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EDITORIALS

Kidney Injury Molecule 1: In Search of Biomarkers of Chronic Tubulointerstitial Damage and Disease Progression

Related Article, p. 16

Chronic kidney disease (CKD) requiring renal replacement therapy is increasing worldwide and is emerging as a major global health threat.[1] CKD is characterized by progressive decline in kidney function associated with excess cardiovascular morbidity and mortality. The evidence in animal models that angiotensin-converting enzyme (ACE) inhibitors, in addition to lowering blood pressure, have selective antiproteinuric and renoprotective properties opened a new era for the treatment of patients with CKD. This dictated the current and consolidated therapeutic approach for proteinuric chronic nephropathies based on blockade of the renin-angiotensin system with ACE inhibitors and/or angiotensin II receptor antagonists, which limit proteinuria and reduce kidney function decline and risk of end-stage renal disease more effectively than other antihypertensive treatments.[2,3]

Early detection of CKD may translate into more favorable outcomes, since renoprotective treatments can be implemented in a more timely manner. This implies the need for simple, noninvasive, and specific biomarkers that would serve to monitor the pathophysiologic processes occurring within the kidney. Serum creatinine is widely used in clinical practice to detect CKD and its progression. Nevertheless, most physicians know the limitations of serum creatinine for the detection of early CKD, which are related to patient-dependent factors such as sex, race, age, and muscular mass, as well as standardization of laboratory measurement of the biomarker.[4] Due to these shortcomings, one can monitor kidney function by estimating glomerular filtration rate (GFR) with creatinine-based formulas that account for anthropometrical and biological variation.[5] However, none of the available prediction equations allows a rigorous assessment of kidney function in healthy individuals and in CKD patients.[6] There is substantial imprecision in estimated GFR compared with its measured values when the measured value is 60 mL/min/1.73 m^2 or greater.[7,8] Thus, prediction equations may be misleading in estimating GFR and are probably not ready for early identification of CKD and monitoring of disease progression.

In line with experimental observations is the evidence that in humans with nephropathy, more severe and persistent proteinuria means more rapid progression of disease.[9] A meta-analysis also confirmed that proteinuria strongly correlated with kidney disease progression, and treatments that fail to reduce proteinuria are unlikely to exert significant renoprotection.[10] However, proteinuria is currently not recognized by the US Food and Drug Administration as a surrogate biomarker in CKD and an outcome for CKD treatment. Moreover, proteinuria may not be present in all forms of CKD, such as tubulointerstitial diseases. Thus, novel biomarkers that would better reflect renal injury and predict disease

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progression and response to treatment are currently being explored.

Plasma or urine markers including neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, asymmetric dimethylarginine (ADMA), and liver-type fatty acid–binding protein (L-FABP) are recognized as the most promising potential biomarkers for the early identification and monitoring of acute kidney injury and possibly CKD.[11] Recently, the interest in biomarkers has been focused on kidney injury molecule (KIM)-1, a type I transmembrane glycoprotein with an ectodomain containing an Ig-like domain and a mucin domain, which was discovered in renal tubular epithelial cells.[12] In healthy kidneys, KIM-1 is undetectable, but this protein is abundantly expressed in proximal tubular cells after ischemic and nephrotoxic injury.[12,13] In rodents and in humans, the ischemic or toxic insults to the kidney cleave the KIM-1 ectodomain, which is quantified in the urine as a biomarker for acute kidney injury.[14] Recent evidence documented that KIM-1 is also upregulated in tubules of patients with various chronic proteinuric kidney diseases, such as focal glomerulosclerosis, IgA nephropathy, membranoproliferative glomerulonephritis, and diabetic nephropathy, and is associated with renal fibrosis and inflammation.[15] Since proteinuria has been proposed to cause tubular injury and interstitial fibrosis,[16] urinary KIM-1 excretion could become a noninvasive biomarker of chronic tubulointerstitial damage contributing to kidney disease progression and could indicate when target renoprotective therapies are needed.

In this issue of the *American Journal of Kidney Diseases*, by a post hoc analysis of a randomized, double-blind, placebo-controlled crossover trial, Waanders et al[17] tested the hypothesis that reduction in proteinuria by therapeutic interventions is associated with decreased urinary KIM-1. In 34 nondiabetic, proteinuric patients, the authors found that the urinary excretion of KIM-1 was significantly reduced by antiproteinuric regimens including losartan alone or in combination with hydrochlorothiazide. Reduction in urinary KIM-1 did parallel the decline in proteinuria, but not in blood pressure. On the contrary, the reduction in urinary *N*-acetyl-β-D-glucosaminidase (NAG)—another biomarker of acute tubular injury—was not closely related to proteinuria. The authors conclude that lowering urinary KIM-1 reflects amelioration of proteinuria-associated tubulointerstitial damage. These observations extend to humans previous experimental evidence in uninephrectomized rats with overload proteinuria, a model of tubulointerstitial damage caused by repeated intraperitoneal injections of bovine serum albumin.[18] In this model, KIM-1 expression was limited to areas with inflammation, fibrosis, and tubular damage, and urinary KIM-1 level was significantly greater in animals with overload proteinuria than controls. Although the clinical findings suggest that urinary KIM-1 may serve as a marker of proteinuria-induced kidney damage, there is no proof that the reduction of KIM-1 in the urine is indeed associated with improvement of tubulointerstitial injury. The change in urinary KIM-1 could simply reflect the direct effect of lowering proteinuria on the tubular expression and shedding of the glycoprotein in the urine. Many if not most forms of progressive, noncystic kidney disease are glomerular in origin, and yet, the intensity of accompanying or evolving injury of the tubulointerstitial compartment, rather than the extent of glomerular changes, is what predicts overall decline in kidney function.[19] Given this functional/structural relationship and KIM-1 being considered a biomarker of tubular damage, the observed reduction in urinary KIM-1 should be associated with improvement of kidney function. In fact, also considering the known limitations involved in measuring kidney function with creatinine clearance, kidney function did not change during the 6-week observation period despite significant decline of the daily excretion rate of KIM-1.

Thus, at the present time, KIM-1 can merely be added to the long list of promising novel biomarkers of CKD, but more investigations are required before translation to clinical practice. It will be important in future studies to validate the sensitivity and specificity of KIM-1 as a biomarker of chronic tubulointerstitial injury in clinical samples from large cohorts and from multiple types of CKD. Moreover, further studies should elucidate the predictive value of shed KIM-1 in the urine for disease progression, and more important, as a surrogate marker for early detection of chronic kidney injury. Such studies will be facilitated by first assessing the reproducibility of urinary KIM-1 measurements as well as by defining the best way to collect urine samples for this biomarker by comparing different approaches (eg, spot morning, random sampling, overnight, or 24-hour collections). More importantly, there is a need to standardize and validate clinical assays of urinary KIM-1 ectodomain, which would allow reproducible measurements of the biomarker across different laboratories.

Should cleaved KIM-1 be able to be reproducibly measured in the urine and used as a biomarker of ongoing tubular kidney damage, it would be useful to explore whether monitoring the urinary levels of this glycoprotein can be a valid, noninvasive tool to assess in vivo the tissue repairing properties of current renoprotective therapies. Indeed, intriguing recent experimental[20] and clinical[21,22] observations have shown that regression of glomerular structural changes and remodelling of the glomerular architecture is achievable with renin-angiotensin system blockade. Moreover, cell therapy with exogenous mesenchymal stem cells—as recently documented in experimental models of acute tubular injury[23]—would be a promising future alternative to repair chronic glomerular and tubulointerstitial injury and promote renoprotection.

In the meantime, the search for early, predictive, and noninvasive biomarkers of CKD should continue, and the new "omics" techniques—transcriptomics, proteomics, and metabolomics, which are expected to provide more insight into the pathophysiology of human CKD—will be rewarding for this task.

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