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Review Article

The Newer Markers of Acute Kidney Injury

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Abstract: Diseases of the kidney are diverse, ranging from Acute Kidney Injury (AKI) to End Stage Renal Disease (ESRD). The treatment of kidney disease poses a major challenge to the health care system and the global economy. Hence the detection and management of kidney diseases in the early, reversible and potentially treatable stages is of paramount importance. AKI refers to a syndrome that results from multiple causative factors and occurs in a variety of clinical settings. AKI presents with varied clinical manifestations that range from a minimal elevation in serum creatinine to anuria. AKI is largely asymptomatic and establishing the diagnosis relies on functional biomarkers such as serial serum creatinine measurements. Unfortunately, serum creatinine is a delayed and unreliable indicator of AKI due to various reasons. Serum creatinine does not accurately depict kidney function until a steady state has been reached which could take several days. Animal studies have identified interventions that can prevent and/ or treat AKI if identified early in the course of disease, even before the serum creatinine begins to rise. The paucity of early biomarkers has hampered our ability to translate these promising therapies to human AKI. Also lacking are reliable methods to assess the efficacy of protective or therapeutic interventions and early predictive biomarkers of drug toxicity. The pursuit of improved biomarkers for the early diagnosis of AKI and its outcome is an area of intense contemporary research. Understanding the early stress response of the kidney to acute injury has revealed a number of potential biomarkers. Some of the biomarkers are Neutrophil Gelatinase Associated Lipocalin (NGAL) , Cystatin C, Interleukin-18 (IL-18) , Liver type Fatty Acid Binding Protein(L-FABP) , Kidney Injury Molecule – 1 (KIM-1) etc.
Keywords: Acute Kidney Injury, Neutrophil Gelatinase Associated Lipocalin (NGAL), Cystatin C, Interleukin-18 (IL-18).

INTRODUCTION

Acute Kidney Injury (AKI) is a heterogeneous syndrome characterized by a rapid decline in the glomerular filtration rate (GFR) resulting in the retention of metabolic waste products, like urea and creatinine and dysregulation of fluid, electrolyte and acid base homeostasis[1]. AKI represent a broad constellation of pathophysiologic process of varied severity and etiology. These include decrease in GFR as a result of hemodynamic disturbances that disrupt normal renal perfusion without causing parenchymal injury, partial or complete obstruction to urine flow and a spectrum of processes with characteristic patterns of glomerular, interstitial, tubular or vascular parenchymal injury [2].

The term Acute Kidney Injury has largely replaced the older term Acute Renal Failure. The term AKI attempts to bring the small acute and transient decrements in kidney function with serious adverse outcomes [2].

In 2002, the Acute Dialysis Quality Initiative (ADQI) Group proposed the first consensus definition of AKI. They proposed a classification of scheme with three strata based on the magnitude of the increase in serum creatinine level and/or the duration of oliguria. The first stratum would provide the greatest sensitivity for diagnosing AKI, whereas the higher strata would provide increasing specificity of diagnosis. These three strata were combined with two outcome stages defined by the need for and duration of renal replacement therapy which resulted in the RIFLE classification (Risk of Renal Dysfunction, Injury to kidney and Failure of kidney function along with two outcome stages, Loss of kidney function and End stage kidney disease[3]. More recently Acute Kidney Injury Network (AKIN) has proposed a modification of RIFLE classification that includes the Risk, Injury and Failure criteria with the addition of a 0.3mg/dl or higher increase in the serum creatinine level to the criteria that define Risk [4].

The utility of diagnostic criteria such as the RIFLE classification and AKIN definition of AKI is limited by the fact that they rely on the serum creatinine concentration, which can increase in cases of prerenal azotemia when there is no tubular injury and can be unchanged under conditions of significant tubular injury, particularly when patients have good underlying kidney function and significant kidney reserve [5].

Even though routinely used and considered as a gold standard biomarker of kidney function, serum creatinine does not detect injury or dysfunction early enough to allow prompt therapeutic intervention[7]. Recently many novel technologies in the field of genomics, proteomics and metabolomics have made it easier to interrogate potential biomarkers [8]. A renewed interest in discovering novel biomarkers have been reported for Acute Kidney Injury [7]. Some of the biomarkers are Neutrophil Gelatinase Associated Lipocalin (NGAL) , Cystatin C, Interleukin-18 (IL-18) , Liver type Fatty Acid Binding Protein(L-FABP) , Kidney Injury Molecule – 1 (KIM-1) etc. None have been adequately validated to justify their use in patient care decisions but a few look quite promising [7].

NGAL

Neutrophil Gelatinase Associated Lipocalin is also known as

- Human Neutrophil Lipocalin (HNL)
- Migration Stimulating Factor Inhibitor (MSFI)
- Alpha -1 microglobulin related protein
- Siderocalin
- Uterocalin
- 24p3

NGAL is a 25kDa glycoprotein of the lipocalin family. It contains 178 aminoacid residues. It is encoded by a gene located on the chromosome locus 3p11. Human serum NGAL levels are increased in the order of 7 to 16 fold and urinary NGAL levels increase by 25 to 100 fold [9] which has led to the development of assays for NGAL for the early detection of renal tubular injury[10] .

Preclinical transcriptome profiling studies identified Ngal to be one of the most upregulated genes in the kidney very early after acute injury in animal models [11]. Downstream proteomic analyses also reveal Ngal to be one of the most highly induced proteins in the kidney after ischemic or nephrotoxic AKI in animal models [12]. The finding that Ngal protein is easily detected in urine soon after AKI in animal studies has initiated a number of translational studies to evaluate NGAL as a non-invasive biomarker in human AKI. A marked increase in both urinary and serum NGAL was documented by Western Blotting in a cross sectional study of adults with established AKI from various etiologies [13]. Urine and serum NGAL correlated with serum creatinine and the kidney biopsies in subjects with AKI demonstrated intense accumulation of immuno reactive NGAL in the cortical tubules. This confirmed NGAL as a sensitive index of established AKI in humans. A number of subsequent studies have now implicated NGAL as an early biomarker for AKI in various clinical settings [7].

CYSTATIN C

Serum cystatin C is more sensitive than serum creatinine to detect changes in GFR since it is less subjective to extra renal factors and may be superior to serum creatinine in both acute and chronic kidney diseases [14]. Cystatin C is a low molecular weight protein produced at a constant rate by all nucleated cells and eliminated exclusively by glomerular filtration. It is small in size, with a molecular weight of 13kDa and a positive charge at physiological pH. It is neither secreted nor reabsorbed by renal tubules but undergoes almost complete catabolism by proximal tubular cells and thus little appears in urine under normal circumstances. Any impairment of absorption in proximal tubules can lead to marked increase in urinary cystatin C levels in humans and animals. There have been a number of studies on the diagnostic potential of both serum and urinary cystatin C level in acute and chronic kidney disease in humans [5, 15].

Because of its short half -life of approximately two hours and other properties described earlier serum cystatin C levels reflects GFR better than creatinine concentration [15]. Cystatin C may be a better marker of kidney function in elderly persons and in the setting of mild kidney dysfunction [16, 17]. Although Cystatin C level is increasingly reported as an end point in studies, the diagnostic and prognostic characteristics of this marker for AKI are yet to be defined. In a mixed critical care population serum cystatin C levels enabled the diagnosis of AKI 1.5 days earlier than creatinine concentration and had moderate ability to predict dialysis requirement. In a study of intensive care unit patients cystatin C showed excellent predictive value for AKI, when AKI was defined by RIFLE criteria. Cystatin C level was shown to be capable of detecting a decrease in GFR earlier after contrast agent administration than the serum creatinine value in adult patients who underwent coronary angiography[17]. Urinary cystatin C / urinary creatinine ratios of more than 11.3 mg/mmol were significantly associated with proteinuria. Urinary cystatin C levels had no diagnostic value on two days before the development of AKI. Furthermore cystatin C is not always a reliable marker of renal function because its synthesis is increased in smokers, hyperthyroidism, and glucocorticoid therapy and cardio vascular disorders [5, 18].

INTERLEUKIN -18

Interleukin-18 (IL-18) is an 18kDa proinflammatory cytokine produced by renal tubule cells and macrophages. It is a mediator of acute tubular injury, including both neutrophil and monocyte infiltration of

renal parenchyma [19, 20]. In the kidney IL-18 is induced and cleaved mainly in the proximal tubules and released into the urine. IL-18 has been shown to participate in a variety of renal disease processes including ischemia-reperfusion injury, allograft rejection, infection, autoimmune conditions and malignancy. Several studies have demonstrated the usefulness of IL-18 as a biomarker for the detection of AKI. Urinary IL-18 levels were reported to be significantly higher in patients diagnosed with acute tubular necrosis than in patients with pre renal azotemia or urinary infection or in healthy control subjects with normal renal function [21]. Patients with diabetic kidney disease and proteinuria had higher IL-18 levels in renal tubular cells compared to patients with nondiabetic proteinuric disease [22].

Increased urinary concentrations of IL-18 were reported by several groups in AKI. In a pediatric critical care population, elevated urinary IL-18 concentrations were associated with an increased risk of developing AKI during the subsequent 48 hours with a sensitivity of less than 40% [23]. In patients undergoing cardiac surgery, urinary IL-18 levels showed modest predictive performance [24, 25]. It was also found that urinary IL-18 levels correlated with the duration of cardiopulmonary bypass but did not predict AKI after bypass [25]. In critically ill adult patients admitted to ICU, urinary IL-18 concentrations did not predict the development of AKI but predicted poor clinical outcomes including death and the need for short term dialysis [26]. IL-18 concentrations accurately predicted the need for dialysis in transplant recipients and also the graft recovery upto 3 months later. Urinary IL-18 was significantly increased at 24 hours after the procedure in those who developed contrast medium induced nephropathy. It showed a better performance in early diagnosis of contrast nephropathy than serum creatinine [27].

The clinical utility of IL-18 as a biomarker to predict or diagnose AKI in other settings such as drug induced kidney injury has not been evaluated. The pathophysiology of IL-18 is not well elucidated and its role may be a mediator of specific injury subtypes rather than a marker of injury. Further studies are required to demonstrate the usefulness of IL-18 as a biomarker in AKI [5].

KIDNEY INJURY MOLECULE-1

Kidney Injury Molecule-1 (KIM-1) also referred as T cell immunoglobulin and mucin domains-containing protein-1 (TIM-1) and hepatitis A virus cellular receptor 1 (HAVCR-1), is a type I transmembrane glycoprotein with an ectodomain containing a 6 cysteine immunoglobulin like domain, 2 N glycosylation sites and a mucin domain[28] . KIM-1 was shown to be significantly expressed in kidneys specifically in proximal tubular cells of humans after ischemia injury, whereas it was virtually absent or present at low levels in healthy kidneys. The ectodomain of KIM-1 is cleaved by metalloproteinases and sheds from cells both in vitro [29] and in vivo into the urine in rodents and humans after proximal tubular kidney injury [30, 31]. The full length form of KIM-1 is 104 kDa whereas the molecular weight of the shed form of KIM-1 ectodomain is approximately 90kDa. The selective KIM-1 expression by injured proximal tubular cells and the shedding of its ectodomain into urine provided a strong impetus for testing KIM- 1 as a biomarker of kidney damage.

KIM-1 mRNA levels are highly correlated with urinary KIM-1 excretion in rats exposed to ischemia for various periods, which indicates that kidney is the only source of KIM-1 production following a renal insult [30, 31]. Since that observation KIM-1 has evolved as a marker of proximal tubular injury, the hallmark of virtually all proteinuric, toxic and ischemic renal diseases. KIM-1 has been shown to be a highly sensitive and specific marker of kidney injury in several rodent models, including models of injury due to ischemia, Cisplatin, folic acid, gentamycin, mercury, chromium[31], cadmium[32], contrast agents[33] , cyclosporine[34] and protein overload[35]. The finding that KIM-1 protein was easily detected in urine soon after AKI in animal studies has motivated a number of translational studies to evaluate KIM-1 as a non-invasive biomarker for human AKI.

Urinary levels of KIM-1 with AKI correlated with the severity of acute tubular necrosis and corresponding levels of KIM-1 ectodomain in the urine of patients with clinically significant AKI [36]. Urinary KIM-1 predicted the adverse clinical outcomes and was significantly associated with composite endpoint of death or the need for dialysis even after adjustment for the disease severity and comorbid conditions [37]. In patients undergoing cardiac surgery urinary KIM-1 was independently associated with AKI. KIM-1 was predictive of AKI in prospective studies of patients undergoing cardiopulmonary bypass. The specificity of KIM-1 varied from 78% to 89% for 0 hours and from 90% to 96% for 3 hours. The usefulness of KIM-1 has been demonstrated not only as a urinary marker but also as a tool for evaluating kidney injury in kidney biopsy specimens by immunohistochemical methods. The level of KIM-1 protein expression in proximal tubule cells correlated with tubulo interstitial fibrosis and inflammation in kidney tissue specimens for a variety of kidney diseases [38]. KIM-1 also shows promise as a useful biomarker for CKD [39]. Recently the FDA have included KIM-1 in the small list of kidney injury biomarkers that they will now consider in the evaluation of kidney damage of animal studies of new drugs as part of their respective drug review processes[5].

LIVER - TYPE FATTY ACID - BINDING PROTEIN

Urinary fatty acid binding protein-1 (FABP-1) has been proposed to be a useful biomarker for early detection of AKI and monitoring of CKD. It is also known as L-Type or Liver-Type Fatty Acid-binding protein (L-FABP). It was first isolated in the liver as a binding protein for oleic acid and bilirubin. It binds selectively to free fatty acids and transports them to mitochondria or peroxisomes, where free fatty acids are beta oxidized and participate in intracellular fatty acid homeostasis. There are several different types of FABP which are ubiquitously expressed in a variety of tissues. The different FABPs' include liver (L), intestinal (I), muscle and heart (H), epidermal (E), ileal (I1), myelin (M), adipocyte (A), brain (B) and testis (T). L-FABP is expressed in proximal tubules of human kidney and localized in the cytoplasm. Increased cytosolic L-FABP in proximal tubular epithelial cells may be derived not only from endogenous expression but also from circulating L-FABP that might be filtered at the glomeruli and reabsorbed by tubular cells [5].

A number of clinical studies have explored the potential utility of urinary L-FABP as a biomarker for the early diagnosis of AKI. Urinary L-FABP correlated well with the ischemic time of the transplanted kidney and the length of hospital stay in human recipients of living related donor renal transplants [40]. L-FABP predicts the development of AKI in children undergoing cardiac surgery. It was elevated within 4 hours after cardiac surgery and these elevated levels anticipated the subsequent development of AKI with an accuracy of 81% [41]. Urinary L-FABP concentrations reflect the severity of sepsis and response to treatment. Urinary L-FABP levels are predictive of the need for short - term renal replacement therapy, but not hospital mortality [42, 43]. Because L-FABP is also expressed by liver, liver injury can be a potential contributor to increased urinary levels of L-FABP during AKI. Serum L-FABP levels do not have an influence on urinary levels and the urinary L-FABP levels are not significantly higher in patients with liver disease than in healthy subjects [41]. Urinary L-FABP has been investigated as an early diagnostic and predictive marker for contrast medium induced nephropathy [43, 44]. Urinary L-FABP increased significantly after 4 hours and remained elevated up to 48 hours after cardiac catheterization [43]. Several clinical studies suggest a potential role for urinary L-FABP in the clinical evaluation of AKI [44]. Larger multicenter studies that include early serial urine samples and larger patient cohorts are required for further evaluation of this promising marker [45].

N-ACETYLD-GLUCOSAMINIDASE

N-Acetyl-D-Glucosaminidase (NAG) is a lysosomal brush border enzyme that resides in the microvilli of tubular epithelial cells. Damage to these cells results in the shedding of this enzyme into urine. NAG has a high molecular weight of 130kDa, and hence plasma NAG is not filtered by the glomeruli. Its excretion into urine correlates with tubular lysosomal activity. Increased urinary concentrations of NAG have been found in patients with AKI, chronic glomerular disease, diabetic nephropathy, exposure to nephrotoxic drugs, delayed renal allograft function, environmental exposure, contrast medium-induced nephropathy and sepsis, and following cardiopulmonary bypass[37,45,46]. Urinary NAG concentrations were significantly higher in patients with contrast medium-induced nephropathy than in patients without such nephropathy within 24 hours after the administration of a contrast agent [46].

There are some limitations in the use of NAG as a marker of kidney injury. Inhibition of NAG enzyme activity has been reported in the presence of metal ions and at higher urea concentrations in urine. Moreover increased urinary levels of NAG have been reported in several nonrenal diseases, including rheumatoid arthritis and hyperthyroidism as well as in conditions with increased lysosomal activity without cellular damage [47, 48]. Because of concerns about its specificity, the clinical utility of NAG as a biomarker has been limited [5].

CONCLUSION

Of the reported candidates, NGAL is represented as a very promising biomarker for early diagnosis of AKI.

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