Uric acid as a risk factor for progression to chronic kidney disease in patients with lupus nephritis: results from the KORNET registry

D.-J. Park[1], S.-E. Choi[1], H. Xu[1], J.-H. Kang[1], J.-S. Lee[2], Y.-D. Choi[2], S.-S. Lee[1]

[1]Division of Rheumatology, Department of Internal Medicine, [2]Department of Pathology, Chonnam National University Medical School & Hospital, Gwangju, Republic of Korea.

Abstract

Objective

Little is known regarding the effect of hyperuricaemia on the progression of kidney function in patients with lupus nephritis (LN). Thus, we investigated the effect of uric acid (UA) on the long-term outcome of patients with biopsy-proven LN.

Methods

Data were obtained from KORNET, a prospective longitudinal systemic lupus erythematosus registry in the Republic of Korea. All 137 patients with LN included in this study had undergone a kidney biopsy and were subsequently treated with immunosuppressants. The patients were divided into two groups: UA ≤7 mg/dL and >7 mg/dL; their sociodemographic, clinical, treatment-related data, and outcomes were compared. Cox-proportional regression analyses were performed to identify independent predictors of renal outcome in patients with LN.

Results

Among the 137 patients, 37 (27.0%) had UA >7 mg/dL. This higher UA group included fewer women, but more patients with hypertension, proliferative type LN, and a chronicity index >12. The 24-h urinary protein excretion and the creatinine level were higher in this group; haemoglobin, platelet, and albumin levels were lower. During 85.0 months of follow-up, complete remission at 1 year was less frequent in the higher UA group, whereas chronic kidney disease (CKD) and end-stage renal disease were more prevalent. In the Cox proportional hazards regression analysis, UA >7 mg/dL was a significant predictor of progression to CKD in patients with LN (hazard ratio=2.437; p=0.020).

Conclusion

Our findings suggest that hyperuricaemia at LN onset is an independent risk factor that predicts the development of CKD in patients with LN.

Key words

lupus nephritis, uric acid, chronic kidney disease, outcome

Dong-Jin Park, MD, PhD
Sung-Eun Choi, MD
Haimuzi Xu, MD, PhD
Ji-Hyoun Kang, MD, PhD
Ji-Shin Lee, MD, PhD
Yoo-Duk Choi, MD, PhD
Shin-Seok Lee, MD, PhD

Please address correspondence to:
Shin-Seok Lee,
Division of Rheumatology,
Department of Internal Medicine,
Chonnam National University
Medical School & Hospital,
42 Jebong-ro, Dong-gu,
Gwangju 61469, Republic of Korea.
E-mail: shinseok@chonnam.ac.kr

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Introduction

Lupus nephritis (LN) is a major organ manifestation of systemic lupus erythematosus (SLE), which occurs in up to 60% of patients with SLE (1, 2). Despite significant advances in the treatment of LN using newer immunosuppressive agents (*e.g.* mycophenolate mofetil [MMF], tacrolimus, and rituximab), permanent kidney damage, including chronic kidney disease (CKD) and end-stage renal disease (ESRD), develops in the majority of patients with LN (3, 4). Indeed, approximately 20–40% of patients with LN will develop CKD and 10–20% will develop ESRD (5, 6). LN-related renal dysfunction is associated with substantial morbidity and mortality (7), as well as an increased risk of cardiovascular disease (*e.g.* myocardial infarction and stroke), both of which are important causes of mortality in patients with SLE (8). Progression to renal dysfunction is associated with a reduction in the quality of life of patients with LN (9). Therefore, the ability to predict the long-term renal outcome in patients with LN will allow more accurate assessment of disease severity and better treatment.

Several lines of evidence suggest a pathogenic role for hyperuricaemia in the development and progression of CKD, including through induction of renal inflammation and endothelial dysfunction, as well as by activation of the renin-angiotensin system (10, 11). Epidemiological studies in the general population and in patients with CKD have also shown an association of hyperuricaemia with an increased risk of CKD (12-15). Among patients with SLE, case-control studies have revealed an association of LN with higher uric acid (UA) levels, suggesting that hyperuricaemia can serve as a predictor of renal damage in SLE (16, 17). Furthermore, a multivariate analysis revealed that the serum UA level at 12 months of follow-up tended to be related to long-term renal outcome (defined as a mild reduction of renal function as a Modification of Diet in Renal Disease creatinine clearance of 60–89 mL/min/1.73 m^2) in patients with LN, although the association was not statistically significant (18).

However, little is known regarding the long-term effect of hyperuricaemia in patients with LN. Notably, previous studies have shown that the renal prognosis of Asians patients with LN is between that of Caucasian and African American patients with LN (19). Thus, this study was performed to evaluate the impact of hyperuricaemia on long-term renal outcome using data from ethnically homogenous Korean patients with biopsy-proven LN.

Patients and methods

Study design and population

This study was conducted as part of a prospective longitudinal study by the KORean lupus NETwork (KORNET) registry. KORNET is a nationwide, multicentre, hospital-based registry which is designed to evaluate the clinical manifestations of SLE and disease outcomes in Korean patients (9). Data recorded in the registry were retrospectively analysed. Study enrollment was limited to patients with LN who visited Chonnam National University Hospital within 6 months of diagnosis, because of data availability regarding long-term outcome. All patients met the 1997 revised criteria for the classification of SLE (20). Patients were included if they had at least a 1-year follow-up period; furthermore, LN had been confirmed in all patients based on renal biopsy findings. Patients were excluded if they had an advanced comorbidity or other diseases associated with kidney dysfunction, such as diabetic kidney disease or primary kidney disease; patients with a past or present history of gout, the use of drugs affecting the serum UA level, inadequate medical records, or follow-up periods less than 1 year were also excluded from this study. Finally, 137 unselected consecutive patients with LN were enrolled. All patients were followed up at 1- to 3-month-intervals, from the time of renal biopsy until at least 1 year later, via the KORNET database. Informed consent was obtained from all participants prior to registry enrollment. The study was performed in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and its later amendments, and was approved by the Institutional Review

Board of Chonnam National University Hospital (approval no. CNUN-2014-239). The registration number of the study (no. KCT0001253) was assigned by the Clinical Research Information Service, which is the primary registry of the World Health Organization International Clinical Trials Registry Platform.

Data collection

Baseline data were collected at the time of renal biopsy. Demographic data included age at SLE onset, age at LN onset, gender, duration of SLE (from the time of SLE diagnosis until LN development), smoking history, presence of hypertension, and presence of diabetes mellitus. Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg on ≥2 occasions, and/or patient self-reported intake of antihypertensive medications. Diabetes mellitus was defined as a history of a fasting glucose level ≥140 mg/dL or the use of insulin or a hypoglycaemic agent. The SLE disease activity index (SLEDAI)-2000 was also determined at the time of biopsy.

Laboratory findings included white blood cell count, haemoglobin concentration, platelet level, serum albumin level, erythrocyte sedimentation rate, C-reactive protein (CRP), albumin, and serum creatinine levels, urinalysis, and urinary protein excretion (g/day) at the time of renal biopsy. Lipid profiles (total cholesterol and low-density lipoprotein [LDL]-cholesterol) were also measured. Serum UA was measured at biopsy and at follow-up; kidney function was assessed at 1–3-month intervals during follow-up. Serological markers, including autoantibodies and complement (C3 and C4), were also determined. Enzyme-linked immunosorbent assays were used to assess the following autoantibodies: anti-Smith (Sm), ribonucleoprotein (RNP), Ro, and La.

Renal pathology findings were determined from biopsy specimens that had been reclassified separately by two renal pathologists, in accordance with the ISN/RPS classification (21), regardless of any previous WHO or ISN/RPS classification. Activity and chronicity indexes were calculated in accordance with the scoring system of the US National Institutes of Health (22). Both renal pathologists were blinded to the patients' previous biopsy information and clinical findings. Mixed-type cases according to the ISN/RPS classification were assigned based on the predominant class, following a consensus between the two pathologists.

Treatment and outcome

Patients with LN were treated with immunosuppressive drugs, in accordance with an internationally accepted treatment protocol (23, 24). Treatment was non-randomised and was based on the judgment of the treating rheumatologists for each patient. Patients with class I and class II LN received low-to-moderate doses of prednisone (<0.5 mg/kg/day) alone or in combination with oral immunosuppressants in case of the renal response was unsatisfactory. For patients with class III/IV ± V or V LN, high-dose intravenous cyclophosphamide (CYC; 500–1,000 mg/m^2 body surface area each month) or MMF (up to 2–3 g/day), with oral or intravenous corticosteroid (prednisolone; 30–60 mg/day, including intravenous methylprednisolone pulse therapy [500–1,000 mg/day x 3 days]), was preferentially administered as induction treatment for LN, followed by quarterly intravenous CYC, MMF, or other immunosuppressant. If MMF and CYC were unavailable, patients were typically treated with azathioprine, cyclosporine, or tacrolimus. In general, induction treatment was performed for a period of 6–12 months based on the treating physician's clinical impression.

In addition, use of medication that affects kidney function and uric acid levels such as low-dose aspirin, loop diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs) were recorded.

Treatment response after 1 year was defined in accordance with the ACR 2006 clinical trial criteria (25). Complete remission was defined as a normal glomerular filtration rate (GFR; 90 mL/min/1.73 m^2) or a >25% increase from baseline; or, if the baseline estimated GFR (eGFR) was abnormal, a urinary protein-to-creatinine ratio <0.2, dipstick test of 0 to trace, and inactive urinary sediment (≤5 red blood cells/high-power field and ≤5 white blood cells/high-power field and no cellular casts). A partial response was defined as stable eGFR, >50% reduction in the urinary protein-to-creatinine ratio or a range of 0.2–2.0, and inactive urinary sediment. No response was defined as failure to meet any of the remission criteria. Rapid progression of renal function was defined as a loss of eGFR >4 mL/min/1.73 m^2 per year (26). CKD was defined as a GFR of <60 mL/ min/1.73 m^2 for ≥3 months, as recommended by the Kidney Disease Quality Outcome Initiative (27). ESRD or renal failure was defined as either GFR <15 mL/min/1.73 m^2 (generally accompanied by signs and symptoms of uraemia) or a need for kidney replacement therapy (dialysis or transplantation) (27). Lastly, apart from renal functions, death due to any cause was also recorded.

Statistical analysis

Statistical analysis was performed using SPSS Statistics, v. 18 (SPSS Inc., Chicago, IL, USA). Patients were divided into two groups at the time of renal biopsy: UA ≤7 mg/dL and >7 mg/dL. The results are expressed as means ± standard deviations for continuous variables and as counts (percentages) for categorical variables. Continuous variables were compared using Student's *t*-test or the Mann-Whitney U-test; categorical variables were compared using the chi-squared test. Multivariable logistic regression analysis was performed to evaluate association between hyperuricaemia and clinical factors. In addition, Multivariate Cox proportional hazards regression analysis was performed to identify predictors of long-term renal outcome, including CKD and ESRD, in patients with LN. We tested for multicollinearity in the multivariable model by calculating variance inflation factors (VIFs) prior to the analysis; our model showed no multicollinearity. $p<0.05$ was considered statistically significant.

Results

Comparison of baseline epidemiologic features, clinical presentation, and laboratory findings

The mean age of the 137 patients at

LN onset was 32.2±13.3 years, and 119 (89.9%) patients were women. The mean disease duration of SLE before LN onset was 30.5±49.9 months. The mean SLEDAI-2000 score and eGFR were 12.6±5.27 and 100.3±47.9 mL/min/1.73 m^2, respectively (data not shown). Among the 137 patients (27.0%) with LN, 37 had serum UA >7 mg/dL at the time of renal biopsy.

The baseline demographic and clinical characteristics of the two groups are shown in Table I. The high UA group had fewer women than the low UA group (73% *vs*. 92%; p=0.003). Although age at LN onset was similar in the two groups, the duration of SLE at LN onset was shorter in patients in the high UA group than in patients in the low UA group (20.9±42.1 months *vs*. 34.0±52.2 months; p=0.051). The percentage of patients with hypertension at the time of LN was higher in the high UA group (56.8% *vs*. 27.0%; p=0.001). The education statuses and smoking histories of the two groups were similar. Disease activity at the time of LN onset, measured using SLEDAI-2000, tended to be higher in patients without complete remission, but the difference between high and low UA groups was not statistically significant.

Among the laboratory findings, serum haemoglobin and platelet levels at the time of renal biopsy were higher in the high UA group than in the low UA group (both p<0.001), whereas the serum albumin level was lower (p=0.001). LDL-cholesterol was also higher in the high UA group than in the low UA group (p=0.029). Among the indicators of kidney function, the high UA group had a higher creatinine level, lower eGFR, and higher 24-h urinary protein excretion (p<0.001, p<0.001, and p=0.020, respectively).

Table I. Baseline characteristics and laboratory findings of patients with lupus nephritis.

	Uric acid ≤7 mg/dL (n=100)	Uric acid >7 mg/dL (n=37)	*p*-value
Age at LN onset, years	31.8 ± 12.9	33.6 ± 14.3	0.541
Female	92 (92.0%)	27 (73.0%)	0.003
Disease duration at LN onset, months	34.0 ± 52.2	20.9 ± 42.1	0.051
Ever-smoker	4 (4.0%)	4 (10.9%)	0.137
Education, years	12.6 ± 3.36	11.3 ± 4.75	0.269
Hypertension at LN onset	27 (27.0%)	21 (56.8%)	0.001
Diabetes mellitus at LN onset	4 (4.0%)	2 (5.4%)	0.518
SLEDAI-2000 score	12.2 ± 4.86	13.5 ± 6.32	0.207
Laboratory findings			
White blood cells, /mm^3	6042 ± 3181	6235 ± 4471	0.682
Lymphocytes, /mm^3	1250 ± 688.9	1141 ± 664.6	0.354
Haemoglobin, g/dL	10.8 ± 1.78	9.47 ± 2.28	0.001
Platelet, 10^3/uL	223.8 ± 104.8	155.0 ± 87.6	<0.001
ESR, mm/h	44.9 ± 34.2	43.8 ± 35.6	0.747
CRP, mg/dL	0.60 ± 0.83	0.77 ± 0.89	0.240
Albumin, mg/dL	3.25 ± 0.76	2.84 ± 0.98	0.001
Total cholesterol, mg/dL	190.5 ± 60.8	215.5 ± 65.4	0.056
LDL-cholesterol, mg/dL	108.3 ± 41.3	131.2 ± 52.7	0.029
Uric acid, mg/dL	5.05 ± 1.11	9.16 ± 1.57	<0.001
Kidney function			
Serum creatinine, mg/mL	0.72 ± 0.27	1.54 ± 1.08	<0.001
eGFR, mL/min/1.73 m^2	112.7 ± 44.2	66.3 ± 41.2	<0.001
Urinary protein excretion, g/24 h	2.81 ± 2.38	3.64 ± 2.28	0.020
Urinary protein excretion >3.5 g/24 h	30 (30.0%)	17 (45.9%)	0.081
Urine sediment	62 (62.0)	25 (67.6)	0.548

Unless indicated otherwise, values are reported as the mean ± standard deviation.
LN: lupus nephritis; SLEDAI: systemic lupus erythematosus disease activity index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; LDL: low-density lipoprotein; eGFR: estimated glomerular filtration rate.

Table II. Autoantibodies and renal biopsy findings in patients with lupus nephritis.

	Uric acid ≤7 mg/dL (n=100)	Uric acid >7 mg/dL (n=37)	*p*-value
Autoantibodies and complements			
Antinuclear	95 (95.0%)	36 (97.3%)	0.560
Anti-dsDNA, IU/mL	575.2 ± 1488.7	519.2 ± 980.2	0.233
Anti-Sm	43 (43.0%)	13 (35.1%)	0.405
Anti-RNP	47 (47.0%)	17 (47.2%)	0.832
Anti-Ro	66 (66.0%)	21 (56.8%)	0.318
Anti-La	28/99 (28.3%)	11 (29.7%)	0.868
C3 level, mg/dL	57.1 ± 28.8	45.3 ± 26.1	0.042
C4 level, mg/dL	12.0 ± 12.8	8.95 ± 5.45	0.415
ISN/RPS classification			0.027
I	12 (12.0%)	1 (2.7%)	
II	12 (12.0%)	2 (5.4%)	
III	26 (26.0%)	4 (10.8%)	
IV	41 (41.0%)	24 (64.9%)	
V	9 (9.0%)	6 (16.2%)	
Activity index	5.04 ± 3.99	6.78 ± 4.59	0.031
Chronicity index	1.54 ± 1.54	2.32 ± 1.64	0.009
Activity index >12	47 (47.0%)	19 (51.4%)	0.651
Chronicity index >4	10 (10.0%)	8 (5.8%)	0.074

Unless otherwise indicated, values are reported as the mean ± standard deviation.
ISN/RPS: International Society of Nephrology/Renal Pathology Society.

Serologic tests and renal pathology findings

The results of the lupus serological studies at baseline are presented in Table II. The serum complement C3 level, an indicator of SLE disease activity, was lower in the high UA group than in the low UA group (p=0.042), whereas there was no association between C4 and the serum UA level. The presence of antibodies, including anti-nuclear, anti-Sm, anti-RNP, anti-Ro/La, and anti-dsDNA, did not significantly differ between the two groups.

Comparison of pathologic features, including the ISN/RPS classification and the activity and chronicity indexes, revealed a significant difference in the ISN/RPS classification distribution between the two groups (p=0.027). In the high UA group, class IV disease was present in 24 (64.9%) patients, class V in six (16.2%) patients, class III in four (10.8%) patients, class II in two (5.4%) patients, and class I in one (2.7%) patient. In the low UA group, class IV disease was present in 41 (41.0%) patients, class III in 26 (26.0%) patients, class I or class II in 12 (12.0%) patients, and class V in nine (9.0%) patients. Both activity and chronicity indexes were higher in the high UA group (p=0.031 and p=0.009, respectively).

Treatments and outcomes

Table III lists the medications and clinical outcomes of patients with LN. There was no significant difference in terms of LN induction treatment; however, with respect to treatment outcome, the complete remission rate after 1-year of immunosuppressive treatment was lower in the high UA group than in the low UA group (18.1% *vs*. 68.0%; p=0.003). Also, loop diuretics were more frequently used by the high- than low-UA group (13.5 *vs*. 3.0%; p=0.033). After a median follow-up of 85.8±47.3 months, greater proportions of patients with LN developed CKD (64.9% *vs*. 25.0; p<0.001) and ESRD (24.3% *vs*. 4.0%; p=0.001) in the high UA group. However, the rates of LN relapse, rapid decline of renal function, and death did not differ significantly between the two groups.

Association between hyperuricaemia and clinical factors

Variables significant at p<0.05 in the univariate analysis were subjected to multivariate logistic regression analysis; these included age, gender, disease duration, hypertension, haemoglobin, albumin, total cholesterol, the eGFR (mL/min/1.73 m^2), the urinary protein excretion level (g/24 h), proliferative LN (ISN/RPS classification), activity and chronicity indexes and loop diuretics use (Table IV). We found that male gender (odds ratio [OR]=7.863; 95% confidence interval [CI]: 1.545–40.017; p=0.013), the eGFR (OR=0.964; 95% CI: 10.942–0.986; p=0.001), and loop diuretics use (OR=14.311; 95% CI: 1.492–137.30; p=0.021) were associated with hyperuricaemia in patients with LN after adjustment.

Table III. Treatment and clinical outcomes in patients with lupus nephritis.

	Uric acid ≤7 mg/dL (n=100)	Uric acid >7 mg/dL (n=37)	p-value
Treatment			
Induction therapy			0.414
CYC	34 (34.0%)	17 (45.9%)	
MMF	36 (36.0%)	10 (27.0%)	
Other induction therapies	30 (30.0%)	10 (27.1%)	
Medications affecting uric acid levels			
Low-dose aspirin	21 (21.0%)	7 (18.9%)	0.789
Loop diuretics	3 (3.0%)	5 (13.5%)	0.033
NSAIDs	4 (4.0%)	1 (2.8%)	0.738
Outcomes			
CR at 1 year	68 (68.0 %)	15 (18.1%)	0.003
Relapse	45 (45.5%)	19 (51.4%)	0.540
Rapid decline of renal function	54 (54.0%)	16 (43.2%)	0.263
CKD	25 (25.0%)	24 (64.9%)	<0.001
ESRD	4 (4.0%)	9 (24.3%)	0.001
All-cause death	2 (2.0%)	2 (5.4%)	0.295

CYC: cyclophosphamide; MMF: mycophenolate mofetil; NSAIDs: non-steroidal anti-inflammatory drugs; CR: complete remission; CKD: chronic kidney disease; ESRD: end stage renal disease.

Table IV. Multivariable logistic regression analyses of predictors of hyperuricaemia in patients with lupus nephritis.

Variables	Multivariate analysis	
	OR (95% CI)	p-value
Male	7.863 (1.545-40.017)	0.013
eGFR, mL/min/1.73 m^2	0.964 (0.942-0.986)	0.001
Loop diuretics	14.311 (1.492-137.30)	0.021

Variables significant at p<0.05 in the univariate analysis were subjected to multivariate logistic regression analysis; these included age, gender, disease duration, hypertension, haemoglobin, albumin, total cholesterol, the eGFR (mL/min/1.73 m^2), the urinary protein excretion level (g/24 h), proliferative LN (ISN/RPS classification), activity and chronicity indexes and loop diuretics use.
CKD: chronic kidney disease; OR: Odds ratio; eGFR: estimated glomerular filtration rate; LN: lupus nephritis; ISN/RPS: International Society of Nephrology/Renal Pathology Society.

Predictors of CKD

Multivariable Cox proportional hazards regression analysis was performed to identify predictors of CKD in patients with LN using clinically meaningful factors, including significant at p<0.05 in univariable analyses (Supplementary Table SI). Several factors (*i.e.* age, education, diabetes mellitus, hypertension, UA >7 mg/dL, eGFR (mL/min/1.73 m^2), 24-hour urinary protein excretion (g/24 h), activity and chronicity indexes, loop diuretics, complete remission at l-year, and relapse) were included in multivariable analysis, which was adjusted for the effects of gender (men) and disease duration (Table V). The analysis showed that UA >7 mg/dL was significantly associated with development of CKD in patients with LN (hazard ratio [HR]=2.437; 95% CI: 1.150–5.162; p=0.020). Although not shown in the table, we also analysed the dose-effect relationship between the uric acid level and CKD development; the uric acid level was divided into ≤7, 7–9, and >9 mg/dL in the multivariate model. A uric acid level >7 and ≤ 9 mg/dL (HR=2.307; 95% CI 1.002-5.309; P 0.049), and a level >9 mg/dL (HR=3.189; 95% CI 1.236–8.214; p=0.015), were independent predictors of CKD, supporting the utility of the uric acid level to predict CKD development in LN patients. However, in LN patients with normal eGFRs,

Table V. Multivariate Cox-proportional regression analysis to identify predictors of progression to CKD in patients with lupus nephritis.

Variable	Multivariate analysis	
	HR (95% CI)	*p*-value
Age	1.002 (0.972-1.033)	0.882
Male	1.577 (0.612-4.063)	0.345
Disease duration	1.002 (0.995-1.009)	0.505
Educational level	0.946 (0.873-1.025)	0.173
Diabetes mellitus	4.713 (1.040-21.350)	0.044
Hypertension	0.759 (0.369-1.560)	0.453
Uric acid >7 mg/dL	2.437 (1.150-5.162)	0.020
eGFR, mL/min/1.73 m^2	0.984 (0.972-0.997)	0.015
Urinary protein excretion, g/24 h	1.063 (0.885-1.128)	0.513
Activity index	0.655 (0.318-1.360)	0.257
Chronicity index	1.097 (0.880-1.367)	0.411
Loop diuretics use	0.592 (0.126-2.792)	0.508
CR at 1 year	0.323 (0.153-0.685)	0.003
Relapse	1.343 (0.636-2.836)	0.439

CKD: chronic kidney disease; HR: hazard ratio; eGFR: estimated glomerular filtration rate; CR: complete remission.

hyperuricaemia was not an independent risk factor for CKD development. We also performed sensitivity analysis on female LN patients only. In the multivariable Cox proportional hazard model, a uric acid level >9 mg/dL (HR=3.187; 95% CI 0. 1.074–9.456; p=0.037) was an independent risk factor for CKD in these patients.

An additional analysis was performed to identify predictors of complete remission at 1 year, as well as predictors of ESRD. However, the analysis failed to identify UA >7 mg/dL as a predictor of either complete remission at 1 year (HR=2.424; 95% CI: 0.400–14.673; p=0.335) or of ESRD (HR=1.858; 95% CI: 0.236–14.601; p=0.556) in patients with LN.

Discussion

To the best of our knowledge, this is the first study to demonstrate an association of serum UA at LN onset with the development of CKD in patients with biopsy-proven LN. Although serum UA is often overlooked, our study shows that it can aid in the prediction of the long-term outcome of LN.

Serum UA is commonly elevated in patients with CKD; however, there remains controversy regarding whether hyperuricaemia plays a role in CKD development or is only a marker of renal impairment. Recent studies have suggested causal relationships of hyperuricaemia with CKD development and progression. Several of these studies, including epidemiologic studies, evaluated the role of serum UA as an independent risk factor for CKD. Their results were nearly uniform in showing that elevated serum UA is an independent predictor of the development of CKD, including ESRD, in individuals with normal kidney function (28). In patients with diabetes and preserved renal function, elevated serum UA (even within the normal range) is a strong predictor for the development of diabetic nephropathy and CKD (12, 13). Elevated serum UA also increases the risk of kidney injury following surgery or radiocontrast exposure (29, 30). However, some studies have shown that an elevated UA level is independently associated with more rapid CKD progression in patients with established CKD (14, 15), this has not been demonstrated in other studies (15, 31, 32). Observational and interventional studies identified a potential nephroprotective effect of lowering the UA level in patients with CKD. This effect has been demonstrated by recent randomised and prospective trials, which showed that the use of xanthine oxidase inhibitors to lower the UA level was able to slow the decline in GFR in patients with CKD (33, 34). However, the UA level has been of limited interest in treatment of patients with SLE and LN, such that data regarding the long-term effect of hyperuricaemia in patients with LN are scarce. Therefore, our study evaluated the impact of hyperuricaemia on long-term renal prognosis in patients with LN.

Hyperuricaemia, defined as serum UA ≥7 mg/dL, was detected in 37 of our 137 patients (27.0%) with LN; it was associated with lower GFR and higher 24-h urinary protein excretion at LN onset. Although the definition of hyperuricaemia varies among different studies, cross-sectional studies have shown that 20–40% of patients with SLE or LN have hyperuricaemia (16, 17, 35); moreover, a higher serum UA level has been reported in patients with SLE who have LN, compared to such patients who do not have LN. Those results suggest that hyperuricaemia is a potential risk factor for LN (16, 17, 36). Yang *et al*. showed that UA was an independent risk factor for LN (odds ratio=1.01; 95% CI: 1.005–1.014; p<0.0001) (16). Similarly, a multivariate analysis conducted by Calich *et al*. revealed that high UA was independently associated with LN (p<0.001) (17); another study of patients with LN showed that serum UA was positively correlated with serum creatinine and negatively correlated with eGFR (35). Our study also demonstrated an association of hyperuricaemia with severe renal disease activity in patients with LN.

Notably, the present study showed that a greater proportion of patients with LN who had hyperuricaemia exhibited proliferative type LN; moreover, patients with LN had higher activity and chronicity indexs. Thus far, only two studies have reported relationships of serum UA level with renal pathology findings. Xie *et al*. recently described associations of hyperuricaemia with renal pathology scores, including activity and chronicity indices, as well as with tubulointerstitial lesions in patients with LN (35). In a study by Okba *et al*., although the sample size was small, LN activity index scores were higher in patients with SLE who had hyperuricaemia, compared to such patients without hyperuricaemia (36). Therefore, our findings further support a relationship between renal functional decline and renal pathological damage in patients with LN who have hyperuricaemia. Both *in vitro* and *in vivo* studies have shown

that serum UA induces renal injury via mechanisms that include renal inflammation, oxidative stress, endothelial dysfunction, and renin-angiotensin system activation (10, 11).

An additional study demonstrated that hyperuricaemia was associated with the long-term prognosis of patients with LN, as well as with renal disease severity at LN onset. Among our patients with LN, a greater proportion of those with hyperuricaemia (compared to those without hyperuricaemia) did not exhibit complete remission after immunosuppressive treatments; they were also more likely to develop CKD and ESRD during follow-up. In a multivariable Cox proportional hazards regression model, hyperuricaemia was identified as an important predictor of CKD development in patients with LN, independent of other risk factors. Although the prognosis of patients with LN with hyperuricaemia is unclear, there is evidence to support hyperuricaemia as a prognostic factor. Reategui-Sokolova *et al*. demonstrated that higher UA levels contributed independently to new development of acute renal damage (measured with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index) in patients with SLE (37). In a study of patients with LN by Ugolini-Lopes *et al*., serum UA levels at baseline and 6 months did not distinguish good and poor long-term renal outcomes; however, serum UA level at the 12-month follow-up was a predictor of good long-term renal outcome (defined as creatinine clearance ≥90.0 mL/min/1.73 m^2) (p=0.02) (18). A retrospective study revealed that serum UA was significantly associated with LN progression (*i.e*., initiation of dialysis or kidney transplantation) in women; however, this association was not present in men (38). In conclusion, consistent with the previously reported association between serum UA and the development of CKD in individuals without SLE (12, 13, 28), we showed that the serum UA level at LN onset was a long-term predictor of CKD in patients with LN. Nevertheless, prospective studies with long-term follow-up data are needed to confirm the value of the serum UA level in predicting renal outcome in patients with LN.

This study had several limitations. First, because it was conducted during routine clinical practice, LN treatment could not be controlled. Second, because only patients with follow-up data for at least 1 year were included, non-responders to immunosuppressive drugs were excluded more often, compared to responders. Third, there is no universally accepted definition of hyperuricaemia; moreover, this study did not consider the effect of female hormones, which reduce serum UA levels by increasing UA excretion from the kidneys (39), on uric acid metabolism in our female patients. In previous clinical studies, hyperuricaemia was defined as serum UA concentration >7.0 mg/dL in men and ≥6.0 mg/dL in women (39, 40). Although UA is soluble up to 6.4 mg/dL under physiological conditions, its solubility increases to 7.0 mg/dL in the presence of UA-binding proteins, before reaching a supersaturated state (41). Accordingly, hyperuricaemia occurs at a serum UA level of >7.0 mg/dL; at that point, UA begins to crystallise within the human body (41). Therefore, it is reasonable to define hyperuricaemia as serum UA >7 mg/dL (41), in accordance with the approach used in several prior studies; this concentration is used in the Japanese guideline for the management of hyperuricaemia or gout in both men and women (42-44). Nonetheless, a sex-related difference in serum UA levels should be considered. As in other studies identifying hyperuricaemia as a risk factor for CKD, we were concerned that serum UA levels were affected by kidney function, with a possible influence of confounding factors (44, 45). As mentioned above, we found that hyperuricaemia was not an independent risk factor for CKD in LN patients with a normal eGFR. We suggest that the effect of hyperuricaemia on renal function, and the risk of CKD progression, were greater in subjects with impaired kidney function. However, further research is required to confirm this. Finally, although adjustments were made for confounding factors (*e.g*. kidney function and response to immunosuppressive agents) in the multivariable analysis, other confounders were not considered, such as metabolic and other risk factors. However, data from 21,475 healthy volunteers followed prospectively for a median of 7 years showed that the UA level remained a risk factor for CKD, despite adjustments for baseline eGFR, age, gender, antihypertensive drugs, and components of metabolic syndrome (*i.e*. waist circumference, cholesterol, blood glucose, triglycerides, and blood pressure) (44). Therefore, the ability of hyperuricaemia to predict long-term renal outcome in patients with LN was presumed to be adequately demonstrated in the present study.

In conclusion, this study showed that patients with LN who have hyperuricaemia exhibit severe renal disease activity, and that hyperuricaemia is a potential predictor of CKD in patients with LN. Serum UA measurement is an inexpensive test that is easily available in clinical practice and should be included in clinical monitoring of LN. Our results suggest that an increased serum UA level contributes to the prediction of long-term renal outcome in patients with LN. Accordingly, clinicians should carefully monitor hyperuricaemia in their patients with LN during the early course of the disease, as this may help to prevent later renal dysfunction. However, further, large-scale studies are needed to confirm these findings.

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