Kidney Injury Marker 1 and Neutrophil Gelatinase-Associated Lipocalin in Chronic Kidney Disease

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Key Words

Biomarker · Cardiovascular · Proximal tubular cell · Kidney injury

Abstract

The current categorization of chronic kidney disease (CKD) is based on biomarkers of the glomerular function (estimated glomerular filtration rate, eGFR) and injury (urinary albumin creatinine ratio, UACR) and provides information on the risk of death and of progression of kidney disease. However, there are gaps in knowledge regarding the risk stratification of elderly patients with eGFR 45–60 ml/min/1.73 m² and of younger patients with higher eGFR but physiological albuminuria. In this regard, most of the kidney cell mass is composed of tubules. Recent studies have explored whether biomarkers derived from the acute kidney injury literature, which are mainly tubular injury markers, may improve the information provided by eGFR and UACR. We now review the potential role of kidney injury molecule 1 (KIM-1), hepatitis A virus cellular receptor 1, T-cell immunoglobulin and mucin domain-1 and neutrophil gelatinase-associated lipocalin (NGAL)/lipocalin 2 as biomarkers for kidney or cardiovascular outcomes in CKD patients. In general, neither uri-

nary KIM-1 nor urinary NGAL (uNGAL) outperform or add relevant information to eGFR or UACR. However, promising results were obtained for circulating KIM-1 prediction of renal outcomes in type 1 diabetes. Additionally, uNGAL may have some value in non-proteinuric patients and increased values have been observed in persons at risk for Mesoamerican nephropathy. Further studies are warranted in these niche populations.

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Introduction

Chronic kidney disease (CKD) is categorized based on biomarkers of the glomerular function (estimated glomerular filtration rate, eGFR) and injury (urinary albumin creatinine ratio, UACR) that provide information on risk of death and of progression of kidney disease. However, for certain populations, the current risk categoriza-

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tion may benefit from additional information regarding risk of CKD progression. As an example, kidney injury in non-albuminuric CKD (e.g. certain tubulointerstitial and vascular nephropathies) is not represented in the glomerular-based risk categorization until eGFR falls <60 ml/min/1.73 m². Tubular injury markers may be better suited for risk categorization in early stages in these patients. Kidney injury molecule 1 (KIM-1), hepatitis A virus cellular receptor 1 (HAVCR1), T-cell immunoglobulin and mucin domain 1 (TIM-1) and neutrophil gelatinase-associated lipocalin (NGAL)/lipocalin 2 (Lcn2) are tubular injury biomarkers that were among the earliest described biomarkers for acute kidney injury (AKI). Both may also add information on the persistence of renal injury in AKI and the risk of progression to CKD. We now review the potential role of KIM-1 and NGAL as biomarkers for kidney or cardiovascular outcomes in CKD patients.

Kidney Injury Molecule 1

The protein encoded by the HAVCR1 gene has received different names: KIM-1, HAVCR1 or TIM-1. We will refer to the protein as KIM-1 [1]. KIM-1 is a cell surface receptor in epithelial and lymphoid/myeloid cells. It behaves as a scavenger receptor for oxidized LDL and phosphatidylserine and as Ebola and Hepatitis A virus entry receptor in epithelial cells [2]. Kim-1 binding to phosphatidylserine allows the phagocytosis of apoptotic cells. In addition, KIM-1 regulates Th2, Th1, and Th17 differentiation. Kim-1 is markedly upregulated in proximal tubules in AKI and CKD. Indeed, the urinary excretion of the KIM-1 ectodomain was qualified by the Federal Drug Administration and by the European Medicines Agency for preclinical assessment of nephrotoxicity and on a case-by-case basis for clinical evaluation. While an acute increase in KIM-1 expression has adaptive anti-inflammatory effects in experimental animals [3], chronic overexpression in proximal tubules may be maladaptive in mice and lead to MCP-1-mediated interstitial inflammation and fibrosis [4].

KIM-1 (Urinary KIM-1) as a Biomarker in CKD

A number of recent studies have evaluated the biomarker potential of urinary KIM-1 (uKIM-1) in CKD (table 1). uKIM-1 was higher in patients with proteinuria and normal renal function than in non-proteinuric individuals, and antiproteinuric drugs decreased uKIM-1, consis-

tent with improved proteinuria-induced tubular injury [5]. In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort of adults with normal renal function, uKIM-1 was associated with the future (5 years) risk of incident CKD stage 3 and/or rapid renal function decline, independently of UACR or NGAL levels [6]. However, the Atherosclerosis Risk in Communities Study (ARIC) evaluating non-proteinuric patients with normal renal function found no association between uKIM-1 levels and incident CKD stage 3 [7] and it did not improve the risk prediction for end-stage renal disease (ESRD) after adjusting for renal function and UACR [8]. Type 2 diabetes mellitus (T2DM) Pima Indians with macroalbuminuria had higher concentrations of uKIM-1/Cr but uKIM-1/Cr did not add to renal disease or mortality risk prediction [9]. In the Health, Aging, and Body Composition cohort, the highest quartile of uKIM-1 was associated with heart failure risk, but the association was weaker than for UACR [10]. Furthermore, uKIM-1 had a modest association with all-cause mortality but not with cardiovascular death, whereas UACR was associated with both [11].

Circulating KIM-1 is also increased in kidney disease. In cardiopulmonary bypass, plasma KIM-1 levels increased within 2 days after surgery only in patients who developed AKI [12]. In patients with T1DM and proteinuria with normal renal function, the serum KIM-1 level at baseline strongly predicted the rate of eGFR loss and risk of ESRD after adjusting for baseline UACR, eGFR and HbA1c [13, 14].

Neutrophil Gelatinase-Associated Lipocalin

The Lcn2 gene encodes Lcn2, also known as NGAL. NGAL was originally identified in neutrophils, but it is a rapid response gene also expressed in kidneys and other organs in response to tissue injury. NGAL contributes to antibacterial defense by scavenging iron through binding to the siderophores that bacteria use to uptake extracellular iron [15]. The NGAL-Fe-siderophore complex is processed by tubular cells, increasing the cytoplasmic iron concentration and activating iron-dependent processes [16]. However, NGAL also binds iron through eukaryotic ligands such as catechol. Binding to NGAL decreases oxidative stress induced by the catechol-Fe complex [17]. In contrast, free NGAL may transport intracellular iron to the extracellular space [18]. Finally, NGAL promotes epithelial growth in various organs including the kidney through a yet-to-be characterized, iron-independent mechanism [17, 19]. NGAL expression

Table 1. Key clinical studies assessing the role of uKIM-1 and NGAL in CKD

Reference	Design	Number	Diabetes, %	eGFR, ml/min/1.73 m ²	UACR, mg/g	Marker	Result	Improves prediction over eGFR/UACR
ARIC [8]	Case-control	321	52–63	71–58	13–73	uNGAL	No association with incident ESRD	No
						uKIM-1	Increased KIM-1/Cr associated with incident ESRD	No
ARIC [7]	Case-control	286	15–18	83±16	3.1–3.5	uNGAL	Not association with incident CKD3 and/or rapid kidney function decline in multivariable analysis	No
						uKIM-1	Not associated with incident CKD3 and/or rapid kidney function decline	No
MESA [6]	Case-control	686	18	75±11	>30 in 6–17%	uNGAL	No association with incident CKD3 and/or rapid kidney function decline	No
						uKIM-1	Association with incident CKD3 and/or rapid kidney function decline	Independent of albuminuria but lower predictive value than albuminuria
Pima Indians [9]	Prospective cohort (14 years)	260	100	149±45	28	uNGAL	Association with incident ESRD and all-cause mortality	Very modestly improves prediction
						uKIM-1	No association with all-cause mortality or ESRD	No
CRIC [20]	Prospective cohort	3,386	48	42±14	24 h urine protein: 1.1±2.4 g	uNGAL	Association with halving of eGFR and/or incident ESRD	Very modestly improves
Academic study [21]	Prospective cohort (2 years)	158	25	32±11	62 (18–398)	uNGAL	Associated with risk of progression to ESRD and risk of rapid decline of renal function at 1 year, but no to all-cause mortality	Improved risk prediction for primary/secondary endpoints only in low-level urinary protein
[23]	Cross-sectional	200 Ages 12–18 years	ND	ND	0–29: 92% 30–300: 7.5% >300: 0.5%	uNGAL	uNGAL higher in children from regions with increased Mesoamerican nephropathy CKD risk	NA
[22]	Longitudinal cohort	284	ND	114±17	2.9±3.5	uNGAL	Before and after 6-month harvest season: increased uNGAL/Cr associated with decreased GFR	Not assessed
[24]	Crossover RCT	34	No	CrCl 89±5 ml/min/1.73 m ²	3,800±400 mg/day	uKIM-1	Decreased uKIM-1 paralleled decreased in proteinuria	NA
Health ABC [10]	Retrospective cohort	2,917	24	79 (21)	8 (5–19)	uKIM-1	Higher uKIM-1 associated independently with incident heart failure	Not assessed
Health ABC [11]	Retrospective cohort	3,010	24	79 (21)	8 (5–20)	uKIM-1	Modest association of uKIM-1/Cr with all-cause mortality, but not with cardiovascular disease	Not assessed. Albuminuria better predictor of mortality and cardiovascular disease than uKIM-1

Data expressed as mean (SD) or median (interquartile range). When 2 numbers available, first corresponds to controls and second to cases.

Health ABC = Health, aging, and body composition; CRIC = chronic renal insufficiency study; NA = not applicable; ND = no data; CrCl = creatinine clearance.

is increased during AKI, leading to high urine and serum levels in animals and patients. Most research supports a protective role for NGAL in AKI. However, in CKD progression NGAL may have a deleterious role [19].

NGAL as a Biomarker in CKD

Overall, studies have not found urinary NGAL (uNGAL) to be a strong predictor of renal outcomes in ESRD that adds relevant information on top of currently available markers. Added information, if present, was very modest (table 1). In the ARIC cohort, higher uNGAL levels were associated with incident CKD3, but significance was lost on multivariate analysis [7] and uNGAL/Cr did not associate with incident ESRD [8]. Likewise, in the MESA cohort of North American adults free of cardiovascular disease with eGFR >60 ml/min/1.73 m², uNGAL did not associate with the risk of incident CKD3 or rapid kidney function decline at 5-year follow-up [6]. In the Chronic Renal Insufficiency Study cohort of CKD 2–4 adults, uNGAL was an independent risk factor of CKD progression but did not substantially improve outcome prediction [20]. In T2DM Pima Indians, uNGAL did not add clinically to death/ESRD risk prediction despite mild changes in C-statistics [9].

However, uNGAL may improve the prediction of CKD progression in elderly Caucasian CKD 3–4 patients with low-grade proteinuria over conventional established cardiovascular and renal risk factors [21]. Assessment of uNGAL might also provide information in Mesoamerican nephropathy, currently characterized as a chronic tubulointerstitial nephropathy. Sugarcane workers with the largest increases in uNGAL/Cr ratios had declines in eGFR levels, measured before and after a 6-month harvest season [22], and in healthy adolescents, uNGAL but not

proteinuria was increased in those regions with highest Mesoamerican nephropathy incidence [23]. Potential implications of these findings include using NGAL to identify risk factors and subclinical damage leading to Mesoamerican nephropathy.

Circulating NGAL is also increased in cardiovascular conditions, sepsis and cancer and thus is unlikely to provide information specific for CKD.

Conclusions

In conclusion, uKIM-1 and uNGAL are markers of tubular injury and AKI that are also increased in CKD. Available studies suggest that in the CKD context, uKIM-1 or uNGAL generally do not outperform or add information to eGFR and UACR for prediction of risk of death, progression of CKD or other adverse cardiovascular outcomes. However, further research is needed on whether there might be a niche in which these biomarkers may add information, such as uNGAL for patients with normoalbuminuria or chronic tubulointerstitial nephropathy and circulating KIM-1 in diabetes.

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Disclosure Statement

None reported.

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