

## Role of NGAL for the Early Detection of Acute Kidney Injury

Zohreh Rostami<sup>1\*</sup>, Mahboob Lessan-Pezeshki<sup>2</sup>

<sup>1</sup>Nephrology and Urology Research Center, Baqiyatallah University of Medical Sciences, Tehran, I.R. Iran

<sup>2</sup>Department of Nephrology, Tehran University of Medical Sciences, Tehran, I.R. Iran

The incidence of acute kidney injury (AKI) is estimated to be from 5% of hospitalized patients to 30–50% of patients in intensive care units, and nowadays there is significant evidence of an increase in its incidence (1, 2). The incidence of both AKI (formerly, acute renal failure) and chronic kidney disease (CKD) has already developed epidemic proportions. In both conditions, early intervention can substantially improve the prognosis. However, the lack of early, predictive and non-invasive biomarkers may lead to delayed initiation of potentially useful therapies for these common clinical settings (3). The diagnosis of AKI is usually based on increases in serum creatinine levels; however, it is a poor indicator of acute deterioration of kidney function. In addition, serum creatinine concentration is greatly influenced by numerous non-renal factors (such as lean muscle mass, race, age, gender, hydration status, medications, muscle metabolism, and protein intake). Measurement of serum creatinine is not ideal marker of renal function in AKI, because these patients are not in steady state. Therefore, changes in serum creatinine may lag far behind renal injury. Thus, considerable rises in serum creatinine are often not apparent until 48–72 h after the initial insult to the kidney. In addition, no significant changes in serum creatinine concentrations may be seen until about 50% of renal function has already been lost. It means that the significant renal disease can exist with minimal or no changes in serum creatinine because of renal reserve, enhanced tubular secretion of creatinine, and compensated lower rates of glomerular

filtration (1, 2, 4, 5).

However, some urinary biomarkers such as casts, filtered high molecular weight proteins, fractional excretion of sodium and tubular proteins or enzymes are not enough sensitive and specific for the early diagnosis of AKI (3). Biomarkers for early AKI diagnosis represent a unique opportunity for an intervention to save the kidney from additional insults and avoid tissue damage. If we wait for the present paraclinical data which can certainly help, we will always be late. Therefore, we need a novel and more sensitive biomarker for the diagnosis of AKI in order to treat it as soon as possible (5). This biomarker must also be specific, practically easy to detect and measure, reproducible, feasible at bedside, correlative with severity, quantitatively describing the intensity of renal damage even when typical clinical signs are absent and is appropriate to indicate the initiation of the therapy (5).

Fortunately, promising methods such as functional genomics and proteomics have discovered new candidates as biomarkers (3, 6), and among them neutrophil gelatinase-associated lipocalin (NGAL), which is a small molecular size (25 kDa) protein and resistance to degradation (7), is a promising biomarker. It usually excreted in urine, accumulates in human kidney cortical tubules which significantly

*\*Correspondence:*

Zohreh Rostami, MD

Nephrology and Urology Research Center, Baqiyatallah University of Medical Sciences, Molla Sadra St. Vanak Sq. Tehran, I.R. Iran

Email: [rostami@ijnu.ir](mailto:rostami@ijnu.ir)

Received: 25 Mar 2010

Accepted: 2 Apr 2010

augmented in epithelial damage and also increases in plasma following nephrotoxic or ischemic injury (7-10). During reepithelialization, NGAL is probably a regulator of epithelial morphogenesis as it can be detected in the mature kidney after tubular damage, and in some stage of nephrogenesis as it is an iron-transporting protein. (11). Several studies have reported that in patients with AKI, NGAL rises very high compared to matching controls (6, 11, 12). In addition, NGAL enhancement occurs in different studies at 24 to 48 hours sooner than the increase in creatinine. Both urinary and plasma NGAL are excellent early markers of AKI with an area under the receiver operator characteristic curve (AUC) in the range of 0.9. Nowadays, many studies are being performed to illuminate exact correlation between NGAL and AKI (5).

According to a cross-sectional study, among intensive care unit patients with established acute renal failure, plasma NGAL concentration and urine NGAL concentration were 10-folds and more than 100 times higher than the normal levels (13). Additionally, elevated serum creatinine concentrations in patients had immuno-reactive NGAL in 50 % of the cortical tubules in kidney biopsy samples and have been associated with high plasma and urine NGAL concentrations (3). High level of NGAL not only presented in AKI, but also it can predict delayed graft function, as NGAL staining has been obtained 1 hour after vascular anastomosis in kidney transplant biopsies which progress to DGF (14). Interestingly, urine NGAL concentrations substantially increased in biopsy proven tubulitis or other tubular pathologies as well as in subclinical tubulitis (7, 15).

Early intrinsic tubule cell damage and subsequently inability to filtered NGAL reabsorption can cause urinary NGAL rising following tubular damage (7). Also several investigators have examined the role of NGAL as a predictive biomarker of nephrotoxicity following contrast administration and postischemic kidney (7, 16) However, urinary NGAL cannot be

detected in anuric patients (7). Further studies are required to depict:

- 1- Does the NGAL actually enable to distinguish between various AKI subtypes (prerenal, intrinsic renal, or postrenal)? Is NGAL more efficient than other methods (BUN/Cr, urine osmolality, fractional excretion of Na, needle biopsy, etc) in evaluation of AKI subtypes? Can we hope not to need an invasive procedure for the early detection of AKI etiology in future?
- 2- NGAL staining in biopsy samples is presented in several conditions such as cisplatin, ACE inhibitors, bisphosphonate or cephalosporin therapy which can lead to false positive in critical conditions (11). How does the NGAL enable to recognize the AKI etiologies (ischemia, toxins, ATN, rejection, sepsis, DGF or a combination of them)? There is a positive association between NGAL staining intensity and cold ischemia time, peak post-transplant plasma creatinine, and DGF (17). How can NGAL staining intensity in early protocol biopsies differentiate between these and other risk factors of graft loss?
- 3- NGAL expression is noticeably elevated in acute systemic disease or urinary tract infections (14). How can NGAL discriminate AKI from other forms of acute kidney disease (e.g. urinary tract infection, glomerulonephritis and interstitial nephritis)?
- 4- How can we evaluate the accuracy and reliability of serum and/or urinary NGAL for the diagnosis of established AKI, for the early diagnosis, and risk stratification of AKI? How can we predict the AKI severity with NGAL?
- 5- Is it possible to monitor the course of AKI and its response to interventions with NGAL?
- 6- NGAL is normally secreted at very low concentration in several human tissues, such as kidney, lungs, stomach, and colon. NGAL expression is markedly elevated in injured epithelia (14, 15). On the other hand, NGAL measurements may be influenced by a number of coexisting variables, such as preexisting

renal disease (13, 16). Also urinary NGAL concentrations significantly correlate with proteinuria (3). How can we omit these contributing factors?

7- What is the cutoff point, sensitivity, specificity and ROC for the urinary and plasma NGAL in early detection of AKI?

8- Elevated serum NGAL in kidney transplant recipients could be due to the enhanced synthesis by injured kidneys, impaired kidney clearance, and nephrotoxicity of immunosuppressive drugs (calcineurin inhibitors) (8). Regarding narrow difference in diagnosis of acute rejection and calcineurin inhibitors nephrotoxicity which have diverse treatment (8), how can NGAL make distinction between these conditions ?

9- Are there any differences between brain dead deceased donors and living donors in NGAL expression?

10- Can the level of urinary or serum NGAL or staining for NGAL in deceased donors be predictive of DGF in recipients?

## References

1. Bosch JP. Renal reserve: a functional view of glomerular filtration rate. *Semin Nephrol.* 199;15:381-5.
2. Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. *Kidney Int.* 2008;73:1008-16.
3. Devarajan P. Neutrophil gelatinase-associated lipocalin (NGAL): a new marker of kidney disease. *Scand J Clin Lab Invest Suppl.* 2008;241:89-94.
4. Herrera J, Rodriguez-Iturbe B. Stimulation of tubular secretion of creatinine in health and in conditions associated with reduced nephron mass. Evidence for a tubular functional reserve. *Nephrol Dial Transplant.* 1998;13:623-9.
5. Ronco C. N-GAL: diagnosing AKI as soon as possible. *Crit Care.* 2007;11:173.
6. Devarajan P. Emerging biomarkers of acute kidney injury. *Contrib Nephrol.* 2007;156:203-12.
7. Lebkowska U, Malyszko J, Lebkowska A, et al. Neutrophil gelatinase-associated lipocalin and cystatin C could predict renal outcome in patients undergoing kidney allograft transplantation: a prospective study. *Transplant Proc.* 2009;41:154-7.
8. Cowland JB, Borregaard N. Molecular characterization and pattern of tissue expression of the gene for neutrophil gelatinase-associated lipocalin from humans. *Genomics.* 1997;45:17-23.
9. Zappitelli M, Washburn KK, Arikan AA, et al. Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. *Crit Care.* 2007;11:R84.
10. Schmidt-Ott KM, Mori K, Kalandadze A, et al. Neutrophil gelatinase-associated lipocalin-mediated iron traffic in kidney epithelia. *Curr Opin Nephrol Hypertens.* 2006;15:442-9.
11. Mishra J, Ma Q, Kelly C, et al. Kidney NGAL is a novel early marker of acute injury following transplantation. *Pediatr Nephrol.* 2006;21:856-63.
12. Wagener G, Jan M, Kim M, et al. Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. *Anesthesiology.* 2006;105:485-91.
13. Nguyen MT, Devarajan P. Biomarkers for the early detection of acute kidney injury. *Pediatr Nephrol.* 2008;23:2151-7.
14. Pisitkun T, Johnstone R, Knepper MA. Discovery of urinary biomarkers. *Mol Cell Proteomics.* 2006;5:1760-71.
15. Xu S, Venge P. Lipocalins as biochemical markers of disease. *Biochim Biophys Acta.* 2000;1482:298-307.
16. Mitsnefes MM, Kathman TS, Mishra J, et al. Serum neutrophil gelatinase-associated lipocalin as a marker of renal function in children with chronic kidney disease. *Pediatr Nephrol.* 2007;22:101-8.
17. Parikh CR, Jani A, Mishra J, et al. Urine NGAL and IL-18 are predictive biomarkers for delayed graft function following kidney transplantation. *Am J Transplant.* 2006;6:1639-45.