 1. Moreover, patients refusing to provide tissue for research were excluded. Nevertheless, the fact that 78% of patients with a UPCR 0.5–1 had either proliferative, membranous or mixed pathology, of whom 39% had no findings on sediment, indicates that an aggressive approach to renal biopsy is warranted in these patients.

In summary, this prospective study showed that nearly 80% of patients with a UPCR between 0.5 and 1 and suspected LN have proliferative or membranous histology and AI and CI similar to patients with higher levels of proteinuria, and that neither serologies nor urinary sediment can reliably predict kidney histology in these patients. These results support renal biopsy at thresholds lower than a UPCR of 1 irrespective of sediment or serologic abnormalities, since histologic findings can inform therapeutic decisions.

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Data availability statement

All data relevant to the study are included in the article and its supplementary material.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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