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Research Article

Hyperuricemia as an independent predictor and prognostic factor in the development of lupus nephritis

Background: Lupus nephritis (LN) can increase morbidity and mortality risk in systemic lupus erythematosus (SLE) and 25% of the patients with LN will advance to end-stage renal disease. Objective: To evaluate if hyperuricemia is independently associated with the prediction and prognosis of LN. Methods and finding: This cohort study included 80 SLE patients. SLE patients were divided according to uric acid levels in two groups: "Hyperuricemia SLE" group (n=40) and "No Hyperuricemia SLE" group (n=40). Serum uric acid ≥ 6.0 mg/dL in female and ≥ 7.0 mg/dL in male were indicative of hyperuricemia. SLE Disease Activity Index (SLEDAI) scores, serum level of uric acid, renal activity and chronicity index results were collected and recorded. Median value of serum uric acid level for patients with hyperuricemia was 8.6 mg/dl (4.3-10.4) and for patients without hyperuricemia was 4.2 mg/dl (3.3-5.3). LN was observed in 62.5% of group I (SLE with hyperuricemia) in comparison to 20% of group II (SLE without hyperuricemia)" with p<0.001. A statistically significant relation between hyperuricemia and the occurrence of LN was detected. There was also an inverse correlation between serum level of uric acid and both serum C3 level and estimated glomerular filtration rate (p<0.001); however, there was positive correlation of serum level of uric acid with SLE activity and proteinuria, with statistical significance (p<0.001). Renal activity index in hyperuricemic patients (median=7) was higher than that in patients without hyperuricemia. Conclusion: There is a link to be considered between hyperuricemia and the development of new renal damage in SLE affecting both LN activity and severity.

Keywords: activity index • chronicity index • hyperuricemia • lupus nephritis • systemic lupus

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Introduction

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disorder identified by the production of autoantibodies and immune complex deposition [1]. It presents with a variety of unpredictable flares of disease activity and irreversible organ damage [2]. Half or more (45%-85%) of patients with SLE will develop Lupus Nephritis (LN) over the course of their lifetime, which is a major concern [3,4]. Despite advanced immunosuppressive therapy, the 5-year survival rate of SLE patients with severe renal damage (11%-33%) is usually very low [5].

Hence, early prediction and diagnosis of LN are of great value. So far, renal biopsy remains to be the gold standard tool for diagnosis of LN [6] and assumes a vital role in its management and prognosis. However, renal biopsy can have various complications including hemorrhage and infection. Besides, some patients have contraindications for renal biopsy, which indicates the requirement for noninvasive markers for evaluating renal dysfunction and its grade [7].

Elimination of serum uric acid (sUA), the circulating end-product of purine metabolism, occurs *via* both renal and extra-renal (gastrointestinal tract) pathways [8]. Kang and colleagues [9] have reported that elevated serum uric acid may also be a risk factor for progression of renal disease, in spite of the fact that it is considered as one of the markers of renal dysfunction. Elevated serum uric acid itself can lead to kidney damage without the deposition of uric acid crystals as reported in different studies [10]. Other studies strongly suggest to consider the concept of "asymptomaticity" for chronic hyperuricemia and hence to check the normal level of serum uric acid levels [11].

Hyperuricemia can be observed in patients with diabetic nephropathy [12], IgA nephropathy [13], metabolic syndrome [14] and cardiovascular diseases [15]. In addition, a noteworthy positive relationship was detected between serum level of uric acid and new onset lupus nephritis. Elevated sUA has been observed as an independent risk factor for the development of LN [16,17]. The correlation between sUA and the degree of renal dysfunction in LN patients was previously analyzed but in a few studies as in Calich and colleagues study who reported an association between lupus nephritis and high serum UA [18]. Therefore the aim of the current

study was to evaluate serum uric acid level and detect if hyperuricemia can independently predict and affect prognosis of LN among Egyptian population.

Methods

Study population

This cohort study included 80 adult SLE patients diagnosed according to the Systemic Lupus International Collaborating Clinics (SLICC) criteria for SLE [19]. We first consequently selected the SLE patients who had hyperuricemia (group I: 40 patients) then we selected suitable group-matched SLE patients without hyperuricemia (group II: 40 SLE patients without hyperuricemia). They were recruited from the immunology clinic of Ain Shams University hospital. The main inclusion criteria were patients who fullfiled criteria for SLE, age between 18 and 45 years old with no proteinuria or RBCs or WBCs casts in urine and estimated glomerular filtration rate ≥ 90 mL/min/1.73 m2. We followed up with the patients for two years. We advised patients to avoid vigorous exercise and purine-rich food (organ meats, mushrooms, fish and seafood, dried peas and beans) prior to the study.

Exclusion criteria included past or present history of primary gout, using drugs affecting serum level of uric acid (loop diuretics and losartan, aspirin, other medicines that contain salicylate, cyclosporine, levodopa, hydrochlorothiazide, vitamin B-3, chemotherapy or radiation therapy) or those with hypertension, diabetes or chronic kidney diseases of other etiologies. The study was approved by the Ain Shams University research ethics committee. All patients did sign an informed written consent.

Study design

We recorded data of all participants including detailed history, clinical examination findings, assessment of SLE disease activity by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)-2K score and results of investigations. Routine investigations were done including renal function tests (Blood Urea Nitrogen (BUN) and serum creatinine). The simplified Modification of Diet in Renal Disease (MDRD) equation was used to calculate the estimated glomerular filtration rate (eGFR) [20,21]. An eGFR more than 90 mL/min/1.73 m2 is considered normal for adults, according to the National Kidney Foundation [22]. Urine analysis was performed using standard urine strip test. Urinary protein:urinary creatinine ratio (mg/dL) and urinary protein concentration were determined, then the protein/creatinine (P/C) ratio was computed by dividing the urinary protein value by the urinary creatinine value (mg/dL).

Erythrocyte Sedimentation Rate (ESR) was analyzed using Westergren method via imaging starter Kit. C-Reactive Protein (CRP) evaluation using CRP (Human) Enzyme-Linked Immunosorbent Assay (ELISA) was done by means of turbidimetric immunoassay technique. Anti-Nuclear Antibody (ANA) was measured using ELISA ANA kit and Anti-dsDNA was analyzed using an immunoenzyme dot assay method. Serum C3 and C4 levels were detected by means of complement fixation test using immunodiffusion plates (FAR Ven Fermi, 12-Italy).

Assessment of patients by means of SLE disease activity index

We assessed the patients by the SLE Disease Activity Index score-2K (SLEDAI score). It consists of 24 variables (9 organ systems and some immunological tests) each of which are scored according to weights derived. The scores of the descriptors ranged from 1 to 8. The total score for all 24 variables is 105 [23].

Renal biopsy

We classified lupus nephritis patients into 6 classes according to 2003 International Society of Nephrology-Renal Pathology Society (ISN/RPS) classification. It includes 6 classes: class I (minimal mesangial), class II (mesangial proliferative), class III (focal), class IV (diffuse), class V (membranous), and class VI (advanced sclerosis) [24]. Renal pathological scores of Activity Index (AI), Chronic Index (CI) and tubulointerstitial lesions (TIL) were assessed by staining renal biopsy specimens with hematoxylin-eosin stain, Masson's trichrome stain, and Periodic Acid-Schiff stain [25].

Serum uric acid

Uric acid level in the serum was quantified using the uricase method via AU680 (BECKMAN COULTER, USA). sUA levels ≥ 6.0 mg/dL in female patients and ≥ 7.0 mg/dL in male patients were considered indicative of hyperuricemia [8].

Statistical methodology

Analysis of data was performed using Stata® version 14.2 (StataCorp LLC, College Station, TX, USA). Normality of numerical data

distribution was examined using the Shapiro-Wilk test. Non-normally distributed numerical data were presented as median and interquartile range and intergroup differences were compared using the Wilcoxon rank sum test. Categorical data were presented as number and percentage or ratio and differences were compared using either Fisher's exact test (for nominal data) or the chi-squared test for trend (for ordinal data). Correlations were tested using the Spearman rank correlation. The correlation coefficient (Spearman rho) was interpreted as follows: < 0.2, very weak; 0.2-.39, weak; 0.4-.59, moderate; 0.6-.79, strong and 0.8-1, very strong.

The diagnostic value of serum uric acid was measured by Receiver-Operating Characteristic (ROC) curve analysis. The area under ROC curve (AUC) is interpreted as follows 0.9-1.0, excellent; 0.8-.89, good; 0.7-.79, fair and 0.6-.69, poor. Multivariable binary logistic regression analysis was utilized to pinpoint the relation between hyperuricemia and development of LN with adjustment for possible confounding factors. Sensitivity, specificity, diagnostic efficiency, positive and negative predictive values and accuracy were calculated. Sensitivity=true positive/true positive+false negative. Specificity=true negative/true negative+false positive. Positive predictive value=true positive/true positive+false positive. Negative predictive value=true negative/true negative+false negative. Accuracy=true positive+true negative/all cases examined. The significance value (P) was categorized as follows: P>0.05, insignificant; P<0.05, significant and P<0.01, highly significant.

Results

Regarding the demographic data, non-statistically significant difference was found between the two studied groups. Table 1 shows the biochemical and hematological data, in which group 1 (SLE with hyperuricemia) had statistically significant lower hemoglobin levels and eGFR than group 2 (SLE without hyperuricemia) with P < .001. Group I (SLE with hyperuricemia) had statistically significant elevated SLEDAI score, urinary P/C, serum levels of creatinine and BUN than group II (SLE without hyperuricemia) with P < .001, < .001, 0.001, 0.001 respectively. LN was detected in 62.5% of group I (SLE with hyperuricemia) and 20% of group II (SLE without hyperuricemia) with P value < .001 as shown in Table 2. Regarding renal biopsy of patients who developed LN in group I (SLE with hyperuricemia), 6 (15%) was Class II, 11 (27.5%) was Class III, 5 (12.5 %) was Class IV and 3 (7.5 %) was Class V. While in group II (SLE without hyperuricemia), 3 (7.5 %) was Class II, 2 (5%) was Class III and 3 (7.5%) was Class IV.

Regarding hyperuricemia and the development of LN, a statistically significant direct relation (P-value = <.001) was found as shown in Figure 1. Using Receiver-Operating Characteristic (ROC) curve, serum uric acid level >9.1 mg/dl could be considered as a predictor for the development of LN in males with 57.14% sensitivity, 100% specificity, 100% PPV (positive predictive value) and 66.7 % NPV (negative predictive value) (area under curve: 0.738). Serum uric acid level > 5.5 mg/dl could be considered as a predictor for the development of LN in females, with 63.64% sensitivity, 88.24% specificity, 84% PPV and 71.4% NPV (area under curve: 0.781).

LN activity index grades were more elevated in SLE with hyperuricemia than in SLE without hyperuricemia. This reflects a statistically significant direct relation between increased LN activity index and hyperuricemia (P=.004). LN chronicity index grades were higher in patients with SLE with hyperuricemia than in SLE without hyperuricemia but were without statistical significance (P=.076) as shown in Table 3. Regarding the multivariable binary logistic regression analysis for the relation between hyperuricemia and LN in SLE patients, both hyperuricemia and high SLEDAI score could be considered as an independents predictor for the development of LN in SLE patients (P<.001).

A statistically significant inverse correlation was found between serum uric level and hemoglobin level (P<0.001) while a non-statistically significant inverse correlation was observed with WBCs and platelet count. There was a statistically significant positive correlation between serum uric levels and both serum creatinine and BUN level in LN patients. Serum uric level was negatively correlated with both serum C3 level and eGFR (P<.001, P<.001 (respectively)) and positively correlated with SLE activity and proteinuria with P<.001, P<.001 respectively. A non-significant positive correlation between serum uric level and CRP level (P=0.61) while a significant positive correlation with ESR (P<0.001) was also detected.

Discussion

Clinical presentation of systemic lupus erthrymatosis ranges from subtle manifestations

Table 1. Hematological and biochemical assays of the studied groups.					
	SLE without hyperuricemia (n=40)		SLE with hyperuricemia (n=40)		
Variable	Median	IQR	Median	IQR	p-value¶
Uric acid (mg/dl)	4.2	3.3 - 5.3	8.6	4.3 - 10.4	<.001
BUN (mg/dl)	18	15 - 20	31	16 - 66	0.001
Creatinine (mg/dl)	0.7	0.6 - 1.0	1.2	0.7 - 2.8	0.001
GFR (ml/min)	98.8	71.7 - 133.5	56.9	22.8 - 104.4	<.001
C3 (mg/dl)	116	91 - 145	51	40 - 88	<.001
Urinary P/C ratio	0.1	0.0 - 0.1	1.9	1.0 - 4.5	<.001
SLEDAI (activity) score	11	9 - 12	22	16 - 33	<.001
WBC (x1000/mm^3)	6.7	4.8 - 9.1	6.9	4.6 - 9.7	0.814
Hemoglobin (g/dl)	12	10 - 12	10	8 - 11	0.001
Platelets (x1000/mm^3)	202	151 - 236	226	158 - 302	0.095
Data are median and interquartile range (IQR). ¶Jonckheere-Terpstra trend test.					

Table 2. Prevalence of lupus nephritis (LN) in the two groups of SLE.			
Variable	SLE with hyperuricemia (n = 40)	SLE without hyperuricemia (n = 40)	p-value¶
LN	25 (62.5%)	8 (20.0%)	< .001
LN class			
Class II	6 (15%)	3 (7.5 %)	
Class III	11 (27.5%)	2 (5%)	
Class IV	5 (12.5 %)	3 (7.5%)	
Class V	3 (7.5 %)	0	
Data are presented as number and (%). ¶Fisher's exact test.			

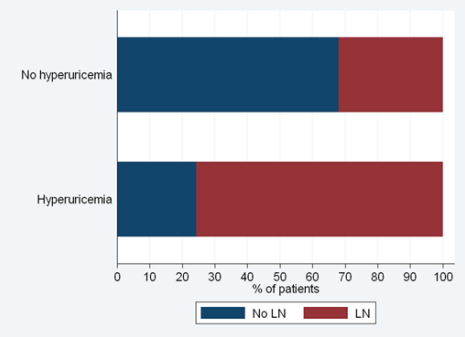

Figure 1. Relation between hyperuricemia and development of Lupus Nephritis (LN).

to life-threatening multiorgan involvement according to site of immune complex deposition [26,27]. Among the different affected organs, kidney affection causes significant morbidity and mortality in a great number of cases. The 5-year survival in patients with renal affection is very low even with treatment [28]. Proteinuria, urinary protein-to-creatinine ratio, creatinine clearance and complement levels are markers for LN but they are unsatisfactory markers [29]. Renal biopsy is still the cornerstone in LN diagnosis; however, it is an invasive procedure [30].

There is a link between alteration of sUA homeostasis and diversity of diseases. This alteration of sUA homeostasis may directly affect disease development or progression [31,32]. But there is still a debate about whether hyperuricemia is a marker of renal dysfunction or a risk factor for renal damage in SLE patients. Actually, hyperuricemia can both initiate and accelerate renal disease. It affects the kidney through various mechanisms as endothelial dysfunction (renin-angiotensin system activation and reduced nitric oxide levels), oxidative stress (increased function of NADPH oxidase), antiangiogenesis (inhibition of endothelial proliferation and augmentation of endothelial apoptosis), renal auto regulation malfunction [33] and encouragement of smooth muscle cells proliferation [34].

These mechanisms could trigger or even promote the progression of renal injury in SLE. The current challenge was to identify the role of serum uric acid in lupus nephritis. Hence the rationale of the present study was to evaluate serum level of uric acid and its relation to different disease variables including lupus nephritis activity and chronicity.

The existence of hyperuricemia in SLE patients may be due to the direct relationship between hyperuricemia and inflammatory markers (high CRP, TNF-α or IL-6) [35,36]. In addition, uric acid can directly cause TNF-α release as observed

Table 3. Relation between hyperuricemia and renal activity and chronicity indices in SLE patients with LN.

	SLE patients				
	without hyperuricemia		With Hyperuricemia		
Variable	Median	IQR	Median	IQR	p-value¶
Renal activity index	4	3 - 6	7	4 - 10	0.004
Chronicity index	2	2 - 2	2	2 - 4	0.076

IQR, interquartile range.
¶Wilcoxon rank sum test.

by Netea and colleagues, the serum levels of TNF-α increased after the infusion of soluble uric acid into mice [37]. Moreover, cell culture experiments have emphasized the contribution of uric acid in SLE pathogenesis through the illustration of its role in inflammation. It induces signal transduction within the apoptotic pathway and stimulates mononuclear cells to produce TNF-α [38].

Toll-Like Receptors (TLRs), which are mediators of innate immunity, can recognize and identify the naked Microcrystalline uric acid (MSU) crystals. This is considered a major factor in ascertaining the MSU crystal deposits' inflammatory effect [39]. UA crystal deposits stimulate dendritic cells in the presence of NF-κB signaling, thus promoting the release of Th17 cytokines. This novel role of UA in driving pro-inflammatory Th17 suggests that sterile inflammation can affect both early innate responses and modulate adaptive immunity [40]. Besides, MSU can prompt CD8+ T cells which are involved in SLE pathogenesis [41].

Our study detected development of lupus nephritis in 62.5% of group I (SLE with hyperuricemia) in comparison to 20% in group II (SLE without hyperuricemia) with a statistically significant difference (P<0.001). These findings are in line with the results of the study conducted by Xie and colleagues, which included 177 patients with LN, 77 with and 100 without hyperuricemia. They detected a direct significant relation between hyperuricemia and the development of LN [8]. Similar results were found by Yang et al. who performed a study on 130 SLE patients of whom 73 patients developed LN and when they correlated serum UA with LN, they found that UA was an independent risk factor for development of LN [16]. However, our results indicated that both UA and high SLEDAI score can be independent risk factors for development of LN. Our results are also in harmony with those of Yang and coworkers who studied the relation between LN and serum uric acid in 191 SLE patients. They found a significant relation between elevated serum uric acid level and development of LN. These results indicate that UA may be involved in SLE nephropathy pathogenesis [17].

In addition, Calich and coworkers evaluated serum uric acid levels in LN, by comparing 46 SLE patients with normal renal function, with and without nephritis in comparison to 28 healthy individuals. They found significantly higher serum uric acid in LN+ compared to LN– and healthy participants. Their statistics confirmed that high UA was an independent variable related to LN ($p < 0.001$) and the cut-off value for UA was 4.47 mg/dL [18].

Hyperuricemia doesn't only promote the development of LN but also causes more renal damage as shown in the present study. Besides a statistically significant negative correlation between serum uric level and both eGFR and C3 in LN patients, there was a statistically significant positive correlation between serum uric acid level and proteinuria, serum creatinine and BUN levels (P<.001, P<.001, P<.001, respectively). Comparable findings were observed by Xie et al. who found that the levels of serum BUN and creatinine were significantly more elevated in the LN patients with hyperuricemia (P<0.05) and eGFR was lower in the LN patients with hyperuricemia, with statistical significance (P<0.05) [8].

The prevalence of hyperuricemia was found to be higher in LN patients with chronic kidney disease (CKD) in comparison with the general population with CKD [42]. This is also in line with the results of the study conducted by Tsumuraya and colleagues which concluded that the prevalence of hyperuricemia in LN patients with CKD was more in patients with CKD of other etiologies (40.11% versus 23.3%) [43]. Previously, sUA was known to cause renal damage through the deposition of intra-luminal crystal in the collecting duct of the nephron. However, it has been shown that UA can also

induce inflammation, endothelial dysfunction, oxidative stress leading to renal arteriolopathy and tubulointerstitial fibrosis [44]. In fact, UA was considered an independent risk factor for new-onset lupus nephritis, due to its close association with C3 consumption, which suggests that C3 could be activated by elevated UA levels through classical and alternative pathways [17].

Our results are also in harmony with the results of Reátegui-Sokolova and colleagues who conducted a study on one hundred and eighty-six patients. During their follow-up, LN evolved in 16 (8.6%) patients. In addition, in other uni-variable and multivariable analyses, baseline serum uric acid level predicted the development of new onset renal affection [45].

Xie and colleagues also demonstrated that activity index and chronicity index scores of renal biopsies in LN patients were significantly elevated in the LN with hyperuricemia group in contrast to the LN without hyperuricemia group (P=0.01, and P<0.01 respectively) [8]. These results are in accordance with the results of our current study as, there is a significant direct relation between hyperuricemia and LN activity index scores (P=.004) and a direct relation between the presence of hyperuricemia and chronicity index but without statistical significance (P=.076). Uric acid leads to renal damage primarily by causing hypertension in both systemic and glomerular blood vessels [46]. However, the effects of increased uric acid levels on advancement of renal affection can occur despite the absence of crystals in the kidney in SLE patients. This can be explained by the fact that soluble urate has been proven to act as a proinflammatory mediator [47] which might be involved in the inflammatory process of the development of LN. Uric acid is considered as a mediator of inflammation due to the existence of a direct relationship between serum uric acid and markers of systemic inflammation [48].

Besides, a non-significant positive correlation between hyperuricemia and CRP levels was detected and this contradicts the results of Yang, et al. who detected that no correlations were found between serum UA and CRP in LN patients [16]. Positive correspondence between serum uric acid and CRP can be elucidated by the close association between increased sUA and systemic inflammation [49]. Besides, our study detected a statistically considerable positive correspondence between serum uric levels and ESR (P<.001) which is also an inflammatory marker.

The present study found that serum level of uric acid was negatively correlated with C3 (P<.001), which was compatible with the results of the studies conducted by Li, et al. [14] and Yang, et al. [17]. This can be related to the activation of C3 by hyperuricemia in LN, through both classical and alternative pathways [50]. In turn, complement activation product's deposition aggravates the renal tissue injury and the progression of LN. Hyperuricemia in our study had a statistically significant positive correlation with SLE activity (SLEDAI- 2K score) in LN patients (P<.001) which opposes the results of Yang et al., who found that hyperuricemia had no association with SLE disease activity (SLEDAI score) [16] and the study by Xie and colleagues who found that SLEDAI scores were dissimilar but had no statistically significant difference in the two groups (P>0.05) [8]. Our results can be explained by the positive correlation between hyperuricemia and proteinuria, thrombocytopenia and leucopenia which are SLEDAI score descriptors.

Besides, we realized that hyperuricemia was positively associated with anemia in LN patients, with statistical significance difference (P<.001) which is similar to the results of Yang and his group who had 191 SLE patients in the study and noticed that increased serum levels of uric acid were only directly associated with decreased red blood cells (P=0.018) [17]. Our present study demonstrated that hyperuricemia had a close association with SLE disease activity (high SLEDAI-2K scores) and showed correlation with LN renal activity and chronicity index of renal biopsy, low serum C3 levels, and high urinary protein: creatinine ratio indicating that hyperuricemia might contribute to the development and progression of LN in SLE patients.

Conclusion

Hyperuricemia contributes with other factors in LN development and could be considered as a prognostic factor for the worse progression of LN (i.e. higher levels of serum creatinine & BUN, low serum C3, higher LN activity index and more proteinuria). Serum UA concentration should be applied in medical practice during evaluation of SLE patients and elevated serum UA levels can be used as a provisional prognostic marker of LN in SLE patients. Further studies may be needed on a larger scale for evaluation of the definitive role of hyperuricemia in the

pathogenesis of LN among SLE patients. Evaluation of significance of early detection and treatment of hyperuricemia for improvement of clinical outcome of LN should be assessed.

Conflict of interest

There was no funding and none of the authors have any personal relationship that could be considered a conflict of interest.

References

1. Nasonov E, Soloviev S, Davidson JE, *et al.* The prevalence and incidence of systemic lupus erythematosus (SLE) in selected cities from three Commonwealth of Independent States countries (the Russian Federation, Ukraine and Kazakhstan). *Lupus.* 23(2), 213–219 (2014).
2. Yuan W, DiMartino SJ, Redecha PB, *et al.* Systemic lupus erythematosus monocytes are less responsive to interleukin-10 in the presence of immune complexes. *Arthritis. Rheum.* 63(1), 212–218 (2011).
3. Borchers AT, Leibushor N, Naguwa SM, *et al.* Lupus nephritis: A critical review. *Autoimmun. Rev.* 12(2), 174–194 (2012).
4. Zubair A, Frieri M. Lupus nephritis: Review of the literature. *Curr. Allergy. Asthma. Rep*. 13(6), 580–586 (2013).
5. Koutsokeras T, Healy T. Systemic lupus erythematosus and lupus nephritis. *Nat. Rev. Drug. Discov.* 13(3), 173–174 (2014).
6. Chan TM (2015) Treatment of severe lupus nephritis: The new horizon. *Nat. Rev. Nephrol.* 11(1), 46–61 (2015).
7. Cameron JS, Hicks J. The introduction of renal biopsy into nephrology from 1901 to 1961: A paradigm of the forming of nephrology by technology. *Am. J. Nephrol.* 17(3-4), 347–358 (1997).
8. Xie T, Chen M, Tang X, *et al.* Hyperuricemia is an independent risk factor for renal pathological damage and poor prognosis in lupus nephritis patients. *J. Cent. South. Univ.* 41(10), 1052–1057 (2016).
9. Kang DH, Nakagawa T, Feng L, *et al.* A role for uric acid in the progression of renal disease. *J. Am. Soc. Nephrol.* 13(12) 2888–2897 (2002).
10. Desideri G, Castaldo G, Lombardi, *et al.* Is it time to revise the normal range of serum uric acid levels? *Eur. Rev. Med. Pharmacol. Sci.* 18(9), 1295–1306 (2014).
11. Mazzali M, Hughes J, Kim YG, *et al.* Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension.* 38, 1101–1106 (2001).
12. Liu P, Chen Y, Wang B, *et al.* Allopurinol treatment improves renal function in patients with type 2 diabetes and asymptomatic hyperuricemia: 3-year randomized parallel-controlled study. *Clin. Endocrinol.* 83(4), 475–482 (2015).
13. Cheng GY, Liu DW, Zhang N, *et al.* Clinical and prognostic implications of serum uric acid levels on IgA nephropathy: a cohort study of 348 cases with a mean 5-year follow-up. *Clin. Nephrol.* 80, 40–46 (2013).
14. Li C, Hsieh MC, Chang SJ. Metabolic syndrome, diabetes and hyperuricemia. *Curr. Opin. Rheumatol.* 25, 210–216 (2013).
15. Sertoglu E. Serum uric acid: An independent predictive marker for coronary artery disease. *Clin. Rheumatol.* 34(9), 1659–1659 (2015).
16. Yang Z, Liang Y, Xi W, *et al.* Association of serum uric acid with lupus nephritis in systemic lupus erythematosus. *Rheumatol. Int.* 31(6), 743–748 (2011).
17. Yang Z, Liang Y, Li C, *et al.* Associations of serum urea, creatinine and uric acid with clinical and laboratory features in patients with systemic lupus erythematosus. *Rheumatol. Int.* 32(9), 2715–2723 (2012).
18. Calich AL, Borba EF, Ugolini-Lopes MR, *et al.* Serum uric acid levels are associated with lupus nephritis in patients with normal renal function. *Clin. Rheumatol.* 37(5), 1223–1228 (2018).
19. Inês L, Silva C, Galindo M, *et al.* Classification of systemic lupus erythematosus: Systemic lupus international collaborating clinics versus American college of rheumatology criteria. A comparative study of 2,055 patients from a real-life, international systemic lupus erythematosus cohort. *Arthritis. Care. Res.* 67(8), 1180–1185 (2015).
20. Levey AS, Coresh J, Balk E, *et al.* National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Ann. Intern. Med.* 139(2), 137–147.
21. Stevens LA, Coresh J, Feldman HI, *et al.* Evaluation of the modification of diet in renal disease study equation in a large diverse population. *J. Am. Soc. Nephrol.* 18(10), 2749-2757 (2007).
22. Delanaye P, Mariat C. The applicability of eGFR equations to different populations. *Nat. Rev. Nephrol.* 9(9), 513–522 (2013).
23. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J. Rheumatol.* 29(2), 288–291 (2002).
24. Weening JJ, D'Agati VD, Schwartz MM, *et al.* The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney. Int.* 65(2), 521–530 (2004).
25. Austin HA, Boumpas DT, Vaughan EM *et al.* Predicting renal outcomes in severe lupus nephritis: Contributions of clinical and histologic data. *Kidney. Int.* 43, 544–550 (1994).
26. Luis M, Rashidi S, Ricardo MV, *et al.* Presence of antibodies against cyclic citrullinated peptides in patients with 'rhupus': a cross-sectional study. *Arthritis. Res. Ther.* 8, R144 (2006).
27. Sherif Z, Wasef Y. Gender differences in systemic lupus erythematosus. *Gender. Medicine.* 1(1), 12–17 (2004).
28. Korbet SM, Lewis EJ, Schwartz MM, *et al.* Factors predictive of outcome in severe lupus nephritis. Lupus Nephritis Collaborative Study Group. *Am. J. Kidney. Dis.* 35(5), 904–914 (2000)
29. Mok CC, Cheung TT, Lo WH. Minimal mesangial lupus nephritis: A systematic review. *Scand. J. Rheumatol.* 39, 181–189 (2010).
30. Christopher-Stine L, Siedner M, Lin J, *et al.* Renal

biopsy in lupus patients with low levels of proteinuria. *J. Rheumatol.* 34(2), 332–335 (2007).

31. Chen C, Jian-Ming L, Qizhi Y. Hyperuricemia-related diseases and xanthine oxidoreductase (xor) inhibitors: An overview. *Med. Sci. Monit.* 22, 2501–2512 (2016).
32. Yan D, Tu Y, Jiang F, *et al.* Uric acid is independently associated with diabetic kidney disease: A cross-sectional study in a Chinese population. *PLoS One.* 10, 129–797 (2015).
33. Ejaz AA, Mu W, Kang DH, *et al.* Could uric acid have a role in acute renal failure? *Clin. J. Am. Soc. Nephrol.* 2(1), 16–21 (2007).
34. Kohagura K, Kochi M, Miyagi T, *et al.* An association between uric acid levels and renal arteriolopathy in chronic kidney disease: A biopsy-based study. *Hypertens. Res.* 36(1), 43–49 (2013).
35. Lee YJ, Lee JH, Shin YH, *et al.* Gender difference and determinants of C-reactive protein level in Korean adults. *Clin. Chem. Lab. Med.* 47, 863–869 (2009).
36. Lyngdoh T, Marques-Vidal P, Paccaud F, *et al.* Elevated serum uric acid is associated with high circulating inflammatory cytokines in the population-based colaus study. *PLoS ONE.* 6(5): e19901 (2011).
37. Netea MG, Kullberg BJ, Blok W, *et al.* The role of hyperuricemia in the increased cytokine production after lipopolysaccharide challenge in neutropenic mice. *Blood.* 89, 577–582 (1997).
38. Bordoni V, de Cal M, Rassu M, *et al.* Protective effect of urate oxidase on uric acid induced-monocyte apoptosis. *Curr. Drug. Discov. Technol.* 2(1), 29–36 (2005).
39. Liu-Bryan R, Scott P, Sydlaske A, *et al.* Innate immunity conferred by Toll-like receptors 2 and 4 myeloid differentiation factor 88 expression is pivotal to monosodium urate monohydrate crystal-included inflammation. *Arthritis. Rheum.* 52, 2936–2946 (2005).
40. Conforti-Andreoni C, Spreafico R, Qian HL, *et al.* Uric acid-driven Th17 differentiation requires inflammasome-derived IL-1 and IL-18. *J. Immunol.* 187(11), 5842–5850 (2011).
41. Shi YJ, Evans E, Rock KL. Molecular identification of a danger signal that alerts the immune system to dying cells. *Nature.* 425, 516–521 (2003).
42. Simeng L, Yijun G, Hong R, *et al.* The prevalence, subtypes and associated factors of hyperuricemia in lupus nephritis patients at chronic kidney disease stages 1–3. *Oncotarget.* 8(34), 57099–57108 (2017).
43. Tsumuraya Y, Hirayama T, Tozuka E, *et al.* Impact of hyperuricaemia on the chronic kidney disease-associated risk factors in a community-based population. *Nephrology.* 20, 399–404 (2015).
44. Toda A, Ishizaka Y, Tani M *et al.* Hyperuricemia is a significant risk factor for the onset of chronic kidney disease. *Nephron. Clin. Pract.* 126, 33–38 (2014).
45. Reátegui-Sokolova C, Ugarte-Gil M, Gamboa-Cardenas R, *et al.* AB0440 Serum uric acid levels predict new renal damage in systemic lupus erythematosus patients. *Ann. Rheum. Dis.* 75, 1057 (2016).
46. Mazzali M, Kanellis J, Han L *et al.* Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. *Am. J. Physiol. Renal. Physiol.* 282: 991–997 (2002).
47. Crisan TO, Cleophas MC, Oosting M, *et al.* Soluble uric acid primes TLR-induced proinflammatory cytokine production by human primary cells via inhibition of IL-1Ra. *Ann. Rheum. Dis.* 75, 755– 762 (2016).
48. Billiet L, Doaty S, Katz JD, *et al.* Review of hyperuricemia as new marker for metabolic syndrome. *ISRN Rheumatol.* 16, 852954 (2014).
49. Ruggiero C, Cherubini A, Miller E, *et al.* Usefulness of uric acid to predict changes in C-reactive protein and interleukin-6 in 3-year period in italians aged 21 to 98 years. *Am. J. Cardiol.* 100, 115–121 (2007).
50. Terkeltaub R, Tenner AJ, Kozin F, *et al.* Plasma protein binding by monosodium urate crystals. Analysis by two-dimensional gel electrophoresis. *Arthritis. Rheum.* 26, 775–783 (1983).