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Assessing the Health of the Nephron in AKI: Biomarkers of Kidney Function and Injury

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Abstract

Purpose of review: Serum creatinine and urine output continue to be the mainstays of diagnosis of acute kidney injury, though both of these measures have significant limitations, especially in acutely hospitalized patients. Biomarkers in both blood and urine have been studied extensively in the research setting and are on the verge of clinical practice to improve diagnosis of AKI.

Recent findings: Blood and urine biomarkers can be localized to specific areas or functions within the nephron. Biomarkers can help to characterize glomerular or tubular function; glomerular, tubular, or interstitial injury; inflammation; or repair. Further, biomarkers can improve diagnosis of AKI in various clinical settings including acute interstitial nephritis, acute tubular injury, and hepatorenal syndrome, and cardiorenal syndrome.

Summary: Biomarkers are becoming more prevalent in both research and getting close to clinical use. Both blood and urine biomarkers can help to localize impairment in nephron health by either location or function within the nephron and among various etiologies of AKI.

Keywords

biomarkers; AKI; AIN; ATN; hepatorenal syndrome; cardiorenal syndrome; precision medicine

I. Introduction

Acute kidney injury (AKI) remains a major health burden of increasing global incidence with significant impact on morbidity and mortality.[1-5] Until 2002, there was no standardized definition of AKI. This changed with the initial RIFLE criteria, later with the Acute Kidney Injury Network (AKIN) criteria and most recently with the widely adopted Kidney Disease Improving Global Outcomes (KDIGO) staging, which takes into account changes in serum creatinine as well as urine output over the course of 7 days, as well as need for renal replacement therapy.[6, 7]

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Dr. Parikh is a member of the advisory board of RenalytixAI and own equity in the same.

The limitations in the use of serum creatinine and urine output for AKI diagnosis are well established.[8] Acute changes in these two markers may provide some indication of kidney dysfunction but does not discriminate the etiology of the kidney injury and guide clinical management. Further, serum creatinine can be falsely elevated in number of conditions and contribute to incorrect diagnosis of AKI. Creatinine may additionally be falsely low especially in hospitalized patients with rapidly changing use of IV fluids, titrations of medications that may affect tubular secretion.

In 2016, the Food and Drug Administration (FDA) and National Institutes of Health (NIH) convened a joint leadership council to clearly define a glossary of terms surrounding biomarkers.[9] Specifically this counsel established the BEST (Biomarkers, EndpointS, and other Tools) Resource to improve and harmonize terms used throughout the literature. This council defined a biomarker as a defined characteristic measured as an indicator of normal biological or pathogenic processes, or responses to an exposure or intervention. Biomarkers encompass not only laboratory testing but radiographic testing and histological testing as well. Categories of biomarkers can provide information on disease diagnosis, prognosis, risk prediction, and response to therapy. Biomarkers are distinct from clinical outcome assessments.[9, 10] Further, biomarkers should not be confused with surrogate markers of disease *a priori*.[10] While a valid biomarker should correlate with a given outcome, for a biomarker to serve as a surrogate, changes in biomarker level should imply a change in clinical outcome.

The purpose of this review is to evaluate the current landscape of biomarker use in the diagnosis and risk stratification of AKI, and to highlight the added benefit this approach provides to the current standard of serum creatinine and urine output-based measures of kidney injury. In this review, we do not intend to enumerate the exhaustive list of biomarkers being used or developed currently in the setting of AKI but to highlight representative or key biomarkers for each pathway and its clinical application.

II. Current biomarkers in the evaluation of nephron health

II.a. Biomarkers of nephron health – glomerular function

Biomarkers to assess the health of the nephron, including both function and injury, can be further sub-classified into those of involving the glomerulus or tubules primarily, as well as biomarkers for inflammation and repair (Table 1). Traditional biomarkers for the diagnosis of kidney function include serum creatinine and cystatin C, as well as urine output, which are most useful in the evaluation of glomerular filtration. Both serum creatinine and cystatin C are affected by numerous clinical conditions and do not accurately reflect true changes in glomerular filtration. In contrast to creatinine however, serum cystatin C is independent of age, gender and in certain situations can serve as a more appropriate marker of glomerular function.[11]

II.b. Biomarkers of nephron health – tubular function

The fractional excretion of sodium (FENa) was first described in the 1970s as a test to differentiate proximal tubular injury from other causes of clinical AKI where tubular

function is preserved, with a defined cutoff of >1% specific for proximal tubular injury.[12, 13] The use of a furosemide challenge to evaluate kidney tubular function and has been well described since the 1970s.[14] In recent years this technique has been formalized into a furosemide stress test, initially developed in the ICU setting.[15] Chawla and colleagues described administration of a one-time dose of furosemide with prediction of severity of AKI based on urine output response within 2 hours.[15] The benefit of the furosemide stress test in assessing tubular function more globally has been described in detail by Koyner and colleagues.[16, 17] In order for the furosemide stress test to work, the proximal tubule segment must be intact so furosemide can be secreted in the tubular lumen. Further, successful response to furosemide stress test also necessitates intact function of the Na-K-2Cl receptor at the level of the thick ascending Loop of Henle. Therefore, the furosemide stress test can serve as a marker of more general tubular function.

II.c. Biomarkers of nephron health – tubular injury

The use of urine microscopy is a readily accessible tool that can be used to evaluate injury to the kidney in various ways, and commonly is a quick tool to assess for the presence of tubular injury.[18] The presence of granular casts and renal tubular epithelial cells or casts indicate acute tubular injury. Further, a scoring system that includes the presence of casts and quantification of renal tubular epithelial cells has been shown to provide additional diagnostic information in the evaluation of patients with suspected acute tubular injury.[19] In recent years, biomarkers have become more available that can better localize injury to various sections of the nephron, including proximal vs. distal tubule. Biomarkers such as kidney injury molecule-1 (KIM-1) indicated are central to the kidney's response to proximal tubular injury.[20] KIM-1 is significantly upregulated in proximal tubular cells in the setting of injury or ischemia.[21, 22] In early studies of the use of KIM-1 for detection of tubular injury, a one-unit increase in KIM-1 conferred greater than 12-fold higher odds of having acute tubular necrosis (ATN) on kidney biopsy. Liver fatty acid binding protein (L-FABP) is present exclusively in the proximal tubule, released in the setting of oxidative stress and ischemia.[23-25] Elevations in L-FABP can therefore localize injury further to proximal tubule.[26]

Urine insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) have gained increasing traction in recent years in the diagnosis of AKI.[27, 28] First described in the Discovery Study, a multi-center cohort study of critically ill patients at risk for AKI, and validated using the Sapphire Study, both IGFBP7 and TIMP-2 were significantly elevated in patients with AKI, in both cohorts. Risk prediction improved with a combination test of both markers, with an AUC of 0.80 in validation. Both IGFBP7 and TIMP-2 induce G_1 cell cycle arrest, a critical pathway in the development of AKI. The clinical use of the TIMP-2xIGFBP7 score, or NephroCheck™, has been proposed with cutoffs of ≤0.3, 0.3-<2, and ≥2, and has been tested in various settings including sepsis and following cardiac surgery.[29-31] In patients with scores ≤0.3, the risk of AKI over the ensuing 12 hours would be considered low and continued standard of care management should be pursued. With scores >0.3, patients would be considered moderate to high risk, with closer monitoring and potentially nephrology consultation warranted. Recent research in a murine AKI model has demonstrated the likely mechanism

of elevated TIMP-2 and IFGPB7 levels include decreased proximal absorption as well as increased leakage of TIMP-2 and IGFPB7, suggesting NephroCheck is another robust marker for proximal tubular injury.[32] However, the clinical application and utility of this test requires further exploration in studies to evaluate improvement in clinical outcomes.

Uromodulin, also referred to as Tamm-Horsfall protein, is expressed by renal tubular cells localized to the thick ascending loop of Henle and is the most abundant protein found in the urine.[33, 34] As it is produced exclusively in the kidney, it can serve as a very specific marker in evaluating kidney health. It is suggested that under normal physiological conditions, uromodulin can protect against urinary tract infections and stone formation.[35, 36] There has been renewed interest in uromodulin recently, with the discovery of mutations in the UMOD gene leading to a number of rare genetic diseases now referred to as autosomal dominant tubulointerstitial diseases.[37] However in the context of AKI, decreased urine levels of uromodulin have been demonstrated in the post- cardiac surgery and ICU settings and it has been hypothesized that the expression of uromodulin is down-regulated, with the excretion decreased, in the setting of AKI.[38, 39] Further, in the pediatric setting, patients with the lowest pre-operative urine uromodulin levels were noted to have greatest risk of AKI post-cardiac surgery.[40]

Urinary neutrophil gelatinase-associated lipocalin (NGAL) had been touted as a potential troponin of the kidney, with levels elevated early in the course of AKI.[41] Most circulating NGAL is reabsorbed in the proximal tubule, and elevated levels may indicate proximal tubular injury. However, the production of NGAL is significantly elevated in the loop of Henle and distal tubule in the setting of AKI, up to 1000-fold.[42] Significantly elevated urinary NGAL may therefore localize the injury to distal tubular injury.[43]

II.d. Biomarkers of nephron health – inflammation

Biomarkers of inflammation have been studied extensively in AKI. In early mouse models, AKI lead to a significant increase in urine levels of Interleukin-18 (IL-18), which then mediates neutrophilic activation.[44, 45] We previously demonstrated that urine IL-18 levels are elevated in the setting of AKI in humans.[46] We later showed that urine IL-18 can serve as an early diagnostic marker of AKI and predicts mortality across various clinical settings, including patients in the ICU and following cardiac surgery.[47, 48]

Monocyte chemoattractant protein-1 (MCP-1) plays a central role in ischemic and toxic kidney injury. Its use as a potential biomarker for AKI was first described in urine samples in a mouse model and validated in patients in the ICU.[49] We later demonstrated that elevated levels of urine MCP-1 were significantly associated with AKI and death following cardiac surgery.[50] Specifically those patients in the highest tertile of MCP-1 had a 1.43 higher odds of AKI compared to those in the lowest tertile.

Tumor necrosis factor receptor 1 (TNF-r1) serves as a cell membrane receptor which binds TNF-α and accentuates endothelial inflammation.[51] TNF-r1 has been associated with progression to ESRD and mortality in patients with diabetes mellitus type 1 and type 2 beyond established risk factors including proteinuria, and implicated in other kidney diseases including various glomerulonephritides, obstructive kidney injury, and kidney

transplant rejection.[51-54] The presence of higher circulating TNF-r1 is a very acute and sensitive marker for inflammation, up-regulate in the setting of elevated TNF-α. It may therefore be a more sensitive marker of kidney inflammation with a more rapid rise than serum creatinine. More recently TNFr-1 has been implicated in the inflammatory response to AKI.[55]

II.e. Biomarkers of nephron health – repair

YKL-40 is a chitinase 3-like-1 gene product which was first implicated in repair after AKI in the setting of kidney transplantation.[56] We demonstrated that levels of both urine and blood YKL-40 were elevated in recipients post-transplantation and predicted need for subsequent dialysis.[56] YKL-40 activates the Akt pathway in renal tubular epithelial cells to limit tubular cell apoptosis in response to ischemia/reperfusion injury. Initially shown to predict animal survival after ischemia reperfusion in a murine model, blood and urine YKL-40 levels were then measured in a cohort of patients undergoing deceased donor kidney transplantation. Relatively higher levels of YKL-40 were noted in patients who suffered delayed graft function (DGF), requiring subsequent dialysis, compared to those patients with immediate or even slow graft function. We determined that YKL-40 could serve as an indicator of peri-transplantation ischemia/reperfusion injury. A follow-up study showed in fact that higher levels of donor YKL-40 were associated with improved outcomes, including reduced risk of DGF regardless of AKI status at the time of organ procurement.[57] Further, in recipients who did develop DGF, those who received donor kidneys with higher YKL-40 concentration had a better 6-month eGFR and lowe risk of graft failure, strengthening the argument that the presence of YKL-40 indicates repair after injury and can prognosticate recovery following injury. We also demonstrated that elevated levels of urine YKL-40 were also elevated in native kidneys in response to injury of any cause and associated with significantly higher odds of AKI progression or death.[58]

III. Application of biomarkers in various clinical settings of AKI

III.a. Subclinical AKI

The concept of subclinical AKI was first introduced by Parikh *et al* in the early 2000s and has been increasingly validated over the years with the increased use of biomarkers to evaluate patients with AKI.[59-63] Subclinical AKI is defined as true kidney injury despite functional measures of kidney function remaining normal. Subclinical AKI may serve as a milder form of kidney injury in which damage to some parts of the kidney, such as tubular injury, are compensated by other functioning nephrons to maintain overall glomerular filtration (GFR) in the normal range. Additionally, subclinical AKI may represent an earlier stage of kidney injury in which serum creatinine will later rise but with the well-established delay in elevation due to various factors. Biomarkers that successfully detect AKI at earlier stages can have a significant impact on reducing overall kidney injury, improving long-term outcomes and preventing progression to chronic kidney disease. Such biomarkers could also help to identify patients that may improve with early intervention, even before AKI becomes clinically detectable. Importantly, patients with subclinical AKI are at greater risk for adverse outcomes including mortality and need for dialysis.[60, 62]

III.b. Acute interstitial nephritis (AIN)

We have recently demonstrated the use of urine biomarkers TNF-α and interleukin-9 (IL-9) in the evaluation of AKI and differentiation between acute interstitial nephritis and other forms of AKI.[64] With the hypothesis that AIN is mediated by specific helper T cells, T-cell related cytokines should be elevated in AIN compared to other forms of AKI that are driven through other mechanisms. Instead, we demonstrated that mast cell derivatives TNF- α and IL-9 were significantly elevated in patients with biopsy-proven AIN compared to patients without AIN over two sub-cohorts of patients. Additionally, these biomarkers were independently associated with higher odds of AIN compared to other kidney diseases such as ATN, glomerular diseases, and diabetic kidney disease. Further, addition of these two biomarkers to clinical practice improved discrimination over and above a clinician's pre-biopsy diagnosis based on clinical impression alone.

III.c. Cirrhosis

AKI is common in patients with cirrhosis, leading to significantly worse outcomes including higher mortality, particularly in patients who develop hepatorenal syndrome (HRS), independent of MELD score. The differential diagnosis of AKI in patients with cirrhosis also commonly include acute tubular injury and pre-renal azotemia. We have explored the use of urine and blood biomarkers in the evaluation of patients with cirrhosis who develop AKI.[65] Urinary NGAL, IL-18, KIM-1, L-FABP, and albuminuria were significantly higher in patients who had AKI progression and death compared to patients who did not progress. These markers were also significantly elevated in patients with ATN compared to patients with HRS and pre-renal azotemia. We further demonstrated that in patients with cirrhosis, a markedly low FENa (<0.2) was more specific for a diagnosis of HRS and helps differentiate from other etiologies such as ATN and pre-renal azotemia.[66]

III.d. Cardiorenal syndrome

Cardiorenal syndrome remains a challenging clinical syndrome in which patients have both acute decompensated heart failure (ADHF) and concurrent AKI.[67] Management decisions for patients with AKI often surround the aggressiveness of diuresis, which is often complicated by rises in serum creatinine, and the use of biomarkers in this setting can be helpful.[68] Urine biomarkers including urinary angiotensinogen, NGAL, IL-18, and KIM-1 measured at the time of CRS diagnosis show improved risk stratification in determining which patients will progress to adverse outcomes.[69] Further, there is growing evidence that the use of urine biomarkers such as NGAL is a more reliable marker of true structural kidney injury compared to creatinine, and that diuresis in the setting of ADHF may lead to a rise in creatinine without true renal tubular injury.[70, 71] Instead, the rise in creatinine often noted with aggressive diuresis may be a more accurate reflection of hemodynamic changes. Thus, low levels of biomarkers can guide continuation of diuretic therapy and RAAS inhibitors for optimal decongestion and management of ADHF.

IV. Conclusion, future directions

The National Institute of Diabetes and Digestive and Kidney Disease has sponsored the Kidney Precision Medicine Project (KPMP) to improve the care of patients with kidney

disease by developing new strategies to apply precision medicine approaches in nephrology. The use of biomarkers to aid in the diagnosis and characterization of kidney disease will be central in this endeavor, for both AKI and CKD. One of the main goals of the KPMP is to improve clinical phenotyping of AKI through the use of research biopsies. With advanced tissue processing including genomic processing and RNAseq, tissue cores from kidney biopsies in multiple sites across the US will be used to build a kidney tissue atlas. This will highlight the many ways biomarkers can be used clinically to further phenotype cases of AKI.

Beyond clinical characterization and phenotyping of AKI, the use of biomarkers for earlier diagnosis of AKI can facilitate earlier intervention and help to individualize treatment of patients. One such clinical scenario in which biomarkers can enrich diagnosis and intervention is in the field of nephrotoxin-associated AKI. A number of electronic medical record systems have constructed alert systems to flag patients who develop in-hospital AKI. However, in recent years, programs aimed at identifying *at-risk* patients prior to the development of AKI have gained such traction. One such program developed by Goldstein and colleagues is the Nephrotoxic Injury Negated by Just-in-Time Action (NINJA) program, first used in the University of Cincinnati Children's Hospital and later expanded to other sites nation-wide.[72] This program aims to identify patients who are exposed to three or more potentially nephrotoxic medications, including IV contrast, with a pharmacy-led intervention to explore alternative medication strategies in an effort to reduce the incidence and severity of AKI.

Adapting a system such as NINJA more broadly, the addition of biomarker measurement for at-risk or injured patients following nephrotoxic exposure can improve clinical decision-making. Patients with nephrotoxic exposure and elevated levels of TNF- α and IL-9, for example, may be started earlier on steroids for likely AIN compared to patients with no biomarker elevation and the delayed rise in serum creatinine before an intervention is begun.

The increasing use of biomarkers in the evaluation of patients, from detection of early injury to recovery or progression after clinical AKI is diagnosed, will continue to be of extreme importance in the age of precision medicine. The use of biomarkers added to clinical and laboratory data, including the use of kidney biopsies, has the potential to significantly improve long-term patient outcomes.

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Key Points:

- Blood and urine biomarkers to interrogate the health of the nephron have garnered increasing interest in recent years.
- Biomarkers can localize specific functions of the nephron as well as location of injury within the nephron.
- The use of biomarkers can help to differentiate various forms of AKI in several clinical scenarios including AIN, hepatorenal syndrome, and cardiorenal syndrome.
- In the future, biomarkers may be used to better inform clinical decision-making and impact long-term patient outcomes.

Table 1:

Biomarkers in various settings of AKI

Mechanism	Biomarker	Potential Clinical Application
Glomerular function	Creatinine, Cystatin-C	- Diagnosis of AKI
Tubular function	FENa, furosemide stress test	- Differentiation of HRS from ATN and pre-renal azotemia in cirrhosis - Recovery from ATN
Tubular injury	Urine microscopy, KIM-1, L-FABP, IGFBP7, TIMP-2, Uromodulin, NGAL	- Early diagnosis of AKI - Differential Diagnosis of ATN - Diagnosis of subclinical AKI
Inflammation	TNF-alpha, IL-9	- Diagnosis of AIN
Repair	YKL-40	- Prognosis after AKI for long term outcomes