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ORIGINAL ARTICLE

Serum uric acid levels contribute to new renal damage in systemic lupus erythematosus patients

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Abstract This study aims to determine whether uric acid levels contribute to new renal damage in systemic lupus erythematosus (SLE) patients. This prospective study was conducted in consecutive patients seen since 2012. Patients had a baseline visit and follow-up visits every 6 months. Patients with ≥2 visits were included; those with end-stage renal disease (regardless of dialysis or transplantation) were excluded. Renal damage was ascertained using the SLICC/ACR damage index (SDI). Univariable and multivariable Cox-regression models were performed to determine the risk of new renal damage. Uric acid was included as a continuous and dichotomous (per receiving operating characteristic curve) variable. Multivariable models were adjusted for age at diagnosis, disease duration, socioeconomic status, SLEDAI, SDI, serum creatinine, baseline use of prednisone, antimalarials, and immunosuppressive drugs. One hundred and eighty-six patients were evaluated; their mean (SD) age at diagnosis was 36.8 (13.7) years; nearly all patients were mestizo. Disease duration was 7.7 (6.8) years. Follow-up time was 2.3 (1.1) years. The SLEDAI was 5.2 (4.3) and the SDI 0.8 (1.1). Uric acid levels were 4.5 (1.3) mg/dl. During follow-up, 16 (8.6%) patients developed at least one new point in the renal domain of the SDI. In multivariable analyses, uric acid levels (continuous and dichotomous) at baseline predicted the development of new renal damage (HR 3.21 (1.39–7.42), p 0.006; HR 18.28 (2.80–119.48), p 0.002; respectively). Higher uric acid levels contribute to the development of new renal damage in SLE patients independent of other well-known risk factors for such occurrence.

Keywords Renal damage · Systemic lupus erythematosus · Uric acid

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease of unclear etiology characterized by autoantibody production and protean organ system manifestations. The incidence of SLE rises steadily from childhood to mid-adulthood, especially among females [1]. SLE can involve various organ or systems; renal involvement is one of the more serious manifestations of SLE and is associated with increased morbidity and mortality [2].

Uric acid is the poorly soluble circulating end product of the purine nucleotide metabolism in human beings. Serum uric acid is determined by the net balance between its production and either reabsorption by the kidney and secretion by the intestine [3]. Over the last few years, emerging roles for serum uric acid levels in human disease have been demonstrated. Uric acid is linked to the development of coronary heart disease [4] and stroke [5]. Data from several studies have associated hyperuricemia with increased incidence and/or progression of chronic kidney disease (CKD) [6, 7].

Hyperuricemia has been found in 5.6 to 10.1% of patients with psoriatic arthritis, rheumatoid arthritis, and diffuse connective tissue disorders compared to 3.8% of healthy individuals [8]. High uric acid levels have been reported in SLE patients to be associated with the occurrence of stroke,

peripheral neuropathy [9], and pulmonary hypertension [10]. Focusing on the kidney, Yang et al. performed a study with the objective to assess the association between elevated serum uric acid (UA) and lupus nephritis (LN) in Chinese systemic lupus erythematosus (SLE) patients. Patients with diabetes mellitus, hypertension, and cardiovascular diseases were excluded from this study because UA levels could be influenced by these diseases; 130 patients were included, and 73 developed LN. As expected, the SLEDAI scores and anti-dsDNA positivity were significantly higher in SLE patients with LN than in those without it ($p < 0.001$ and $p < 0.04$, respectively) whereas the levels of serum C3 were significantly lower in SLE patients with LN than in those without it ($p < 0.001$). The levels of serum UA were also significantly higher in SLE patients with LN than in those without it ($p < 0.001$); in fact, an increment of 1 mol/l in serum UA concentration was associated with a 1.01 increase in the risk of LN, concluding the authors that uric acid levels in SLE patients are independently associated with the development of nephritis [11]. Finally, Xie et al. have recently demonstrated that hyperuricemia is associated with renal pathological scores, including the activity and chronicity indices and tubulointerstitial lesions in Chinese patients with LN [12].

These data taken together indicate that uric acid plays an important role in SLE pathogenesis and suggest that persistently high uric acid levels may be predictive of damage in SLE patients. To our knowledge, the relationship between uric acid and development of renal damage in SLE patients has not been previously evaluated. We have now conducted such analyses in a primarily mestizo SLE patient population taken into consideration other well-known risk factors that may also affect damage in this condition.

Methods

We studied SLE patients from The Almenara Lupus Cohort [13]; all patients met the 1997 ACR criteria at enrollment. This cohort was started in January 2012 and has been previously reported. The constitution of this cohort has been approved by the hospital's institutional review board (IRB). Patients who signed the informed consent were recruited into this cohort and followed every 6 months with a protocol which included an interview, medical records review, physical examination, and laboratory tests. For these analyses, written informed consent was waived by the IRB and the patient records and information were anonymized.

For this study, patients with at least two visits were included. Patients with end-stage renal disease (regardless of dialysis or transplantation) were excluded for these analyses. Uric acid was measured in milligram per deciliter. For this study, the demographic data included were gender, age at diagnosis, and socioeconomic status by the Graffar's method [14].

The laboratory variable included was serum creatinine, complement, and AntiDNA-ds levels. Clinical variables included were disease activity (ascertained with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)) [15], disease damage (ascertained with the System Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index (SDI)) [16], disease duration, metabolic syndrome comorbidities, and lupus nephritis at baseline or during follow-up. Therapeutic variables included were glucocorticoid, reported as current dose and time of exposure, antimalarial and immunosuppressive drugs use at baseline reported as current, past, or never. The primary end point was defined as the incidence of new renal damage, which is an increase in at least one point in the renal domain of the SDI during the follow-up.

Statistical analyses

Patients who developed and those who did not develop new renal damage were compared. Values for categorical variables are given as numbers (percentages) and values for continuous variables are given as means and standard deviations. We calculated the optimal cut-off value of uric acid for a higher likelihood of developing new renal damage using the corresponding receiver–operating characteristic (ROC) curve (Fig. 1); we used this value to dichotomize the uric acid variable to evaluate whether higher uric acid levels contributed to the risk of new renal damage during the patient's follow-up.

Kaplan-Meier plots and the log rank test were performed to evaluate the effect of time on the occurrence of renal damage in both groups. Univariable and multivariable Cox-regression models were performed to determine the risk of new renal damage. Results are expressed as hazard ratios (HR). Uric acid values were examined both, as a continuous and as a dichotomous variable. A p value (two-sided) < 0.05 was considered significant in all analyses.

All statistical analyses were performed using SPSS v. 21.0 (IBM, Chicago, IL).

Results

One hundred and eighty-six patients were included in these analyses; 172 (92.5%) were female and almost all were mestizo (mixed Amerindian and European ancestry). Their mean (SD) age at diagnosis was 36.8 (13.7) years. Their disease duration was 7.7 (6.8) years. At baseline, uric acid levels were 4.5 (1.3) mg/dl, the SLEDAI was 5.2 (4.3), and the SDI 0.8 (1.1). Sixty-one (32.8%) patients had low complement, and 69 (37.1%) had Anti-dsDNA positive. One hundred and two (55.4%) patients had lupus nephritis at baseline; of them, 80 (43.0%) had renal biopsy. Fifty-three patients had proliferative

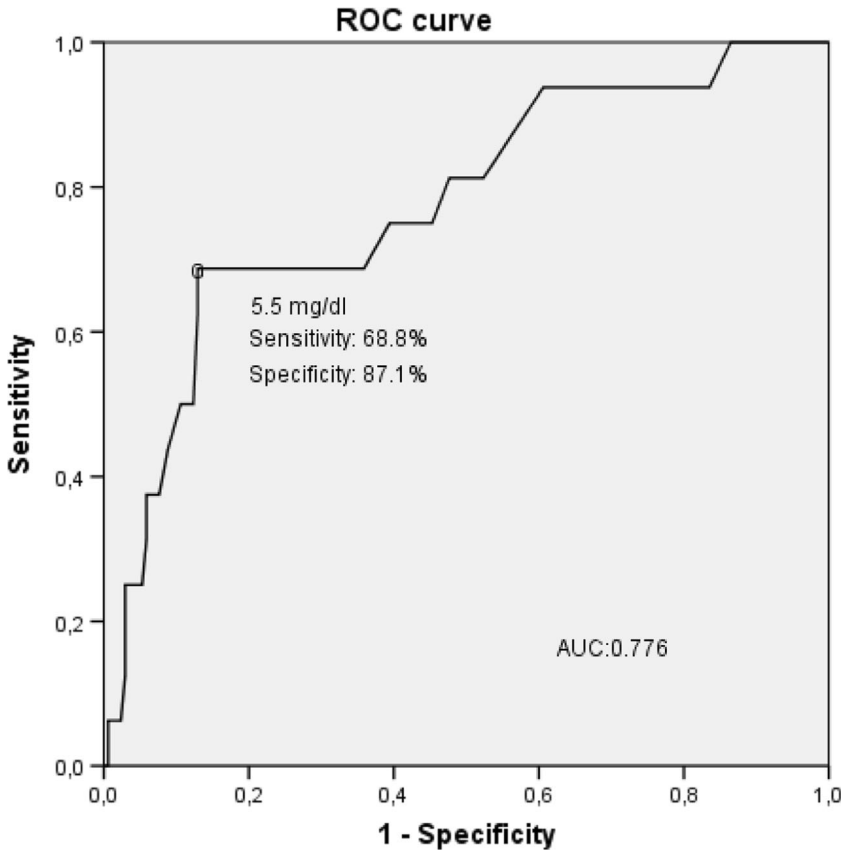

Fig. 1 Receiver–operating characteristic (ROC) curve of uric acid for predicting new renal damage

LN (classes III and IV), and 11 (5.9%) had class V alone. There were no patients affected by membranous-proliferative changes in renal biopsies. Two of 84 patients (2.4%) developed lupus nephritis during their follow-up. In the scope of the treatment, only one (1.9%) patient was taken drugs that decrease serum uric acid levels (allopurinol). Fifty patients (26.9%) were using mycophenolate mofetil at baseline, 21 (11.3%) azathioprine, 10 (5.4%) cyclophosphamide, 8 (4.3%) tacrolimus, 6 (3.2%) cyclosporine, 4 (2.2%) methotrexate, 2 (1.1%) rituximab, and 1 (0.5%) leflunomide. Ninety of the 186 patients (48.4%) had hypertension, 20 (10.8%) had diabetes mellitus or elevated fasting glucose, 166 (89.2%) had obesity, 56 (30.1%) had hypertriglyceridemia, and 94 (50.5%) had high LDL levels and 110 (59.1%) low HDL levels. These comorbidities, separately, had no significant association as predictors of new renal damage in both, univariable and multivariable analyses ($p > 0.05$).

Sixteen (8.6%) patients had one point in the renal domain at baseline and two patients (1.1%) had two. During the follow-up period of 2.3 (1.1) years, there were 3.4 (1.1) visits per patient, and 16 patients developed at least one new point in the renal domain of the SDI. Comparison of baseline characteristics between patients with and without renal damage is depicted in Table 1. The cut-off point derived from the ROC curve was 5.5 mg/dl (sensibility 68.8%, specificity 87.1%). Kaplan-Meier plots of the event-free proportion between the high and low uric acid groups who were followed for the occurrence of new renal damage are shown in Fig. 2. In those with uric acid lower than 5.5 mg/dl, renal damage free survival was 99.2% in the first year, 99.2% in the second year, and 96.4% in the third year and in those with uric acid higher than 5.5 mg/dl, renal damage free survival was 88.3% in the first year, 78.4% in the second year, and 68.2% in the third year; $p < 0.001$.

In univariable and multivariable analyses, when baseline uric acid levels were examined as continuous variable, they predicted the development of new renal damage (HR 2.24 (95% CI 1.50–3.34), $p < 0.001$; HR 2.82 (95% CI 1.05–7.57), $p = 0.040$; respectively). Other factors that predicted the development of new renal damage were serum creatinine (HR 5.98 (95% CI 2.84–12.61), $p < 0.001$ and HR 8.13 (95% CI 1.65–40.13), $p = 0.010$ in the univariable and multivariable analyses, respectively). Prednisone doses at baseline, however, was not a predictor (HR 1.00 (95% CI 0.92–1.09), $p = 0.986$; HR 0.82 (95% CI 0.71–0.95), $p = 0.009$; in the univariable and multivariable analyses, respectively).

These data are depicted in Table 2. When uric acid levels were examined as a dichotomous variable, higher baseline uric acid levels (>5.5 mg/dl) also predicted renal damage in univariable (HR = 8.36; 95% CI 2.88–24.26; $p < 0.001$) and multivariable analyses (HR = 16.36; 95% CI 1.91–139.95; $p = 0.011$). These data are depicted on Table 3.

Table 1 Comparison of baseline characteristics between SLE patients with and without renal damage on follow-up

	Without renal damage (*N* = 170)	With renal damage (*N* = 16)	*p* value
Uric acid (mg/d, mean (SD))	4.37 (1.22)	5.74 (1.37)	<0.001
Age at diagnosis (years, mean (SD))	36.93 (13.59)	35.22 (15.31)	0.356
Female gender (*N* (%))	157 (92.4)	15 (93.8)	0.840
Disease duration (years, mean (SD))	7.56 (6.72)	8.82 (7.60)	0.568
Socioeconomic status (*N* (%))			0.091
High	72 (42.4)	3 (18.8)	
Medium	61 (35.9)	10 (62.5)	
Low	37 (21.8)	3 (18.8)	
SLEDAI (mean (SD))	5.05 (4.17)	7.38 (5.15)	0.043
SDI (mean (SD))	0.74 (1.10)	1.19 (1.38)	0.116
Cr (mg/dl, mean (SD))	0.78 (0.34)	1.24 (0.60)	0.001
PDN current dose (mg/d, mean (SD))	7.27 (6.68)	7.50 (7.25)	0.927
PDN time of exposure (years, mean (SD))	7.01 (6.13)	9.63 (8.68)	0.333
Antimalarials use (*N* (%))			0.690
Never	18 (10.6)	1 (6.3)	
Past	21 (12.4)	3 (18.8)	
Current	131 (77.1)	12 (75.0)	
Immunosuppressive drugs use (*N* (%))			0.172
Never	46 (27.1)	2 (12.5)	
Past	38 (22.4)	2 (12.5)	
Current	86 (50.6)	12 (75.0)	

PDN prednisone, *Cr* creatinine, *SDI* SLICC/ACR damage index, *SLEDAI* systemic lupus erythematosus disease activity index, *N* number, *SD* standard deviation

Discussion

Utilizing the baseline serum uric acid levels from a primarily mestizo SLE cohort, we have examined their contribution to new renal damage occurrence, which indeed was the case, even after adjusting for other well-known risk factors for the occurrence of renal damage in SLE, particularly serum creatinine levels at the outset. To the best of our knowledge, this is the first longitudinal study examining this.

Serum uric acid values between 3.5 and 7.2 mg/dl in adult males and postmenopausal women and between 2.6 and 6.0 mg/dl in premenopausal women have been identified as normal in several countries [17]. Experimental and clinical studies indicate that serum uric acid levels are associated with

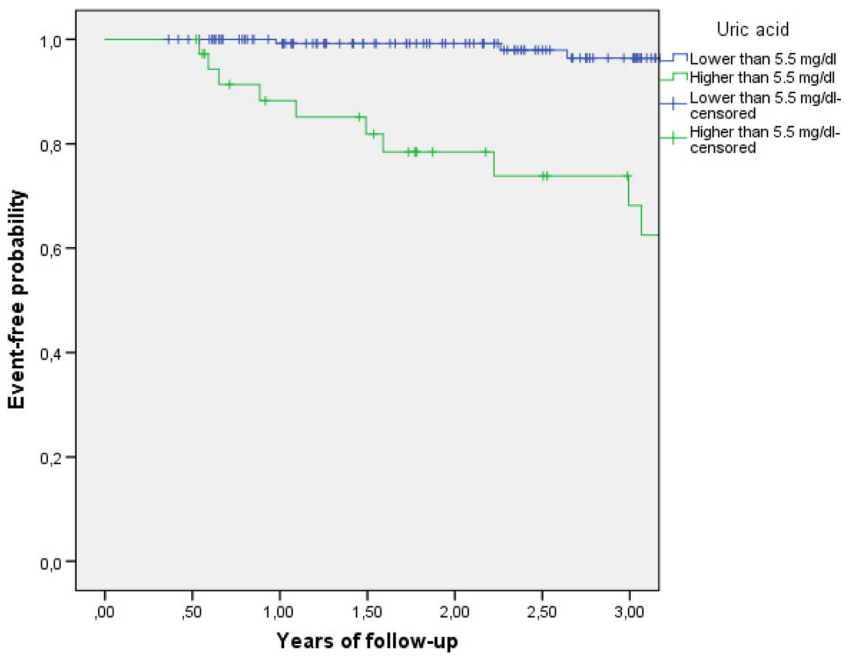

Fig. 2 Kaplan-Meier curve of the probability of renal damage free survival in SLE patients with uric acid higher and lower than 5.5 mg/dl

Table 2 Predictor of new renal damage (univariable and multivariable analyses)

Variables at baseline	HR (CI 95%)	*p* value	HR (CI 95%)	*p* value
Uric acid (mg/dl)	2.24 (1.50–3.34)	<0.001	2.82 (1.05–7.57)	0.040
Age at diagnosis (years)	0.99 (0.96–1.03)	0.751	1.02 (0.95–1.08)	0.616
Gender (male)	0.53 (0.07–4.25)	0.550	0.21 (0.01–3.49)	0.274
Disease duration (years)	1.03 (0.96–1.10)	0.451	0.86 (0.70–1.06)	0.147
Socioeconomic status				
High	Ref.		Ref	
Medium	2.97 (0.49–17.80)	0.235	9.83 (0.44–215.06)	0.147
Low	6.58 (1.43–30.26)	0.016	11.04 (0.68–142.06)	0.065
SLEDAI	1.12 (1.02–1.23)	0.019	1.02 (0.86–1.18)	0.817
SDI	1.33 (0.95–1.87)	0.095	0.67 (0.37–1.23)	0.196
Creatinine level (mg/dl)	5.98 (2.84–12.61)	<0.001	8.13 (1.65–40.13)	0.010
Prednisone current dose (mg/d)	1.00 (0.92–1.09)	0.986	0.82 (0.71–0.95)	0.009
Time of exposure to prednisone (years)	1.03 (0.97–1.10)	0.289	1.09 (0.96–1.25)	0.193
Antimalarials use				
Never	Ref.		Ref.	
Past	3.11 (0.32–30.00)	0.327	1.27 (0.04–44.84)	0.896
Current	2.28 (0.30–17.61)	0.429	1.25 (0.07–22.40)	0.881
Immunosuppressive drugs use				
Never	Ref.		Ref.	
Past	1.41 (0.20–10.03)	0.735	0.83 (0.05–15.01)	0.901
Current	3.66 (0.82–16.38)	0.090	13.71 (1.00–188.00)	0.050
Lupus nephritis	2.61 (0.84–8.11)	0.096	0.78 (0.76–5.22)	0.778
Hypertension	2.39 (0.83–6.90)	0.106	1.94 (0.41–9.16)	0.402
Diabetes/glucose intolerance	0.93 (0.21–4.09)	0.918	0.44 (0.04–4.44)	0.487
Central obesity	0.50 (0.11–2.28)	0.373	1.43 (0.09–22.37)	0.798
Hypertriglyceridemia	2.32 (0.84–6.43)	0.106	0.92 (0.19–4.42)	0.915
Low HDL	2.30 (0.74–7.15)	0.150	2.83 (0.50–16.00)	0.240
High LDL	0.65 (0.24–1.76)	0.397	0.84 (0.16–4.44)	0.836

several risk factors for CKD including diabetes [18], hypertension [19], and inflammation [20] and with a poor prognosis; in stage 3–5 CKD patients, hyperuricemia was associated with a higher risk of renal replacement therapy, rapid renal progression, and hospitalization for all causes [7].

Hyperuricemia is also a risk factor for diabetic kidney disease (DKD) with serum uric acid levels within the high-normal range being independently associated with DKD (OR (95%CI) = 1.005 (1.004–1.007)) [21].

In terms of SLE, it has been reported that steady hyperuricemia may predict the future development of pulmonary hypertension (PH) in patients with normal pulmonary artery systolic pressure at baseline (RR = 8.50 (1.00 to 72.00)) [22]. A significant number of SLE patients in rheumatology practice have undiagnosed PH with few discernible symptoms. Serum uric acid levels may be useful as a surrogate marker for screening for PH in these patients [10]. Hyperuricemia in SLE patients has been also independently associated with the occurrence of stroke (OR (95%CI) = 2.38 (1.20–7.24)) and peripheral neuropathy (OR (95%CI) = 3.49 (1.52–12.23)). It has also been independently associated with hypertension (OR (95%CI) = 7.76 (2.72–15.76)), hyperlipidemia (OR (95%CI) = 5.05 (1.59–11.32)), and history of arterial thrombosis (OR (95%CI) = 4.95 (1.98–15.34)), which are the major stroke and myocardial infarction risk factors in SLE patients [9]. Finally, uric acid levels have been shown to be independently associated with the development of LN in SLE patients [11] (OR (95%CI) = 1.01 (1.005–1.014)) and with more serious renal pathological findings in those SLE patients who already have LN [12].

A growing body of evidences demonstrates that uric acid might play a pathophysiological role in many metabolic disorders, which seems to be independent of the deposition of monosodium urate crystals [17]. Interestingly, the threshold value of serum uric acid associated with hypertension seems to be as low as 5.0–5.5 mg/dl, clearly below its supersaturation value, thus being probably independent of the formation of monosodium urate crystals [23]. Experimental studies suggest the possibility that an elevated concentration of uric acid itself can lead to kidney disease without the deposition of uric acid

Table 3 Predictors of new renal damage by univariable and multivariable analyses

Variables at baseline	HR (CI95%)	*p* value	HR (CI95%)	*p* value
Uric acid higher than 5.5 mg/dl	8.36 (2.88–24.26)	<0.001	16.36 (1.91–139.95)	0.011
Uric acid lower than 5.5 mg/dl	Ref.			
Age at diagnosis (years)	0.99 (0.96–1.03)	0.751	1.03 (0.96–1.10)	0.423
Gender (male)	0.53 (0.07–4.25)	0.550	0.14 (0.01–2.49)	0.179
Disease duration (years)	1.03 (0.96–1.10)	0.451	0.87 (0.61–1.07)	0.180
Socioeconomic status				
High	Ref.		Ref	
Medium	2.97 (0.49–17.80)	0.235	14.55 (0.58–365.38)	0.104
Low	6.58 (1.43–30.26)	0.016	16.33 (0.91–292.96)	0.058
SLEDAI	1.12 (1.02–1.23)	0.019	0.98 (0.83–1.16)	0.847
SDI	1.33 (0.95–1.87)	0.095	0.91 (0.52–1.64)	0.781
Creatinine level (mg/dl)	5.98 (2.84–12.61)	<0.001	4.46 (0.84–23.74)	0.079
Prednisone current dose (mg/d)	1.00 (0.92–1.09)	0.986	0.87 (0.76–1.00)	0.048
Time of exposure to prednisone (years)	1.03 (0.97–1.10)	0.289	1.06 (0.94–1.20)	0.329
Antimalarials use				
Never	Ref.		Ref.	
Past	3.11 (0.32–30.00)	0.327	1.56 (0.05–52.08)	0.804
Current	2.28 (0.30–17.61)	0.429	1.76 (0.10–31.82)	0.703
Immunosuppressive drugs use				
Never	Ref.		Ref.	
Past	1.41 (0.20–10.03)	0.735	1.05 (0.06–18.77)	0.973
Current	3.66 (0.82–16.38)	0.090	5.92 (0.44–79.44)	0.180
Lupus nephritis	2.61 (0.84–8.11)	0.096	1.40 (0.18–11.10)	0.753
Hypertension	2.39 (0.83–6.90)	0.106	2.57 (0.53–12.57)	0.243
Diabetes/glucose intolerance	0.93 (0.21–4.09)	0.918	0.37 (0.03–4.16)	0.417
Central obesity	0.50 (0.11–2.28)	0.373	0.38 (0.03–4.81)	0.456
Hypertriglyceridemia	2.32 (0.84–6.43)	0.106	1.08 (0.25–4.65)	0.916
Low HDL	2.30 (0.74–7.15)	0.150	1.98 (0.36–11.03)	0.435
High LDL	0.65 (0.24–1.76)	0.397	0.56 (0.10–3.18)	0.513

Serum uric acid values were dichotomized as per ROC (See Fig. 1)

SDI SLICC/ACR damage index, *SLEDAI* systemic lupus erythematosus disease activity index

crystals [24]. In our study, we also found that high normal values are predictive of the occurrence of renal damage in SLE patients. These findings strongly suggest to carefully reconsider the concept of "asymptomaticity" for chronic hyperuricemia and to consequently revise the serum uric acid levels' normal range [17].

Another important effect of studying serum uric acid levels in relation to kidney damage in SLE is that pharmacologic interventions could be used to prevent further damage. Goicoechea et al., for example, reported that allopurinol treatment slowed renal disease in comparison with control group (HR = 0.53; (0.28 to 0.99); *p* 0.048) [25]. Kanbay et al. also reported that allopurinol treatment resulted in a decrease in serum uric acid, a decrease in systolic blood pressure, an increase in flow-mediated dilation, and an increase in estimated glomerular filtration rate compared with baseline values [26].

The physiopathological role of hyperuricemia in kidney disease is still not completely understood. A variety of mechanisms have been implicated, but at the present time most of the evidence is derived from experimental models. For example, Kim et al., reported that hyperuricemia has a direct role in activating NLRP3 inflammasomes in macrophages, promoting chemokine signaling in the proximal tubule and contributing to the progression of diabetic nephropathy through cross talk between macrophages and proximal tubular cells [27]; there is also evidence of the relationship between uric acid and endothelial cell dysfunction in vitro and in vivo, and this is associated with mitochondrial alterations and decreased intracellular ATP [28]. Furthermore, Corry et al., have reported that uric acid stimulates proliferation, angiotensin II production, and oxidative stress in vascular smooth muscle cells through the tissue renin-angiotensin system (RAS) [29].

Finally, Sánchez-Lozada et al. have demonstrated that, in rodent models, hyperuricemia led to afferent arteriolopathy, which impairs the autoregulatory response of afferent arterioles, resulting in glomerular hypertension. Thickening of the afferent arteriole produces severe renal hypoperfusion; the resulting ischemia is a potent stimulus that induces tubulointerstitial inflammation and fibrosis [30]. These studies taken together provide evidence for a deleterious effect of uric acid on inflammation and vascular function, and possible repercussion on renal damage.

Utilizing the baseline serum uric acid levels from a primarily mestizo SLE cohort, we have examined their contribution to new renal damage occurrence, which indeed was the case, even after adjusting for other well-known risk factors for the occurrence of renal damage in SLE, particularly serum creatinine levels at the outset, a value expected to be associated with renal damage accrual. In fact, it has been shown that SLE patients with severe lupus nephritis a baseline serum creatinine levels ≤1.0 mg/dl are associated with a higher remission rate than those with higher levels [31], and it has also been demonstrated that lower glomerular filtration rate (<30 ml/min/1.73 m2) is associated with a lower response to treatment in lupus nephritis [32].

Our study has several limitations; first, as this is not an inception cohort, we cannot be sure if high uric acid levels could have occurred before renal involvement or if they increased as a consequence of renal involvement; in fact, patients who went on to develop new renal damage, had higher levels of serum creatinine than the ones that did not go on to develop it. Second, this cohort is relatively small, and ethnically homogeneous, so we cannot be sure if uric acid levels impact on renal damage in patients from other ethnic/racial groups. Nevertheless, we consider relevant to report this association, which should prompt the conduct of other longitudinal studies with a larger number of patients in order to confirm our findings and if so, if treatment with allopurinol or other drugs could prevent the occurrence of renal damage. Furthermore, the association between renal damage and uric acid levels could help us understand its underlying pathogenesis in SLE patients.

In conclusion, we describe for the first-time uric acid levels as a contributing factor to new renal damage occurrence in SLE patients, independently of age at diagnosis, gender, disease duration, socioeconomic status, disease activity, damage, serum creatinine levels, presence of lupus nephritis, comorbidities, use of prednisone, antimalarials, and immunosuppressive drugs at baseline.

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Compliance with ethical standards

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Disclosures None.

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