Kidney involvement is common in systemic lupus erythematosus (SLE) and is a major cause of morbidity and mortality. About 50% to 70% of adults and 37% to 82% of children with SLE develop lupus nephritis (LN). A kidney biopsy is generally performed to confirm a diagnosis of LN and to inform treatment in SLE patients who develop proteinuria with or without hematuria and/or impaired kidney function. Proteinuria is considered to be the key clinical diagnostic marker of LN, and in the absence of proteinuria above a certain threshold, kidney biopsies in SLE patients are often not performed. For example, the current American College of Rheumatology (ACR) guidelines suggest that a kidney biopsy be performed in patients with proteinuria >1.0 g/d, or proteinuria >0.5 g/d accompanied by hematuria or cellular casts. However, there have been a handful of reports describing significant kidney pathology in SLE patients with no or minimal proteinuria, raising the question of what constitutes an appropriate threshold for performing a kidney biopsy. We examined proteinuria levels at the time of kidney biopsy in our LN population to determine whether the proteinuria threshold for biopsy should be <0.5–1 g/d.

We characterized 222 SLE patients who underwent a kidney biopsy for suspicion of LN between 2008 and 2017 at the Hospital de Clinicas, University of Buenos Aires. Most patients (79%) had proteinuria ≥0.5 g/d, and all except 7 patients had evidence of glomerular hematuria (acanthocytes) on examination of the urine sediment. However, 46 patients with a urine protein level <0.5 g/d underwent biopsy. All of these patients had glomerular hematuria, and 5 had a serum creatinine concentration >1 mg/dl (1.1–1.3 mg/dl). All patients were Hispanic and of European ancestry. The demographic and clinical characteristics of the patients with low (<0.5 g/d) proteinuria and the patients with proteinuria (≥0.5 g/d) are compared in Table 1, and the kidney biopsy findings are listed in Table 2. The subgroups of patients with low proteinuria plus a serum creatinine concentration >1 mg/dl and of patients with very low proteinuria (<0.25 g/d) are described in Table 3.

About 85% of the patients with proteinuria <0.5 g/d and 76% with proteinuria <0.25 g/d had class III or IV (±V) LN. None of these patients had class I LN, and only 11% and 20% had class II in the <0.5 g/d and <0.25 g/d proteinuria groups, respectively. The patients with low proteinuria generally had moderate histologic activity, with only 7 (15%) having an activity index ≤1. In addition, despite no prior history of nephritis, most of the patients with low proteinuria had already accrued chronic kidney damage, and only 8 (17%) had a chronicity index of 0. Histologic activity and chronicity were significantly worse in the patients with >0.5 g/d proteinuria. In this group, 2 patients had an activity index of 1 and the rest were all ≥2. Similarly, 2 patients had a chronicity index of 0, and the rest were ≥1.

Compared to the SLE patients with >0.5 g/d proteinuria, there were numerically more male patients in the low-proteinuria group, but this was not significant. The overall duration of SLE was the same for both groups, with a median of about 1 year, but a very wide range. LN was diagnosed within 2 months of an SLE diagnosis in 15% of the low-proteinuria patients and 20% of the patients with >0.5 g/d proteinuria. Patients at both levels of proteinuria were of similar age, all were anti-nuclear antibody–positive, and there were no differences between groups in complement consumption or the proportion of patients who were double-stranded DNA antibody–positive. However,
patients with proteinuria <0.5 g/d did have significantly better kidney function than patients with proteinuria >0.5 g/d. These observations demonstrate that in patients with SLE and glomerular hematuria, the kidney may harbor significant pathology without much proteinuria. One interpretation of these findings is that the patients were identified very early in the course of their LN. Although that may be the case and although it cannot be determined from our cohort, their overall duration of SLE was 12 months, their kidney biopsy samples showed more than minimal histologic activity, and their kidneys already had evidence of chronic damage. These findings support making an early diagnosis of LN with rapid treatment to avoid chronic renal injury and progressive kidney dysfunction.5,7

It is important to emphasize that our patients do not have silent lupus nephritis, which describes patients with no urinary abnormalities and proteinuria ≤300 mg/24 h. Between 60% and 70% of patients with silent LN were found to have class I or II LN histology, whereas only 15% to 20% had class III or IV.5,8 In contrast, class IV LN was the most common International Society of Nephrology/Renal Pathology Society (ISN/RPS) class found in our patients with glomerular hematuria (46%), closely followed by class III LN (30%). Similarly, class III or IV LN was found in 14 of 24 (58%) patients with SLE, proteinuria <0.25 g/d, and an active urine sediment, and in 57% of 21 patients who had a kidney biopsy for 24-h proteinuria <1 g/d with or without hematuria.5

This study has several limitations. It is a retrospective analysis and cannot be used to define the incidence or prevalence of proliferative LN in patients with minimal proteinuria. There were too few patients with class II or V LN to be able to identify predictors to differentiate LN classes in a population of patients with glomerular hematuria and low-grade proteinuria. Finally, and most importantly, all of the most patients with class III and IV LN were treated aggressively with corticosteroids and an immunosuppressive agent (cyclophosphamide or mycophenolate mofetil), precluding any determination of whether patients with

Table 1. Cohort demographics, clinical characteristics, and laboratory data at biopsy

| Cohort characteristics | Proteinuria <0.5 g/d (n = 46) | Proteinuria ≥0.5 g/d (n = 176) | P value* |
|------------------------|-------------------------------|-------------------------------|---------|
| Female                 | 36 (78.5)                    | 155 (88)                      | 0.097   |
| Age, yr                | 31.5 (18–66)                 | 32 (66–168)                   | 0.72    |
| Duration of lupus, mo  | 12 (2–60)                    | 11 (1–186)                    | 0.84    |
| Glomerular hematuria present | 48 (100)         | 169 (96)                      | 0.36    |
| Proteinuria, g/d       | 0.23 (0.0–0.42)              | 3.60 (0.5–20)                 | <0.0001 |
| Serum creatinine, mg/dl| 0.70 (0.4–1.3)               | 0.9 (0.4–7.8)                 | <0.0001 |
| ANA-positive           | 46 (100)                     | 176 (100)                     | —       |
| Anti-dsDNA-positive    | 31 (67.4)                    | 114 (64.8)                    | 1       |
| C3, mg/dl              | 66 (15–174)                  | 69 (14–180)                   | 0.97    |
| C4, mg/dl              | 12 (1–43)                    | 9 (1–46)                      | 0.89    |

Table 2. Histologic findings at biopsy

| Histologic parameter | Proteinuria <0.5 g/d (n = 46) | Proteinuria ≥0.5 g/d (n = 176) | P value* |
|----------------------|-------------------------------|-------------------------------|---------|
| ISN/RPS class        |                               |                               |         |
| II                   | 5 (10.9)                      | 0                             | —       |
| III                  | 14 (30.4)                     | 18 (10.2)                     | 0.002   |
| IV                   | 21 (45.7)                     | 135 (76.7)                    | 0.0001  |
| V                    | 2 (4.3)                       | 3 (1.7)                       | —       |
| III or IV +V         | 4 (8.7)                       | 19 (10.8)                     | —       |
| VI                   | 0                             | 1 (0.6)                       | —       |
| Activity index       | 6 (0–14)                      | 9 (1–21)                      | <0.0001 |
| Chronicity index     | 2 (0–4)                       | 3 (0–8)                       | <0.0001 |

Table 3. Demographic, clinical, and histologic findings of patients with very low levels of proteinuria

| Cohort characteristics | Proteinuria <0.25 g/d (n = 25) | Both proteinuria <0.25 g/d and serum creatinine ≥1 mg/dl (n = 5) | Both proteinuria <0.25 g/d and serum creatinine <1 mg/dl (n = 20) | P value* |
|------------------------|-------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------|
| Female                 | 21 (84)                       | 5 (100)                                                      | 16 (80)                                                      | NS      |
| Age, yr                | 32 (18–65)                    | 24 (22–42)                                                   | 32 (18–65)                                                   | NS      |
| Duration of lupus, mo  | 12 (2–56)                     | 12 (4–44)                                                    | 5 (2–56)                                                     | NS      |
| Glomerular hematuria present | 25 (100)                 | 5 (100)                                                      | 20 (100)                                                     | NS      |
| Proteinuria, g/d       | 0.05 (0.05–0.23)              | 0.20 (0.05–0.23)                                             | 0.05 (0.05–0.23)                                             | NS      |
| Serum creatinine, mg/dl| 0.70 (0.5–1.1)                | 0.63 (0.5–0.9)                                               | 0.0008                                                       |         |
| ANA-positive           | 25 (100)                      | 5 (100)                                                      | 20 (100)                                                     | NS      |
| Anti-dsDNA-positive    | 19 (76)                       | 4 (80)                                                       | 15 (75)                                                      | NS      |
| C3, mg/dl              | 64 (15–174)                   | 44 (15–79)                                                   | 87.5 (20–174)                                                | 0.032   |
| C4, mg/dl              | 12 (1–43)                     | 3 (1–14)                                                     | 12 (1–43)                                                   | NS      |
| Activity index         | 5 (0–10)                      | 6 (6–7)                                                      | 4 (0–10)                                                     | NS      |
| Chronicity index       | 2 (0–4)                       | 2 (2–3)                                                      | 1 (0–4)                                                      | NS      |
| ISN/RPS class II       | 5 (20)                        | 0 (0)                                                        | 5 (25)                                                       | NS      |
| ISN/RPS class III + V  | 6 (24)                        | 1 (20)                                                       | 5 (25)                                                       | NS      |
| ISN/RPS class IV       | 1 (4)                         | 0 (0)                                                        | 1 (5)                                                        |         |
| ISN/RPS class V        | 12 (48)                       | 4 (80)                                                       | 8 (40)                                                       |         |

ANNA, anti-nuclear antibody; anti-dsDNA, anti–double-stranded DNA antibody; C3, complement C3; C4, complement C4; ISN/RPS, International Society of Nephrology/Renal Pathology Society; NS, not significant.*Comparing patients with proteinuria <0.5 g/d to patients with proteinuria ≥0.5 g/d. Data are expressed as number of patients (% of group) or as median (range).
these characteristics may respond adequately to less intense immunosuppression.

In summary, patients with lupus and evidence of an active urine sediment but low levels of proteinuria (<0.5 g/d) may have important kidney pathology that warrants aggressive treatment. Despite current guidelines that recommend a proteinuria threshold of >0.5 to 1 g/d, a diagnostic kidney biopsy in SLE patients with low-grade proteinuria should be considered.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)
Supplementary Methods.
Figure S1. Study design and cohort flowchart.

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