Looking for the early marker of renal injury

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Acute Kidney Injury is a complex and increasingly common syndrome. Practically all available markers reflect functional impairment rather than a true direct mark of cellular injury. An ideal AKI biomarker should be accurate, reliable, easy to measure with a standard assay, noninvasive, reproducible, and sensitive and specific with defined cutoff values. Studies have identified a relatively small number of genes that are specifically altered in acute renal tubular injury. Kim-1 is one of the best-characterized urinary biomarkers to date in both experimental animals and humans with renal disease. Also NGAL is at the top of many researchers' lists. Other biomarkers include IL-18, N-acetyl-β-d-glucosaminidase, and urinary liver-type fatty acid binding protein.

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Introduction

The World Kidney Day for the year 2013 adopted 'Stop Acute Kidney Injury' as the main theme because of its significant implication on the renal and general outcome in affected individuals. Acute kidney injury (AKI) is a complex and increasingly common syndrome, the diagnostics and treatment of which have remained essentially unchanged for decades, to the great frustration of clinicians and researchers. Serum creatinine, as a marker of global renal functional affection, fractional excretion of sodium, suggestive of acute tubular necrosis (ATN), fractional excretion of urea, as another sensitive marker to differentiate prerenal azotemia from ATN, have all been used with variable significance. Sensitivity and specificity of fractional excretion of urea were 48 and 75% in patients not on diuretics and 79 and 33% in patients on diuretics. The sensitivity and specificity of fractional excretion of sodium were 78 and 75% in patients not on diuretics and 58 and 81% in those who received diuretics [1,2]. Practically all available tests reflect functional impairment rather than a true direct mark of cellular injury.

However, cardiac troponin assays have made a tremendous impact on the management of acute coronary syndrome as they facilitate risk stratification and early diagnosis of acute coronary syndrome, thereby improving patient care and outcome [3].

Now, many experts predict that the field is poised for transformation over the next decade. Novel urine and serum biomarkers will be central to this revolution in care.

Markers of kidney injury

An ideal AKI biomarker should be accurate, reliable, easy to measure with a standard assay, noninvasive, reproducible, and sensitive and specific with defined cutoff values [4,5]. Urine represents an ideal body fluid for AKI biomarker assessment as it can be obtained noninvasively and repeatedly from a spontaneously voided sample or from an indwelling bladder catheter. The road to AKI biomarker validation spans discovery in preclinical studies on bodily fluids, assay development, retrospective study in completed trials, and prospective screening in ongoing trials.

Microarray technology has been used to identify novel genes that ideally are present at low levels in normal renal tissue but are upregulated in renal tissue of rats exposed to a broad range of nephrotoxic chemicals but not in renal tissue of rats exposed to non-nephrotoxic chemicals and chemicals that cause hepatic damage. These were typically large studies conducted in pharmaceutical companies or multicenter collaborative projects in which clinical chemistry, renal pathology, and gene changes were monitored in the same animals. These studies have identified a relatively small number of genes that are specifically altered in acute renal tubule injury. The front-runners are genes, such as osteopontin, clusterin, glutathione S-transferase α, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (Kim-1), tissue inhibitor of metalloproteinase-1, interleukin 18 (IL-18), and cystatin C [6–8].

Most early AKI biomarker validation studies have occurred in patients after cardiopulmonary bypass [9] or renal transplantation [10]. The reasons for selecting these populations are clear: the timing of kidney

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injury is known; biomarkers can be assessed repeatedly after the event; and the AKI event rates after these procedures are well documented. In addition, many early trials assessed AKI biomarkers in children, as they do not have many of the comorbidities (chronic kidney disease, diabetes, chronic inflammatory diseases) that could potentially confound AKI studies.

Kim-1 is one of the best-characterized urinary biomarkers to date in both experimental animals and humans with renal disease. In ischemic injury, Kim-1 expression is most prominent in the S3 segment in the corticomedullary region, which is the part of the nephron most susceptible to ischemic injury. Kim-1 not only functions as a biomarker but also has predictive value for acute renal injury; for example, Liangos *et al.* [11] showed in a cohort of 201 hospitalized patients with acute renal failure that urinary Kim-1 was predictive of adverse clinical outcome. Patients within the highest Kim-1 quartile had a 3.2-fold odds ratio for dialysis or hospital death compared with patients in the lowest quartile. Kim-1 has also been shown to have prognostic significance in transplant recipients; renal Kim-1 expression is more sensitive than histology for detecting early tubular injury in human allografts [12–14].

Of the many potential markers, NGAL is at the top of many researchers' lists. Also known as lipocalin-2 or siderocalin, NGAL is a protein in neutrophils that rises within 2–4 h after kidney injury. Arguably the most studied emerging marker of AKI, NGAL has been investigated across a broad range of clinical settings, including postcardiac surgery, critical and emergency care, and in adult and pediatric populations [15]. Other biomarkers considered by some researchers to be the most promising for AKI diagnosis, treatment, and prognosis include urine IL-18, N-acetyl-β-D-glucosaminidase, and urinary liver-type fatty acid binding protein. IL-18 is a proinflammatory cytokine indicative of renal tubular inflammation that has been found in significantly higher concentrations in patients with ATN in comparison with a variety of other conditions. N-acetyl-β-D-glucosaminidase is a high-molecular-weight lysosomal enzyme with considerable activity in renal proximal tubular cells and has been shown to increase in urine when there is proximal tubular cell necrosis. Liver-type fatty acid binding protein binds unsaturated fatty acids and lipid peroxidation products during tissue injury from hypoxia and has been shown to be significantly higher in patients with poor AKI outcomes. Preclinical studies also have shown renal papillary antigen 1 and 2 (RPA-1 and RPA-2) to be promising site-specific markers for drug-induced nephrotoxicity [16].

The next challenge for AKI biomarkers is to test their ability to direct therapeutic intervention or other clinical management. Yet, the heterogeneity of patient populations and varying precision of AKI biomarkers noted above presents a significant risk for inappropriate use of AKI biomarkers to decrease their utility. A recent concept of a prodome of 'renal angina' has been proposed to direct biomarker assessment only in patients who fulfill a combination of illness severity/risk and small changes in kidney function (creatinine changes or fluid overload) [17,18].

Conclusion

Considerable progress has been made in the last decade in identifying biomarkers of renal tubular injury in experimental animals and more importantly in humans with acute renal injury and in some cases of chronic renal injury. Improved analytical techniques and studies on micro RNA excretion in urine are exciting prospects for adding to our biomarker armory. New treatment strategies will add better value for early intervention in patients with AKI.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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