

# Biomarkers in Chronic Kidney Disease

By Nisha Bansal and Chi-Yuan Hsu

There has been considerable interest in studying novel biomarkers in chronic kidney disease (CKD) beyond the conventional clinical indices, such as serum creatinine, blood urea nitrogen, and urine protein or urine albumin. The motivation for this is similar to what has been outlined in other articles in this issue of *ASN Kidney News*. For example, novel biomarkers may improve our ability to better risk classify patients and guide clinical actions (e.g., closer follow-up and more intense treatment for patients at higher risk of progression of CKD), to identify high-risk patients for enrollment into clinical trials (as enriched enrollment of patients who are more likely to progress will enhance study power), and to better understand underlying biological pathophysiological mechanisms (which may in turn identify novel targets for treatment).

Under the sponsorship of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a CKD Biomarker Consortium was formed in 2009. The consortium consists of investigators from more than a dozen academic medical centers and research institutions around the country, analyzing clinical data and stored biosamples and from numerous longitudinal cohorts.

## Biomarkers of renal injury in the setting of CKD

One area of focus for the CKD Biomarker Consortium is to evaluate—among patients with CKD or those at high risk for CKD—urine injury biomarkers, many of which were initially identified in the arena of acute kidney injury (AKI). Examples of these urine injury biomarkers include urine kidney injury molecule-1 (KIM-1), urine neutrophil gelatinase associated lipocalin (NGAL), liver-type fatty acid binding protein (L-FABP) and beta-N-acetylglucosaminidase (NAG).

Preliminary results show that injury biomarkers are in fact often detectable in the urine of patients with CKD, albeit usually at concentrations much lower than that seen in the setting of AKI. Interestingly, a minority of seemingly stable ambulatory CKD patients have very high levels (1,2). Several studies have shown that elevations of these levels of urine injury biomarkers are independent risk factors for more rapid loss of kidney function in subsequent years (1–3). For example, in the Chronic Renal Insufficiency Cohort (CRIC) study, although median urine NGAL concentration was only 17.2 ng/mL (in 3386 patients), 5 percent of readings were between 178.9 ng/mL and 3069.6 ng/mL (1). In that study, even after adjusting for potential confounders such as baseline estimated glomerular filtration rate (eGFR) or urine protein, high urine NGAL level remained an independent risk factor for progression of CKD, defined as halving of eGFR or end stage renal disease (Table 1). However, this novel marker only very modestly improved prediction of outcome events (1).

## Urine injury biomarkers may be associated with nonrenal outcomes

Kidney dysfunction, as traditionally assessed by eGFR and urine albumin-creatinine ratio, is strongly linked with higher future risk of cardiovascular disease and death (4,5). Recent investigations have also noted that urine injury biomarkers may also be associated with cardiovascular disease and death. A study of approximately 3000 older adults in the Health, Aging and Body Composition cohort with and without CKD (mean eGFR 79 mL/min/1.73 m<sup>2</sup>) found that higher urine KIM-1 was independently associated with a 32 percent higher risk of incident heart failure, while there was no association of interleukin-18 (IL-18) with heart failure (6). In this same cohort, there was a modest association of higher urine KIM-1 with all-cause mortality (7). There was no association of KIM-1 with atherosclerotic disease and no association of IL-18 with atherosclerotic disease or death. However, the magnitude of the association of KIM-1 with these outcomes was smaller than that seen with urine albumin-creatinine ratio (6,7). These initial studies suggest that urine injury may possibly signal risk of numerous nonrenal outcomes. While these studies are observational and do not indicate causality, these data provide novel information about the link between kidney dysfunction and cardiovascular disease. Further studies are needed to explore these associations in different populations, including patients with known CKD.

## Urine injury biomarkers in unique patient populations

Urine injury biomarkers have also been examined in unique populations, such as patients infected with the human immunodeficiency virus (HIV).

In a study of 908 HIV-infected women with preserved kidney function (mean eGFR 88 mL/min/1.73 m<sup>2</sup>), high urine IL-18 levels were independently associated with 88 percent greater risk of all-cause mortality (8). There was no association of KIM-1 with higher risk of mortality (8). In this same cohort, IL-18 and KIM-1 were also independently associated with subsequent rapid decline of kidney function (9).

Interestingly, it has been suggested that elevations in urine injury biomarkers may also be an earlier manifestation of kidney injury induced by tenofovir, a commonly used nephrotoxic medication used to treat HIV. Among this cohort of HIV-infected women, three urine tubular biomarkers (NGAL, NAG and  $\beta$ -2-microglobulin) were measured before and after starting tenofovir (10). There were no differences in NGAL or NAG; however,  $\beta$ -2-microglobulin was 19 times more likely to be elevated after tenofovir initiation (10). In a cross-sectional study of 99 patients with HIV, of whom approximately half were on tenofovir therapy, spot concentrations of retinol-binding protein (RBP)—a low-molecular weight protein normally reabsorbed by the proximal tubule—were significantly higher in tenofovir users (11). As our understanding of these urine injury biomarkers increases, there may be further opportunities to study these biomarkers in other high-risk patient populations. ●

## Disclosures

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## References

- Liu KD, et al. Urine neutrophil gelatinase-associated lipocalin levels do not improve risk prediction of progressive chronic kidney disease. *Kidney Int* 2013; 83:909–914.
- Fufaa GD, et al. Association of urinary KIM-1, L-FABP, NAG, and NGAL with incident end-stage renal disease and mortality in American Indians with type 2 diabetes mellitus [Abstract]. *J Am Soc Nephrol* 2013; 24:427A.
- Bolignano D, et al. Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. *Clin J Am Soc Nephrol* 2009; 4:337–344.
- Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351:1296–1305.
- Gerstein HC, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; 286:421–426.
- Driver TH, et al. Urinary Kidney Injury Molecule 1 (KIM-1) and Interleukin 18 (IL-18) as risk markers for heart failure in older adults: The Health, Aging, and Body Composition (Health ABC) Study. *Am J Kidney Dis*. doi: 10.1053/j.ajkd.2014.01.432.
- Sarnak MJ, et al. Association of urinary injury biomarkers with mortality and cardiovascular events. *J Am Soc Nephrol*. doi:10.1681/ASN.2013070713.
- Peralta C, et al. Urinary biomarkers of kidney injury are associated with all-cause mortality in the Women's Interagency HIV Study (WIHS). *HIV Med*. doi: 10.1111/hiv.12113.
- Shlipak MG, et al. Urinary markers of kidney injury and kidney function decline in HIV-infected women. *J Acquir Immune Defic Syndr* 2012; 61:565–573.
- Oboho I, et al. Tenofovir use and urinary biomarkers among HIV-infected women in the Women's Interagency HIV Study (WIHS). *J Acquir Immune Defic Syndr* 2013; 62:388–395.
- Hall AM, et al. Subclinical tubular injury in HIV-infected individuals on antiretroviral therapy: a cross-sectional analysis. *Am J Kidney Dis* 2009; 54:1034–1042.