

Neutrophil Gelatinase Associated Lipocalin-Ngal: An Emerging Biomarker for Acute Kidney Injury

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Abstract: *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 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. 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. Fortunately, understanding the early stress response of the kidney to acute injury has revealed a number of potential biomarkers. Neutrophil Gelatinase Associated Lipocalin (NGAL) is one among them. This paper highlights the role of NGAL as a biomarker of AKI.*

Keywords: AKI, biomarker, creatinine, early, NGAL

1. 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].

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]. AKI is largely asymptomatic and establishing the diagnosis is based on functional biomarker such as serial serum creatinine measurements ^[3]. It is considered as “the gold standard” biomarker of kidney function ^[4]. 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^[3]. Recently many novel technologies in the field of genomics, proteomics and metabolomics have made it easier to interrogate potential biomarkers ^[5]. A renewed interest in discovering novel biomarkers have been reported for Acute Kidney Injury ^[3]. A number of new biomarkers have been proposed and researched to predict AKI at an early stage. 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 ^[3]. Of the reported candidates, NGAL is represented as a very promising biomarker for early diagnosis of AKI. NGAL belongs to the lipocalin family.

2. NGAL

NGAL has been identified and investigated extensively as an early biomarker of AKI ^[3]. Human NGAL was originally identified as a novel protein isolated from secondary granules of human neutrophils ^[6]. It is a 25kDa protein covalently bound to neutrophil gelatinase ^[7]. NGAL

expression is markedly induced in injured epithelial cells including kidney, colon, liver and lung ^[8]. The biological role of NGAL induction is one of the marked preservation of function, attenuation of apoptosis and an enhanced proliferative response ^[9]. Preclinical transcriptome profiling studies have identified Ngal gene to be one of the most upregulated genes in the kidney very early after acute injury in animal models ^[10]. Also the downstream proteomic analyses revealed NGAL to be one of the most highly induced proteins in the kidney after ischemic or nephrotoxic AKI in animal studies ^[11]. This has led to a number of studies for evaluating NGAL as a noninvasive biomarker in human AKI ^[3].

Emerging experimental and clinical evidence indicate that in the early phases of AKI from diverse etiologies, NGAL accumulates in two distinct pools, a systemic and a renal pool. The increased NGAL mRNA expression in the distant organs like liver and spleen, the overexpressed protein is released into the circulation. The release of NGAL from neutrophils, macrophages and other immune cells (NGAL is an acute phase reactant) and the decrease in the clearance of NGAL due to the decrease in GFR following AKI constitute the systemic pool. The rapid up regulation of NGAL mRNA in the thick ascending limb of the loop of Henle and the collecting ducts with the resultant synthesis of NGAL protein in the distal nephron constitute the renal pool. The secretion into the urine comprises the major fraction of urinary NGAL ^[12], ^[13]. Although urinary diagnostics have several advantages, including the non-invasive natured sample collection and few interfering proteins, some disadvantages also exist. These include difficulty in obtaining samples from patients with oliguria, potential changes in urinary biomarker concentration induced by the overall fluid status and diuretic therapy, and the fact that several urinary biomarkers have in the past shown insufficient sensitivity or specificity. Serum based diagnostics have revolutionized intensive care medicine ^[14]. Both plasma and urinary NGAL levels were found to be increased and useful in predicting AKI ^[3].

NGAL for the Prediction of AKI

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 noninvasive 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^[15]. 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^[3].

NGAL in Cardiac Surgery associated AKI

The value of NGAL as a clinical marker was first demonstrated in a prospective study of children undergoing cardiopulmonary bypass. Both serum and urinary NGAL levels were upregulated within two hours in patients who developed AKI. A cut off value of 50 microgram/ L was 100% sensitive and 98% specific in predicting AKI^[16]. Another follow up study in children showed that 2 hour postoperative serum NGAL levels were predictive of AKI (with AUC of 0.96) and correlated with postoperative changes in serum creatinine concentration, duration of AKI and length of hospital stay. NGAL level at 12 hours strongly correlated with mortality. The NGAL levels revealed a 10 fold or more increase in urine and plasma of patients with AKI^[17]. Other studies also showed that urine and plasma NGAL levels were excellent independent predictors of AKI in the 2-6 hour specimen with AUC of the ROC of over 0.9^{[18], [19]}. These findings have now been confirmed in prospective studies of adults who developed AKI after cardiac surgery. Urinary and plasma NGAL levels were significantly elevated 2-6hours after surgery^[20]. However AUC-ROCs for the prediction of AKI have been rather disappointing when compared with pediatric studies and have ranged widely from 0.61 to 0.96. This somewhat inferior performance in adult populations may be reflective of confounding variables such as older age groups, preexisting kidney disease, prolonged bypass times, chronic illness and diabetes. The predictive performance of NGAL also depends on the definition of AKI employed, as well as on the severity of AKI. The predictive value of plasma NGAL post cardiac surgery was higher for more severe AKI compared with less severe AKI^[21]. Similarly the discriminatory ability of NGAL for AKI increased with increasing severity as classified by the RIFLE criteria^[22]. Also urinary NGAL levels but not serum creatinine concentrations correlated with cardiopulmonary bypass time and aortic cross clamp time^{[23], [24]}. Further the predictive power of urinary NGAL for AKI after cardiac surgery varied with baseline renal function with optimal discriminatory performance in patients with normal preoperative renal function. A metaanalysis of published studies in all patients after cardiac surgery revealed an overall AUC-ROC of 0.78 for prediction of AKI when NGAL was measured within 6 hours of initiation of cardio pulmonary bypass and AKI was defined as greater than 50% increase in serum creatinine^[25].

NGAL IN AKI IN CRITICAL CARE SETTING

In the intensive care unit setting the main problem is to establish the time of renal insult. Often, the baseline kidney function also remains unknown. This patient population is extremely heterogeneous and the etiology is often unclear^[26]. Upto 60% of patients may have already sustained AKI on admission to the intensive care unit^[27]. Sepsis accounts for 30-40% of all AKI encountered in critically ill patients and generally portend a poorer prognosis with lower survival^{[28], [29]}. Other etiologies for AKI in this setting include exposure to nephrotoxins, hypotension, kidney ischemia, mechanical ventilation and multi organ disease. These etiologies are associated with distinct mechanisms of injury that are active at different times with different intensities and may act synergistically^[3].

In Critically ILL Multiple Trauma Patients

Acute Kidney Injury (AKI) is a frequent complication of severe trauma. In a retrospective cohort of 1033 critically ill adult trauma patients, the prevalence of AKI was 23.8%. Although only 10% of these patients were in need of renal replacement therapy, the presence of even mild AKI was associated with a 2-fold increase in intensive care unit mortality and length of stay. In a homogenous trauma population within 24 hours from injury and before the appearance of secondary complications such as sepsis, urinary NGAL was found to serve as an early and reliable predictive marker of AKI from the 1st day of injury^[29].

In Critically Ill Patients with Septic Shock

AKI is very common and potentially devastating problem in critically ill children and adults. The reported incidence of AKI in this population varies greatly due to lack of a standard consensus definition. AKI affects between 5% and 50% of critically ill patients in reported series. The mortality and morbidity remain high in these patients. Studies have shown that both serum and urinary NGAL were significantly increased within 24 hours of admission to pediatric intensive care unit in critically ill children^[30]. Serum NGAL values of critically ill children with septic shock were increased compared with healthy controls and those with Systemic Inflammatory Response Syndrome (SIRS). It has also been suggested that NGAL may be a marker of Multi Organ Dysfunction Syndrome (MODS) similar to C reactive protein, procalcitonin or interleukin – 6^{[30], [31]}.

In studies of adult intensive care patients, plasma NGAL concentrations on admission constituted a very good to outstanding biomarker for development of AKI within the next 2 days^{[32], [33]}. Also in patients undergoing liver transplantation, a single plasma NGAL level obtained within 2 hours of reperfusion was highly predictive of subsequent AKI^[34]. In a study of adults in emergency department setting, a single measurement of urinary NGAL at the time of initial presentation predicted AKI and strictly distinguished prerenal azotemia from intrinsic AKI and from chronic kidney disease^[35]. Thus NGAL is a useful early AKI marker that predicts the development of AKI, even in heterogeneous group of patients with multiple comorbidities and with unknown timing of kidney injury. However

patients with septic AKI display the highest concentrations of both plasma and urine NGAL, when compared to those with nonseptic AKI^{[3], [36]}.

NGAL in Contrast Induced Nephropathy (CIN)

The need for contrast enhanced imaging has increased in all fields of modern medicine. While the contrast enhanced procedures are fairly safe in the healthy population, patients with preexisting impaired renal and/or cardiac function are prone to develop a reversible form of acute kidney injury called contrast induced nephropathy. It begins soon after the contrast is administered^[37]. The underlying pathology is believed to be acute tubular necrosis, with renal vasoconstriction resulting in medullary hypoxemia and direct cytotoxic effects of the contrast agents^[38]. The reported incidence of CIN varies widely ranging from 0% to over 50%. This variability is due to the presence or absence of risk factors (primarily CKD), definition of contrast induced nephropathy, the amount and type of contrast agent administered, prospective or retrospective design and whether other causes of acute renal failure unrelated to contrast media were excluded^[39]. Percutaneous coronary intervention (PCI) was associated with low risk of CIN even in patients with CKD^[40]. Serum NGAL was significantly increased after 2, 4 and 8 hours while urine NGAL was increased 4, 8 and 24 hours after procedure in both diabetic and non-diabetic individuals. NGAL levels were significantly higher in patients with CIN starting 2 hours (serum NGAL) as 4 hours (urinary NGAL) after PCI. Even after 48 hours, serum and urinary NGAL levels were significantly higher in patients with CIN when compared to patients without CIN^[41].

NGAL in AKI of Kidney Transplantation

Delayed Graft Function (DGF) is defined as renal failure persisting after transplantation^[42]. The definition of DGF refers to oliguria or the requirement for dialysis in the first week after transplantation. The two major pre renal causes immediately after transplantation are hypotension and volume depletion. Post ischemic acute tubular necrosis or reperfusion injury is usually the most common cause of DGF^[43]. Studies have shown that urinary NGAL may represent an early predictive biomarker of DGF. It was found that in patients with DGF, peak postoperative serum creatinine requiring dialysis typically occurred 2-4 days after transplantation whereas urine NGAL values on day 0 were maximally elevated in the DGF group compared to the groups with prompt graft function^[44]. Monitoring NGAL levels might allow for the prediction of graft recovery and the need for hemodialysis after kidney transplantation from a donor after cardiac death. A dramatic fact in serum NGAL was observed on the first postoperative day after transplantation from a living related donor and it reached normal range on the 10th postoperative day. All the patients after cadaveric kidney transplantation required hemodialysis for 5-22 days^[45]. Recently, it was found that serum NGAL decreased significantly as early as day 1 after kidney transplantation, prior to a fall in cystatin C and creatinine. However for the patients who developed DGF, a fall in NGAL, cystatin C or creatinine was not observed^[46]. Urinary levels of NGAL were found to be early noninvasive

and accurate predictors of both the need for dialysis within the first week of kidney transplantation and 3 month recovery of graft function^[47].

NGAL for Monitoring Trials in AKI

NGAL is emerging as an early biomarker in interventional trials because of its high predictive properties for AKI. For example, reduction in urine NGAL was employed as an outcome variable in clinical trials demonstrating the improved efficacy of a modern hydroxyethyl starch preparation over gelatin or albumin in maintaining renal functions in cardiac surgery patients^[48]. Urine NGAL levels have also been utilized to document the efficacy of a miniature cardiopulmonary bypass system in the preservation of kidney function when compared to standard cardiopulmonary bypass^[49]. Adults, who developed AKI after aprotinin use during cardiac surgery, displayed a dramatic rise in urine NGAL in the immediate postoperative period attesting to the potential use of NGAL for the prediction of nephrotoxic AKI^[50]. NGAL measurements are currently included as an outcome variable in several ongoing clinical trials. The use of predictive and sensitive biomarker such as NGAL in clinical trials will result in a reduction in required sample size and also on the cost^[3].

NGAL in the Prognosis of AKI

Studies have shown that the early measurements of NGAL levels are used for predicting the severity and clinical outcomes of AKI. In children undergoing cardiac surgery, early postoperative plasma NGAL levels strongly correlated with the duration and severity of AKI, length of hospital stay, dialysis requirement and death^[51]. In a multicenter study of children with diarrhea associated hemolytic uremic syndrome, urine NGAL obtained early during the hospitalization, predicted the severity of AKI and hemodialysis requirement with high sensitivity^[52]. Early urine NGAL levels also predicted the duration of AKI in a heterogeneous cohort of critically ill pediatric patients^[195]. In adults undergoing cardiopulmonary bypass, urine NGAL was found to be highest in those patients who subsequently required renal replacement soon after surgery^{[17], [20]-[22]}. Similar results were observed in the adult critical care setting also^[32-35]. A number of studies conducted in the cardiac surgery and critical care populations have identified early NGAL measurements as a very good mortality marker. Serum NGAL measured at the inception of renal replacement therapy was an independent predictor of 28 day mortality^[49]. In kidney transplant patients undergoing either protocol biopsies or clinically indicated biopsies, urine NGAL measurements were found to be predictive of tubulitis or other tubular pathologies^[53] suggesting the possibility that NGAL might represent a noninvasive screening tool for the detection of tubulointerstitial disease in the early months following kidney transplantation^[3].

3. Conclusion

NGAL has been extensively investigated as an early biomarker for AKI in various clinical settings like cardiac surgery, intensive care unit, contrast induced nephropathy, kidney transplantation etc. NGAL also satisfies a number of

characteristics of an ideal AKI biomarker. These include noninvasiveness, rapidity of measurements, sensitive to facilitate early detection and allow for risk stratification, amendable to clinical assay platforms and the results predict clinical outcomes, efficacy of therapies and expedite drug development process.

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