Elevated urine neutrophil gelatinase-associated lipocalin can diagnose acute kidney injury in patients with chronic kidney diseases

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To the Editor: Hsu *et al.* evaluated the association between chronic kidney disease (CKD) and risk of acute kidney injury (AKI). They demonstrated several important findings: (1) CKD is an important risk factor for the development of AKI; (2) even early CKD stage 3 kidney dysfunction is a risk factor for the development of AKI; and (3) AKI risk increased in a step-wise relationship with worsening kidney disease.[1] The public health implication of their investigation is immense. In 2000, 20 million adults in the United States were affected by kidney disease,[2] and as the prevalence of CKD increases, the incidence of AKI will also continue to increase.[3]

An important issue concerning the diagnosis of AKI is that the clinical standard, the serum creatinine, is a suboptimal method to evaluate AKI in CKD. In the setting of CKD, serum creatinine levels are already elevated and may fall in advanced disease secondary to changes in extrarenal clearance.[1,4,5] Furthermore, serum creatinine levels are known to vary as a function of muscle mass, gender, race, medications, and comorbid conditions. Given these well-known limitations, it is not surprising that Hsu *et al.*[1] found that serum creatinine cannot distinguish between natural progression of CKD and acute-on-chronic disease.

Neutrophil gelatinase-associated lipocalin (NGAL) is a biomarker of AKI. We recently demonstrated in a large-scale prospective trial that a single spot urine NGAL is able to predict the subsequent development of AKI on presentation to the emergency department (ED).[6] We conducted a secondary data review of this cohort to determine the characteristics of NGAL in all patients with CKD, with and without AKI.

We included all-comers to the ED in order to enroll a representative sample of women, racial/ethnic minorities, and patients without insurance. CKD was defined according to the National Kidney Foundation Chronic Kidney Disease guidelines (estimated glomerular filtration rate (eGFR) <60 ml/min). The modified Modification of Diet in Renal Disease was used to determine eGFR.[7] Baseline kidney function was determined by reviewing electronic medical records for serum creatinine measurements between 1 and 12 months before ED presentation. AKI was defined according to minimal risk, injury, failure, loss, end-stage (RIFLE) criteria established by the Acute Dialysis Quality Initiative.[8]

Table 1 demonstrates our findings. A total of 156 patients were enrolled with an eGFR <60 ml/min, of these 15 (10%) developed AKI. On average, patients with CKD who developed AKI were significantly younger and more likely to be of black race. In agreement with Hsu *et al.*, patients with CKD who developed AKI had significantly worse baseline kidney function than those patients who did not develop AKI (27.5 ± 13.0 vs 41.2 ± 12.7 ml/min; *P*-value <0.001 for AKI and non-AKI groups, respectively). Spot urine NGAL levels at ED presentation were significantly higher in those patients with CKD who developed AKI (434.6 ± 233.1 vs 21.9 ± 36.9 μg/g; *P*-value <0.001, respectively). In our series, six patients (40%) with AKI on CKD required inpatient hemodialysis.

These data strongly suggest that in the setting of CKD, elevated urine NGAL levels are associated with the development of AKI. Therefore, in patients with CKD, urine NGAL may provide both a rapid diagnosis of AKI and differentiate AKI from changes in GFR due to chronic disease progression. Early and rapid AKI diagnosis in this patient population will allow for appropriate triage (to admit or discharge the patient) and avoidance of potentially nephrotoxic medications.

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Table 1 | Patient characteristics

Characteristic	Acute injury on CKD (*n*=15)	Stable CKD (*n*=141)	*P*-value
Mean age (s.d.) (years)	57.3 (13.6)	69.8 (15.4)	0.003
Women (%)	66.7	56.7	0.6
Black race (%)	53.3	25.5	0.03
Mean baseline eGFR (s.d.) (ml/min per 1.73 m^2)	27.5 (13.0)	41.2 (12.7)	<0.001
Mean ER eGFR (s.d.) (ml/min per 1.73 m^2)	15.3 (8.3)	37.4 (14.6)	<0.001
Mean NGAL level (s.d.) (μg/g creatinine)	434.6 (233.1)	21.9 (36.9)	<0.001

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NGAL, neutrophil gelatinase-associated lipocalin.

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Response to 'Elevated urine neutrophil gelatinase-associated lipocalin can diagnose acute kidney injury in patients with chronic kidney diseases'

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We thank Dr. Sise and co-workers very much for their letter and interest in our recent publication.[1] We appreciate them sharing their stratified analysis among the subset of their patients with chronic kidney disease from their provocative study.[2]

We would like to make a clarification regarding the statement 'it is not surprising that Hsu *et al.* found that serum creatinine cannot distinguish between natural progression of CKD and acute-on-chronic disease.' What we had said was that 'Among patients with very advanced chronic kidney disease, it may be difficult to distinguish between the final stages of progression to end-stage renal disease from potentially reversible acute-on chronic renal failure so the very high odds ratio observed among those with estimated GFR of <15 ml per min per 1.73 m^2 must be interpreted with caution.'[1] Using direct medical records review of a random sample of 100 patients with baseline estimated GFR <45 ml/min per 1.73 m^2, we demonstrated that we were able to identify accurately cases of acute-on-chronic kidney disease. As described in the paper, a board-certified nephrologist confirmed that 100% of the time, our algorithm captured true cases of acute renal failure/acute kidney injury and did not mistakenly include cases of progression of chronic kidney disease. The etiology of these 100 cases of acute on chronic renal failure are shown below and are comparable to that reported in prior studies.[3]

Etiology	
Decreased renal perfusion (including volume contraction, congestive heart failure, hypotension, cardiac arrest)	76
Medication related	0
Radiocontrast media	6
Postoperative	6
Sepsis	21
Others	6
Total exceeds 100 as some cases had more than one contributing etiology	

We agree completely that neutrophil gelatinase-associated lipocalin and other biomarkers are an exciting area of research in acute kidney injury. Currently these biomarkers are being validated against 'gold standard' definitions of acute kidney injury as determined by changes in serum creatinine.[2,4,5] Our understanding of the epidemiology of acute kidney injury and the role of biomarkers should be greatly enhanced with the anticipated launch of the NIH-NIDDK sponsored study of the natural history of acute kidney injury (http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-07-009.html).

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Does postmenopausal hormone therapy influence renal function?

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To the Editor: Ahmed *et al*[1] investigate a facet of postmenopausal hormone therapy (HT) hereunto unaddressed by the Women's Health Initiative, but their epidemiologic approach raises several questions.

The authors chose age 66 as the minimal age for enrollment (mean age >70), and subjects were largely plagued by various chronic ailments and renal compromise (estimated glomerular filtration rate <90 ml/min per 1.73 m^2). As younger ($<$ age 60) women with normal renal function account for the overwhelming majority of HT utilization, why did the investigators select a markedly