Serum uric acid is associated with damage in patients with systemic lupus erythematosus

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ABSTRACT

Introduction Serum uric acid levels have been reported as predictors of cardiovascular, pulmonary, neurological and renal morbidity in patients with SLE. However, their role in cumulative global damage in these patients has not yet been determined.

Objective To determine whether serum uric acid levels are associated with new damage in patients with SLE.

Methods This is a longitudinal study of patients with SLE from the Almenara Lupus Cohort, which began in 2012. At each visit, demographic and clinical characteristics were evaluated, such as activity (Systemic Lupus Erythematosus Disease Activity Index-2K or SLEDAI-2K) and cumulative damage (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index or SDI). Treatment (glucocorticoids, immunosuppressive drugs and antimalarials) was also recorded. Univariable and multivariable Cox regression models were used to determine the impact of serum uric acid levels on the risk of new damage.

Results We evaluated 237 patients, with a mean age (SD) at diagnosis of 35.9 (13.1) years; 220 patients (92.8%) were women, and the duration of the disease was 7.3 (6.6) years. The mean SLEDAI-2K and SDI scores were 5.1 (4.2) and 0.9 (1.3), respectively. Serum uric acid level was 4.5 (1.4) mg/dL. Follow-up time was 3.1 (1.3) years, and 112 (47.3%) patients accrued damage during follow-up. In univariable and multivariable analyses, serum uric acid levels were associated with new damage (HR=1.141 (95% CI 1.016 to 1.282), p=0.026; HR=1.189 (95% CI 1.025 to 1.378), p=0.022, respectively).

Conclusion Higher serum uric acid levels are associated with global damage in patients with SLE.

INTRODUCTION

In humans, uric acid is the final product of purine metabolism. At physiological pH, uric acid is found predominantly (98%–99%) as a deprotonated anion. The solubility of uric acid at normal physiological pH is generally given at 6.8 mg/dL, with reference ranges for uric acid of 3.5–7.2 mg/dL (210–430 μmol/L) and 2.6–6.0 mg/dL (155–360 μmol/L) in younger men and premenopausal women, respectively.[1] Hyperuricaemia is the result of increased production or decreased excretion of uric acid.[2] Uric acid levels have been associated with increased risk of heart mortality,[3] increased risk of kidney disease[4] and as a predictor of metabolic syndrome.[5]

In patients with SLE, uric acid has been recognised as a potential marker of endothelial dysfunction and renal disease, as an association has been found between active lupus nephritis and hyperuricaemia,[6] as well as with cerebral infarction and peripheral neuropathy.[7] Likewise, uric acid levels are useful in predicting the future development of pulmonary hypertension in patients with SLE with normal basal systolic pulmonary artery pressure.[8] In addition, serum uric acid levels have been reported as predictor of increased risk of kidney damage.[9]

Thus, the objective of this study was to determine whether serum uric acid levels are associated with the occurrence of new damage in patients with SLE.

METHODS
Patients

Starting in January 2012, all patients with SLE presenting to the Rheumatology Department of the Hospital Guillermo Almenara Irigoyen in Lima, Peru, have been invited to participate in the Almenara Lupus Cohort.

All patients met the 1997 American College of Rheumatology (ACR) criteria when entering the cohort. Patients with at least two visits were included. Demographic data included gender, age at diagnosis,

socioeconomic status according to the Graffar method, and educational level defined as years of formal education. On the other hand, clinical variables included disease activity (evaluated using the Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K)),[10] damage (assessed using the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI)),[11] disease duration and comorbidities using the Charlson Comorbidity Index.[12] Therapeutic variables included the use of glucocorticoids (current dose and time of exposure). Similarly, the use of immunosuppressive and antimalarial drugs was recorded as current, past or never administered. A past user was defined as those patients receiving treatment until the day before the assessment. All variables were assessed at baseline, with the exception of new damage, which was assessed at subsequent visits.

Statistical analyses

Univariable and multivariable Cox regression models were performed to determine the impact of serum uric acid level on the risk of new damage. Multivariable models were adjusted for age at diagnosis, disease duration, socioeconomic status, educational level, SLEDAI-2K, SDI, comorbidities, and use of prednisone, immunosuppressive and antimalarial drugs. $P<0.05$ was considered significant in all analyses. All statistical analyses were performed using SPSS V.26.0.

RESULTS

Two hundred and thirty-seven patients with SLE were evaluated. The mean age (SD) at diagnosis was 35.9 (13.1) years, 220 patients (92.8%) were women, almost all were Mestizo (European and Native American ancestry), and the disease duration at baseline was 7.3 (6.6) years. The mean SLEDAI-2K and SDI scores were 5.1 (4.2) and 0.9 (1.3), respectively. Charlson Comorbidity Index score was 0.5 (0.9). Serum uric acid levels were 4.5 (1.4) mg/dL; 24 (10.1%) patients had uric acid levels above the normal limit. The current mean dose of prednisone was 7.1 (6.4) mg/day. Time of exposure to prednisone was 6.9 (6.2) years, and follow-up time was 3.1 (1.3) years. One hundred and twelve (47.3%) patients accumulated some type of damage during follow-up. Patient characteristics are shown in table 1.

Organ damage per domain is described in table 2.

In univariable and multivariable analyses (adjusting for variables known to have an impact on damage accrual), serum uric acid levels were associated with new damage (HR=1.141 (95% CI 1.016 to 1.282), p=0.026; HR=1.189 (95% CI 1.025 to 1.378), p=0.022, respectively), as shown in table 3.

DISCUSSION

The association between uric acid levels and damage accrual in patients with SLE was evaluated, and serum uric acid level was found to be associated with the development of new damage in these patients. Previous studies

Table 1 Characteristics of patients with SLE

	Mean or n	SD or percentage
Age at diagnosis (years)	35.9	13.1
Gender, male	17	7.2
Socioeconomic status		
High	46	19.4
Medium	96	40.5
Low	95	40.1
Educational level (years)	13.1	3.2
Disease duration (years)	7.4	6.7
Uric acid level (mg/dL)	4.6	1.5
SLEDAI-2K	5.2	4.3
SDI	1.0	1.3
Charlson Comorbidity Index	0.5	0.9
Prednisone current dose (mg/day)	7.2	6.4
Time of exposure to prednisone (years)	6.9	6.2
Antimalarial use		
Never	20	8.4
Past	28	11.8
Current	189	79.7
Immunosuppressive drug use		
Never	60	25.3
Past	60	25.3
Current	117	49.4
Follow-up time	3.1	1.3

SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2K.

have found an association between hyperuricaemia and hypertension,[13] metabolic syndrome[14] and renal disease,[2] as well as with organ failure or damage,[15] especially renal.[16]

In several autoimmune diseases, high serum uric acid levels play an important role in the development and risk of certain comorbidities; for example, in rheumatoid arthritis, uric acid is a cardiovascular risk factor reflected in the increased thickness of the carotid artery.[17] On the other hand, in systemic sclerosis, Gigante et al[18] found that serum uric acid levels were higher in those with more microvascular damage as compared with those with less microvascular damage.

Taraborelli et al[19] examined the effect of disease duration of 511 patients with SLE on damage; this study showed that, at 1 year of follow-up, about 40% of patients had some damage: usually mild or moderate. The prevalence of damage progressively increased over time, starting from a mean SDI score of 0.6 (SD: 0.89) at 1 year to 0.9 (SD: 1.19) at 5 years and 3.7 (SD: 1.5) at 35 years of follow-up. Bruce et al[20] found that increasing age had a significant influence on the probability of

Table 2 Damage per domain

	Not new damage		New damage		P value
	n (%)	Uric acid, mean (SD)	n (%)	Uric acid, mean (SD)	
Global score	125	4.37 (1.36)	112	4.83 (1.46)	0.014
Domains					
Ocular	223	4.58 (1.48)	14	4.61 (1.27)	0.942
Neuropsychiatric	197	4.63 (1.52)	40	4.38 (1.11)	0.323
Renal	198	4.31 (1.21)	22	5.88 (1.57)	<0.001
Lung	215	4.58 (1.44)	22	4.66 (1.71)	0.796
Cardiac	233	4.61 (1.46)	4	3.43 (0.87)	0.109
Peripheral vascular	235	4.59 (1.47)	2	3.75 (0.49)	0.418
Gastrointestinal	231	4.61 (1.47)	6	3.53 (0.73)	0.074
Musculoskeletal	200	4.51 (1.44)	37	4.98 (1.57)	0.078
Cutaneous	236	4.59 (1.47)	1	4.80	0.884
Gonadal	115	4.15 (1.10)	6	5.20 (0.78)	0.023
Diabetes	223	4.56 (1.45)	3	4.40 (0.36)	0.852
Cancer	233	4.57 (1.46)	4	5.43 (1.50)	0.248

damage accrual, and is also the case for ethnicity. For example, compared with Caucasians from Europe or Canada, US patients of African ancestry had a higher risk of evolving from no damage to damage and also of progressing from baseline damage to higher damage,[20] and the case is the same for Hispanic patients.[21] Moreover, Shaharir et al[22] investigated the associated factors of disease damage among patients with lupus nephritis

Table 3 Factors associated with the occurrence of new damage (univariable and multivariable analyses)

Variables	HR (95% CI)	P value	HR (95% CI)	P value
Uric acid level (mg/dL)	1.141 (1.016 to 1.282)	0.026	1.197 (1.020 to 1.403)	0.028
Age at diagnosis (years)	1.023 (1.009 to 1.038)	0.001	1.038 (1.018 to 1.058)	<0.001
Gender (male)	1.005 (0.489 to 2.065)	0.989	1.027 (0.455 to 2.321)	0.949
Socioeconomic status				
High	Ref		Ref	
Medium	1.239 (0.745 to 2.061)	0.409	0.461 (0.174 to 1.223)	0.120
Low	1.422 (0.950 to 2.129)	0.087	1.023 (0.579 to 1.805)	0.938
Educational level (years)	0.940 (0.889 to 0.993)	0.027	0.885 (0.793 to 0.988)	0.029
Disease duration (years)	1.032 (1.008 to 1.055)	0.007	1.056 (1.006 to 1.109)	0.029
SLEDAI-2K	1.040 (1.000 to 1.082)	0.051	1.018 (0.971 to 1.068)	0.457
SDI	1.283 (1.147 to 1.435)	<0.001	1.095 (0.836 to 1.208)	0.960
Creatinine level (mg/dL)	0.993 (0.882 to 1.118)	0.907	0.979 (0.817 to 1.175)	0.823
Charlson Comorbidity Index	1.030 (0.854 to 1.243)	0.755	0.853 (0.646 to 1.128)	0.265
Prednisone current dose (mg/day)	0.993 (0.964 to 1.023)	0.637	1.000 (0.965 to 1.037)	0.994
Time of exposure to prednisone (years)	1.032 (1.006 to 1.058)	0.016	1.001 (0.952 to 1.053)	0.957
Antimalarial use				
Never	Ref		Ref	
Past	0.970 (0.466 to 2.017)	0.934	1.372 (0.584 to 3.226)	0.468
Current	0.708 (0.409 to 1.225)	0.217	1.106 (0.587 to 2082)	0.756
Immunosuppressive drug use				
Never	Ref		Ref	
Past	1.021 (0.597 to 1.744)	0.940	1.191 (0.654 to 2.170)	0.568
Current	1.420 (0.916 to 2.202)	0.117	1.649 (0.997 to 2.728)	0.051

Ref, reference; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2K.

and found that higher daily prednisolone dose predicted disease damage.

In SLE, serum uric acid levels have been reported to be associated with several impairments, including renal, cardiovascular, pulmonary and neurological, which when analysed together may explain the impact on damage. Yang et al[23] found that serum uric acid level was associated with the development of lupus nephritis and previously we have reported that serum uric acid level predicts increased kidney damage.[9] In the same way, Ugolini-Lopes et al[24] found that serum uric acid levels <6.05 mg/dL at 12 months of follow-up were a predictor of good long-term renal outcome in lupus nephritis. Likewise, in the study by Sabio et al,[25] patients with hyperuricaemia presented a worse cardiovascular risk profile that included hypertension, obesity, high cholesterol levels, renal damage and metabolic syndrome; in addition, serum uric acid levels correlated with high levels of erythrocyte sedimentation rate, C reactive protein, fibrinogen and homocysteine. Similarly, Castillo-Martínez et al[8] demonstrated that serum uric acid levels greater than 7 mg/dL would increase the risk of developing pulmonary hypertension by 8.5 times.[8] Similar findings have been reported by Kim et al,[26] where a value greater than 6.5 mg/dL of uric acid would be reasonably accurate in predicting the presence of pulmonary hypertension. In addition, hyperuricaemia has been shown to be related to factors that would increase the risk of stroke, such as high blood pressure, hyperlipidaemia and history of arterial thrombosis, and has been independently associated with the occurrence of cerebrovascular events and polyneuropathy.[7]

Uric acid can generate urate radicals when it is exposed to oxidising agents[27] and itself has been shown in an in vitro study to stimulate the synthesis of monocyte chemoattractant protein-1, interleukin-1b, intereukin-6 and tumour necrosis factor-a, all of which are proinflammatory molecules.[28] In contrast, it also represents one of the most important low-molecular-mass antioxidants in the human biological fluids.[29–31] It is a powerful scavenger of peroxyl radicals, hydroxyl radicals and singlet oxygen,[29] and may contribute to increased lifespan in humans by providing protection against oxidative stress-provoked ageing and cancer. Also, uric acid is an oxidisable substrate for hem protein/H_2O_2 systems and is able to protect against oxidative damage by acting as an electron donor.[32] Despite this, we did not demonstrate how low the uric acid level needs to be to avoid damage in patients with SLE.

Keeping uric acid levels low is recommended to avoid damage in SLE, as it has been observed in studies that increasing uric acid is related to anaemia in SLE,[33] and also associated with the occurrence of stroke, peripheral neuropathy, hypertension, hyperlipidaemia and history of arterial thrombosis.[7] Even normal values of uric acid have been associated with renal damage in patients with SLE.[9 24]

This study has some limitations. As it is not an inception cohort, it is not possible to define if the interaction between serum uric acid levels and damage is bidirectional, that is, damage increases the level of serum uric acid and this in turn determines new damage. Other limitations include the fact that randomisation was not possible in terms of the type of treatment that patients received. In addition, some medications have not been recorded in the database, such as losartan. Finally, the cumulative dose of steroids could not be obtained since this is not an inception cohort. On the other hand, being a cohort of mostly Mestizo patients, the results cannot be extrapolated to patients from other ethnic groups. An important strength of this study, however, is that for the first time it is reported that higher serum uric acid levels are associated with global damage. It will be necessary to conduct longitudinal studies with a larger number of patients to confirm these findings.

In conclusion, we describe for the first time the association between uric acid levels and global damage in patients with SLE, independently of age at diagnosis, sex, disease duration, socioeconomic status, disease activity, comorbidities, prednisone use, antimalarials and immunosuppressive drugs at baseline.

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