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Review Article

Exploring the unseen: Asymptomatic hyperuricemia and its role in the pathogenesis of lupus nephritis, a narrative systematic review

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Abstract. Lupus nephritis (LN) is a major cause of morbidity in systemic lupus erythematosus, yet the impact of asymptomatic elevations in serum uric acid (SUA) on its onset and progression remains unclear. This narrative systematic review synthesizes data from observational cohorts, pathology studies, and mechanistic investigations to clarify the role of hyperuricemia in LN. We first describe the high prevalence of elevated SUA among biopsy-proven LN patients and its consistent association with worse renal function, more severe proteinuria, and higher disease activity indices. We then examine histopathological studies linking hyperuricemia to greater activity and chronicity scores, suggesting that uric acid may exacerbate glomerular and tubulointerstitial injury. Proposed mechanisms include DAMP-mediated inflammasome activation, endothelial dysfunction, and promotion of fibrotic pathways. Although several reports identify hyperuricemia as a risk factor for chronic kidney disease progression or end-stage renal disease in LN—particularly in women—results vary by cohort, making its independent prognostic value uncertain. Finally, we review evidence on urate-lowering therapies in LN, noting that routine treatment is not yet justified in the absence of gout or nephrolithiasis. We conclude that SUA holds promise as a biomarker of LN severity but advocate for prospective trials to determine whether targeted urate reduction can improve renal outcomes.

Keywords: Asymptomatic hyperuricemia, biomarkers, lupus nephritis, serum uric acid, urate-lowering therapy.

Introduction

The relationship of serum uric acid (SUA) activity with lupus nephritis (LN), the severe renal presentation of systemic lupus erythematosus (SLE), is increasingly becoming understood as an area of multimodal and quite significant complexity for managing this autoimmune condition. Although elevated SUA has been linked to CKD of diverse etiology, its specific role in the context of LN-specifically, its correlation with disease activity, renal damage, and prognosis—remains a subject of deep research and debate.[1-3]. This comprehensive review will explore the multidimensional relationship between SUA and LN from the provided sources to examine the occurrence of hyperuricemia in LN, if it is related to clinical and pathological parameters, its predictive effectiveness, potential pathogenic mechanisms, and the urgent need for additional research in this direction.

Hyperuricemia, characterized by an elevated SUA level, is common among patients with lupus nephritis (LN). The incidence rates have been different in various populations, as reflected by studies. For instance, in a large observational single-center cohort study of 1,297 LN patients, hyperuricemia was observed in 50.04% of the participants.[4] In another similar study of 578 Korean LN patients that was retrospectively analyzed, 37.3% of the patients had hyperuricemia on the renal biopsy day.[5] A second investigation using a Southern Chinese population with LN documented by biopsy reported an even greater prevalence, with 58.5% of 123 patients exhibiting hyperuricemia.[6] These findings affirm that many patients with LN also present elevated SUA, suggesting an association between the two. The definitions for hyperuricemia may vary among studies, thus explaining the identified disparity. For example, a study defined hyperuricemia as SUA ≥416 μmol/L (7 mg/dL) in men and postmenopausal women and ≥357 μmol/L (6 mg/dL) in premenopausal women.[6]

Materials and Methods

The facts presented in this paper originate from a critical assessment of the following sources: original research studies, systematic reviews, and clinical trial studies examining the relationship between hyperuricemia and various aspects of kidney disease, with a particular focus on lupus nephritis. The studies were selected based on their relevance to the definition, epidemiology, clinical

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significance, and management of hyperuricemia within the broader context of chronic kidney disease (CKD), specifically for patients with lupus nephritis.

Results

Association with Clinical and Laboratory Parameters

Numerous studies have studied the relationship between SUA levels and clinical and laboratory parameters in patients with lupus nephritis (LN). Results show that LN patients experiencing hyperuricemia frequently exhibit worse renal function, as indicated by decreased estimated glomerular filtration rates (eGFR) and increased serum creatinine and blood urea nitrogen (BUN) levels.[5-7] Research on Korean LN patients discovered meaningfully elevated creatinine levels in the hyperuricemia group compared to controls.[5] Likewise, a study of Egyptian SLE patients with LN indicated remarkably reduced GFR and higher creatinine and BUN levels in those with hyperuricemia.[7]

Hyperuricemia in lupus nephritis (LN) is associated with some negative clinical features. Studies show a correlation between hyperuricemia and the severity of hematuria and proteinuria.[7] Elevated SUA levels are associated with more lupus disease activity scores, i.e., SLEDAI and SLEDAI-R.[6, 8] Studies have established correlations between hyperuricemia in LN and hypertension, high triglycerides, and decreased hemoglobin and serum albumin levels.[7] Interestingly, in a single study, more LN patients with hyperuricemia were positive for antiphospholipid antibodies.[9] The findings indicate that hyperuricemia may not only be produced by renal injury in LN but might also be related to more diffuse systemic inflammation and immunologic dysregulation in SLE. Revealing these correlations could lead to future therapies to manage systemic inflammation and immunological imbalance or to create target therapies against hyperuricemia in LN.

Hyperuricemia and Renal Pathology in Lupus Nephritis

The relationship between SUA level and severity, and some of the characteristics of renal pathological damage in LN, has also been investigated. Positive correlations between increased levels of SUA and higher renal pathological scores, including activity index, chronicity index, and tubulointerstitial lesions, have been demonstrated by some studies.[4, 10]One study found that the hyperuricemia group of LN patients was associated with more crescents, mesangial matrix, endothelial cell proliferation, and inflammatory cell infiltration compared to the non-hyperuricemia group.[4] However, this study did find no difference in the overall LN pathological grade between the two groups. Another study found a statistical difference in the pathological type constituent ratio between LN patients with and without hyperuricemia. In particular, elevated SUA levels have been associated with higher frequencies of class IV+V and lower frequencies of class V LN in some populations.[11] These findings suggest that hyperuricemia may be involved in specific renal damage patterns in LN, but more research is needed to clarify these correlations and the mechanisms involved fully.

Prognostic Value of Serum Uric Acid in Lupus Nephritis

The prognostic significance of the concentration of SUA in estimating long-term renal function in LN remains a relevant area of investigation. Some research has suggested hyperuricemia on disease presentation as an independent risk factor for the occurrence of CKD and the progression to ESRD.[6, 12] It has been determined in a study with Korean LN patients that hyperuricemia is a potential predictor of CKD in these patients.[12] Similarly, one study in a Southern Chinese population showed that elevated levels of SUA, both as continuous and as categorical variables, were predictive of risk for progression of LN. This relationship was maintained in women but not always in men.[6] Furthermore, one study found an increase in SUA by 100 μmol/L correlated with a 10% rise in risk for progression of LN (ESRD or death).[13]

Nevertheless, other research has yielded inconsistent findings. A major retrospective cohort study found that while half of the LN patients had hyperuricemia, it was not an independent risk factor for poor clinical outcomes. According to this study, low eGFR could independently predict adverse outcomes in LN patients with hyperuricemia.[4] Interestingly, a female effect seems to exist, which is linked at an accelerated rate with LN disease progression compared to males [5]. As a result, this sexual dimorphism influencing the management strategies of LN could have significant importance in customizing treatment regimens differently for patients based on their gender background. Additional investigation has revealed that 12-month follow-up SUA levels could have predictive potential for long-term outcomes in the disease process in this renal manifestation, LN.[14] Additionally, research has shown that the combination of both high SUA levels and renal arteriolar injury results in a markedly higher risk for progression to ESRD or death in LN patients [13]. The variation in these findings is a reason for additional large-scale and longitudinal research to finally determine the independent prognostic significance of SUA in LN in varying populations and at different stages of the disease.

Potential Mechanisms Linking Hyperuricemia to LN and Renal Damage

Multiple mechanisms have been proposed to explain how elevated serum uric acid (SUA) levels can trigger and exacerbate lupus nephritis (LN) and associated kidney damage. Uric acid is recognized for its pro-inflammatory effects; it acts as a danger-associated molecular pattern (DAMP) that activates the NLRP3 inflammasome, releasing pro-inflammatory cytokines that may worsen kidney inflammation linked to LN.[15] Additionally, uric acid plays a role in endothelial dysfunction by inhibiting nitric oxide (NO) production and increasing oxidative stress.[16] The activation of the renin-angiotensin system (RAS) may also contribute to hypertension and worsen

renal injury. [17]

Furthermore, uric acid can impact renal cells directly. It has been demonstrated to induce oxidative stress and elevate pro-fibrotic factor production in tubular epithelial cells, potentially resulting in tubulointerstitial fibrosis, a common characteristic of progressive LN.[18] While uric acid crystal accumulation is usually related to gout, it can occur in renal tissues during hyperuricemia, leading to inflammation and damage without apparent gout symptoms. In systemic lupus erythematosus, where immune complex deposition significantly contributes to renal damage, the pro-inflammatory properties of uric acid may further intensify existing inflammation, perpetuating a harmful cycle for the kidneys.[19] Moreover, increased SUA levels may disrupt insulin receptor substrate-1, causing insulin resistance and metabolic complications that could adversely affect renal health.[20] The link between elevated SUA levels in SLE and pulmonary hypertension highlights the broader systemic effects of hyperuricemia in this autoimmune disorder.[21]

Urate-Lowering Therapy in the Context of Lupus Nephritis

Urate-lowering therapy (ULT) in hyperuricemic LN patients is an emerging area. While ULT, as allopurinol and febuxostat, mainly xanthine oxidase inhibitors, has been demonstrated to be effective in the gout treatment and has been shown to slow CKD progression in selected non-SLE populations, its impact on renal outcomes in the context of hyperuricemic LN patients remains to be definitively established.[3, 22] There are several complicating issues. First, hyperuricemia in LN may be secondary to reduced renal function, so it is not sure that lowering SUA would independently benefit the kidney.[23-25] Second, the presumed benefits of ULT must be balanced against the risks and side effects in the SLE setting, where patients frequently receive multiple immunosuppressive drugs.[26]

Some studies have approximated the nephroprotective effect of allopurinol among patients with CKD and hyperuricemia, and findings were inconclusive. For instance, the CKD-FIX and PERL trials failed to demonstrate a significant effect of allopurinol on eGFR decline among some patients with CKD.[27, 28] Nonetheless, in a meta-analysis, it was suggested that urate-lowering therapy (ULT) could considerably help prevent renal function reduction among patients with CKD and asymptomatic hyperuricemia.[29] Currently, based on currently available evidence, urate-lowering therapy is not usually recommended for asymptomatic hyperuricemia in CKD and/or hypertensive patients, particularly lupus nephritis patients, unless it is necessary, e.g., for the treatment of gout or prophylaxis for recurrent kidney stone formation. There is a requirement for further adequately designed, controlled trials in hyperuricemia patients with lupus nephritis to correctly decide the risks versus benefits of ULT in patients with lupus nephritis.[1, 12] It should be noted that treating hyperuricemia in patients with pre-existing gout and CKD, for example, lupus nephritis, can involve the treatment of gout flares aggressively.[30]

Serum Uric Acid as a Biomarker in Lupus Nephritis

As there is a general association of raised SUA levels with LN and potential correlations with disease activity and renal damage, the function of SUA as a biomarker for LN has been researched. Some research studies have reported potential cut-off values for SUA that would be correlated with the presence or development of LN. For instance, a study has set a cut-off value of SUA 4.47 mg/dL for predicting LN in SLE patients with normal renal function.[24] A study has differently graded hyperuricemia in men, postmenopausal women, and premenopausal women.[31] Though SUA is inexpensive and readily available, it cannot be used as an independent diagnostic test for LN because of the multifactorial nature of the disease. However, monitoring levels of SUA in LN patients can be helpful in evaluating renal function and possibly disease course, especially in the setting of other clinical and laboratory parameters.[12] Further studies are needed to establish the utility of SUA as a helpful monitoring or prognostic marker in various subsets of LN patients.

Other Associations of Hyperuricemia in SLE

Apart from its association with LN and CKD, SLE hyperuricemia has also been associated with other clinical manifestations. Elevated SUA levels have been reported in SLE patients with pulmonary hypertension (PH).[32] In a study, serum UA levels in SLE patients with PH were similar to those in idiopathic pulmonary arterial hypertension (IPAH) patients.[21] This suggests hyperuricemia may play a role in the pathogenesis or development of PH in SLE. However, the mechanisms involved are still not fully understood or studied. Further, as brought out in our discussion history, hyperuricemia is a proven risk factor for cardiovascular disease, and SLE patients are already at increased risk of cardiovascular events.[33] Therefore, hyperuricemia in SLE may be the culprit behind this increased cardiovascular risk, but further research is needed that directly addresses this interaction.

Factors Influencing Serum Uric Acid Levels in SLE

These factors include changing levels of SUA in patients with SLE. As highlighted above, damage to renal functions is a strong determinant because the kidney has to excrete most uric acid.[1, 34] Some medications common in SLE, e.g., prednisolone, influence the SUA level as well.[9] Consumption of food patterns, particularly the diet rich in purines, is believed to increase the creation of uric acid.[35] Inherited factors are the regulators of uric acid metabolism.[26] In patients with LN, the extent of glomerular and tubular damage may significantly affect the kidneys' capacity to handle uric acid.[24] Therefore, the interpretation of SUA in LN should consider these many contributory variables.

Limitations and Future Directions

The current evidence supporting SUA's pathogenic function in LN is essentially from observational and

retrospective studies, which have limitations, such as the inability to determine causality and confounders.[1, 5] The heterogeneity of LN concerning clinical and pathological presentation and the heterogeneity of the patients included in the studies also contribute to the variability of findings.[36] In addition, no large randomized controlled trials can measure the impact of ULT on renal function in patients with LN and hyperuricemia.[1]

Such investigations should overcome these limitations in subsequent work. Standardization of endpoints and use of proper cohorts of characterized patients need to be adopted in prospective long-term follow-up studies to further elucidate the independent prognostic value of SUA at all stages and LN subtypes.[1, 6] Additionally, an examination of the underlying mechanisms by which uric acid could contribute to SLE-related renal inflammation and injury is required.[1, 24] Lastly, well-designed clinical trials must ascertain if ULT positively impacts renal outcomes in specific subgroups of patients with hyperuricemia and LN, balancing the risks and benefits of their underlying autoimmune disease and other comorbid conditions.[12] Specifying specific patient subgroups most likely to benefit from SUA monitoring or ULT may lead to more efficient and targeted treatment algorithms for LN.

Conclusion

Serum uric acid concentrations are elevated in patients with lupus nephritis and seem to correlate with several adverse clinical and pathological observations like poorer renal function and perhaps more significant renal damage. Even though various studies indicate that hyperuricemia may predict poor renal outcomes independent of another disease in LN, particularly in women, results have not been consistent between cohorts. The mechanisms through which uric acid is associated with LN pathogenesis are its pro-fibrotic and pro-inflammatory effects. The effectiveness of urate-lowering therapy in enhancing renal prognosis in LN patients with hyperuricemia is uncertain and should be further investigated. Subsequent studies should clarify the complex interaction between SUA and LN to delineate its unique role in the pathogenesis of the disease and outline therapeutic interventions based on uric acid metabolism in this recalcitrant autoimmune disease.

Conflicts of Interest

The authors declare that they have no conflicts of interest relevant to this manuscript.

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