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Comprehensive Assessment of Kidney Health in Acute Kidney Injury: Can we achieve?

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Abstract

Acute kidney injury (AKI) is a frequent event in hospitalized patients, with an incidence that continues to rise, reaching as much as 70-80% in intensive care settings. The need for dialysis and progression to end-stage kidney disease (ESKD) after an episode of AKI is relatively low, from 5 to 20%. However, it is now recognized that patients with AKI may have very different kidney outcomes, varying from complete recovery, incipient chronic kidney disease (CKD), to progression to end-stage kidney disease (ESKD). Recent studies have shown that even mild AKI episodes can be associated with a 90% increased risk of developing CKD during long-term follow-up. There is a significant need to focus our efforts on factors that could mitigate the progression of kidney dysfunction and ultimately improve outcomes from AKI. The first step toward this goal encompasses a better understanding of tubular and glomerular alterations during and following an AKI episode. Our current approach, based solely on GFR, is flawed since the loss of kidney function does not correspond to the degree of decline in estimated GFR, and eGFR does not reflect tubular function. Changes in tubular concentration, reabsorptive and secretory capacity are recognized in AKI; however, they have not been incorporated in clinical assessments of overall kidney function. Here we review few canditates to assess glomerular filtration/permeability, tubular dysfunction, and injury and how we expect these markers to alter during the development and recovery phase of AKI.

Introduction

Recent advances in urinary and serum biomarkers of kidney damage have provided new tools to identify tubular injury that can be mapped to specific sites; however, these injury markers have not been correlated with alterations in tubular function[1]. The combination of tubular function assessment in conjunction with kidney injury, glomerular filtration, and permeability markers would provide a more accurate overall evaluation of kidney health[2]. This overall assessment would enable clinicians to be better equipped to diagnose kidney disease and manage patients with kidney dysfunction [3-5].

Despite the improvement in AKI classification systems and putative biomarkers for AKI, timely diagnosis and assessment of AKI severity remain challenging [6]. Alterations in kidney

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function are generally assessed by serum creatinine (sCr), the most common surrogate for GFR, which has limitations since GFR poorly reflect tubular function, the main site of injury in AKI. Renal tubule cells perform many of the essential kidney functions, including reabsorption, electrolyte transport, secretion of endogenous molecules and medications, acid/base balance control, and concentration and dilution of urine [7]. In this minireview, we will discuss some key pathophysiological mechanisms and key markers of kidney glomerular and tubular function, including filtration, absorption, secretion, and concentration that could provide a comprehensive evaluation of kidney function (Table 1).

The concern about the limitation of serum creatinine and the difficult to find a reliable GFR

Our most recent diagnostic criteria for AKI, the KDIGO classification system [8], still relies on changes of serum creatinine and urine output [9]. Serum creatinine has standardized assays widely available and is of easy interpretation by all providers. However, sCr is not only filtered, but also secreted by the tubules, and affected by age, gender, muscle mass, muscle metabolism, medication, and hydration status [10]. Thus, serum creatinine based evaluation of filtration is inaccurate. The more precise exogenous markers of filtration, inulin, iothalamate, CrEDTA or iohexol, can provide more reliable filtration estimation, but need be injected, making the process time consuming and costly.

Urine and plasma Uromodulin as a marker of Tubular reserve

Uromodulin, also called Tamm-Horsfall protein, is a glycoprotein expressed in the thick ascending limb (TAL) and distal convoluted tubule of the kidneys. It is excreted as the most abundant urinary protein in healthy kidneys [11], and released into the circulation through the peritubular capillary network [12,13]. Different than other markers for kidney function, uromodulin is exclusively produced by TAL cells, thus it can be linked to tubular health and reserve [14-16]. Levels of urine and serum uromodulin has been correlated with kidney health and few experimental studies have suggested that it may a down regulation effect on systemic and kidney inflammation, playing a protective role in AKI [17]. In cardiac surgery, studies have shown that low urine uromodulin is associated with higher odds of AKI and higher peak serum creatinine in the post-operative period [18,19]. Plasma uromodulin can also be assessed and have two main advantages; less prone to enzymatic degradation by proteases[20] and does not requrire correction for urinary concentration [21].

Plasma Cystatin C: more accurate filtration marker

Cystatin C is a low molecular weight, 13.36 kDa non-glycosylated protein, freely filtered through the glomerulus, reabsorbed and metabolized in the proximal renal tubule, not suffering renal or extrarenal secretion. Unlike creatinine, serum levels of cystatin C are not significantly affected by sex, race or muscle mass. However, concentrations of cystatin C concentration is affected by age high glucocorticoids levels, thyroid disorders, inflammation, cigarette smoking, and some proliferative disorders. In addition, in sepsis, the production of cystatin C is decreased, and the nonrenal clearance is increased.

Proenkephalin is an early biomarker of kidney injury not influenced by inflammation.

Proenkephalin (proENK), is a monomeric peptide (approximately 4.5 kDa). It is a stable surrogate marker for endogenous enkephalins; it is cleaved from the precursor peptide preproenkephalin A alongside enkephalins (endogenous opioids) and filtrated by the glomerulus. PENK has been associated with worsening of kidney during AKI and is accurately represent glomerular filtration rate in patients with sepsis. In a retrospective study including 101 patients admitted to the emergency department with suspected sepsis, in patients without AKI ENK levels were mainly within the normal range, despite the presence of inflammation[22]. In the post-operative period of cardiac surgery, pro-ENK was an early marker of AKI development, while NGAL was elevated above the normal range for almost all patients without AKI [23].

Albuminuria as a marker of glomerular and tubular dysfunction

Urine albumin is a well-known marker glomerular permeability. The structure of the fenestrated endothelial layers, negative charge basement membrane, and podocytes do not allow albumin to enter the tubule. The presence of albumin in the urine reflects damage to this delicate and complex structure, being a useful marker of endothelial dysfunction, CKD progression, and an independent risk factor for cardiovascular disease and cardiovascular mortality[24-26]. However, the mechanism of albuminuria is complex as the normal glomerulus filters substantial amounts of albumin that is then processed by proximal tubular cells. Dysfunction in retrieval pathway dysfunction is associated with nephrotic range proteinuria. Small amount of filtered albumin that are not retrieved undergo lysosomal degradation. In AKI the dysfunction in the degradation pathway can lead to non-nephrotic proteinuria, and be a marker of tubular dysfunction as well.

Urinary Cystatin as a marker of tubular injury

Serum cystatin C is a more accurate marker of glomerular filtration, whereas, urinary cystatin C can be an early marker in tubular injury. Few studies have shown that serum cystatin C can provide an earlier AKI diagnosis than serum creatinine[27]. In the study by Park et al.[28] the urinary cystatin C and creatinine were measured in 213 patients with AKI diagnosis, classified as pre-renal AKI and intrinsic AKI. The authors found that values of urinary cystatin C increased in intrinsic AKI. Contradictory findings were reported in other studies. Royakkers et al. [29], found that urinary cystatin C had no diagnostic value in the days prior to the diagnosis of AKI by serum creatinine (AUC <0.50) and the plasma and urinary cystatin C on the first day of AKI diagnosis were poor predictors of the need for dialysis (AUC = 0.66).

Changes in urine α1-microglobulin levels are associated with tubular exposure to nephrotoxin

In contrast to other biomarkers produced by proximal tubular epithelial cells, α1-microglobulin (α1m), a 26-kD lipocalin, is filtered at the glomerulus but fully reabsorbed by proximal tubular epithelial cells, where it is degraded. With kidney tubule dysfunction, elevated urine α1m levels indicate decreased proximal tubular reabsorptive capacity. Utilizing samples from Multicenter AIDS Cohort Study, a large cohort of men with normal

kidney function and HIV infection, Jotwani el al, showed the association of tenofovir (TDF) exposure and higher urine levels of α1m [30]. Among HIV-infected men, cumulative TDF exposure was associated with incrementally higher α1m levels, whereas time since TDF treatment discontinuation was associated with progressively lower α1m levels.

These findings, in conjunction with the prior work demonstrating the prognostic significance of urine α1-m for CKD progression, highlight α1m as a promising biomarker of tubular function compromise.

Urine hippurate levels can estimate tubular secretion function

The combination of protein-binding and tubular secretion allows the kidney to clear some solutes at rates exceeding the renal plasma flow, and thus, is a more efficient mechanism than glomerular filtration and especially important for drug elimination. In astudy using an untargeted mass spectrometry approach in healthy controls and dialysis patients, 13 endogenous solutes that are efficiently cleared by renal tubule secretion were identified [31]. Hippurate, was found to have a renal clearance 12 fold higher than serum creatinine in healthy controls (mean hippurate clearance 1,868 ml/min), and was elevated more than 30 fold in dialysis patients relative to healthy controls. Similar to para-amino hippurate (PAH), hippurate is known to be actively secreted into the urinary filtrate by proximal tubule cells, and yet, unlike PAH, hippurate is an endogenous compound that can be measured in serum and urine in humans without the need for intravenous loading. In a prospective cohort study of 298 patients with kidney disease, hyppurate was measured by liquid chromatography-tandem mass spectrometric assays, in serum and timed urine samples[32]. They show that tubular secretion rate modestly correlated with mGFR and was associated with fractional excretion of electrolytes. Lower levels of hippurate in the urine was associated with higher risk of death independent of eGFR. Thus, measuring tubular secretion may add information on overall kidney health.

Of note, in a small study, tubular secretion function assessment by spot serum and urine samples was compared with 24-hour urine samples[33]. Fractional excretion (FE) of tubular secretion markers were shown to be relatively stable, supporting the use of spot urine specimens to assess tubular secretion.

Lower urine ammonium measured in spot urine samples can reflect decreased tubular function

In patients with CKD, the ability to adapt urinary ammonia excretion to increased or normal acid load is impaired. In a cohort study with 1065 patients CKD stages 1–4, GFR by 51Cr-EDTA, venous total CO_2 concentration and urinary ammonia excretion were assessed, over 24hs and in fasting spot samples, for a median follow-up period of 4.3 years [34]. Urinary ammonia concentration (in spot urine) decreased with GFR; for every 10mEq/L decrease in fasting NH4 urinary concentration. As the net endogenous acid production was the same at any mGFR level, the decrease in ammonia was likely due to an impaired ability of the the tubules to generate ammonium and not a consequence of decreased acid load. Similar associations with CKD progression and death were found using 24-hour urine or spot specimens. In acute worsening of kidney function, low ammonium may reflect a decreased

ability of the tubules to generate ammonium, or perhaps to secrete hydrogen and keep ammonium in the urinary space.

Conclusion

The sequential assessment of the components of tubular health, before and during the course of AKI, could provide us with a unique opportunity to understand their pattern during AKI. The panel biomarkers discussed above offer a more comprehensive assessment of kidney health. Understanding the pattern of change of the components of tubular function and its correlation with tubular injury during an AKI episode can provide insights into the etiology and prognosis of AKI. Knowledge of the degree of dysfunction on the different components of tubular function can have clinical implications in drug dosing and prevention of toxicity. Whether the assessment of overall tubular health can improve the prediction of severity, non-recovery, and risk of CKD progression is a still challenge for the AKI research field.

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Table 1.

Biomarkers rational for clinical use in acute kidney injury setting and/ or chronic kidney disease.

Biomarkers:		Mechanism in AKI	Limitations/ Confounding factors
Functional/ Filtration	**Scr**	freely filtered by glomerulus, also secreted by tubular cells	affected by age, gender, muscle mass, muscle metabolism, medication, hydration status, sepsis and liver disease.
	Cys C	freely filtered by glomerulus, reabsorbed and metabolized in the proximal tubular cells	affected by age, high glucocorticoids levels, systemic inflammation, cigarette smoking, hyperbilirubinemia, hypertriglyceridemia, malignance and thyroid and proliferative disorders.
	Pro-ENK	is an endogenous polypeptide hormone filtrated by the glomerulus; associated with GFR, is increased in AKI (sepsis and transplant)	also elevated in cardiovascular failure, systemic inflammation and pain.
Permeability/ Tubular injury	**Albuminuria**	filtered by glomerulus, reabsorbed and metabolized in the proximal renal tubule; prediction of cardiovascular risk and CKD progression.	affected by protein metabolism (drugs or liver diseases) and cardiovascular disease.
Tubular Injury	**KIM-1**	transmembrane glycoprotein produced after ischemic/ nephrotoxic insults; is increased in AKI and associated with CKD progression (fibrosis).	Increase in renal cell carcinoma, chronic proteinuria, CKD and sickle cell nephropathy.
	NGAL	a 25KDa polypeptide protease of the lipocalin superfamily; can predict AKI before sCr elevation. Also involved in tubular repair.	levels also increase in sepsis, COPD, cardiac dysfunction, malignancy, age, urinary tract infection, pancreatitis and endometrial hyperplasia.
Tubular Inflammation	**IL-18**	pro-inflammatory cytokine; increased in ischemic and inflammatory AKI.	affected by other factors including; psoriasis, heart failure, inflammatory bowel disease, multiple sclerosis and metastatic melanoma.
Tubular Stress	**TIMP-2/ IGFBP7**	proteins released in urine in response to stress (inflammation and ischemia); useful in AKI prediction	also increases in inflammation, ischemic events in other organs and cancer (prostate, colorectal)
Reabsorption	α1m	low molecular weight protein, its presence reflects proximal tubular damage; studies in nephrotoxic AKI and CKD progression	is found in other tissues: lungs, intestine and placenta and could be affected in sepsis.
Secretion	**Fe Hippurate**	handle by organic anion transporters on the basolateral membrane, decreased secretion reflects tubular dysfunction. Low excretion has been associated with CKD progression.	obesity, diabetes, gastrointestinal diseases, psychological disorders, autism, toxicity and parasitic infection affect excretion
	Fe ammonium	low ammonium reflects a decreased ability of the tubules to generate ammonium	also affected by dietary acid load, and changes in plasma potassium concentration.

Scr (serum creatinine), AKI (acute kidney injury), CKD (chronic kidney disease), eGRF (estimated glomerular rate filtration), Cys C(cystatin C), Pro-enk. (Pro- enkephalin), Alb. (Albuminuria), KIM-1 (kidney injury olecule-1), NGAL (neutrophil gelatinase associated a lipocalin), IL-18 (interlekine-18), TIMP-2 (Tissue inhibitor of metalloproteinase 2), IGFBP 7 (Insulin-like growth factor-binding protein 7), a-1M (alpha 1-macroglobulin), Fe (fractional excretion), HA (hipurate)