Delayed Consequences of Acute Kidney Injury

Sharidan K. Parr and Edward D. Siew

Acute kidney injury (AKI) is an increasingly common complication of hospitalization and acute illness. Experimental data indicate that AKI may cause permanent kidney damage through tubulointerstitial fibrosis and progressive nephron loss, while also lowering the threshold for subsequent injury. Furthermore, preclinical data suggest that AKI may also cause distant organ dysfunction. The extension of these findings to human studies suggests long-term consequences of AKI including, but not limited to recurrent AKI, progressive kidney disease, elevated blood pressure, cardiovascular events, and mortality. As the number of AKI survivors increases, the need to better understand the mechanisms driving these processes becomes paramount. Optimizing care for AKI survivors will require understanding the short- and long-term risks associated with AKI, identifying patients at highest risk for poor outcomes, and testing interventions that target modifiable risk factors. In this review, we examine the literature describing the association between AKI and long-term outcomes and highlight opportunities for further research and potential intervention.

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INTRODUCTION

Acute kidney injury (AKI) is an increasingly common disease that complicates up to 1 in 5 hospitalizations.[1-8] The conventional belief that AKI is "self-limited" has been challenged by studies showing an association between AKI and progressive kidney disease,[9-13] cardiovascular events,[14-16] and short- and long-term mortality.[1,7,17-20] The combination of population growth, increasing AKI incidence,[8] and improved short-term survival[7,21,22] has resulted in an expanding population of AKI survivors at risk for these outcomes. In this review, we will examine literature describing the association between AKI and incident and progressive chronic kidney disease (CKD), end-stage renal disease (ESRD), cardiovascular events, and mortality. We will also discuss processes that may modify the course of disease in the post-AKI period (Fig 1), and future research that will be needed to identify potential interventions and define optimal care.

INCIDENT CKD AFTER AKI

The traditional belief that AKI survivors often experience full recovery is likely rooted in early clinical observations that young patients with presumed normal baseline kidney function who experienced severe AKI often had a good *clinical* recovery, resuming their occupations and prior functional capacity.[23,24] However, carefully performed physiologic measurements demonstrated that renal recovery was often incomplete. Using thiosulphate and para-aminohippurate clearances, Lowe and colleagues[23] demonstrated that kidney function remained below the lower limit of normal in most of the patients over a 3-year follow-up period. Using para-aminohippurate and inulin clearances, Finkenstaedt and Merrill[24] also reported that "clearance values remained below the lower limit of normal in most patients… consistent with permanent renal damage of mild degree." These studies were small and lacked appropriate controls and measures of baseline kidney function, but indicated that AKI may not truly be "self-limited".

Following these early reports, experiments in animal models of AKI have elucidated potential mechanisms for post-AKI residual kidney impairment including interstitial inflammation, capillary rarefaction, and chronic hypoxia, leading to tubulointerstitial fibrosis and progressive nephron loss.[25-27] Physiologic derangements that potentially lower the threshold for subsequent injury have also been reported, including hyperfiltration, urinary concentrating defects, impaired sodium-handling, enhanced pressor response, and impaired autoregulation of renal blood flow (Fig 1).[25,26]

Some evidence suggesting a potential link between AKI and future kidney disease in humans comes from pediatric studies. Although adult populations who experience AKI often have "reduced renal reserve" and comorbidities (ie, diabetes and hypertension) that confound the association between AKI and CKD, the low prevalence of these conditions in the pediatric population supports a link between AKI and future CKD. Mammen and colleagues[28] evaluated a pediatric intensive care unit population with AKI for subsequent development of CKD, defined as albuminuria or glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2. The distribution of Acute Kidney Injury Network Stages 1, 2, and 3 were 35%, 37%, and 28%, respectively.

From the Tennessee Valley Healthcare System (TVHS), Geriatric Research Education and Clinical Centers (GRECC), Nashville, TN; TVHS, Veterans Administration (VA) Medical Center, Veterans Health Administration, Nashville, TN; Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; and Vanderbilt Center for Kidney Disease (VCKD), Nashville, TN.

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Address correspondence to Edward D. Siew, MD, MSCI, Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, 1161 21st Avenue South, MCN S-3223, Nashville, TN 37232. E-mail: edward.siew@vanderbilt.edu

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Over a median follow-up period of approximately 1 year, the incidence of CKD was 10% overall, and increased in a graded manner with AKI severity from 5% to 17%. In addition, 47% of patients were identified as being at increased risk for future CKD based on hypertension, mildly decreased glomerular filtration rate, or hyperfiltration. In another study by Garg and colleagues,[29] 19 children recovering from hemolytic-uremic syndrome were compared with a control group of 64 healthy children. At 5-year follow-up, hemolytic-uremic syndrome survivors had a higher prevalence of microalbuminuria compared with controls (20% vs 3%) with a relative risk of 6.0. Collectively, these and other pediatric studies[30,31] suggest a potentially causal role of AKI in future development of CKD and highlight hypertension and albuminuria as important modifiable factors in the follow-up period. However, most of these studies were limited by small sample size and lack of a control population.

Several studies in adults have also demonstrated evidence of an association between hospitalized AKI and future incident CKD (Table 1). Within a large integrated health care system in Northern California, Lo and colleagues[13] evaluated the risk for developing Stage 4 or 5 CKD in patients with baseline eGFR > 45 mL/min/1.73 m^2 (including 68% with eGFR > 60) who experienced dialysis-requiring AKI and were dialysis-independent 30 days after discharge. After matching and adjusting for multiple clinical factors, including baseline eGFR, an episode of dialysis-requiring AKI was independently associated with a 28-fold increase in risk for developing Stage 4 or higher CKD over 10,344 person-years of follow-up. Although 84% of patients who survived the index hospitalization recovered to become dialysis-independent, they had a substantially increased risk of developing advanced CKD.

The association between less severe AKI and future CKD has also been examined. In 29,388 Veteran patients undergoing cardiac surgery, Ishani and colleagues[33] evaluated the relationship between magnitude of acute postoperative serum creatinine increase and the risk for incident CKD (persistent eGFR < 60 mL/min/1.73 m^2). AKI severity was categorized by a proportional increase in serum creatinine from baseline, defined as class I (1%-24%), class II (25%-49%), class III (50%-99%), or class IV (≥100%). The investigators observed a graded association between magnitude of postoperative creatinine increase and risk for incident CKD. Risk was greatest at 3 months after surgery, with creatinine increase classes I to IV conferring hazard ratios (HRs) of 2.1 to 6.6. The persistence of these associations at 5 years, although attenuated (HRs 1.5-2.4), provides further evidence linking less severe AKI with future CKD risk.

To evaluate the hypothesis that even reversible AKI may have long-term consequences, Bucaloiu and colleagues[34] studied patients with normal baseline kidney function and without proteinuria who experienced reversible AKI, defined as a return of creatinine to within 90% of baseline within 90 days of AKI, and compared them to matched non-AKI controls. Survivors of AKI had a significantly increased risk of developing incident CKD over a median follow-up time of 3.3 years, with an HR of 1.91. Among patients experiencing AKI, 71% had Acute Kidney Injury Network Stage I AKI, and the duration was less than 24 hours in 75% of patients, suggesting that even mild, transient AKI predicts risk for future CKD. However, it is unclear whether mild AKI *causes* incident CKD, or whether AKI is simply more likely to occur in patients with higher comorbidity burden and subtle underlying renal abnormalities who are already predisposed to develop CKD.

CKD PROGRESSION AND ESRD AFTER AKI IN ADULTS

Given observations that progression to ESRD is frequently nonlinear and punctuated by AKI episodes,[11,35] it is important to consider the potential contribution of AKI to the advanced CKD burden. Multiple studies have demonstrated the association between AKI and progressive CKD and/or ESRD, several of which have been included in Table 2. Ishani and colleagues[33] examined CKD progression after cardiac surgery. Progression was assessed using a moving average eGFR and defined by a persistent reduction in eGFR constituting an increase in CKD stage. The risk of CKD progression was highest 3 months postoperatively with adjusted hazard ratios (aHRs) of 2.5 to 8.0 depending on the magnitude of postoperative increases in serum creatinine. Although misclassification of recovering AKI as progressive CKD in the months after discharge is possible, the persistence of this association at 5 years (aHRs 1.5-2.4) supports the robustness of these findings.

Wald and colleagues[38] examined the risk for chronic dialysis in a population-based study using administrative data in Ontario, Canada. In this study, patients who recovered from dialysis-requiring AKI and survived at least 30 days after discharge were matched with hospitalized patients who did not have AKI. The incidence rate of chronic dialysis was 2.63 per 100 person-years in patients with dialysis-requiring AKI, vs 0.91 per 100 person-years in controls (aHR 3.23) over a median follow-up time of 3 years. An episode of dialysis-requiring AKI was associated with an approximately 2-fold and 15-fold higher risk for developing chronic dialysis in patients with and without underlying CKD, respectively, compared to hospitalized patients without dialysis-requiring AKI.

CLINICAL SUMMARY

- The number of acute kidney injury (AKI) survivors is increasing rapidly due to the combined effects of population growth, a rising incidence of AKI, and improved short-term survival.
- AKI is associated with subsequent elevation in blood pressure, cardiovascular events, incident and progressive CKD, ESRD, and mortality.
- Optimal care for AKI survivors is not well defined and will require understanding the long-term implications of AKI, identifying patients at highest risk for these outcomes, and targeting modifiable risk factors for intervention.