



Beyond Serum Creatinine: Emerging Biomarkers for Early Detection of Progressive Kidney Injury

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Mini Review

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Abstract

Serum creatinine remains one of the most widely used indicators of kidney function, but its limitations have become increasingly recognized. Creatinine concentrations may remain within apparently acceptable ranges despite substantial structural kidney injury and can be influenced by muscle mass, age, sex, diet, hydration, and medication use. This creates a diagnostic gap in which kidney damage may progress before conventional functional measurements become abnormal. Emerging biomarkers offer the possibility of identifying renal injury earlier and providing information about specific pathological processes. Biomarkers such as cystatin C, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, tissue inhibitor of metalloproteinase-2, insulin-like growth factor-binding protein 7, and urinary albumin provide complementary information regarding filtration, tubular injury, cellular stress, and glomerular damage. In addition, newer approaches involving metabolomics, proteomics, transcriptomics, and multi-biomarker panels may improve prediction of progressive kidney disease. This mini-review discusses the limitations of serum creatinine and evaluates emerging biomarkers that may contribute to earlier detection and risk stratification of progressive kidney injury.

Keywords: Kidney Injury; Serum Creatinine; Biomarkers; Cystatin C; NGAL; KIM-1; Renal Disease; Chronic Kidney Disease; Early Detection

Introduction

Early identification of kidney injury is essential because renal damage can progress silently for prolonged periods. Chronic kidney disease (CKD) frequently develops without obvious symptoms until substantial functional impairment has occurred. Serum creatinine and estimated glomerular filtration rate (eGFR) remain central components of routine kidney assessment, but they primarily reflect filtration rather than direct structural injury [1].

A significant increase in serum creatinine may occur only after considerable reduction in kidney filtration capacity. Consequently, a patient may have ongoing tubular or glomerular injury while serum creatinine remains relatively stable. This limitation has encouraged researchers to search for biomarkers capable of identifying kidney damage before substantial functional decline becomes evident [2].

The development of sensitive biomarkers may allow clinicians to distinguish between reduced filtration, active

tubular injury, inflammation, and cellular stress. Such information could support earlier intervention and more accurate prediction of disease progression.

Limitations of Serum Creatinine

Serum creatinine is inexpensive, widely available, and clinically useful, but it is not a perfect marker of kidney injury. Creatinine production depends substantially on muscle mass and is therefore affected by age, sex, body composition, nutritional status, and physical activity. Changes in hydration and medications can also influence serum creatinine concentrations. More importantly, serum creatinine generally increases after a significant reduction in glomerular filtration has already occurred. Another limitation is that creatinine reflects kidney function rather than necessarily indicating the location or mechanism of injury. Two patients with similar creatinine levels may have very different underlying renal pathologies.

These limitations have stimulated interest in biomarkers that respond more rapidly to renal injury and provide information about specific biological pathways.

Cystatin C

Cystatin C is an endogenous low-molecular-weight protein produced by most nucleated cells. It is freely filtered by the glomerulus and is subsequently reabsorbed and metabolized within the proximal tubule.

Compared with creatinine, cystatin C is less dependent on muscle mass and may provide a more reliable estimate of filtration in selected populations. Combining creatinine and cystatin C can improve estimation of kidney function in situations where creatinine alone may be misleading. However, cystatin C is also influenced by factors unrelated to filtration, including inflammation, thyroid function, and certain medications. Therefore, it is best considered a complementary marker rather than a universal replacement for creatinine [3].

Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is one of the most extensively studied biomarkers of acute tubular injury. It can be detected in plasma and urine and may rise earlier than serum creatinine following certain forms of kidney injury. NGAL is associated particularly with tubular stress and injury. Its potential value has been investigated in acute kidney injury, postoperative patients, critical illness, and other high-risk settings. Despite promising findings, NGAL is not entirely kidney-specific. Infection, systemic

inflammation, and other conditions can influence NGAL concentrations. Differences in assay methods and patient populations have also contributed to variable diagnostic performance [4].

Kidney Injury Molecule-1

Kidney injury molecule-1 (KIM-1) is a transmembrane protein that becomes markedly expressed in injured proximal tubular epithelial cells. Urinary KIM-1 has therefore attracted attention as a marker of tubular injury. Unlike serum creatinine, which mainly reflects filtration, KIM-1 may provide information about structural tubular damage. This makes it potentially valuable for identifying injury at an earlier stage. KIM-1 has been studied in drug-induced nephrotoxicity, ischemic injury, and various renal diseases. However, further validation is required before it can be routinely incorporated into everyday CKD screening.

TIMP-2 and IGFBP7

Tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) represent biomarkers associated with cellular stress and cell-cycle arrest. The urinary combination of TIMP-2 and IGFBP7 has been investigated particularly for predicting the development of moderate to severe acute kidney injury. These biomarkers may identify tubular epithelial cells experiencing stress before irreversible injury becomes apparent. Their importance lies in the concept that early kidney injury may involve cellular stress and adaptive responses before measurable changes in filtration occur. Nevertheless, their principal clinical applications currently remain concentrated in acute kidney injury risk assessment rather than routine population screening for CKD [5].

Albuminuria and Emerging Protein Biomarkers

Urinary albumin remains an important indicator of glomerular barrier dysfunction. Increased albumin excretion is associated with kidney disease progression and cardiovascular risk, even when eGFR is relatively preserved. Beyond albumin, proteomic technologies have identified numerous urinary and circulating proteins potentially associated with inflammation, fibrosis, tubular dysfunction, and extracellular matrix remodeling. Multi-protein signatures may eventually provide more comprehensive information than individual biomarkers. The advantage of biomarker panels is that kidney disease is biologically heterogeneous. A combination of markers may therefore identify different aspects of injury more effectively than any single molecule [6].

Omics-Based Biomarkers

Advances in proteomics, metabolomics, lipidomics, and transcriptomics are expanding the search for kidney disease biomarkers. These approaches can detect complex molecular patterns associated with renal injury and disease progression. Metabolomic studies may identify changes in small molecules produced or modified during impaired renal metabolism. Transcriptomic approaches can reveal altered gene-expression patterns associated with inflammation, fibrosis, and cellular stress. Although these technologies remain largely research-oriented, they may eventually support personalized renal risk assessment. Their translation into clinical practice will require standardized methodologies, large validation cohorts, and cost-effective testing platforms [7].

Clinical Applications and Challenges

Emerging biomarkers could potentially support earlier detection of kidney injury in patients with diabetes, hypertension, exposure to nephrotoxic drugs, critical illness, or other risk factors. However, biomarker implementation faces several challenges. A useful biomarker must demonstrate reproducibility, specificity, clinical relevance, and improvement over existing tests. Biological variability, differences between laboratory assays, and the influence of comorbid conditions can complicate interpretation. Importantly, detecting an abnormal biomarker is only clinically valuable if it leads to an effective intervention. Future research should therefore connect biomarker detection with treatment strategies and patient outcomes.

Future Perspectives

The future of kidney injury detection is likely to involve combinations of conventional and emerging biomarkers rather than replacement of serum creatinine by a single new test. Artificial intelligence may help integrate biomarker concentrations with eGFR, albuminuria, imaging, medications, clinical history, and longitudinal patient data. Such models could potentially identify individuals at high risk of progressive renal injury before conventional markers demonstrate substantial deterioration. Point-of-care and minimally invasive testing may further increase the accessibility of biomarker-based kidney monitoring.

Conclusion

Serum creatinine remains fundamental to clinical nephrology, but its limitations highlight the need for

complementary indicators of renal injury. Cystatin C, NGAL, KIM-1, TIMP-2, IGFBP7, albuminuria, and emerging omics-derived signatures provide information that may extend beyond conventional filtration measurements. The greatest future potential may lie in integrated biomarker panels capable of distinguishing early structural injury, cellular stress, inflammation, and progressive fibrosis. Before widespread clinical adoption, however, these biomarkers require rigorous validation and demonstration of meaningful benefits for patient management. Moving beyond serum creatinine could ultimately enable earlier recognition of kidney injury and create new opportunities for preventing irreversible renal decline.

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