CHAPTER 24

The Role of Biomarkers in the Diagnosis and Management of Acute Kidney Injury

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OBJECTIVES

This chapter will:

1. Review the role of biomarkers in AKI diagnosis and management and discuss how they can be used in current clinical practice.
2. Discuss the contribution of susceptibility and exposures to risk for AKI.
3. Discuss the roles biomarkers can play in risk stratification, diagnosis, and management of AKI.
4. Review special considerations for pediatric patients.

Acute kidney injury (AKI) is a common and serious complication of acute illness and injury that is associated with several adverse outcomes. Serum creatinine is used widely in diagnosing AKI, but it is a late marker of change in kidney function with poor sensitivity. Thus different urinary and serum proteins have been investigated intensively as possible biomarkers for the early diagnosis of AKI. AKI is a complex process, and biomarkers could be used for different roles in the different stages. In addition to facilitating early diagnosis, AKI biomarkers can provide valuable insight into risk stratification for vulnerable patients. Furthermore, biomarkers could also function as molecular phenotyping tools that could be used to guide clinical intervention. However, effective use of biomarkers requires an understanding of their strengths, limitations, and individual performance characteristics. This chapter reviews the role of a variety of biomarkers in AKI management and discusses how they can be used in current clinical practice.

ROLE OF BIOMARKERS IN ACUTE KIDNEY INJURY RISK STRATIFICATION

Risk for AKI is determined by multiple factors: those inherent to the patient (susceptibility), such as age and comorbid conditions, and those that are imposed on the patient by the circumstances (exposures). Patients with high susceptibility may develop AKI even when the exposure is relatively small, whereas large exposures can result in AKI even in patients with low susceptibility. Understanding an individual's AKI risk profile may offer the opportunity for prevention or early intervention. Examples of susceptibilities for AKI include chronic liver disease/hepatic failure, hypertension, diabetes, and advanced age. Common exposures include sepsis, nephrotoxins, and cardiopulmonary bypass. Effective risk stratification to identify these patients is essential.

Several AKI risk prediction scores and kidney-specific scoring models have been developed and validated in the setting of cardiac surgery; however, most of these scores fail to predict milder forms of AKI. Currently available risk scores to predict AKI are often not sensitive or specific enough to identify high-risk individuals and poorly predict AKI progression. Recently, risk stratification of AKI has been evaluated and refined by the use of functional and damage biomarkers. These candidate biomarkers were identified based on AKI pathophysiology, usually by use of animal models. Creatinine is a functional marker, a surrogate for changes in glomerular filtration rate, which often occurs late in the time course of AKI. Injury biomarkers can detect AKI up to 12 to 66 hours before increases in serum creatinine. Subclinical AKI is marked by a lack of change in serum creatinine or urine output and by changes in damage biomarkers.

Cardiac surgery is a major risk factor for AKI, resulting from a complex set of exposures including cardiopulmonary bypass, tissue damage, cardiac dysfunction, and hemolysis.[1,2] Urinary and serum cystatin C have been studied in the Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) cohort, one of the largest studies in patients undergoing cardiac surgery. Preoperative serum cystatin C, but not urinary cystatin C, performed better than serum creatinine at predicting the risk of AKI.

Risk stratification for AKI[3] is important for acute decompensated heart failure (ADHF). For predicting AKI on the first day of intensive care unit (ICU) admission, a combination of serum cystatin C and urine kidney injury molecule-1 (KIM-1) yielded an excellent area under the receiver operating characteristic curve with high sensitivity and specificity. In patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention, urinary neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C at presentation were predictive of AKI. In addition, high serum levels of these biomarkers were associated with an elevated risk and more advanced stage of AKI. Combining urinary NGAL with a novel creatinine-based metric, both available soon after completion of surgery, may provide previously unavailable early and effective risk stratification for serious adverse outcomes after cardiac surgery.

Urinary insulin-like growth factor binding protein-7 (IGFBP7) and tissue inhibitor of metalloproteinase (TIMP)-2 were found to be increased in the urine of patients at high risk for AKI from a variety of causes.[4] In 2014 the US Food and Drug Administration approved a test based on [TIMP-2] [IGFBP7] (the product of TIMP-2 and IGFBP7 concentrations) to determine whether critically ill patients are at risk for developing moderate to severe AKI (equivalent to stage II to III). Urinary [TIMP-2] · [IGFBP7] values of 0.3 $(ng/mL)^2/1000$ or greater identify patients at high risk and those $>2(ng/mL)^2/1000$ at highest risk for AKI, and provide new information to support clinical decision making. For postoperative surgical ICU patients, the urinary [TIMP-2]·[IGFBP7] test accurately identified patients at risk

for developing AKI within the ensuing 12 hours, and its inclusion in clinical risk prediction models significantly enhances their performance.

ROLE OF BIOMARKERS IN EARLY DIAGNOSIS OF ACUTE KIDNEY INJURY

Conventional diagnosis of AKI depends on oliguria and increases in serum creatinine, both of which may be insensitive or delayed markers of kidney damage. Delayed diagnosis of AKI in the critically ill patient is likely related to increased morbidity and mortality, prolonged length of stay, and cost escalation. There are promising candidate biomarkers that reflect kidney function, detect an early and graded increase in tubular epithelial cell injury, and distinguish dehydration from AKI.

NGAL, which is detectable in the urine as early as 3 hours after renal injury, shows promise as a biomarker to help diagnose early AKI. NGAL has been tested in multiple studies of patients at risk for AKI resulting from sepsis, cardiac surgery, exposure to contrast media, or after renal transplantation. In these studies, the average sensitivity and specificity of NGAL measured 1 to 3 days before AKI diagnosis was 76% and 77%, respectively, for cardiac surgery patients, and 73% and 80%, respectively, for patients admitted to the ICU.[5] In a prospective study of patients undergoing cardiac surgery, urine cystatin C, NGAL, KIM-1, alpha glutathione S-transferases (α-GST), and π-GST demonstrated ability to diagnose stage III AKI at various postoperative time points.[6] Preoperative KIM-1 and α-GST predicted the development of stage I and stage III AKI. KIM-1 was very useful in differentiating acute tubular necrosis from other forms of AKI.

[IGFBP7] · [TIMP-2] biomarker panel best predicted AKI at 12 hours with area under the receiver operating characteristics curve (AUROC) of 0.80. These markers performed well in patients with sepsis (AUROC 0.82) and postoperatively (AUROC 0.85) when compared with traditional biomarkers and improved risk stratification for AKI well ahead of clinical manifestations (azotemia and oliguria). Urinary excretion of urinary liver-type fatty acid-binding protein (L-FABP) reflects stress of proximal tubular epithelial cells and correlates with severity of ischemic tubular injury. A meta-analysis of 15 prospective cohort studies demonstrated that L-FABP can discriminate AKI in hospital-based cohorts of high-risk patients. Other potential biomarkers for diagnosis of AKI include proteomics, microRNAs, urinary tubular enzymes, and urinary low-molecular-weight proteins. Further studies are needed to clarify the role of these markers.

Biomarkers in conjunction with clinical judgment may be ideal for determining the likelihood that a patient will develop AKI in the next 24 hours. A clinical model of renal angina index (RAI) has been developed to identify which critically ill patients would be at the greatest risk of development of AKI.[7,8] Renal angina is a model that uses patient demographic risk factors and clinical context in addition to early signs of injury such as oliguria or fluid overload to develop a practice to identify patients at high risk for AKI. The identification should heighten vigilance in monitoring of kidney function and signal care providers to use tactics to improve renal outcomes by increasing kidney perfusion and avoiding nephrotoxins.[9] RAI has a high negative predictive value to rule out AKI. When biomarkers were combined with the RAI, either individually or in pairs, the predictive performance for diagnosis of AKI significantly improved (AUC 0.80 RAI alone, increased to 0.84–0.88; $p < .05$ for each). In addition, the AUC for a single measurement of [IGFBP7]·[TIMP-2] to predict AKI at 12 hours was 0.82 (95% CI 0.76–0.88) for biomarkers alone and 0.86 (95% CI 0.80–0.90) when biomarkers were combined with clinical variables.[10] The furosemide stress test (FST) can be used for the purpose of evaluating tubular integrity and nephron function in the absence of a kidney biopsy. This combined serial testing, including initial testing with a strong negative predictive value (e.g., renal angina, biomarkers) followed by a more selective testing technique with higher positive predictive values (e.g., biomarkers, FST) could improve the diagnostic value for AKI.[11]

ROLE OF BIOMARKERS IN ACUTE KIDNEY INJURY INTERVENTION

Biomarkers may be useful in selecting patients who could benefit from various treatment modalities for AKI. Clinicians can use these biomarkers to determine which patients may be candidates for novel therapeutic strategies intended to improve kidney outcomes. Remote ischemic preconditioning (RIPC) with upper-arm blood pressure cuff inflations before surgery was used to prevent or decrease ischemic reperfusion induced AKI in patients for cardiac surgery. In those who had an increase in [TIMP-2] · [IGFBP7] after RIPC and before cardiopulmonary bypass, the incidence of AKI was reduced compared with the incidence in those who did not have elevated cell cycle arrest biomarkers.[12] This suggests that increases in biomarkers may be used to predict which patients will respond to RIPC, a potential therapeutic intervention for the prevention of AKI.[13] Measurement of urinary angiotensinogen could play a role in identifying patients with AKI who are likely to develop chronic kidney disease (CKD) and could potentially benefit from the renin-angiotensin system (RAS) blockade.[14,15]

Biomarkers also may be able to guide decision making for initiation of renal replacement therapy (RRT) in patients with AKI. Selected studies demonstrated that NGAL, cystatin C, N-acetyl-β-D-glucosamininidase (NAG), KIM-1, and alpha 1-microglobulin had the potential to distinguish patients in whom RRT was needed.[8] This would imply that these biomarkers may be integrated into clinical decision algorithms and synergistically could improve current ability to identify patients in whom RRT should be initiated early.[16,17] However, published studies have many recognized limitations, which preclude the ability to adapt their findings into clinical practice today. Although currently available data are not sufficient to conclude that biomarkers should be used routinely for clinical decision making for RRT initiation, additional data may in the future significantly modify the clinical variability for initiation of RRT and potentially translate into improved outcomes and cost effectiveness. A potential approach to future biomarker strategies for RRT initiation, integrating these biomarkers with traditional clinical factors, has been proposed.[8,16]

Biomarkers could be used to exclude those participants at low risk for an outcome, to enrich the study population sampled and increase the event rate during clinical trials.[18] Using biomarkers to aid in the selection of a higher-risk patient group for a study could lead to a focus on those more likely to benefit from an intervention. In the recent ELAIN trial, KDIGO classification combined with plasma NGAL (>150 ng/dL) was used to randomize patients for early versus late RRT.[19] Similarly, the use of enrichment is

also important clinically because efforts to improve clinical outcomes will be most effective when focused on the highest risk groups.[18]

ROLE OF BIOMARKERS IN ACUTE KIDNEY INJURY PROGNOSIS

The ability of biomarkers to predict AKI progression to CKD or renal recovery has been investigated. Proteinuria and microalbuminuria, classical markers of CKD progression, have been used and validated for the progression of AKI to CKD. KIM-1, NGAL, and urinary cystatin C could play a role in prediction of renal recovery. The role of biomarkers, including NGAL, KIM-1, and nephronectin (NPNT), in the recovery process has been studied, but it has not reached the point of widespread clinical implementation.[19] Activation of RAS has long been recognized as an important contributor to chronic renal injury. Urinary angiotensinogen has been proposed as a marker of intrarenal RAS activity, and it is predictive of progression of CKD.[14,15] Information regarding specific biomarkers of renal repair or progression is scarce but growing.[20]

Many studies have established an association between AKI biomarkers and short-term outcomes defined by need for RRT, prolonged hospitalizations, and death. The TRIBE investigators have demonstrated that the highest tertile of peak urinary NGAL, IL-18, KIM-1, LFABP, and albumin was associated independently with a 2.0- to 3.2-fold increased risk for mortality compared with the lowest biomarker tertile. Preoperative and postoperative plasma NGAL were associated with long-term outcomes such as 3-year mortality rates. A [TIMP-2] · [IGFBP7] value greater than 2 $(ng/mL)^2/1000$ was associated with increased mortality or a need for RRT over the next 9 months. Measurement of urinary angiotensinogen may allow the prediction of severe AKI and other adverse outcomes in the ICU. The combination of urinary angiotensinogen and renin predicts progression to very severe disease in patients with early AKI after cardiac surgery. NGAL was useful for predicting renal recovery, defined as being alive, not requiring dialysis during hospitalization.

BIOMARKERS IN ACUTE KIDNEY INJURY: PEDIATRIC PERSPECTIVE

The incidence of AKI in critically ill children varies between 8% and 89%, depending on the definition of AKI, although undoubtedly has significant associated morbidity and mortality independent of degree of critical illness.[21] Children can provide a unique cohort in AKI research given the relative lack of comorbidities and chronic kidney disease as compared with adult populations. With the changing epidemiology of pediatric AKI from intrinsic renal diseases to systemic illnesses and nephrotoxic medication exposure, monitoring for AKI in critically ill children has become essential. Even small increases in serum creatinine are associated with increased pediatric morbidity and mortality,[22] highlighting the need for early detection, effective supportive care, and/or intervention. There is a variability in serum creatinine with size, gender, and gestational age at birth, which prove to be particularly problematic in neonates, infants, and children. Premature neonates are at high risk for AKI and are vulnerable to renal injury,[23] but detection of AKI continues to be problematic in this population. The challenge is determining appropriate alternative biomarkers that are sensitive and specific to detect AKI in heterogeneous populations across age groups.

Many of the studies in pediatric AKI started with the population of children who underwent cardiopulmonary bypass, because the time of renal insult is defined. Six urinary biomarkers, including NGAL, KIM-1, L-FABP, IL-18, TIMP-2, and IGFBP7, have been validated as predictive of AKI in this population before any noticeable rise in serum creatinine.[24] A prospective study assessing pediatric critically ill children showed that when biomarkers are used in clinical context, their ability to accurately predict AKI increases, analogous to the use of troponins in adult patients with chest pain to predict acute coronary syndrome. Urinary NGAL was the biomarker that provided the highest level of discrimination for the prediction of severe AKI in the pediatric critically ill population for this study. Assessing biomarkers in children who are at highest risk for development of AKI (those with critical illness, requiring cardiorespiratory support, history of transplantation, and fluid overload) increases clinical efficacy. This RAI can risk stratify patients for subsequent development of severe AKI, with the potential to be used as a quick bedside tool.

The use of biomarkers for detection and diagnosis of AKI is valuable in the general pediatric population and those presenting to an emergency department. Biomarkers that have the ability to distinguish the relative timing of renal insult could be incredibly beneficial in diagnosis and prognosis for patients who have unknown chronology of kidney injury. The potential for rapid detection assays could prove beneficial. The utility of using multiple biomarkers to increase accuracy of AKI diagnosis has been pursued in several studies, one of which showed better ability to predict severe or persistent AKI when urinary NGAL and plasma cystatin C were used as a composite risk.[17] Incorporation of biomarkers with the RAI could be used for prediction of severe AKI in critically ill children.[24]

AKI prognosis becomes especially important in the pediatric population given the relative longer life expectancy. Unfortunately, AKI has significant effects on childhood morbidity with associated increased length of hospital stay and longer duration of mechanical ventilation in addition to increased mortality. Urinary IL-18 and L-FABP can remain elevated at 7 years in children who underwent cardiopulmonary bypass with associated AKI, although clinical relevance of the elevated urinary biomarkers is unclear.[25]

In conclusion, traditional parameters provide some guidance for the diagnosis of AKI, but early, more sensitive, affordable, specific, clinically acceptable biomarkers of AKI also are needed. As the development of proteomics, metabolomics, and basic biologic understanding of AKI progresses, more and more novel biomarkers will be identified. The combination of biomarkers indicating kidney dysfunction and damage is likely to have higher sensitivity and specificity. Clinical experience with biomarkers is expanding rapidly.

Key Points

1. Acute kidney injury (AKI) is a common problem in clinical practice, but the diagnosis is delayed because of the inherent limitation of current diagnostic tools.

2. Biomarkers have the potential to be used for AKI risk stratification, early diagnosis, guidance for intervention, and outcome prognosis, but their performance has been variable.
3. Combining biomarkers with clinical judgment scores may improve the AKI detective ability.
4. Few biomarkers are in widespread clinical use, and only one test has yet been cleared by the US Food and Drug Administration. New markers for disease progression, cause, and response to therapy are being developed.

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