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Harm! Foul! How AKI SHReDDs Patient Futures

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Abstract

Purpose of review: Transition from acute kidney injury (AKI) to chronic kidney disease (CKD) is increasingly accepted. Less well recognized, but supported by very similar data, is development of disease of other organ systems after AKI. Awareness of other-organ sequelae of AKI may inform efforts to improve the care of patients after AKI.

Recent findings: Stroke, Hypertension, Reproductive risk, Dementia, and Death (SHReDD) are sequelae which occur with increased risk relative to that of non-AKI within 6 months-3 years after AKI diagnosis, and which are supported by preclinical/mechanistic study. Adjusted hazard ratios for these sequelae are strikingly similar to that of AKI-CKD, ranging from 1.2–3.0. Mechanistic studies suggest kidney-centric mechanisms including sodium regulation, volume status regulation, and the renin-angiotensin system are drivers of long-term, extra-renal, change.

Summary: Further clinical characterization and mechanistic insight is necessary, and may have considerable translational impact. Programs which screen or follow post-AKI patients may increase clinical utility if focus is expanded to include the SHReDD complications.

Keywords

AKI sequelae; reproductive sequelae of AKI; cardiovascular sequelae of AKI; Post-AKI screening

Introduction:

The doctrine “no harm, no foul” directs basketball referees not to penalize players for transgressions which are unlikely to affect the game’s outcome. Derived from 17th-century English legal doctrine *de minimis non curat lex*—“the law is not troubled by trifles” [1, 2], “no harm, no foul” also became a medical aphorism applied to transient rise in serum creatinine. However, in the last 15 years, observational studies and mechanistic basic science have refuted this aphoristic approach. Strong mechanistic studies have increased recognition of acute kidney injury to chronic kidney disease (AKI-CKD) transition. Although it may no longer be surprising that AKI initiates chronic disease in the kidney, an increasing body of

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literature suggests we may yet be surprised to find that AKI can initiate long-term disease *beyond* the kidney. Although in some cases data are sparse, cardiovascular disease, all-cause mortality, reproductive, and cognitive function may be impacted after AKI. Because of the potential for causality, identification of AKI represents a critical moment at which it may be possible to act to prevent or at least identify the burden of future disease. Thus, as with AKI-CKD transition, enumerating and characterizing the transition between AKI and chronic other-organ disease, AKI-C**x**D, is a first step, which could greatly improve human health. Critical questions include temporality, comorbid risks including concomitant CKD, and impact. New data prior to the COVID-19 pandemic indicates that AKI incidence is high and increasing, perhaps as high as 2 per 1000 population [3]. Since COVID-19 caused worldwide increase in AKI, it is likely the case that long-term outcomes of AKI will have high impact on population health.

Here, we review evidence for AKI-C**x**D with significant potential human health impact: Stroke, Hypertension, Reproductive risk, Dementia, Death (SHReDD). We summarize mechanisms, estimate impact, propose observational and preclinical investigational strategies, and provide rationale for screening. Our hypothesis is that by viewing AKI-C**x**D as a single entity with diverse manifestations, the importance of kidney-centered investigation, and thus the probability of successful intervention, may be increased.

Stroke

Stroke is the third leading cause of death due to cardiovascular disease [4]. The annual cost of stroke in the United State is about $103 billion [5]. Multiple reports indicate AKI as a predisposing factor for stroke. Wu et al [6] reported that patients recovered from AKI have a higher incidence of stroke than the patients without AKI. They studied 4,315 propensity-matched recovered, dialysis-requiring AKI and non-AKI patients. After mean follow-up of 3.36 years, the rate of incident stroke was significantly higher in the AKI-recovery patients than in the non-AKI patients (15.6 vs 11.5 per 1,000 person-years). Regarding mechanism, Liu et al reported inflammation and functional changes in the brain after ischemic AKI in mice [7]. They revealed that AKI increased the microvascular permeability in the brain, which resulted in leaky blood–brain barrier. They also reported that ischemic AKI led to increased levels of the proinflammatory chemokines including granulocyte colony stimulating factor which have been implicated in the pathogenesis of stroke [8]. Experiments in a severe rodent renal IRI model (60 minutes bilateral IRI) and *in vitro* modeling confirm that AKI dysregulates the blood brain barrier, induces neuronal transcriptional change, and induces inflammation, including activation of microglia [9, 10]. A hopeful preclinical insight is provided by Zhao et al; using IRI as a model, they demonstrated direct brain microvascular effect of AKI, which persists at least a week. Brain arterioles of IRI-subjected animals lose angiotensin II (AngII) responsiveness and alter expression of fibroblast growth factor 2, suggesting direct AKI-induced change in vascular physiology which could potentially be amenable to renin-angiotensin system-targeted treatment [11]. The suggestion that AKI induces intracranial inflammation and vascular changes implicated in stroke pathogenesis may prove a starting point toward further clinical investigation and screening. Significant advances in assessment of intracranial inflammation such as novel-

contrast MRI, molecular imaging, and cerebrospinal fluid biomarkers may provide avenues for translational study [12, 13].

Hypertension

Hypertension is among the most common and serious health problems; worldwide it is the most common cause of CKD, and an initiator of additional cardiovascular disease [4]. A bidirectional relationship between hypertension and kidney disease has long been suspected; accordingly, clinical and animal studies strongly suggest that AKI causes hypertension. Using retrospective design, Hsu et al studied 2,451 AKI patients without history of hypertension [14]. Blood pressure elevation was observed in 30.6% of AKI patients at 180 days, and 46.1% at 730 days after AKI; this was a significantly greater proportion than in non-AKI patients. AKI was independently associated with elevated blood pressure during follow-up, with more severe AKI associated with higher adjusted risk. Based on this data, it is estimated that AKI potentially causes 22.1 incident hypertension events per 100 person/years [14, 15]. Of greater impact is the increase in hypertension caused by pediatric AKI, reported by Askenazi et al [16]. 6 of 29 (20.6%) hospitalized children developed hypertension within 3–5 years after AKI, highlighting the increased burden of chronic disease initiated in childhood.

Animal studies that demonstrate hypertension developing after AKI suggest potential pathophysiologic mechanisms. Soranno et al reported ischemic AKI-induced hypertension in mice [17–19]. AKI induced by 25-minute bilateral ischemia-reperfusion injury (IRI), caused elevated systolic blood pressure and left ventricular diastolic dysfunction at 1 year in males, but not females. Histone deacetylase (HDAC) inhibition ameliorated the male-only blood pressure elevation and cardiac dysfunction, without changing long-term loss of glomerular filtration rate (GFR). It is unclear whether other regulatory effects of HDAC inhibition might be involved but the lack of change in long-term GFR loss, despite prevention of adverse cardiovascular consequence, argues that cardiovascular disease initiated by AKI may be GFR-independent. Similarly, Spurgeon-Pechman et al reported development of salt sensitive hypertension in rats subjected to IRI [20]; this did not occur in sham-treated rats. Salt-sensitive hypertension and then albuminuria developed a week after initiation of the high-salt diet, suggesting that albuminuria was driven by hypertension; high-salt induced glomerular damage was noted on histologic sections. A subsequent study demonstrated loss of pressure natriuresis and renal medullary autoregulation; it is suggested these together result in the observed salt-sensitive hypertension [21].

Overall, preclinical and clinical data provide strong evidence for AKI-induced hypertension. Additional preclinical investigation in translational models of AKI such as cecal ligation and puncture (a sepsis model) and cardiac arrest/cardiopulmonary resuscitation (a model of acute cardiorenal syndrome) would be expected to inform further clinical investigation [22, 23]. As IRI is considered a translational model of renal transplant, investigation of the clinical course of postoperative hypertension and natriuresis in renal transplant patients may also provide important data.

Reproductive Risk

Evidence suggests that even mild changes in renal function such as that in living kidney donors and those with mild CKD may increase risk for pregnancy complications [24]. Two recent studies by Tangren et al strongly support that AKI may worsen future pregnancy outcomes. In the first, investigators identified that recovered AKI conferred increased risk of preeclampsia (adjusted odds ratio 2.9) and adverse fetal outcomes (adjusted odds ratio 2.4) including fetal growth restriction, even after matching for demographics, BMI, diastolic blood pressure, and other comorbidities. The mean time from AKI to pregnancy was 32 months. Sensitivity analysis restricted to patients with documented normal prepartum creatinine demonstrated similar result, as did subgroup analysis in nulliparous people, suggesting the association was specific to AKI. Interrogation of the cohort after accrual of additional parturients revealed additional risk of preterm birth, and further demonstrated a dose-response relationship between severity of AKI and subsequent risk of preeclampsia for KDIGO stages 2–3 [24–26].

The mechanism of AKI-reproductive risk is unclear but strong support for the phenomenon and suggestion of mechanism is provided by Gillis et al. Rats with a history of recovered ischemia-reperfusion-induced AKI demonstrated complicated pregnancies similar to those observed by Tangren. Recovered AKI-exposed dams had fewer, smaller litters with fetal growth restriction and increased preterm death. Involvement of the renin-angiotensin system was suggested by impaired response to sodium loading during pregnancy, reduced plasma volume, and increased uterine artery resistance index in AKI-exposed dams [27]. Observational studies support direct and indirect mechanisms. A direct AKI-preeclampsia mechanism could be inferred from studies of preeclampsia and CKD, in which a linkage is better understood [28]. Molina-Pérez et al. found that women with CKD and angiogenic imbalance were more likely to have preeclampsia [29]. The study enrolled 171 pregnant patients with CKD and assessed the balance of soluble Fms-Like Tyrosine Kinase-1 (sFlt-1) to placental growth factor (PlGF), which associates with preeclampsia risk [30]. Risk of preeclampsia associated with increasing sFLT-1 to PlGF ratio. Overexpression of sFlt1 results in parallel rise of AngII [31]; since increased AngII sensitivity is suggested in mechanistic studies of AKI [32], the potential for connection to pregnancy risk should be investigated. AKI-induced hypertension could also indirectly lead to reproductive risk, as hypertension has a well-described role in complications of pregnancy, including preeclampsia [33].

To our knowledge, no investigation addresses effects of AKI on fertility. However, CKD decreases fertility in both sexes: impaired spermatogenesis, erectile dysfunction, and reduced ovulation. As these effects are negated by renal transplant [34, 35], post-AKI infertility deserves further investigation.

In 2012, the total cost burden of preeclampsia in the United States was $2.1 billion in the first year following birth alone [36]. The potential for lifelong disease greatly increases the impact of adverse maternal health. Although studies on AKI parental effects after birth have largely centered on AKI that occurs during pregnancy, as recovered AKI increases the rate of preeclampsia, patients with recovered AKI who give birth are likely at higher risk for

future renal, metabolic, and cardiovascular diseases [37]. Studies expanding knowledge on the impact of recovered AKI on parental and offspring outcomes enable longitudinal risk assessment and provide mechanistic avenues for treatment, potentially reducing long-term disease in AKI survivors and their offspring. Prospective study of AKI survivors for fertility disorders and reproductive risk are likely to have high impact given the risk of lifelong disease in offspring.

Dementia

The most common cause of dementia in the elderly is Alzheimer's disease, which affects 5.8 million people in the United States and more than 55 million people worldwide [38, 39]. Global costs of dementia were estimated as approximately $1.3 trillion in 2019 and rising rapidly [38, 40]. Several population studies demonstrate association between recovered AKI (as determined from coding data or dialysis requirement) and later onset of dementia, with surprisingly consistent hazard ratios of 1.88–3.04. Because CKD also associates with dementia, all three studies controlled for CKD using exclusion, sensitivity analysis, and/or propensity scoring; AKI associates with dementia independently of preexisting or subsequent CKD, although subsequent CKD increases risk. The transition to dementia may occur quickly – mean time to onset of dementia was reduced in AKI patients compared with controls, and Kaplan-Meier curves diverge within two years. One study reported mean time to diagnosis of dementia in the AKI group as 1.9 [0.2–4.1] years (median [interquartile range]), quite similar to that reported for AKI-CKD transition [41–43]. Mechanisms are poorly characterized but studies describe cognitive and behavioral changes induced by AKI, supporting interaction with the neural circuits affected in dementia. Cognitive/behavioral tests in rodents are altered in the acute phase of several AKI models, although changes do not appear to persist [44, 45]. Vanderlinden et al. found that AKI patients assessed nearly 7 months after AKI demonstrated greater evidence of neurocognitive impairment than hospitalized, non-AKI controls [46]. Together, growing evidence connects a history of AKI and early cognitive impairment. Important questions remain regarding the influence of comorbid organ failure and mechanism. However, early diagnosis of dementia may improve quality of life and slow progression; since all current medical therapy targets slowed progression, earlier diagnosis may also improve benefit from therapy [47].

Mortality

AKI impacts both short- and long-term mortality. Numerous clinical reports have suggested that AKI complicating cardiovascular events [48, 49], progression of CKD [50, 51], and recurrence of AKI [52, 53], increase long-term mortality. Odutayo et al reported AKI associated with an 86% increased risk of cardiovascular disease-associated mortality [48]. The seminal AKI-CKD meta-analysis of 13 cohorts by Coca et al which identified the incidence of CKD and ESRD after AKI also demonstrated doubled mortality risk in AKI patients with compared with non-AKI patients [51]. Siew et al demonstrated that patients with recurrent AKI had a higher 1-year mortality (35%) than patients without recurrent AKI (18%)[53]. Increased severity of AKI itself also increases long-term risk of mortality [54, 55]; together these suggest that the vector of recovery may impact long-term mortality. Investigating this hypothesis. Kellum et al identified five recovery patterns. In particular

patients with early reversal of recovery (37.3% of the cohort) demonstrated elevated risk of 1 year mortality compared with patients with sustained recovery [56]. Mechanistic studies of mortality after AKI are lacking. While it seems reasonable to hypothesize that early mortality is due to AKI-induced systemic disease, this relationship may be either more straightforward or more complicated. Observation of perimortem comorbidities in clinical cohorts may be partly revealing and suggest a path for preclinical study.

Surveillance of AKI Survivors:

Characterization of AKI-CKD recently led to the development of guidelines and even clinics for post-hospital surveillance of AKI survivors; however, this practice is the subject of considerable current controversy (reviewed in Vanmassenhove, Vanholder and Lameire [57]). First, AKI is not always recorded as a diagnosis, or coded in the electronic medical record, making it challenging to identify the right patients for follow-up. Second given the incidence of AKI, a requirement for specialist follow-up likely exceeds the capacity of nephrology specialists. Third, AKI survivors suffer urgent comorbidities which often require follow-up and thus may not have capacity for or access to additional medical visits. Fourth, physiologic changes during critical care (for example a fall in serum creatinine due to lost muscle mass) may confound posthospital assessments. Most importantly, two recent studies have demonstrated lack of renal benefit to specialist care following AKI. Silver et al found that randomization to nephrology specialist follow-up after AKI resulted in a clinically insignificant (although statistically significant) *increase* in major adverse kidney events (MAKE), and Thanapongsatorn et al found no difference in eGFR or MAKE with nephrologist-inclusive multidisciplinary follow-up after AKI [58, 59]. The latter study, however, offers a tantalizing hint at success: specialist care resulted in better urinary albumin:creatinine ratio, and better blood pressure control. Rather than impacting overall renal function, post-AKI surveillance may offer the chance to better manage – or possibly prevent – new disease including but not limited to CKD. Figure 1 summarizes the AKI-related cost, incidence, and time-to-appearance of AKI-C**x**D complications.

Conclusion

Together, disease initiated by AKI represents tremendous suffering and cost; AKI is not a trifle. The doctrine should not be "*de minimus*" but rather, "*de magnis curat medicinus*" – *"Physicians care about great things"*. Preclinical and clinical studies should focus and inform each other on mechanisms of transition to chronic disease in multiple organs after AKI (AKI-C**x**D). Investigation of post-AKI screening, seems likely to succeed by focusing on risk of the composite outcome: Stroke, Hypertension, Reproductive risk, Death, and Dementia ("SHReDD"), as each of these has modifiable risk factors and early interventions. With this perspective, the identification of AKI represents a tremendous opportunity to reduce the burden of future disease.

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Abbreviations:

AKI	Acute kidney injury
ANG II	Angiotensin II
CKD	Chronic kidney disease
COVID-19	Coronavirus Disease 2019
CxD	Chronic *other organ* disease
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HDAC	Histone deacetylase
IRI	Ischemia reperfusion injury
KDIGO	Kidney Disease Improving Global Outcomes
MAKE	Major Adverse Kidney Events
mmHg	Millimeters of Mercury
MRI	Magnetic resonance imaging
PlGF	Placental growth factor
sFlt-1	Fms-like tyrosine kinase-1
SHReDD	Stroke, Hypertension, Reproductive Risk, Death, Dementia

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Key Points

- AKI associates with future Stroke, Hypertension, Reproductive risk, Dementia, and Death. These risks are likely independent of incident CKD.
- Preclinical studies support mechanistic connection between AKI and subsequent disease of nonrenal systems, so-called AKI-C**x**D transition.
- Post-AKI screening programs have thus far demonstrated mixed results. Impact would likely be increased by broad screening for kidney-induced disease of the brain, cardiovascular, and reproductive systems

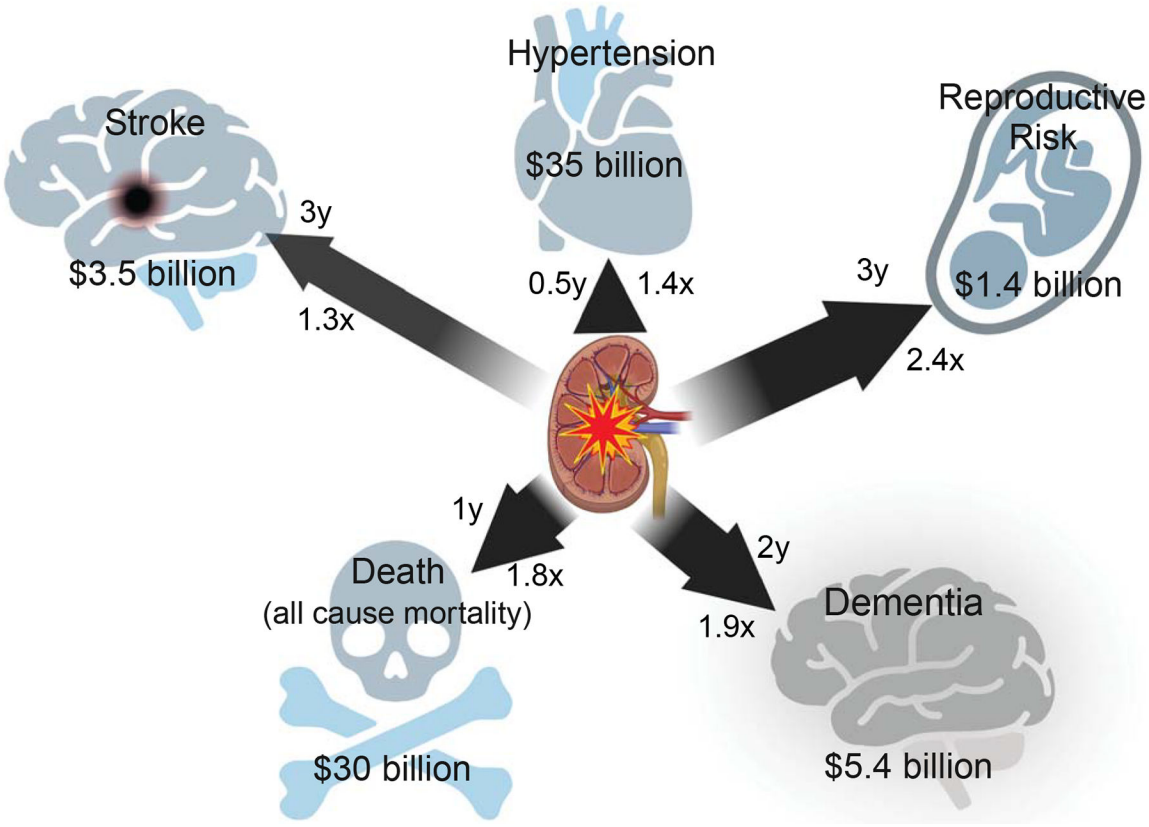

Figure 1:

SHReDD (stroke, hypertension, reproductive risk, dementia, and death) complications of AKI occur rapidly and may have high health care impact. Time-to-discovery, adjusted hazard ratio, and estimated AKI-related cost are depicted. Arrow length is proportional to time-to-discovery, and arrow width to hazard ratio. For reproductive risk, attributable cost is due to preeclampsia only, and only represents one year, not lifetime cost. Attributable cost was estimated using CDC Disease Facts and the most conservative adjusted hazard ratio from sources referenced in the text.