

# Trace Metaluria as a Biomarker of Acute Kidney Injury



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Early detection or rule-out of acute kidney injury (AKI) enables triage and treatment of patients that can both improve outcomes and avoid unnecessary hospital admissions. Because serum creatinine only equilibrates to a new steady-state after a change in renal function after an indeterminate period of time, there has been an ongoing effort to identify biomarkers that can rapidly diagnose AKI through point of care testing in emergency rooms, intensive care units (ICUs), and postsurgical settings. An ideal AKI biomarker derives from injured kidney cells, and has a specific, temporal, and dose-dependent relationship to renal injury. These characteristics enable the application of biomarkers to the determination of pre-procedure AKI risk, diagnosis of AKI, and prognosis after AKI.<sup>1,2</sup>

In this issue of *KI Reports*, for the first time, urinary levels of the trace metals cadmium, copper (Cu), and

zinc (Zn) are linked to AKI.<sup>3</sup> The association of these metals with kidney injury was first suggested via a porcine model in which ischemia-reperfusion injury increased metaluria as measured by mass spectrometry. These results served as the basis for a single-center observational study of postcardiac surgery patients and ICU patients to monitor urinary concentrations of cadmium, Cu, and Zn alongside incidence of AKI in the 24 hours after surgery or ICU admission.

The authors' results in both postcardiac surgery and ICU patients suggest a potential role for urinary metal concentrations in diagnosis and prognosis of AKI. In cardiac surgery patients, urinary Zn had the best performance with area under the receiver operating curve of 0.77, whereas in the ICU patients, Cu performed best with area under the receiver operating curve of 0.76. The negative predictive value for all 3 metals was >90% in the cardiac surgery study, and >80% in the ICU study. The negative predictive value for Cu was >90% in both studies. In multivariate analyses of the ICU study data, both Cu and Zn reached significance for prediction of in-hospital mortality.

One appeal of urinary trace metaluria as an AKI biomarker lies in its potential cost-effectiveness. Whereas many of the biomarkers studied to date are proteins detected by antibody-based methods, urinary trace metal levels could be determined using low-cost screen-printed electrodes with reported limits of detection adequate for the  $\mu\text{g/l}$  concentrations the authors measured using mass spectrometry.<sup>4</sup>

In contrast to biomarkers that are stimulated in response to AKI, in the case of these trace metals, a pre-existing store in the kidney is depleted after injury. The authors' porcine model shows a reduction in kidney Zn stores from  $\sim 180 \mu\text{g/g}$  preinjury to  $\sim 160 \mu\text{g/g}$  8 weeks after ischemia-reperfusion injury. The authors cite evidence that trace metals collect in proximal tubule cells and hypothesize that they are released after acute tubular injury. The size of these trace metal stores appears heterogeneous across individuals. In human nephrectomy samples, the authors report ranges of kidney Cu and Zn levels ranging from  $\sim 5$  to  $15 \mu\text{g/g}$  and  $\sim 50$  to  $240 \mu\text{g/g}$  respectively.

These unique features of urinary trace metals as biomarkers pose both challenges and opportunities. If the degree of trace metaluria after AKI correlates with the amount of stored trace metal preinjury, it is possible that differing baseline kidney stores of metals across individuals could confound a clear dose dependence relationship between urinary trace metal concentrations and severity of kidney injury. Perhaps this underlies the difficulty of establishing a dose response between stage 1 and stage 2/3 AKI in the authors' ICU study. Whether diverse trace metal stores across

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individuals actually have relevance to clinical biomarker interpretation can be tested in larger and multicenter studies.

A similar line of thought suggests an opportunity for application of urinary trace metals as a biomarker to chronic kidney disease. Presumably, recurrent episodes of acute tubular injury would deplete kidney trace metal stores over time. Perhaps then, urine metal concentrations below a certain threshold could be a marker of chronic kidney disease specifically resulting from repeated episodes of acute tubular injury. The authors report supplementary data from a small set of patients showing that urinary Zn concentrations are lower on average in patients with chronic kidney disease than in proteinuric patients without chronic kidney disease. If

the same trend holds in larger data sets, it could suggest a use for urinary trace metal concentrations in diagnosing a history of recurrent acute tubular injury.

Much remains to be determined regarding urinary trace metals, and future multicenter studies will help clarify the application of this novel biomarker to the diagnosis and prognosis of AKI. At present, the potential cost-effectiveness of the approach along with its good performance in ruling out kidney injury as well as in predicting mortality in ICU patients marks it out as a tantalizing area of continued research.

#### DISCLOSURE

The author declared no competing interests.

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