Beyond Proteinuria: Urinary Podocalyxin as a Window into the Histopathological Spectrum of Lupus Nephritis - An Editorial

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Lupus nephritis (LN) remains one of the most serious organ manifestations of systemic lupus erythematosus (SLE), contributing substantially to morbidity, progressive renal impairment and premature mortality. Despite significant advances in immunosuppressive therapy, early recognition and accurate assessment of renal involvement remain major clinical challenges. The clinical presentation of LN is remarkably heterogeneous, ranging from asymptomatic urinary abnormalities to rapidly progressive glomerulonephritis and nephrotic syndrome. This diversity reflects the underlying histopathological spectrum of the disease, which is conventionally classified into six classes according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification[1].

Renal biopsy remains the gold standard for establishing the diagnosis, determining the histological class, and assessing the activity and chronicity of renal lesions. However, kidney biopsy is an invasive procedure, associated with potential complications, and cannot be performed repeatedly at every stage of disease monitoring. Moreover, conventional clinical parameters, particularly proteinuria, serum creatinine and urinary sediment abnormalities, do not always accurately reflect the underlying histological activity. Consequently, identifying reliable, non-invasive biomarkers that can predict renal histopathology has become an important area of research in contemporary nephrology[2].

Urinary podocalyxin: A promising marker of podocyte injury

Podocalyxin is a highly sialylated transmembrane glycoprotein expressed predominantly on the apical surface of glomerular podocytes. It plays an essential role in maintaining podocyte architecture, cellular integrity and the filtration barrier. Podocyte injury, detachment and disruption of the glomerular filtration barrier may result in increased urinary excretion of podocalyxin. Therefore, urinary podocalyxin (uPCX) has attracted attention as a potential non-invasive biomarker of glomerular injury, particularly in diseases involving podocyte damage.

The biological relevance of this marker in LN is supported by previous investigations. Ikuma and colleagues demonstrated that urinary podocyte numbers and urinary podocalyxin levels were significantly associated with histological features of LN. Their study suggested that urinary podocyte measurements were particularly informative in proliferative nephritis, whereas urinary podocalyxin was elevated in both proliferative and membranous forms. The combination of these markers provided additional information regarding histological involvement[3]. Another study involving Egyptian patients with LN demonstrated significantly increased urinary podocalyxin levels and a strong positive correlation with proteinuria and disease activity, further supporting its potential clinical utility[4].

Twenty-four-hour proteinuria: An established but imperfect indicator

Twenty-four-hour urinary protein excretion remains an important conventional parameter for evaluating the severity of renal involvement in LN. The magnitude of proteinuria reflects disruption of the glomerular filtration barrier and is clinically relevant for assessing disease presentation, treatment response and long-term renal outcomes. Higher levels of proteinuria are frequently encountered in proliferative and membranous forms of LN, although the relationship between protein excretion and histological severity is not necessarily linear.

An important limitation is that proteinuria represents the functional consequence of glomerular injury rather than a direct measurement of histological inflammation. Patients with substantial proteinuria may have predominantly chronic glomerular damage, while some patients with active proliferative nephritis may demonstrate relatively modest protein excretion. Similarly, membranous LN (class V) may produce nephrotic-range proteinuria without the same pattern of inflammatory activity observed in class III or IV disease. Thus, proteinuria alone cannot reliably distinguish between histological classes or adequately characterize renal inflammatory activity[2,5].

Combining urinary podocalyxin and proteinuria: A complementary approach

The association between urinary podocalyxin and 24-hour proteinuria offers an interesting opportunity to improve the non-invasive assessment of LN. These two parameters represent different but complementary aspects of glomerular pathology. While proteinuria reflects impaired filtration-barrier function, urinary podocalyxin may provide additional information about podocyte injury and structural disruption.

Their combined assessment may therefore help distinguish patients with different patterns of glomerular involvement. A higher urinary podocalyxin level, particularly when accompanied by significant proteinuria, may indicate substantial podocyte injury and glomerular damage. Conversely, discordance between the two parameters may provide useful biological information, suggesting that protein leakage and podocyte injury do not necessarily progress in parallel.

The potential clinical importance of this relationship lies in its association with histological classification. Proliferative lesions, particularly classes III and IV, are characterized by inflammatory glomerular injury, whereas class V predominantly involves subepithelial immune-complex deposition and glomerular basement membrane alterations. Podocyte injury may occur in both patterns, although its extent and mechanisms may differ. Consequently, evaluating urinary podocalyxin alongside proteinuria may provide a more comprehensive picture of renal involvement than either parameter alone[3,4].

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Received: 15 November 2026
Published Online: 26 November 2026
DOI: 10.5281/zenodo.24550616

Volume: 10, Number: 4, Page: 1318-1319
e-ISSN: 2789-5912
ISSN: 2617-0817

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Clinical implications and future directions

The investigation of urinary podocalyxin and 24-hour proteinuria in relation to LN histological classes is therefore clinically relevant. Such an approach may contribute to identifying patients with significant renal involvement, improving risk stratification and potentially supporting decisions regarding the need for renal biopsy. Nevertheless, these biomarkers should currently be regarded as complementary investigative tools rather than substitutes for histopathological examination.

Several methodological considerations deserve attention. Urinary podocalyxin measurements may vary according to assay methodology, sample handling, urinary concentration and the timing of sample collection. Normalization against urinary creatinine may improve comparability between samples. Furthermore, the association of these biomarkers with histological class should ideally be evaluated alongside the NIH activity and chronicity indices, renal function, serum albumin, urinary sediment and immunological markers. Prospective studies with larger populations and serial measurements are necessary to establish diagnostic accuracy, sensitivity, specificity and predictive values.

The 2024 KDIGO Clinical Practice Guideline emphasizes that clinical findings do not always correspond to the severity of renal histopathology and reinforces the importance of kidney biopsy in guiding treatment decisions[2]. This highlights the need for additional non-invasive biomarkers that can complement conventional clinical assessment.

Ultimately, the association of urinary podocalyxin and 24-hour proteinuria with histological classes of LN represents a promising area of translational nephrology. By integrating a marker of podocyte injury with an established measure of glomerular dysfunction, clinicians and researchers may gain a better understanding of the relationship between clinical manifestations and renal pathology. The future challenge is to establish whether this combination can provide sufficiently reliable information to improve clinical decision-making, monitor disease activity and predict renal outcomes. The goal should not simply be to identify another urinary biomarker, but to move towards a more precise, non-invasive and biologically informed approach to the management of lupus nephritis.

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