Is Tubular Dysfunction a Risk Factor for AKI?

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Keywords

Biomarker · Tubule · Albuminuria · Acute kidney injury

Abstract

Tubular functions are critical for homeostasis maintenance. However, tubular function markers are not typically assessed in routine clinical care. Recent research by our group has revealed that tubular dysfunction at baseline is a risk factor for subsequent acute kidney injury (AKI), independent of estimated glomerular filtration rate and albuminuria. Here, we describe the underlying hypotheses and biological insights and contrast the changes in tubule function versus injury both before and after an AKI episode.

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Contribution from the AKI and CRRT 2020 Symposium at the 25th International Conference on Advances in Critical Care Nephrology, Manchester Grand Hyatt, San Diego, CA, USA, February 24–27, 2020. This symposium was supported in part by the NIDDK funded University of Alabama at Birmingham–University of California San Diego O'Brien Center for Acute Kidney Injury Research (P30DK079337).

Introduction

Acute kidney injury (AKI) is a common clinical syndrome that plays an important role in the nonlinear progression of chronic kidney disease (CKD) [1]. Factors at the time when patients are healthy that predispose to future AKI risk are likely to give insights not only to risk of AKI but also to CKD. Damage to the kidney is not limited to the glomerulus; rather, on kidney biopsy, tubular atrophy and tubulointerstitial fibrosis are common findings in virtually all forms of CKD [2–4], but these markers of tubule disease are poorly correlated with either estimated glomerular filtration rate (eGFR) or albuminuria [5]. Tubular functions are critical to maintain homeostasis. In this review, we will briefly discuss 4 key functions performed by the kidney tubules that are not assessed by the eGFR and albuminuria and describe recent research that illustrates how measurement of these tubule functions can provide insight into future risk of AKI.

Novel measures that reflect different aspects of tubule cell function and that are assessable in the urine have recently been identified. These markers include a wide range of tubular processes, including proximal tubule re-

Fig. 1. Associations of urine markers of tubule cell dysfunction (red) versus injury (blue) with future risk of AKI in SPRINT participants with CKD. AKI, acute kidney injury; umod, uromodulin; α1m, alpha-1 microglobulin; β2m, beta-2 microglobulin; SPRINT, Systolic Blood Pressure Intervention Trial.

absorptive capacity (marked by lower urine concentrations alpha-1 microglobulin [α1m] and beta-2 microglobulin [β2m]), secretion (marked by higher fractional excretion of hippurate, cinnamoylglycine, isovaleryl-glycine, phenylacetylglutamine, suberic acid, tiglyglycine), acid-base control (marked by urine concentrations of ammonium [NH₄⁺]), and defense from infection and tubular protein synthesis (marked by higher urine concentrations of uromodulin [umod]).

Our group and others have recently identified whether these markers are associated with risk of CKD progression independent of eGFR and albuminuria, as well as with common consequences of CKD such as risk of cardiovascular disease and mortality. For example, higher urine α1m concentrations, marking impaired proximal reabsorptive capacity, have consistently been independently associated with kidney function decline and mortality [6]. Dr. Suchy-Dicey and colleagues [7] found that markers of tubular secretion are associated with higher risk of CKD progression and mortality. Dr. Raphael and colleagues [8] found that lower urinary NH₄⁺ excretion precedes the development of overt metabolic acidosis and is strongly associated with risk of CKD progression, independent of eGFR and ACR in the African-American Study of Kidney Disease trial. These findings were evident even among those with normal serum bicarbonate concentration at baseline. Finally, lower urinary umod concentrations have been associated with CKD progression, independent of eGFR and albuminuria [9]. Taken together, across these markers, and when evaluated in different settings, abnormalities in kidney tubule function

appear to consistently associate with greater risk of CKD progression and related comorbidities, independent of eGFR or albuminuria.

In contemporary clinical care, none of these markers of tubular function are routinely assessed, but focuses solely on glomerular function and urine output [10]. We recently hypothesized that community-living individuals with tubule dysfunction that was evident at times of relative health may be less able to compensate to kidney insults than those without tubule dysfunction, despite similar eGFR and albuminuria [11]. We hypothesized that challenges to the kidneys may induce AKI in individuals with tubule dysfunction, whereas persons without tubule dysfunction may be better prepared to compensate to these challenges and may, therefore, be less likely to develop AKI. Among the Systolic Blood Pressure Intervention Trial (SPRINT) participants with eGFR < 60 mL/min/1.73 m², we measured tubule function (α1m, β2m, and umod) and injury (uNGAL, uKIM-1, uIL-18, uMCP-1, and uYKL-40) markers at the participants' baseline study visits, when they presented to the research clinic in their usual state of health. We adjusted models for clinical risk factors for AKI, baseline eGFR, and albuminuria and the other function and injury markers concurrently. We then followed up the 2,351 SPRINT CKD participants for almost 4 years, capturing AKI events that occurred during the trial. We found that lower urine umod and higher urine α1m were each independently associated with subsequent risk of AKI, independent of AKI risk factors, baseline eGFR, and albuminuria. The biological process marked by higher urine α1m is thought to be similar for higher urine β2m. Hence, elevated concentrations of these markers reflect decreased proximal tubule reabsorptive capacity. It is, therefore, unclear why there was lack of association of urine β2m concentrations with future AKI, but we hypothesize that this may be because stability of β2m is dependent upon urine pH. Prior studies have shown that β2m undergoes enzymatic degradation at a pH < 5.5, and urine specimens from SPRINT were not treated with acid or alkali at the time of collection [12, 13]. None of the 5 injury markers were associated with future risk of AKI (Fig. 1). These findings suggested that tubule dysfunction, more so than injury, may identify individuals less likely to compensate for renal insults and may, therefore, be at higher risk of AKI in the future.

We also wondered whether tubule dysfunction or injury was more altered after an AKI episode occurred. Among a random subset of 947 participants, we repeated measurements of tubule dysfunction and injury after 4 years and compared the changes in biomarkers among

the 59 who experienced AKI in the intervening period versus the remainder who did not. In this analysis, we observed statistically significant increases in 3 of 5 injury markers (uNGAL, uIL-18, and uYKL-40), with a fourth injury marker coming close to statistical significance (KIM-1, $p = 0.06$). In contrast, only 1 marker of tubule function ($\alpha 1m$) had increased more in individuals who had AKI compared to the remainder. Thus, overall, injury to the kidneys appeared to increase markers of tubule cell injury, as expected. In contrast, markers of tubule dysfunction were relatively unaltered after the AKI event.

This study demonstrates that tubule dysfunction markers identify individuals at risk of subsequent AKI, independent of eGFR and albuminuria; associations that were stronger than markers of tubule cell injury. In contrast, tubule injury markers are more consistently elevated after AKI episodes than markers of tubule dysfunction. These findings suggest that joint evaluation of tubule function and injury provides novel insights to factors predisposing to AKI and responses to kidney injury, above and beyond eGFR and albuminuria which primarily reflect glomerular function and injury. Such novel biomarker signatures may ultimately help clinicians both identify their patients' risk for subsequent AKI and po-

tentially to understand if an observed decline in eGFR from prior visits may reflect an AKI episode that occurred in the intervening period.

Acknowledgments

A.L.B. was supported by a U.S. Department of Veterans Affairs Office of Research and Development award (IK2 BX004986-01A1), a Ruth L. Kirschstein training grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK; T32DK104717), a pilot grant from the UAB and UC San Diego - O'Brien Center for Acute Kidney Injury Research (P30 DK079337) and a grant from the NIDDK R01DK119528 (PI: J.H.I.). J.H.I. was supported by a midcareer mentoring award from the NIDDK (K24DK110427). The ancillary study measurements and data analysis were supported by an R01 award from the NIDDK to J.H.I. and Michael G. Shlipak (R01DK098234) and an AHA award to J.H.I. (14EIA18560026). The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Conflict of Interest Statement

Dr. Ix served as San Diego site PI for the SPRINT trial.

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