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Neutrophil gelatinase-associated lipocalin (NGAL):

A new marker of kidney disease

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Abstract

The incidence of both acute kidney injury (AKI, previously referred to as acute renal failure) and chronic kidney disease (CKD) is reaching epidemic proportions. In both situations, early intervention can significantly improve the prognosis. However, the paucity of early, predictive, non-invasive biomarkers has impaired our ability to institute potentially effective therapies for these common clinical conditions in a timely manner. The current status of one of the most promising novel biomarkers, namely neutrophil gelatinase-associated lipocalin (NGAL), is presented in this review. The evidence for the role of NGAL measurements in a variety of clinical situations leading to AKI (cardiac surgery, kidney transplantation, contrast nephropathy, haemolytic uraemic syndrome and in the intensive care setting) or to CKD (lupus nephritis, glomerulonephritides, obstruction, dysplasia, polycystic kidney disease, IgA nephropathy) is explored. The emerging utility of standardized clinical platforms for reliable measurement of NGAL in plasma (Triage® NGAL Device; Biosite Incorporated) and urine (ARCHITECT® analyzer; Abbott Diagnostics) is also discussed. It will be important in future studies to validate the sensitivity and specificity of NGAL concentration measurements in clinical samples from large cohorts and from multiple clinical situations. Such studies will be facilitated by the anticipated widespread availability of standardized commercial tools in the near future.

Keywords

Acute kidney injury; acute renal failure; biomarker; chronic kidney disease; contrast nephropathy; kidney transplantation; lipocalin; nephrotoxicity

Introduction

There is an urgent need for early predictive biomarkers of both acute kidney injury (AKI, previously referred to as acute renal failure) and chronic kidney disease (CKD). In both situations, early intervention can significantly improve the prognosis. However, currently

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Disclosures
Biosite® Incorporated has signed an exclusive licensing agreement with Cincinnati Children's Hospital for developing plasma NGAL as a biomarker of acute renal failure and chronic kidney disease. Abbott Diagnostics has signed an exclusive licensing agreement with Cincinnati Children's Hospital for developing urine NGAL as a biomarker of acute renal failure and chronic kidney disease.

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available biomarkers (such as serum creatinine concentrations) are fraught with imprecision, and their delayed response has impaired our ability to institute potentially effective therapies in a timely manner. Fortunately, the application of innovative technologies has identified candidates that are emerging as early biomarkers of AKI and CKD. The current status of one of the most promising novel biomarkers, namely neutrophil gelatinase-associated lipocalin (NGAL), is presented in this review.

Urgent need for early biomarkers in acute kidney injury

The incidence of AKI in all hospitalized patients is approximately 7 % [1]. In critically ill patients, the overall prevalence of AKI requiring dialysis was 5.7 % with a mortality of 60.3 % [2]. An alarming increase in morbidity and mortality associated with AKI has been demonstrated, and AKI is a major risk factor for the development of non-renal complications and an independent contributor to mortality [3]. While recent advances have suggested novel therapeutic approaches in animal models, translational efforts in humans have yielded disappointing results. The reasons for this include an incomplete understanding of the underlying pathophysiology, and the lack of early biomarkers for AKI [4,5]. In current clinical practice, AKI is typically diagnosed by measuring serum creatinine concentrations. Unfortunately, creatinine is an unreliable indicator during acute changes in kidney function. First, serum creatinine concentrations can vary widely with age, gender, muscle mass, muscle metabolism, medications and hydration status. Second, serum creatinine concentrations may not change until a significant amount of kidney function has already been lost. Third, during acute changes in glomerular filtration, serum creatinine concentration does not accurately depict kidney function until steady state equilibrium has been reached, which may require several days. However, animal studies have shown that while AKI can be prevented and/or treated by several maneuvres, these must be instituted very early after the initiating insult, well before the serum creatinine even begins to rise. The quest to improve early diagnosis of AKI is an area of intense research [5,6]. Conventional urinary biomarkers such as casts and fractional excretion of sodium have been insensitive and non-specific for the early recognition of AKI. Other traditional urinary biomarkers such as filtered high molecular weight proteins and tubular proteins or enzymes have also suffered from lack of specificity and a dearth of standardized assays. Fortunately, emerging technologies such as functional genomics and proteomics have uncovered novel candidates that are emerging as biomarkers [5,6].

NGAL in acute kidney injury: preclinical studies

Several investigators have used molecular techniques such as cDNA microarrays and subtractive hybridizations combined with downstream proteomic analysis to identify novel pathways, biomarkers and drug targets in AKI. Supavekin et al. identified neutrophil gelatinase-associated lipocalin (*Ngal*, also known as *lcn2*) as one of the most upregulated genes in the early post-ischaemic mouse kidney [7,8], a finding that has now been confirmed in several other transcriptome profiling studies following ischaemic and nephrotoxic kidney injuries. Downstream proteomic studies have also revealed NGAL to be one of the earliest and most robustly induced proteins in the kidney after ischaemic or nephrotoxic AKI in animal models [9-14]. Importantly, NGAL protein is easily detected in the blood and urine soon after AKI in pre-clinical studies [9-12]. These findings have initiated a number of translational studies to evaluate NGAL as a novel biomarker in human AKI.

NGAL in acute kidney injury: clinical studies

In a cross-sectional study, subjects in the intensive care unit with established acute renal failure displayed a greater than 10-fold increase in plasma NGAL concentration and more than a 100-fold increase in urine NGAL concentration by Western blotting when compared to normal controls [12]. Both plasma and urine NGAL concentrations correlated highly with serum

creatinine concentrations. Kidney biopsies in these patients showed intense accumulation of immuno-reactive NGAL in 50 % of the cortical tubules. These results identified NGAL as a widespread and sensitive response to established AKI in humans.

In a prospective study of children undergoing cardiopulmonary bypass, AKI (defined as a 50 % increase in serum creatinine) occurred in 28 % of the subjects, but the diagnosis using serum creatinine was only possible 1-3 days after surgery [15]. In marked contrast, NGAL measurements by Western blotting and by ELISA revealed a robust 10-fold or more increase in the urine and plasma, within 2-6 h of the surgery in patients who subsequently developed AKI. Both urine and plasma NGAL (at a cut-off value of 50 μg/L) were powerful independent predictors of AKI, with an area under the receiver-operating characteristic curve (AUC) of 0.998 for the 2-h urine NGAL and 0.91 for the 2-h plasma NGAL concentration [15]. On multivariate analysis, the 2-h NGAL concentration was a strong independent predictor of clinical outcomes such as duration of AKI among cases [16]. Thus, plasma and urine NGAL have emerged as sensitive, specific and highly predictive early biomarkers of AKI after cardiac surgery in children. These findings have now been confirmed in a prospective study of adults who developed AKI after cardiac surgery, in whom urinary NGAL concentration was significantly elevated by 1-3 h after the operation [17]. AKI, defined as a 50 % increase in serum creatinine concentration, did not occur until the third postoperative day. Patients who did not encounter AKI also displayed a significant increase in urine NGAL concentration in the early postoperative period, although to a much lesser degree than in those who subsequently developed AKI. The AUC reported in this study was 0.74 for the 3-h NGAL and 0.80 for the 18-h NGAL, which is perhaps reflective of the confounding variables typically encountered in adults.

NGAL has also been evaluated as a biomarker of AKI in kidney transplantation. Biopsies of kidneys obtained 1 h after vascular anastomosis revealed a significant correlation between NGAL staining intensity and the subsequent development of delayed graft function [18]. In a prospective multicentre study of children and adults, urine NGAL concentrations in samples collected on the day of transplant clearly identified cadaveric kidney recipients who subsequently developed delayed graft function and dialysis requirement (which typically occurred 2-4 days later). The ROC curve for prediction of delayed graft function based on urine NGAL concentration at day 0 showed an AUC of 0.9, indicative of an excellent predictive biomarker [19]. In a recent retrospective study of kidney transplant patients undergoing either protocol biopsies or clinically indicated biopsies, urine NGAL concentrations were found to be significantly increased in subjects with tubulitis or other tubular pathologies [20]. Urine NGAL also tended to be increased in subjects with subclinical tubulitis (p=0.06), raising the possibility of NGAL representing a non-invasive screening tool for the detection of tubulo-interstitial disease in the early months following kidney transplantation.

Several investigators have examined the role of NGAL as a predictive biomarker of nephrotoxicity following contrast administration [21,22]. In a prospective study of children undergoing elective cardiac catheterization with contrast administration, both urine and plasma NGAL predicted contrast-induced nephropathy (defined as a 50 % increase in serum creatinine from baseline concentration) within 2 h after contrast administration [22]. Using a cut-off value of 100 μg/L, the AUC for prediction of contrast nephropathy was excellent for the 2-h urine NGAL (0.92) as well as the 2-h plasma NGAL (0.91). By multivariate analysis, the 2-h NGAL concentrations in the urine and plasma were found to be powerful independent predictors of contrast nephropathy [22].

Urine NGAL has also been shown to predict the severity of AKI and dialysis requirement in a multicentre study of children with diarrhoea-associated haemolytic uraemic syndrome [23]. Using a cut-off of 200 μg/L, NGAL in urine obtained soon after hospitalization was

significantly increased in those children who subsequently developed severe AKI requiring dialysis. Recently published results also suggest that plasma and urine NGAL concentrations represent predictive biomarkers of AKI in the intensive care setting, being able to predict this complication about 2 days prior to the rise in serum creatinine concentration [24]. Thus, NGAL is a useful early AKI marker that predicts development of AKI even in a heterogeneous group of patients with unknown timing of kidney injury.

In summary, NGAL is emerging as a centre-stage player in the AKI field as a novel predictive biomarker. However, it is acknowledged that the studies published thus far are small, in which NGAL appears to be most sensitive and specific in relatively uncomplicated patient populations with AKI. NGAL concentrations may be influenced by a number of coexisting variables such as pre-existing renal disease [25] and systemic or urinary tract infections.

All results described thus far have been obtained using research-based assays, which are not a practical option in the clinical setting. The availability of validated clinical tools for NGAL concentration measurements could revolutionize renal diagnostics. In this regard, a standardized point-of-care kit has been devised for the measurement of plasma NGAL (Triage® NGAL Device, Biosite Incorporated). In a pilot study with 40 plasma samples and 12 calibration standards, NGAL measurements by research ELISA and by the Triage® NGAL device were highly correlated (r=0.94). In a subsequent study of 120 patients undergoing CPB, AKI (50 % or greater increase in serum creatinine concentration) developed in 45 patients, but the diagnosis using serum creatinine was delayed by 2-3 days after CPB [26]. In contrast, mean plasma NGAL concentration measured with the Triage® NGAL device increased 3-fold within 2 h of CPB, and remained significantly elevated for the duration of the study. By multivariate analysis, plasma NGAL concentration at 2 h post-CPB time was the most powerful independent predictor of AKI (β=0.004, p<0.0001). For the 2-h plasma NGAL concentration, the area under the curve was 0.96, sensitivity was 0.84 and specificity was 0.94 for prediction of AKI using a cut-off value of 150 μg/L. The 2-h postoperative plasma NGAL concentrations strongly correlated with change in creatinine concentrations (r=0.46, p<0.001), duration of AKI (r=0.57, p<0.001) and length of hospital stay (r=0.44, p<0.001). The 12-h plasma NGAL concentration strongly correlated with mortality (r=0.48, p=0.004) and all measures of morbidity mentioned above [26]. Thus, non-biased measurements of plasma NGAL are obtained using the point-of-care Triage® NGAL device. The assay is facile and performed on the Triage Meter with quantitative results available within approximately 15 min, and requires only microlitre quantities of whole blood or plasma. The assay is auto-calibrated and includes reactive internal controls which run with every sample applied. The assay is deployable directly to the point of patient care. Using this device, plasma NGAL concentration was found to be an early predictive biomarker of AKI, morbidity and mortality after CPB [26].

In addition, a urine NGAL immunoassay has been developed for a standardized clinical platform (ARCHITECT® analyzer, Abbott Diagnostics). In a pilot study with 136 urine samples and 6 calibration standards, NGAL concentrations by research ELISA and by the ARCHITECT assay were highly correlated (r=0.99). In a subsequent study, 196 children undergoing CPB were prospectively enrolled and serial urine NGAL concentrations obtained by ARCHITECT assay [27]. AKI developed in 99 patients, but the diagnosis using serum creatinine concentration was delayed by 2-3 days after CPB. In contrast, mean urine NGAL concentrations increased 15-fold within 2 h, and by 25-fold at 4 and 6 h after CPB. For the 2-h urine NGAL concentration, the area under the curve was 0.95, sensitivity was 0.82 and specificity was 0.90 for prediction of AKI using a cut-off value of 100 μg/L. The 2-h urine NGAL levels correlated with severity and duration of AKI, length of stay, dialysis requirement and death. Thus, non-biased measurements of urine NGAL are obtained using the ARCHITECT platform. This assay is easy to perform with no manual pretreatment steps, a first result available within 35 min and it requires only 150 microlitres of urine. Urine NGAL

concentration measured by ARCHITECT assay was found to be an early predictive biomarker of AKI severity after CPB [27].

A summary of the present status of NGAL for early detection of AKI in various clinical settings is provided in Table 1. Larger multicentre studies to further define the predictive role of plasma and urine NGAL concentrations as a member of the putative "AKI Biomarker Panel" have been initiated using robust assays that have been developed for wide-spread clinical use; the results are awaited with anticipation.

NGAL in chronic kidney disease: clinical studies

As discussed above, NGAL is a promising biomarker of AKI. In CKD, there is a growing literature suggesting that NGAL is also a marker of kidney disease and severity. In 45 subjects with CKD secondary to renal dysplasia, obstructive uropathy and glomerular and cystic diseases, plasma NGAL concentrations were inversely associated with GFR [25]. As kidney function declined to <30 mL/min, NGAL outperformed cystatin C as a biomarker of kidney failure [25]. Another study [28] in subjects with CKD (due to chronic glomerulone-phritis) demonstrated that mean urinary NGAL concentrations were higher in CKD patients (378.28 ±111.13 μg/L vs. 7.38±3.26 μg/L in controls; p=0.01). Furthermore, urinary NGAL concentrations were significantly correlated with serum creatinine concentrations (r=0.588, p-value=0.02), GFR (r=-0.528, p-value=0.04) and proteinuria (r=0.294, p-value=0.01) [28].

Both urine and plasma NGAL represent biomarkers of CKD severity in patients with autosomal dominant polycystic kidney disease [29]. In these subjects, urine and plasma NGAL concentrations correlated with residual GFR, and those with greater severity of cystic disease (measured as number of cysts >10) displayed the highest NGAL values [35]. Urine NGAL has also been shown to represent an early biomarker for degree of chronic tubulointerstitial injury in patients with IgA nephropathy [30].

Conclusions

The tools of modern science have provided us with exciting novel biomarkers for AKI and CKD, and NGAL is one of the most promising ones. It will be important in future studies to validate the sensitivity and specificity of urine and plasma NGAL in clinical samples from large cohorts and from multiple clinical situations. Such studies will be markedly facilitated by the availability of commercial tools for the reproducible measurement of NGAL across different laboratories.

Key points from the discussion

- The control group used for studying the specificity comprised patients who did not develop acute renal failure. Baseline values were measured on all prior to surgery. A normal population was also studied. By using such an early marker, we have earlier warning of potential problems and can prevent potentially harmful interventions such as administration of nephrotoxic agents and contrast media, as well as prompting the initiation of earlier therapeutic interventions.
- NGAL is produced in the distal nephron and its synthesis is up-regulated in response to kidney injury. NGAL is an ion-transporting agent. Markers of damage are potentially better than functional markers. NGAL is also a powerful marker of kidney disease progression. Serum concentrations increase before those of creatinine and it is a powerful tool for monitoring CKD. KIM-1 and NGAL are markers of active tubular pathology. Using creatinine and NGAL together could

create action thresholds for intervention for both patients without known renal disease and for monitoring known disease.

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Table I

Current status of NGAL for early detection of AKI in various clinical settings. The times indicated are the earliest time-points when the NGAL concentrations become significantly elevated from baseline values. AKI is defined as a 50 % increase in serum creatinine concentration from baseline. DGF is delayed graft function, defined as dialysis requirement within 1 week of transplantation. The clinical platforms for urine and plasma NGAL measurement are nearing completion, and have been verified in at least one published study [26,27].

Type of sample	Cardiopulmonary bypass (CPB)	Contrast nephropathy	Sepsis or intensive care unit setting	Kidney transplant (tx)	Commercial assay source
Urine	2 h post-CPB 2-3 days before AKI	2-4 h post-contrast 1-3 days before AKI	48 h before AKI 1-3 days before AKI	12-24 h post-tx 2-3 days before DGF	ARCHITECT Assay (Abbott*)
Plasma	2 h post-CPB 2-3 days before AKI	2 h post-contrast 1-3 days before AKI	48 h before AKI 1-3 days before AKI	Not tested	TRIAGE® NGAL Kit (Biosite*)

* In development.