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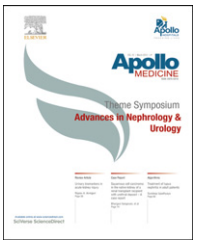

Review Article

Urinary biomarkers in acute kidney injury

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ABSTRACT

Acute kidney injury (AKI) is common in critically ill patients and is associated with high mortality and cost of hospitalization. The standard clinical diagnosis of AKI is based on the estimation of serum creatinine, which is a late and unsatisfactory marker of AKI. An intense search for an early biomarker has yielded considerable success in recent years and several urinary biomarkers to predict AKI early and reliably have been identified. Among these, urinary concentration of neutrophil gelatinase-associated lipocalin (NGAL) holds much promise and has been validated in several population of AKI in intensive care unit (ICU). Concentrations of other urinary biomarkers such as kidney injury molecute-1 (KIM-1), interleukin-18 (IL-18) and Liver fatty acid binding protein (L-FABP) are promising, but await validation. Sensitivity and specificity of urine NGAL (uNGAL) to predict AKI is best in homogeneous population and pediatric patients, but somewhat less in heterogeneous adult population in ICU. In addition, uNGAL predicts severe AKI, renal replacement therapy initiation and mortality in ICU. In future, further studies are likely to clarify and broaden the application of urine biomarkers in research and clinical practice in AKI. Future holds much promise in terms of therapeutic interventions based on biomarkers for primary and secondary prevention in AKI.

1. Introduction

Acute kidney injury (AKI) is common in hospitalized patients, occurring in up to 40% of patients admitted to intensive care unit (ICU) and is associated with high mortality and cost of therapy.[1] Recent studies indicate that even a small increment in serum creatinine (SCr) of 0.3 mg/dl is associated with significant increment in mortality and cost of hospitalization.[2] Till recently there were no uniform criteria to define AKI. Over the last decade, a collaborative effort between nephrologists and intensivists has lead to new criteria to define of AKI based on SCr and urine output. These diagnostic criteria namely risk, injury, failure, loss, and end-stage kidney (RIFLE) and acute kidney injury network (AKIN) have been validated and accepted as standard definitions worldwide.[3,4] However, the new "gold standard" criteria to define AKI appear to be flawed, since they take into consideration only the functional aspect of AKI, but not the structural injury.

SCr is an unsatisfactory criteria to define AKI for following reasons[5]: 1) rise in SCr occurs when glomerular filtration rate (GFR) has already declined by 30–40%, implicating that it is late marker of AKI, 2) creatinine generation is reduced in septic AKI compared to normal population, thereby overestimating GFR in them, 3) fluid overload, often seen in critically ill patients dilutes SCr concentration, thereby underestimating its true concentration in serum, and 4) SCr level is affected by age, gender, muscle mass and some medications that affect the generation and excretion of creatinine.

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All interventional studies in AKI in humans have either failed or are equivocal, in contrast to animal studies where benefit is often seen.[6] It is widely believed that, late intervention based on SCr has been the major stumbling block for the failed trials in human AKI. In this respect, an urgent need for a biomarker of AKI that could accurately detect AKI much before a rise in SCr has been widely felt both by clinicians and researchers. It is expected that interventional trials in AKI applied very early in the course of AKI detected by early biomarkers could yield positive results.

2. Biomarker in AKI: definition and characteristics

A biomarker is an indicator of a biological state. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[7] In the context of AKI, a biomarker is an objective measure of renal tubular injury. This biomarker would be detected in urine or in the blood following AKI and would be expected to quantify the degree of tubular injury thereby predicting the severity of AKI. Also, a biomarker of tubular injury would be useful in distinguishing acute tubular necrosis from pre-renal azotemia, which is easily reversible.

An ideal biomarker of AKI should have all or most of the following characteristics[5]: 1) basal levels should allow risk stratification, 2) remains elevated for a significantly longer period after injury, 3) appear very early, even before a clinical diagnosis of AKI can be made, 4) reliably make a clinical diagnosis of AKI with high sensitivity and specificity, 5) have wide spectrum of values correlating to degree of injury, 6) unaffected by demographics and clinical factors, 7) present in significant concentration in urine or blood, 8) easy to measure in the laboratory, 9) the measurement should be inexpensive and results available rapidly, and 10) able to predict accurately the severity of AKI and need for renal replacement therapy.

3. Early biomarker in AKI: suitable candidates

An intense search for an early biomarker of AKI has resulted in substantial progress in this area. Advances in the molecular biology in the last decade have enabled scientists to identify and test a number of biomarkers in AKI. Several candidates have been identified, but only few have withstood the vigorous test in laboratory and clinical setting.

The biomarkers of AKI can be classified as[8]: 1) Functional markers: SCr, serum cystatin-C (CyC), 2) Upregulated proteins: neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecute-1 (KIM-1), interleukin-18 (IL-18), Liver fatty acid binding protein (L-FABP), heat shock protein-72 (Hsp-72), 3) Low molecular weight proteins: urine CyC and 4) Enzymes: N-acetyl- β-D-glucosaminidase (NAG), alpha-glutathione s-transferase (a-GST) and π-glutathione s-transferase (pi-GST). Among these, urine NGAL (uNGAL) and plasma NGAL (pNGAL) concentrations are by far the most widely studied in clinical setting. My discussion in this paper will mainly focus on uNGAL, with a brief account of other clinically relevant biomarkers.

4. Biology of biomarkers of AKI

The temporal pattern of increase in urinary biomarkers in AKI following cardiac-bypass surgery is shown in Fig. 1.[9]

4.1. *Neutrophil gelatinase-associated lipocalin (NGAL)*

Among all the biomarkers, the measurement uNGAL is the most promising in predicting AKI. NGAL exists as a 25-kD monomer protein, belongs to the lipocalin superfamily. It was initially found in activated neutrophils, and has a role as an innate antibacterial factor. Subsequently, it was shown that several other types of cells, including those in the renal tubule produce NGAL in response to various injuries. Under physiologic conditions, NGAL is expressed in low concentrations in kidney, lung, and gastrointestinal tissue. Circulating NGAL is filtered by the glomerulus, and reabsorbed entirely in the proximal tubule. It is secreted in low concentrations by the thick ascending limb of the renal tubule and the normal urinary concentration of NGAL is very low (<5 ng/mL). In proximal tubular injury, NGAL synthesis is increased and reabsorption may decrease, resulting in increased urinary levels. In distal tubular injury there is increased distal renal tubular expression and synthesis of NGAL and increased urinary levels of NGAL. NGAL is protease resistant and does not seem to be degraded or metabolized after synthesis and secretion into the tubular lumen.[10–12]

The normal plasma NGAL (pNGAL) level in healthy adults is 50–90 ng/mL. The concentration of pNGAL increases in AKI, though the major source of pNGAL in AKI appears to be non-renal. Elevated pNGAL in AKI appears to be due to concomitant hepatic, pulmonary, intestinal tissue injury or release from immune cells such as neutrophils, macrophages, coupled with decreased glomerular filtration of NGAL and reduced proximal tubular absorption of filtered NGAL. However, the relative contribution of these factors causing elevation of plasma NGAL in AKI remains to be determined.[10–12]

Measurement of uNGAL and pNGAL are currently available commercially[13] using several methods such as radioimmunoassay, western blot and enzyme-linked

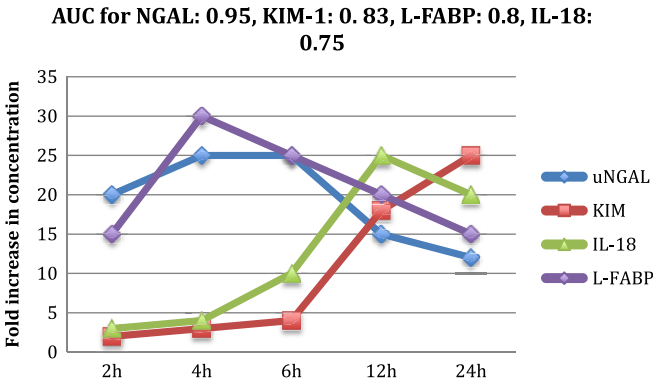

Fig. 1 – Temporal pattern of increase in urine biomarkers in AKI following cardiac-bypass surgery.