Editorial

Kidney Injury Molecule-1 (KIM-1): Biomarker of Tubular Injury and Predictor of Kidney Disease Progression

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To date, the definition and classification of Chronic Kidney Disease (CKD) remain based on two primary criteria: a decline in the estimated Glomerular Filtration Rate (eGFR) derived from serum creatinine, and increased urinary albumin excretion (urine albumin-to-creatinine ratio/ UACR). Serum creatinine is a biomarker of filtration function whose levels rise only after significant renal function loss—when up to 50% of the kidney has sustained irreversible damage.[1] In other words, a CKD diagnosis is established only after extensive tubulointerstitial fibrosis and glomerulosclerosis have already occurred (the "blind spot" phenomenon). Interstitial fibrosis and tubular atrophy (IFTA) serve as the histological markers with the strongest predictive value for progressive loss of kidney function, regardless of the disease's primary etiology.[2] This situation leads to delayed early intervention in both Acute Kidney Injury (AKI) and CKD. "As eGFR is dipping, the clock is ticking."

Consequently, there is a need to shift focus toward the tubulointerstitial compartment, particularly the proximal tubule, a highly metabolically active structure that is consequently very vulnerable to ischemia, toxins, and oxidative stress. Among the various tubular biomarkers, Kidney Injury Molecule-1 (KIM-1) has emerged as the most promising diagnostic and prognostic marker.[3]

KIM-1 in AKI and CKD

KIM-1, also known as Hepatitis A virus cellular receptor-1 (HAVCR-1) or T-cell immunoglobulin and mucin-domain containing-1 (TIM-1), is a type I transmembrane glycoprotein that is virtually unexpressed in proximal tubule cells under healthy renal conditions. However, following injury caused by ischemia or nephrotoxicity, KIM-1 gene expression increases rapidly.[4] Urinary KIM-1 levels correlate strongly with tissue levels and, consequently, with the extent of renal tissue damage. KIM-1 not only serves as an early biomarker for AKI but also holds the potential to predict long-term renal outcomes.[5]

- **In Acute Kidney Injury (AKI):** Detection of uKIM-1 (urine) and pKIM-1 (plasma) offers diagnostic performance for early detection that is far superior to serum creatinine. Recent meta-analyses indicate that uKIM-1 and pKIM-1 exhibit high sensitivity and specificity (AUC ~0.81) for detecting AKI in post-cardiac surgery patients or in cases involving ischemia or drug-induced kidney injury.[6]
- **In Chronic Kidney Disease (CKD):** In CKD, elevated KIM-1 levels reflect ongoing active tubular injury or subclinical tubular stress that goes undetected by

Cite this as:
Samsu N. Kidney Injury Molecule-1 (KIM-1): Biomarker of Tubular Injury and Predictor of Kidney Disease Progression. InaKidney. 2026;3(2):207-209. doi:10.32867/inakidney.v3i2.280

eGFR. KIM-1 provides a true picture of the burden of interstitial damage in diabetic nephropathy, hypertensive nephropathy, and glomerulonephritis.[7]

However, in contrast to previous studies, in this edition of InaKidney, Sari et al. demonstrate that urinary KIM-1 levels have low diagnostic value for AKI in patients with sepsis.[8] This discrepancy in results may indicate pathophysiological differences dependent on the underlying cause of the AKI. Indeed, sepsis-associated AKI is a complex and heterogeneous condition involving various mechanisms, such as microcirculatory dysfunction, systemic inflammatory responses, and cellular metabolic disturbances.[9] Another potential influencing factor is the timing of sample collection relative to the onset of injury; urinary KIM-1 levels can detect AKI in sepsis patients as early as two hours post-injury.[10] Limitations in study design may also play a role, necessitating more careful consideration and rigorous examination.[7]

KIM-1: A Predictor of Progression and Adverse Renal Outcomes

The most crucial role of KIM-1, distinguishing it from classic biomarkers, is its ability to predict long-term renal outcomes. Persistent elevation of KIM-1 expression following AKI is associated with disease progression and contributes to inflammatory damage and interstitial fibrosis in the kidney through extracellular matrix (ECM) deposition and epithelial-to-mesenchymal transition (EMT).[11,12]

Long-term clinical cohort studies confirm that baseline KIM-1 levels (in both plasma and urine) independently correlate with rapid eGFR decline and the risk of progression to end-stage renal disease (ESRD) and cardiovascular mortality in patients with diabetic kidney disease (DKD).[13] Thus, KIM-1 serves as a potent biomarker for the non-invasive assessment of renal tubular injury and disease activity during the progression of CKD, as well as for monitoring therapeutic response. By monitoring KIM-1 levels, clinicians can assess the severity of kidney injury, identify patients at risk of developing CKD, and implement timely interventions.[7]

Integration of Tubular Injury and Glomerular Filtration Biomarkers: Subclinical CKD and Its Implications

This new paradigm integrates two complementary biological compartments of the kidney: biomarkers of proximal tubular injury and biomarkers of precise or early glomerular filtration. This shift drives a proposal to align the classification of CKD using a complementary matrix (function versus structure). Patients with normal eGFR but positive biomarkers for tubular injury (e.g., KIM-1) are categorized as having subclinical CKD, molecular CKD, or pre-CKD. Patients with eGFR < 60 ml/min and positive biomarkers are classified as having progressive CKD (characterized by ongoing tissue damage), whereas those with negative biomarkers are classified as having inactive or stable CKD (characterized by the loss of nephron mass).

However, the utility of KIM-1 extends beyond mere risk stratification; the biomarker also serves as a surrogate marker to assess the efficacy of novel nephroprotective therapies. Consequently, patients with subclinical CKD can receive optimal pharmacological interventions, such as SGLT2 inhibitors, non-steroidal mineralocorticoid receptor antagonists (nsMRAs), or anti-inflammatory/anti-fibrotic agents—to prevent permanent loss of nephron mass.

Shifting the paradigm of CKD management through the use of early biomarkers for tubular injury and glomerular filtration represents an urgent clinical need. Integrating KIM-1 and other tubular biomarkers with early glomerular filtration biomarkers into daily clinical practice enables nephrologists to transition from reactive diagnosis to proactive, precision medical management, moving from an era of merely "slowing the decline of kidney function" to one of "preventing organ failure at an early stage."

Declarations

Competing interest

The author declares no conflict of interest.

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