

Human Models to Evaluate Urinary Biomarkers of Kidney Injury

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It has been several years since the Board of Advisors and the Council of the American Society of Nephrology summarized a series of retreats undertaken to prioritize renal research directions given current resource limitations (1). All five working groups devoted to different areas of research in nephrology highlighted the importance of biomarker development, but two groups—acute renal failure and transplantation—went so far as to recommend the establishment of dedicated biomarker cores to speed up the processes necessary for biomarker discovery and validation. A recurring theme in the nephrology literature is that current clinical indicators of kidney injury (serum creatinine and GFR) are inadequate for timely diagnosis and prognosis, which has severely limited nephrologists' ability to reduce morbidity and mortality further in our patient populations. Supplementing current measures of renal function with well-developed kidney injury biomarkers may ultimately be the key to addressing this demoralizing problem.

In this issue of *CJASN*, two groups report findings on urinary biomarkers of acute kidney injury (AKI) in different populations. In a 123-patient cohort of adults undergoing elective cardiac surgery, Koynert *et al.* (2) measured several of the most frequently reported and promising urinary biomarkers, such as kidney injury molecule 1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and π -glutathione-S-transferase. They demonstrate the superiority of these urinary biomarkers (earlier onset and better discrimination) compared not only with plasma creatinine but also against the fractional excretions of sodium and urea. The second group focused on the transplant population and evaluated several of the same urinary biomarkers. As opposed to protein concentrations, however, Szeto *et al.* (3) quantified mRNA expression from the urinary sediment of 63 kidney transplant recipients with worsening allograft function, and they report that each log of urinary KIM-1 expression is associated with nearly threefold higher risk for graft failure. They also demonstrate that gene expressions of NGAL, KIM-1, and IL-18 in urinary sediment are

significantly different between histologically diagnosed rejection and nonspecific tubular atrophy and interstitial fibrosis as well as 11 healthy control subjects.

These two articles highlight the current focus of renal research. Whereas the nontransplant community has aggressively implemented one of the key recommendations by the acute renal failure working group—assessing biomarkers in patient groups at high risk for AKI (*e.g.*, cardiac surgery, critical illness), the transplant community has been much less aggressive regarding its working group's recommendation for biomarker study. There are currently more than 50 original articles of various biomarkers in the setting of AKI compared with fewer than 10 in kidney transplantation (4). Why is this the case?

We would argue, in fact, that transplantation is a superior model to study kidney injury biomarkers because it does not have several of the limitations that affect other settings of AKI. In deceased-donor kidney transplantation, for example, significant ischemia is uniformly present, with cold-ischemia times averaging 12 to 16 hours. Conversely, in the typical nontransplant setting, AKI is heterogeneous in duration (minutes to days), dosage (relatively few require dialysis support), and type (ischemic, nephrotoxic, inflammatory). Even the nature and timing of the insult itself can be difficult to identify. In addition, although AKI commonly occurs in settings such as cardiac surgery and intensive care, as many as one third of those with serum creatinine elevations have prerenal azotemia with no means to verify structural or histologic injury. This leads to false-negative biomarker results that are based on arbitrary outcome definitions. Such results are less likely in kidney transplantation because almost all cases have varying degrees of overt kidney injury without contamination from prerenal azotemia. Furthermore, transplantation is a timed insult and offers the opportunity to ascertain histology (preimplantation biopsy) at the moment of injury and several times during follow-up. In contrast, the general lack of biopsy data is a severe limitation in most settings of native kidney injury.

The transplant setting also permits the study of biomarkers for important short-term (*e.g.*, delayed graft function, acute rejection) and long-term (*e.g.*, allograft failure) outcomes. These are relatively common outcomes after transplantation, allowing reasonable sample sizes and lengths of follow-up. Short-term events, such as dialysis requirement, can be assessed for native

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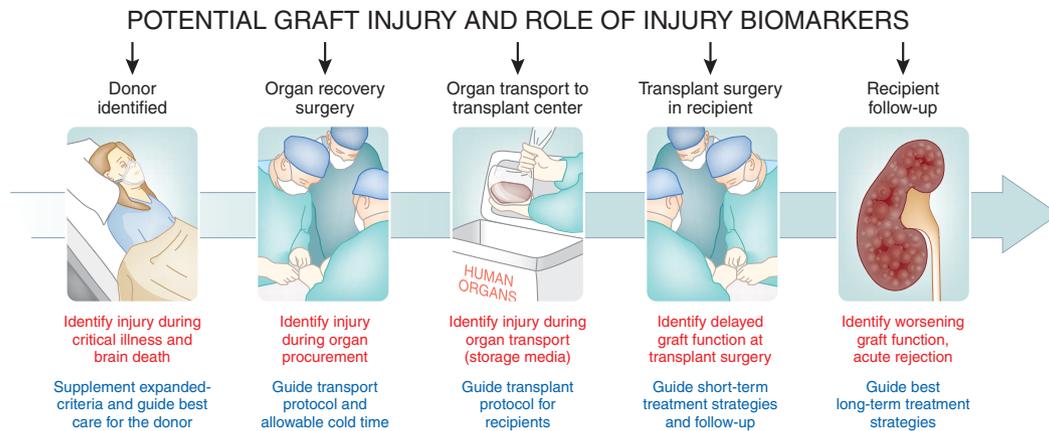


Figure 1. The various time points for which structural kidney injury can potentially occur and be detected and acted upon during the kidney transplant process to determine and/or improve prognosis.

kidneys in AKI, but long-term outcomes (*e.g.*, development of chronic kidney disease, death) are far less common and difficult to study because they require enormous resources. In addition, the availability of national databases for transplanted kidneys, such as the Scientific Registry of Transplant Recipients (5), makes long-term follow-up feasible. Other than these advantages, one possible limitation in the transplant setting is the potential interference of immunosuppressive and/or nephrotoxic medications during renal recovery.

Apart from the issue of whether native or transplant AKI is the superior model, another dilemma is whether we can borrow results from the native kidney setting to describe AKI in transplantation and *vice versa*. Because of the differences in biomarker concentrations observed between the two settings, the likely answer to this is “no.” A recent systematic review of studies in various native AKI settings noted wide variation in optimal cutoff values for NGAL to predict renal replacement therapy but reported a median pooled-optimal NGAL cutoff value of 278.3 ng/ml (6). Conversely, our group noted median urine NGAL levels in kidney transplant recipients with immediate and delayed graft function change from 418.9 and 483.0 ng/ml at the time of transplantation to 60.5 and 1035.0 ng/ml by the first postoperative day, respectively (7).

In addition to benefiting the general field of biomarker research in nephrology, we believe biomarkers of kidney injury are specifically needed to improve the clinical practice of kidney transplantation. Biomarkers may provide a number of windows for useful applications in the transplant setting, from the time leading up to organ procurement to late postoperative course management in the recipient. For example, novel biomarkers might serve as very early prognostic markers at the time of organ procurement, as markers of meaningful kidney injury and dysfunction at the time of transplantation (more accurately define delayed or slow graft function), and as screening tools in recipients to supplement or even replace protocol transplant biopsies (Figure 1). Biomarkers at the time of procurement have the potential to supplement or replace the current approach for determining expanded-criteria donor status. They may prove helpful for deciding allograft transport proto-

cols (*e.g.*, biologically appropriate limits for cold ischemia time, use of machine pump preservation) and for improving organ allocation by identifying viable allografts of otherwise questionable quality on the basis of clinical characteristics alone. The latter point is particularly important in light of highly variable discard rates (some as high as 60%) across the United States, especially for kidneys from donors designated as expanded-criteria using the current system (8). Ultimately, noninvasive biomarkers could aid in the development of large-scale therapeutic trials and guide more effective management strategies across the multiple time frames of kidney transplantation.

As the field of biomarker research in nephrology continues to evolve, it will likely become important to evaluate the individual and potential combined roles for different biomarkers of structural tissue injury (*e.g.*, KIM-1, NGAL, IL-18), of proximal tubular function (*e.g.*, urinary cystatin C), and of filtration function/urine flow (*e.g.*, urinary creatinine). It will be imperative to include biomarker validation and discovery in future controlled trials for the treatment/prevention of AKI. Although the field has been maturing rapidly for AKI caused by cardiac surgery and other settings of native kidney injury, it needs to gain even greater momentum in the transplant setting.

Disclosures

None.

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See related articles, “Urinary Biomarkers in the Clinical Prognosis and Early Detection of Acute Kidney Injury,” on pages 2154–2165, and “Urinary Expression of Kidney Injury Markers in Renal Transplant Recipients,” on pages 2329–2337.