The Promise of Tubule Biomarkers in Kidney Disease: A Review

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For over 70 years, serum creatinine and its derivative equations to estimate glomerular filtration rate (eGFR) have been the primary index for detection and monitoring of kidney disease. Tubulointerstitial damage and fibrosis are highly prognostic for subsequent kidney failure in biopsy studies, yet this pathology is invisible to the clinician in the absence of a biopsy. Recent discovery of biomarkers that reflect distinct aspects of kidney tubule disease have led to investigations of whether these markers can provide additional information on risk of chronic kidney disease (CKD) progression and associated adverse clinical end points, above and beyond estimated glomerular filtration rate and albuminuria. These biomarkers can be loosely grouped into those that mark tubule cell injury (eg, kidney injury molecule 1, monocyte chemoattractant protein 1) and those that mark tubule cell dysfunction (eg, α1-microglobulin, uromodulin). These kidney tubule biomarkers provide new opportunities to monitor response to therapeutics used to treat CKD patients. In this review, we describe results from some unique contributions in this area and discuss the current challenges and requirements in the field to bring these markers to clinical practice. We advocate for a broader assessment of kidney health that moves beyond a focus on the glomerulus, and we highlight how such tools can improve diagnostic accuracy and earlier assessment of therapeutic efficacy or harm in CKD patients.

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However, the severity of tubular atrophy and fibrosis on biopsy had no association with iothalamate-measured GFR accounting for age. Therefore, despite its prognostic importance, tubular disease cannot be reliably detected by the standard clinical measures of glomerular health (eGFR and UACR) and is invisible to the clinician except in the rare instances when biopsies are obtained.

In the past decade, investigators began exploring individual biomarkers that could give insights into unique aspects of kidney tubule health. Similar to the clinically available biomarkers of glomerular health (eGFR and UACR), these newer biomarkers could be characterized into 2 broad groups reflecting aspects of tubule injury and tubule dysfunction. Evaluating individual biomarkers, investigators consistently observed signals with clinically important outcomes including CKD progression, CVD, and mortality that were evident even after accounting for eGFR, UACR, and traditional CKD risk factors. These studies initially evaluated one tubule marker at a time; more recently, however, we and others are exploring the paradigm that we need a global assessment of kidney health using multiple measures concurrently to maximize the diagnosis, treatment, and prevention of CKD (Fig 1). This might improve risk assessment not only for kidney outcomes but also related end points, including CVD and heart failure. Moreover, we hypothesized that these markers could provide new tools to monitor CKD therapy. In this review, we summarize how these hypotheses have been advanced over the past decade and what the challenges are in this area of research. Finally, we propose next steps that will be required to make these measurements available and useful to the practicing clinician.
Kidney tubule biomarkers can be generally classified as either reflecting the processes of direct tissue injury and repair in the tubulointerstitium or as measuring unique functions that are performed by kidney tubule cells. Although some require blood measurements, most can be measured in urine. The kidney damage biomarkers were initially pursued as early indicators of acute kidney injury (AKI) in hospitalized patients, but it has been subsequently demonstrated that they can be measured reliably in the ambulatory setting.

Collectively, this initial group of biomarkers quantifies the severity of tubule cell injury (eg, kidney injury marker 1 [KIM-1]), the capacity for the tubules to repair themselves from injury (eg, epidermal growth factor [EGF]), and the extent of inflammation and fibrotic activity (eg, monocyte chemoattractant protein 1 [MCP-1]) within the tubulointerstitial space. However, the exact pathological correspondence of each biomarker has yet to be fully elucidated. Unique biomarkers that are fit for the purpose are also emerging—for example, evaluating unique cytokines to differentiate the inflammatory response in acute interstitial nephritis (AIN) versus acute tubule necrosis (ATN).

The functions of the kidney tubules are broad because they are critical to homeostatic control. For example, serum sodium, potassium, and calcium concentrations largely reflect aspects of the kidney tubules’ ability to regulate each of these electrolytes in response to unique hormone control. Additional functions of the kidney tubules are not routinely measured clinically but are measurable by research assays. These include assessment of the proximal tubules’ capacity to reabsorb filtered small-molecular-weight proteins (eg, α₁-microglobulin [A1M]), the capacity of the proximal tubule to secrete endogenous metabolites (eg, hippurate) or exogenous compounds (eg, furosemide), the production of proteins required to maintain impermeability of water to distal tubule segments and to protect against infection (eg, uromodulin), and ammonium production as a marker of the kidney tubules’ ability to excrete acid.

These tubule biomarkers should have direct relevance to the prognosis for kidney-specific end points and also for CKD complications such as CVD, heart failure, and mortality. Demonstrating such relationships is a critical first step to demonstrate these markers are truly reflective of the kidney’s health status, even if their intended ultimate clinical utility extends far beyond predicting prognosis. Thus, investigators have used epidemiological studies to learn inductively of their importance as risk factors for CKD adverse outcomes. The usual design for studying novel CKD prognostic biomarkers is to measure one or more in stored frozen specimens and to compare associations with longitudinal adverse outcomes. Promising biomarkers can then be tested for other potential uses, such as for facilitating the selection of the most appropriate treatments, monitoring of effectiveness, monitoring for safety, and distinguishing causes of changes in eGFR (Fig 2).
contrasting cohort of stable kidney transplant recipients from the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial. Among 4 urine tubule markers evaluated, the investigators found strong associations for proximal tubule dysfunction and fibrosis biomarkers with risk of allograft failure, as captured by higher urine A1M (hazard ratio [HR] per 2-fold higher, 1.76 [95% CI, 1.27-2.44]) and MCP-1 (HR, 1.49 [95% CI, 1.17-1.89]) concentrations, respectively. Once more, these associations were independent of eGFR, UACR, transplant- and CKD-related risk factors, and of one another.

Furthermore, Park et al demonstrated that these tubule function and injury markers had independent associations with risk for CVD and mortality in FAVORIT, as in HIV. These findings, confirmed across 2 different settings, suggested that not only could assessing tubule health inform prognosis above and beyond eGFR and UACR, but also assessment of both tubule function and injury could provide distinct and potentially additive information on prognosis.

Additional studies have evaluated urine biomarkers in the high-risk ambulatory settings of diabetes and hypertension. For example, in the Action to Control Cardiovascular Disease (ACCORD) Trial, Nadkarni et al conducted a case-control study with cases defined by a 40% reduction in eGFR over 5 years among adults with type 2 diabetes. The tubule inflammation and fibrosis marker MCP-1 was again strongly associated with reductions in eGFR (HR per 2-fold higher, 2.27 [95% CI, 1.44-3.58]), yet the tubule injury biomarkers (interleukin 18 [IL-18] and KIM-1) were not associated with that outcome in this study. However, these investigators subsequently explored kidney tubule injury biomarkers measured in the blood rather than the urine, and found that higher levels of plasma KIM-1 were strongly associated with CKD progression; these findings suggested that plasma concentrations of biomarkers specific to the kidney tubules may have stronger associations than urine concentrations in some settings.

In the Systolic Blood Pressure Intervention Trial (SPRINT), which recruited participants with hypertension and high CVD risk, the investigators identified participants with eGFR < 60 mL/min/1.73 m² at baseline and measured a panel of 8 urine biomarkers as risk factors for CKD progression. Jotwani and colleagues demonstrated that, among tubule function measures, higher urine uromodulin (UMOD) concentrations (a marker of distal kidney tubule synthetic function) were strongly associated with slower decline in eGFR; among the injury markers, higher levels of urine A1M and lower UMOD were associated with elevated risk for CKD progression in adjusted analyses. Additionally, Garimella et al demonstrated that 2 measures of reduced tubule function—higher A1M and lower UMOD—were strongly and independently associated with risk of CVD events in SPRINT; in fact, these 2 biomarkers improved CVD risk prediction above and beyond traditional CVD risk factors, eGFR, and UACR.

An additional novel marker of tubule dysfunction is epidermal growth factor (EGF). EGF messenger RNA transcripts are selectively expressed in distal tubular epithelial cells, and higher levels are thought to reflect functional tubular mass and regeneration potential. Kidney biopsy studies have correlated lower urine EGF concentrations with more severe tubule atrophy and interstitial fibrosis. EGF is only minimally detectable in
plasma, so urine EGF excretion may be specific to kidney tubule damage and fibrosis. Recent studies have demonstrated that lower urine EGF is associated with CKD progression in populations with CKD at baseline, and more recently in a general population cohort with preserved eGFR at baseline, on average. However, unlike the other biomarkers, most studies evaluated urine EGF individually, so its performance and interrelationship with other tubule function biomarkers are less well established and warrant further research. Nonetheless, the strong signals observed with urine EGF independent of baseline eGFR, albuminuria, and other risk factors make it a promising new addition among markers characterizing tubule cell dysfunction.

Some kidney tubule health biomarkers are detectable in the bloodstream and, as summarized previously, preliminary findings have suggested that blood levels may be more informative than urine levels for some markers, perhaps because of greater precision, regulation, or less influence from changes in urine tonicity. Recent studies have extended this work, evaluating blood levels of soluble urokinase-type plasminogen activator receptor (suPAR), tumor necrosis factor receptor 1 (TNFR1), TNFR2, and KIM-1. Plasma suPAR was found to have strong associations with incident CKD in a community-based cohort of persons undergoing cardiac catheterization. In 2 trials of persons with diabetes, higher plasma TNFR1, TNFR2, and KIM-1 were each associated with risks for progressive loss of kidney function, with effect sizes of approximately 2-fold greater risk per 2-fold higher biomarker concentration. These findings were confirmed for TNFR1 and TNFR2 with similarly strong findings among persons with diabetes and CKD in the CRIC (Chronic Renal Insufficiency Cohort) Study. Finally, among children with CKD in the CKID (CKD in Children) cohort, these same plasma biomarkers were prognostic for CKD progression, with the strongest associations observed for plasma TNFR1 and plasma KIM-1.

These findings are exciting for their utility to predict prognosis. However, because these circulating proteins have strong correlations to eGFR, it can be more challenging to distinguish their pathological connection to kidney tubule damage independent from their linkage to the underlying true GFR. This important area requires additional research to determine what unique insights these blood biomarkers provide into tubule health and what their clinical utility may be.

**Tubule Dysfunction, Risk of AKI, and Differentiation of AKI Etiology**

In addition to CKD progression, kidney tubule function biomarkers have been associated with risk for future AKI events in SPRINT. Interrogating why some individuals develop AKI in response to hemodynamic stressors whereas others do not, Bullen et al hypothesized that worse kidney tubule function may identify kidneys more susceptible to injury that might be missed by assessment of eGFR and UACR alone. The team hypothesized that tubule dysfunction may manifest as AKI events when the kidneys are stressed by hypotension or other insults. Among SPRINT participants with eGFR < 60 mL/min/1.73 m³ at their baseline ambulatory visit, the investigators demonstrated that worse proximal tubule reabsorptive function (higher urine A1M) and reduced tubule synthetic function (lower urine UMOD) had mutually independent associations with future development of AKI during the trial. Interestingly, in contrast to these markers of tubule function, the ambulatory measures of kidney tubule injury did not have associations with risks for future AKI. These injury markers were elevated only after the AKI episodes, as was expected.

Investigators are also harnessing the unique pathologies evident in different etiologies of CKD and AKI. For example, Moledina et al recently evaluated inflammatory markers in the urine of persons admitted with AKI who underwent kidney biopsies for diagnosis of the etiology. Harnessing the unique inflammatory infiltrate of patients...
with AIN, they demonstrated that patients with biopsy-confirmed AIN had higher urine concentrations of IL-9 and tumor necrosis factor α (TNF-α) compared with patients who had ATN, glomerular etiologies, or diabetic nephropathy on biopsy. Higher urine concentrations of these 2 biomarkers also improved the ability to distinguish AIN from ATN. Moreover, among the subset with AIN, higher urine IL-9 was associated with greater interstitial infiltration at the time of kidney biopsy.

In summary, markers of tubule injury and dysfunction demonstrate the potential of these groups of biomarkers to improve characterization and prognostication for persons at risk for or with established CKD. Plasma biomarkers have augmented the strength of these associations but perhaps with less specificity for representing intrinsic kidney damage. Consistently, across biomarkers and across different settings, markers of kidney tubule function and injury have provided additional relevant and prognostic information on risk of CKD and related outcomes above and beyond eGFR, UACR, and clinical risk factors, as we predicted based on prior biopsy studies. These findings confirm that these biomarkers provide novel information about kidney health not captured by eGFR and UACR, which is a critical first step. Yet ultimately their clinical utility will likely be much broader than prognostication for kidney failure (Fig 2).

Tubule Injury and Dysfunction Biomarkers for Monitoring Therapeutic Responses

The biomarkers reflecting tubule injury and dysfunction have provided new opportunities for monitoring drug therapy in CKD patients. Once more, work in this area began with research in the setting of HIV. Tenofovir disoproxil fumarate (TDF), a widely prescribed, highly effective antiretroviral medication, is known to cause both AKI and more rapid CKD progression. TDF induces mitochondrial dysfunction in proximal tubule cells and can cause Fanconi syndrome, which is manifest by the proximal tubule’s failure to reabsorb nutrients and small proteins.

Zhang et al.19 hypothesized that TDF may impair proximal tubule reabsorptive capacity, which would be marked by higher urine concentrations of A1M and similar proteins in the urine. They identified 198 HIV-infected individuals who had urine specimens obtained both before they initiated TDF and 1-year after, and measured a panel of tubule health biomarkers at both time points. Among this panel, 2 biomarkers that represent proximal tubule reabsorptive function were the most dramatically elevated after initiation of TDF; concentrations of trefoil factor 3 increased by 78% and A1M increased by 32%, and these elevations were associated with subsequent declining eGFR.30 Results were similar in men using TDF as part of HIV pre-exposure prophylaxis, among whom urine A1M concentrations increased by 21% after 6 months.31

In SPRINT, hypertensive participants with high risk of CVD were randomized to intensive systolic blood pressure (SBP) lowering (target < 120 mm Hg) versus a standard SBP target (<140 mm Hg). The trial showed that intensive SBP lowering resulted in reductions in a composite CVD endpoint and mortality, but also resulted in more rapid loss of eGFR.32 This has led to concern that intensive SBP lowering may increase long-term kidney risk. An alternative hypothesis is that this acute reduction in eGFR may reflect hemodynamic changes rather than intrinsic injury to the kidney.

Investigators recently evaluated kidney tubule biomarkers to gain insights into the kidney’s response to intensive SBP lowering. Among a subset of 978 SPRINT participants with eGFR < 60 mL/min/1.73 m², Malhotra et al.33 measured a panel of 8 biomarkers of kidney tubule injury and dysfunction at baseline and after 1 year. Some of these markers (UACR, β₂-microglobulin [B2M], and A1M) are filtered at the glomerulus, while others are produced within the kidney tissue in response to injury, inflammation, or repair (urine neutrophil gelatinase-associated lipocalin [NGAL], KIM-1, IL-18, MCP-1, and human cartilage glycoprotein 40 [YKL-40]). Despite the acute decline in eGFR, the investigators found that none of these measures showed significant increases in the intensive versus the standard arm; therefore, intensive SBP lowering did not appear to cause intrinsic tubule cell injury despite the eGFR decline (Fig 4). Among the panel, the 3 biomarkers that are filtered at the glomerulus (urine albumin, B2M, and A1M) were all significantly decreased in response to intensive SBP lowering (Fig 4; left box), whereas none of the biomarkers that are produced within the kidney tissue were significantly different between study arms (Fig 4; right box).34,35 These findings support the hypothesis that the acute reduction in eGFR in response to intensive SBP lowering is due to hemodynamic changes rather than intrinsic kidney injury in most patients. In a separate analysis of SPRINT participants who developed incident CKD during intensive SBP lowering, investigators similarly found no evidence of intrinsic kidney injury.36

Finally, a parallel analysis in ACCORD participants who had diabetes, Nadkarni et al.37 demonstrated that intensive SBP lowering also acutely lowered eGFR without raising any of the biomarkers that would indicate intrinsic kidney tubule cell injury.

Other investigators are making important parallel discoveries using kidney tubule biomarkers for therapeutic monitoring. Previously we described the recent discovery of the diagnostic utility of urine IL-9 and TNF-α concentrations in patients with biopsy-verified AIN versus other causes of AKI. The investigators also reported that higher urine IL-9 was associated with greater interstitial infiltration at the time of biopsy among the subset with AIN. Recently these authors reported that higher baseline IL-9 concentrations at the time of biopsy were associated with a greater response to treatment with
Among the AIN patients who received corticosteroids, there were larger improvements in eGFR over a 6-month follow-up period in the subgroup of patients with higher urine IL-9 levels at baseline, whereas the subgroup with lower IL-9 levels had less interstitial infiltration and did not have improvements in eGFR with corticosteroid treatment over the subsequent 6 months.36

In summary, the etiologies for reductions in eGFR are heterogeneous, and clinicians do not currently have tools to differentiate their causes in clinical practice. Given their concerns for intrinsic kidney injury, clinicians often feel compelled to interrupt beneficial medications, such as antihypertensive or antiretroviral medications, and then rely upon observation time to determine whether the kidney “recovers” based upon the eGFR response. In the case of AIN, many patients require kidney biopsy for definitive diagnosis, which is invasive, expensive, and carries risks of bleeding. By leveraging the unique pathological signatures provided by individual tubule injury and dysfunction biomarkers, emerging evidence suggests that a panel of kidney tubule measures can aid in the noninvasive diagnosis of the etiology of eGFR decline. Even when kidney biopsies are obtained, they are rarely done repeatedly. Thus, observing changes in biomarkers longitudinally may ultimately provide useful tools to monitor changes in kidney health noninvasively in response to drug therapy, as has now been demonstrated using stored urine specimens in the examples of TDF treatment in HIV, intensive SBP lowering, and with corticosteroid treatment for AIN.

**Current Challenges and Developmental Needs Required to Move Kidney Tubule Injury and Dysfunction Biomarkers to the Bedside**

Although these associations of kidney tubule biomarkers with CKD onset and progression have launched a new paradigm for research, the magnitude of the findings have not consistently been strong enough to distinguish categories of risk for future outcomes. One approach to overcome the limits of individual markers will be to combine them into panels that collectively improve prediction. Indeed, several recent studies have found improvements in the area under the receiver operator curve (AUC) on the order of 0.02–0.07 for both CKD progression and CVD end points when evaluating biomarker combinations.17,37,38 Moving forward, in a given population of patients, the biomarker panel could be selected to include markers that indicate both kidney tubule dysfunction and injury while also providing the strongest signals for CKD progression and CVD prognosis. Once a set of relevant biomarkers has been finalized, groups of measurements that have overlapping physiology may be combined using data reduction strategies.38

This review has described data wherein kidney tubule biomarkers have shown promise for therapeutic monitoring in HIV, hypertension, and AIN, yet there are many...
other exciting opportunities to use these markers for similar purposes in other common clinical settings. Additional research is needed to determine the utility of the biomarkers in each of these use cases, and to confirm that changes in biomarkers correlate to contemporaneous changes in kidney pathology.

For clinical application, commercial entities will need to develop precise, high-throughput assays that could be performed in many clinical laboratories affiliated with both ambulatory practices and hospitals. It will be essential that novel testing strategies are not only widely available to clinicians but also reproducible across diverse settings. Finally, if a panel of markers is to be used, it will be important that strategies are developed to integrate the information and guide the clinician to use the information in an unbiased way that will best guide clinical decision making.

Summary

The limitations of serum creatinine as the cornerstone of clinical diagnosis and monitoring of kidney disease have been widely described. Beyond the consequences of its influence by muscle mass, diet, and tubule secretion, serum creatinine changes cannot differentiate between benign hemodynamic changes versus intrinsic kidney injury. Whereas oncology, cardiology, and other fields in medicine have transformed clinical care by embracing biomarkers that provide new pathological insights, nephrology has been slow to adopt and integrate new markers. Within nephrology, each new biomarker is typically held to the standard of whether it, as an individual marker, can improve clinical decision making and quantify prognosis for kidney failure. However, single biomarkers rarely are able to achieve that standard of risk discrimination or diagnostic utility, and estimating prognosis is one of many challenges facing the nephrologist in clinical practice. Arguably, refining diagnosis, and monitoring response to therapy are more commonly needed and utilisable in the clinic.

Collectively, biomarkers of kidney tubule injury and dysfunction hold considerable promise and provide an opportunity to characterize the health of the kidney more fully. Consider the analogy to a liver function panel. Using 6 different biomarkers—aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, serum albumin, and the prothrombin time—the clinician can quickly review the blood concentrations both in absolute terms and in relation to the other 5 markers, and infer the likely cause and severity of liver injury. For example, a patient with hypotension and the combination of marked elevations in AST and ALT but relatively preserved total bilirubin and prothrombin time will lead the clinician to deduce that the patient has likely experienced ischemic liver injury. The combination of elevated total bilirubin and alkaline phosphatase with relatively lower concentrations of the other liver biomarkers in a patient may lead the clinician to obtain imaging to evaluate for etiologies of obstructive jaundice or infiltrative liver disease. Finally, a patient with elevated prothrombin time and low serum albumin may have synthetic dysfunction from chronic cirrhosis. It is inconceivable that clinicians would be willing to diagnose liver diseases while relying solely on the serum albumin concentration, even though costs may be lower and albumin might predict liver failure better than the other markers if compared head to head. The appropriate clinical question is not whether albumin predicts liver-related death independently of the AST concentration; rather the relative pattern of liver function tests allows the clinician to move quickly toward definitive diagnostic tests for the benefit of the patient.

Nephrology clinical practice could be no different, and this is now within reach. Clinicians should demand improvements in diagnostic tests to capture the complexity of kidney diseases. Curiosity is the hallmark of the diagnostician, and the limitations of current diagnostic testing in nephrology derail our quests for the satisfaction to truly understanding the pathophysiology of our patients’ diseases. Wider testing will provide new insights to patterns of diseases, which will facilitate our diagnostic evaluations and will, in all likelihood, improve patient care. For these reasons, our curiosity and our desire to characterize the breadth of kidney disease should be adequate justification to introduce novel biomarkers into CKD care, as it is in other fields of medicine. Although additional research and refinements are needed, kidney tube biomarkers will be essential to provide a global kidney health panel that can improve diagnosis and management for patients at risk or suffering from kidney diseases.

Article Information

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