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Editorial

Early Detection of a Kidney Disease – Where do we Stand Today?

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Abstract

Chronic kidney disease (CKD) represents a major global health burden, with early detection of glomerular injury remaining a persistent clinical challenge. The urinary albumin-to-creatinine ratio (UACR), although widely accepted as a diagnostic and prognostic marker, primarily reflects established structural damage. Urinary nephrin, a podocyte-specific transmembrane protein integral to the slit diaphragm, has emerged as a sensitive and mechanistically precise indicator of early podocyte injury. Detection of nephrinuria precedes the onset of albuminuria and correlates with disease activity across diabetic nephropathy, preeclampsia, and immune-mediated glomerulopathies. Comparative evaluation suggests that nephrinuria provides superior temporal and pathophysiological insight into glomerular injury. Incorporation of urinary nephrin into clinical practice, alongside UACR, holds potential to refine early CKD diagnostics and to facilitate a transition toward precision-based renal risk assessment and timely therapeutic intervention.

Keywords: chronic kidney disease, urinary albumin-to-creatinine ratio, urinary nephrin

Chronic kidney disease (CKD) affects more than 800 million individuals worldwide and continues to rise in prevalence and mortality [1]. Despite major advances in therapeutics and disease management, early detection of glomerular injury remains suboptimal. For decades, the urinary albumin-to-creatinine ratio (UACR) has been the cornerstone for the noninvasive detection of kidney injury, particularly in diabetic kidney disease (DKD). Yet, UACR elevation represents a relatively late event in the course of glomerular pathology, typically reflecting established damage rather than its incipient stages [2]. In the evolving landscape of renal biomarkers, urinary nephrin, a podocyte-specific protein, has emerged as a promising early indicator of glomerular injury. Its detection in urine (nephrinuria) provides direct evidence of podocyte stress or detachment, offering a mechanistically grounded complement, and potentially, a precursor to traditional albuminuria-based diagnostics.

The podocyte and the glomerular filtration barrier

The glomerular filtration barrier (GFB) is a tri-layered structure composed of fenestrated endothelium, the glomerular basement membrane (GBM), and the podocyte slit diaphragm. Its function relies on the structural and molecular integrity of podocytes, highly differentiated epithelial cells that maintain filtration selectivity through their interdigitating foot processes. Podocytes are dynamic cells with specialized junctional complexes, where nephrin, a transmembrane protein encoded by *NPHS1,* serves as both, a structural scaffold and a signaling molecule regulating cytoskeletal organization and cell survival. Experimental models demonstrate that nephrin loss leads to effacement of foot processes, disruption of slit diaphragm continuity, and consequent proteinuria. Damage to podocytes, whether mechanical, metabolic, or inflammatory, represents an early and irreversible event in the progression of glomerular disease. The shedding or leakage of nephrin into the urine thus provides a direct molecular signature of podocyte injury, preceding the onset of albuminuria and measurable renal function decline [3,4].

Urinary Nephrin: The sentinel biomarker of glomerular injury

Under physiological conditions, nephrin is retained within the slit diaphragm and absent from urine. Its appearance in urine indicates podocyte injury or detachment. Detection methods include enzyme-linked immunosorbent assays (ELISA), Western blotting, and, more recently, high-sensitivity chemiluminescent immunoassays [4]. Several clinical studies have established the role of urinary nephrin in diverse kidney disorders. In both type 1 and type 2 diabetes mellitus, nephrinuria occurs in normoalbuminuric patients, preceding microalbuminuria by months or years [5]. Similar findings have been reported in preeclampsia, where po-

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docyte injury drives proteinuria and in immune-mediated glomerulopathies such as lupus nephritis, minimal change disease, and focal segmental glomerulosclerosis (FSGS) and hypertensive nephropathy [3,6,7]. Notably, nephrin levels often correlate with the disease activity and histological indices of glomerular damage, underscoring its potential for monitoring treatment response and disease remission. In this context, urinary nephrin is more than a marker, i.e. it's a window into podocyte biology, capturing early events that precede irreversible structural loss.

UACR: The established but imperfect standard

In the meanwhile, UACR remains a practical and clinically validated tool for detecting glomerular injury. It is simple, reproducible, and cost-effective, correlating strongly with long-term renal and cardiovascular outcomes. However, albuminuria reflects the net effect of multiple pathological processes endothelial dysfunction, GBM thickening, and podocyte injury, without distinguishing among them [8]. Furthermore, UACR is influenced by numerous nonpathological factors, including physical activity, posture, infection, fever, blood pressure, and glycemic fluctuations. This variability limits its precision for detecting subclinical or transient glomerular injury. In early diabetic nephropathy, for instance, significant podocyte loss and nephrin downregulation can occur despite normal UACR values [9, 10]. Thus, while UACR remains the clinical "gold standard", it may be more accurate to regard it as a lagging indicator, one that detects damage only after the glomerular barrier has already been structurally compromised.

Comparative evaluation: urinary nephrin vs. UACR

For better overview urinary nephrin and UACR characteristics have been presented in table 1.

Table 1. Comparative characteristics of urinary nephrin and UACR in glomerular injury detection

Table Feature	Urinary Nephrin	UACR
Source	Podocyte-specific slit diaphragm protein	Plasma protein filtered across the GFB
Pathophysiological insight	Direct marker of podocyte injury	Indirect marker of barrier dysfunction
Temporal appearance	Appears before albuminuria	Elevated in established injury
Specificity	High for podocyte damage	Nonspecific for the cause of injury
Measurement	Immunoassay (ELISA, Western blot)	Routine immunoturbidimetric methods
Clinical use	Research and emerging biomarker	Established diagnostic and prognostic tool

Clinical and research perspectives

Integrating urinary nephrin into clinical workflows could reshape CKD risk assessment and therapeutic monitoring. Its podocyte specificity provides an avenue for assessing early responses to nephroprotective interventions, particularly sodium-glucose cotransporter 2 (SGLT2) inhibitors, renin–angiotensin system blockers, and emerging podocyte-targeted therapies [10,11]. However, challenges remain on how nephrin could be transitioned from a research biomarker towards a routine diagnostic tool. These include the need for assay harmonization, standardized reference ranges across populations, cost-effectiveness analysis, and clarification of biological variability. Expectedly, large-scale longitudinal studies are essential to validate nephrin's predictive performance for CKD onset and progression. Moreover, combining nephrin with UACR or other podocyte-derived biomarkers such as podocalyxin, synaptopodin, or urinary exosomal mRNA could yield composite indices with superior sensitivity and specificity. Such multimarker strategies align with the emerging precision medicine paradigm, where molecular profiles guide individualized risk stratification and early intervention.

In conclusion, urinary nephrin represents a mechanistically specific and temporally early biomarker of podocyte injury, capturing glomerular pathology at a stage when intervention may still be reversible. While UACR continues to serve as a cornerstone of CKD screening and prognosis, it is ultimately a downstream marker reflecting established injury. The complementary use of both biomarkers, nephrin for detection and UACR for monitoring, may offer a more complete picture of glomerular health. As nephrology moves toward earlier and more personalized intervention, urinary nephrin holds promise not merely as a diagnostic innovation but as a redefinition of how clinicians conceptualize kidney disease progression from a reactive detection to a proactive preservation of renal integrity. Future research should focus on standardization of the nephrin measurement, establishing normative data, and exploring its predictive capacity for therapeutic response. The ability to identify glomerular injury before an incipient albuminuria could fundamentally alter the trajectory of CKD management, shifting the paradigm from a late recognition to the genuine prevention.

Conflict of interest statement. None declared.

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