Urine albumin as a biomarker in acute kidney injury

Subhashini Bolisetty, Anupam Agarwal

Department of Medicine, Nephrology Research and Training Center, University of Alabama at Birmingham, Birmingham, Alabama 35294

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Address for correspondence:
Anupam Agarwal, MD
Division of Nephrology, THT 647
University of Alabama at Birmingham
Birmingham, AL 35294
Tel: (205) 996 6670;
Fax: (205) 996 6650
Email: agarwal@uab.edu
Acute kidney injury (AKI) is a common clinical condition that is associated with significantly high rates of morbidity and mortality particularly in critically ill patients (1, 2, 10, 18). Despite fundamental advances in understanding the etiology and pathophysiology of AKI, the current therapeutic approaches remain limited to supportive measures (e.g. dialysis). Treatment for AKI is confounded by several variables including patient demographics, severity of AKI and AKI associated with complex medical and surgical interventions. Therefore, there is a growing need to provide timely and accurate diagnosis to allow for the implementation of potentially novel therapeutic interventions to overcome AKI.

Studies in animal models of AKI have highlighted the therapeutic potential for a number of interventions. However, translation of these potential therapies to humans has yielded inconclusive and equivocal results (2, 5, 12). One of the proposed reasons for such failure is the lack of early markers for AKI and hence an unacceptable delay in initiating therapy. In current clinical practice, identification and severity of AKI is generally based on elevations in serum creatinine levels. Unfortunately, creatinine is an unreliable indicator of early AKI for multiple reasons. For example, a significant decrease (~50%) in GFR may be necessary to raise the serum creatinine above the normal laboratory range (2, 9, 11). In sepsis, production of creatinine from the muscle is reduced and relying on changes in serum creatinine to diagnose AKI in such settings could delay diagnosis of AKI (3). Recent studies have conclusively shown that the morbidity and mortality associated with AKI are correlated with the severity of kidney injury. The data from these studies and animal models indicate that prevention or decrease in the extent of injury could significantly lower negative outcomes related to
AKI (6, 8, 9). Therefore, there is a vital need for the identification of biomarkers that are sensitive, specific and provide timely and early diagnosis of AKI before substantial damage has already been done.

A biomarker is defined as a measurable and quantifiable biological parameter that can serve as an index for health and physiology related assessment. An ideal biomarker for AKI should be specific to the kidney, differentiate between subtypes of AKI (prerenal, intrinsic renal and postrenal), determine the location and severity of injury and most importantly, facilitate early detection of AKI for successful utilization of potential therapeutic agents. In addition, the test should be inexpensive, non-invasive, accurate, easy and rapid to quantify (7, 8, 11). Extensive ongoing research has yielded several potential biomarkers in AKI including neutrophil gelatinase-associated lipocalin (NGAL), liver fatty acid binding protein (L-FABP), kidney injury molecule-1 (KIM-1), interleukin-18, netrin, monocyte chemoattractant protein-1, cystatin C as well as others (4, 7, 10, 13, 16).

In the present issue, Ware and colleagues highlight the importance of urine albumin as a biomarker of AKI (17). Use of albumin excretion has been well established as a diagnostic and prognostic marker to evaluate the degree of severity of glomerular diseases in the progression of chronic kidney disease (14, 15), but only limited studies have suggested the utility of urine albumin as a biomarker for AKI. Using multiple complementary approaches involving five animal models of AKI in mice (three representing renal causes of AKI, one for pre-renal and one for post-renal) the authors show that urine albumin increases as early as 4h following injury only in the intrinsic renal causes of AKI (ischemia reperfusion, nephrotoxin and rhabdomyolysis) and not in
either pre-renal (secondary to endotoxin) or postrenal (obstructive uropathy) conditions.

Increases in urine albumin occurred prior to changes in serum creatinine, which increased only after significant azotemia had developed. These results from animal models of AKI were further corroborated in urine samples from patients with and without AKI and found to be comparable to early changes in NGAL, an extensively validated AKI biomarker. The findings in this work are consistent with recent studies published in rat models of nephrotoxin-induced AKI (19). In the course of investigating urinary trefoil factor 3 as a biomarker (which was significantly decreased in nephrotoxin-induced AKI), Yu and colleagues found urine albumin to outperform serum creatinine and blood urea nitrogen for detecting acute tubular injury in rats. These studies also evaluated isoproterenol toxicity to the heart and skeletal muscle where no renal histological damage occurs and found no change in urinary albumin levels. These results and the work by Ware and colleagues further substantiate the specificity of urine albumin as a biomarker for AKI.

The findings in this work also provide new insights into the regulation of the albumin gene, which is normally silenced in the kidney. During AKI secondary to intrinsic renal causes, there is significant proximal tubular injury. One potential consequence of such tubular injury would be the inability of the proximal tubule to reabsorb albumin, resulting in albuminuria. The authors provide an additional mechanism in this regard that relates to direct increases in albumin gene transcription in the renal cortex in the animal models of intrinsic AKI. Chromatin immunoprecipitation analysis revealed an association of RNA polymerase II with the albumin gene, indicating an increase in the transcriptional activation of albumin, which was also observed in
urine samples from patients with AKI. A 5-fold increase in RNA polymerase II binding to
urinary fragments of the albumin gene was detected in patients with AKI compared to
control subjects without AKI. An increase in the expression of an albumin-like gene, α-
fetoprotein was also noted. Assessment of serum albumin levels would provide further
information on the contribution of albumin gene transcription to increased urine albumin
levels, described in this work. The authors suggest an interesting analogy for this
phenomenon of increased generation of albumin and α-fetoprotein and have termed this
as "renal hepatization" during AKI, a potentially new avenue in AKI research.

The strengths of this paper include the validation of urinary albumin as a specific
biomarker for intrinsic renal causes of AKI as opposed to most other promising
biomarkers that are unable to accurately differentiate the etiology of AKI. Moreover, the
use of AKI and non-AKI associated patient samples provides strong evidence for the
use of this biomarker in clinical practice. Of note, even the ICU patients without AKI had
a modest increase in urine albumin, which may suggest subclinical kidney injury. It
would be interesting to follow these patients and determine if urine albumin increases
over time and if they develop AKI. In the future, it will be essential to validate the
sensitivity and specificity of urine albumin in clinical samples from larger cohorts and
from multiple clinical settings. Although it is not clear from the animal models if levels of
urine albumin could predict the severity of AKI, it may be important to evaluate this in a
clinical setting. Further studies should also evaluate if urine albumin can serve as a
prognostic marker and its use to evaluate outcomes following therapeutic interventions.

In conclusion, it is evident that urine albumin may serve as a biomarker for early
diagnosis of AKI. It is specific to intrinsic causes of AKI and is not altered in pre-renal or
post-renal causes of AKI. The commercial availability of tests for the detection of urine albumin and its low cost gives it an added advantage for routine clinical use. In clinical practice however, the use of a single biomarker may not always be sufficient. As highlighted by several investigators in the literature, a panel of biomarkers would be necessary to identify the severity of injury, the type of insult and also monitor response to therapeutic interventions.
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