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Review Article

Role of renin-angiotensin system in acute kidney injury-chronic kidney disease transition

YU-HSIANG CHOU,[1,2,3] TZONG-SHINN CHU[1] and SHUEI-LIONG LIN[1,3,4,5]

[1]Renal Division, Department of Internal Medicine, [4]Department of Integrated Diagnostics and Therapeutics, National Taiwan University Hospital, [3]Graduate Institute of Physiology, College of Medicine, [5]Research Center for Developmental Biology and Regenerative Medicine, National Taiwan University, Taipei, and [2]Department of Internal Medicine, National Taiwan University Hospital Jin-Shan Branch, New Taipei City, Taiwan

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Correspondence
Dr Shuei-Liong Lin, Graduate Institute of Physiology, No. 1, Jen-Ai Road Section 1, Taipei, Taiwan. Email: linsl@ntu.edu.tw

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SUMMARY AT A GLANCE

Renin-angiotensin system (RAS) is activated after AKI and leads to AKI-CKD continuum. RAS blockade can reduce the ensuing CKD and mortality. Using RAS blockade could be considered for the monitoring and therapeutic strategies after AKI.

ABSTRACT:

Acute kidney injury (AKI) can increase the risk of developing incident chronic kidney disease (CKD). The severity, frequency and duration of AKI are crucial predictors of poor renal outcome. A repair process after AKI can be adaptive and kidney recovers completely after a mild injury. However, severe injury will lead to a maladaptive repair, which frequently progresses to nephron loss, vascular rarefaction, chronic inflammation and fibrosis. Although different mechanisms underlying AKI-CKD transition have been extensively discussed, no definite intervention has been proved effective to block or to retard the transition until recently. In CKD, renin-angiotensin system (RAS) inhibitor has been proved effective to slow down disease progression. Furthermore, RAS needs to be highlighted again in AKI-CKD transition because recent animal studies have shown the activation of intra-renal RAS after AKI, and RAS blockade can reduce the ensuing CKD and mortality. In patients with the complete renal recovery after AKI, administration of RAS inhibitor is associated with reduced risk of subsequent CKD as well. In this article, we will demonstrate the role of RAS in AKI-CKD transition comprehensively. We will then emphasize the promising effect of RAS inhibitor on CKD prevention in patients recovering from AKI based on evidence from the bench to clinical research. All of these discussions will contribute to the establishment of reliable monitoring and therapeutic strategies for patients with functional recovery from AKI who can be most easily ignored.

The global burden of acute kidney injury (AKI) has increased remarkably and leads to high morbidity and mortality.[1–6] Many studies have identified that AKI is a major risk of ensuing chronic kidney disease (CKD).[7–11] The conventional wisdom that AKI survivors with renal functional recovery tend to do well and be uneventful should be abandoned.[12–14] The severity, frequency and duration of AKI have been demonstrated to be associated with the ensuing incident CKD.[7,8,10] AKI and CKD have been seen as interconnected syndrome.[15,16] Patients with unrecovered AKI can be treated as CKD.[17–21] However, there is no consensus regarding reliable monitoring and therapeutic strategies for patients with recovered from AKI and they can be the most easily ignored. As a result, more efforts are needed to clarify the mechanisms of AKI-CKD transition and multiple animal studies have displayed some plausible pathogenesis, such as a maladaptive repair induced by pericyte-myofibroblast transition,[22,23] profibrogenic cytokine production by G2/M cell-cycle arrested tubular cells,[22,24,25] epigenetic changes in myofibroblasts[26–30] and microvascular rarefaction.[23,31–33] Nevertheless, the underlying mechanisms of clinical AKI-CKD continuum remain incompletely discovered. Even though based on the evidence of recent animal and clinical studies, renin-angiotensin system (RAS) plays a crucial role in the pathogenesis of AKI-CKD transition and RAS inhibitor is a potential treatment to impede AKI-CKD transition for patients recovering from AKI.

In this article, we will focus on RAS activation involved in the mechanisms underlying AKI-CKD transition *in vitro* and *in vivo*. We will also demonstrate current clinical evidence and discuss the potential of RAS inhibitor administration as a therapeutic strategy for AKI patients with renal recovery.

In addition, we will emphasize the needs to establish the standardized definition for renal recovery because it is a very important first step towards providing a platform by which comparative epidemiology and clinical outcomes could be judged in the future study.

EPIDEMIOLOGY OF AKI-CKD CONTINUUM

Mounting evidence has shown that ensuing CKD develops in a considerable proportion of patients after AKI even with complete renal recovery. In a meta-analysis of 13 cohort studies, the incidence of ensuing CKD and end-stage renal disease (ESRD) in patients with previous AKI were 25.8/100 and 8.6/100 patient/years, respectively.[34] The risk of ensuing CKD (hazard ratio 8.8) or ESRD (hazard ratio 3.1) is higher in patients with AKI.[34] In Taiwan, Lai et al.[11] reported the median interval between the onset of AKI and the composite endpoints 'stage 3 CKD or death' was 685 days in an analysis of 634 critically ill patients with AKI not requiring dialysis. In our recent study, 39.7% patients with renal functional recovery from cardiac surgery-associated AKI (CSA-AKI) developed ensuing CKD during median follow-up period of 2.99 years.[35]

THE RENIN-ANGIOTENSIN SYSTEM

Physiological actions of RAS in the kidney

The activation of RAS plays a pivotal role in CKD progression through multiple mechanisms.[36] Renin institutes the first step in the activation of RAS through cleaving angiotensinogen to form angiotensin I (Ang I). Renin is secreted from juxtaglomerular apparatus in the kidney and regulated by a renal baroreceptor and sodium chloride (NaCl) delivery to the macula densa. Ang I is subsequently cleaved by angiotensin-converting enzyme (ACE) to form angiotensin II (Ang II). Ang II is the major biologically active product in RAS. All of the RAS components are present in kidney, including proximal tubular angiotensinogen, collecting duct renin, and tubular Ang II type 1a (AT1a) receptors. Most classically recognized physiologic functions of Ang II are mediated by AT1a receptor, which is the predominant subtype in all nephron segments. As a result, intra-renal Ang II is formed independently in kidney and circulating Ang II can also be actively internalized into proximal tubular cells by AT1a receptor-dependent mechanisms. Consequently, Ang II levels in renal tissues are much higher than circulating levels and physiological actions of intra-renal Ang II include constriction of afferent and efferent arterioles, stimulation of reabsorption of renal tubular sodium and regulation of tubuloglomerular feedback.[36]

The role of RAS in AKI-CKD continuum

Prolonged and overactivation of RAS after AKI would result in ensuing CKD through several mechanisms.[16] First, Ang II raises resistance of glomerular arterioles particularly the efferent one and impairs autoregulation by afferent arteriole, thereby leading to hyperfiltration, glomerular hypertension and sclerosis.[37] Moreover, Ang II activates the pro-inflammatory transcription factor nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) through the Rho kinase pathway.[38] Ang II activates Toll-like receptor 4 and then stimulates NF-κB activation in mesangial cells.[39] Ang II also upregulates expression of vascular cellular adhesion molecule-1, intra-cellular adhesion molecular-1, integrin and chemokines, such as monocyte chemoattractant protein-1 and regulated on activation, normal T cell expressed and secreted thereby recruiting inflammatory cells into glomerulus and interstitium.[40] In addition, Ang II leads to renal fibrosis directly by inducing proliferation of renal fibroblasts accompanied with expression of transforming growth factor β1, connective tissue growth factor, fibronectin and type I collagen.[41,42] Ang II also promotes the accumulation of extracellular matrix by upregulating plasminogen activator inhibitor-1 and tissue inhibitor of matrix metalloproteinases-1, which inhibit metalloproteinases.[43]

Recent animal studies have provided evidence that RAS activation during and after injury play a critical role in AKI-CKD continuum. Losartan, an AT1a receptor antagonist, administration during reperfusion phase can maintain glomerular infiltration and accelerate renal recovery after ischemia-reperfusion injury (IRI).[44] AT1a receptor knockout in renal tubular cells leads to reduction of local and systemic tumour necrosis factor-α and amelioration of AKI induced by cisplatin.[45] In addition to the protective effect of RAS inhibitor on the severity of AKI, losartan prior to IRI can also prevent the development of CKD by maintaining early renal blood flow, lesser inflammation and increased hypoxia-inducible factor-1α activity.[46] Downstream mineralocorticoid receptor antagonism before or after IRI also showed similar protective effect on AKI-CKD transition.[47,48] Nevertheless, whether RAS persists activation or is reactivated after functional recovery from AKI is not clear until our recent study.[49] Our data showed that RAS activation persists even after functional recovery from IRI-AKI and treatment with losartan can reduce ensuing CKD and mortality.[49]

Clinical study of RAS inhibitor in AKI-CKD continuum

Many clinical trials have proved the specific renoprotective effect of RAS inhibitor including ACE inhibitor and AT1a receptor blocker in patients with diabetic or proteinuric non-diabetic CKD.[19–21] Nonetheless, the role of RAS activity in acute phase and injury severity of AKI is not clear and

therefore RAS inhibition is usually avoided in acute phase, even though several animal studies reported beneficial effects of RAS inhibition on AKI.

Notably, many clinical studies disclose RAS activation after AKI. In CSA-AKI, the duration of cardiopulmonary bypass corresponding to ischemia time is directly related to the risk for AKI.[50] Intra-renal RAS is overexpressed in patients with AKI based on the finding of increased urinary angiotensinogen. Furthermore, urinary levels of angiotensinogen are associated with the severity of AKI and a strong predictor for AKI.[51,52] RAS activation after AKI also appears to be one of the mechanisms for the elevated blood pressure after AKI in a recent clinical study.[53]

Until now, there has been no large-scale randomized controlled trial to evaluate the effect of RAS blockade on AKI and ensuing CKD. One reason is that different causes of AKI and diverse mechanisms might make the effect of RAS inhibitor less remarkable. Therefore, patients with specific aetiologies of AKI should be specifically grouped for RAS inhibition study. In addition, there are always concerns that excessive dilatation of glomerular efferent arteriole by RAS inhibitor might pose a risk for decreased glomerular filtration and development of AKI. Nevertheless, some observational studies still attempt to delineate the effect of RAS inhibitor in AKI-CKD continuum. A propensity score-based research of 536 patients undergoing coronary artery bypass graft on cardiopulmonary bypass revealed that patients received angiotensin-converting enzyme (ACE) inhibitors pre-operatively are associated with a reduced risk of CSA-AKI.[54] Huang *et al.* also demonstrated the association between pre-operative RAS inhibition and reduced post-operative CSA-AKI after propensity score matching in 1172 patients in National Taiwan University Hospital (NTUH) Surgery Intensive Care Unit Acute Renal Failure (NSARF)Study Group.[55] On the contrary, in a retrospective cohort study of 1358 adult patients who underwent cardiac surgery, pre-operatively receiving long-term treatment with RAS inhibitors is associated with a 27.6% higher risk for AKI post-operatively.[56]

Our recent clinical study, which is the first one to evaluate the effect of RAS inhibitor administered post-operatively, further demonstrates lower rate of ensuing CKD (users *vs* non-users, 26.6 *vs* 42.2%) and longer median CKD-free survival time (users *vs* non-users, 1079 *vs* 520 days) in users of RAS inhibitor, started and continued after clinical renal recovery after CSA-AKI.[35] Therefore, RAS inhibitors, usually avoided during the acute phase of AKI events, are potential to be a powerful and safe agent to improve survival and renal outcome for patients recovering from AKI who are often neglected (Fig. 1).

PERSPECTIVES

The best way to reduce AKI-CKD continuum is to prevent AKI from developing. Nevertheless, the appropriate management for patients who has renal functional recovery is uncertain even many mechanisms of AKI-CKD continuum have been well disclosed. In the future, we should continue to study the causal relationship between the pre-existing comorbidities and mechanisms of AKI-CKD continuum. It is necessary to characterize patients according to different aetiology of AKI to clarify their specific mechanisms. In addition, development of a consensus for a standard definition of AKI recovery is an urgent need for a framework of monitoring and therapeutic strategies. Timely reliable pharmacologic agents should be administered to exhibit their optimal therapeutic effects. In other words, we need a protocol including essential components and precise timing for monitoring patients who suffer from AKI. Traditional renal function tests, such as serum creatinine and estimated glomerular filtration rate are insufficient to precisely reflect the pathophysiological processes in injured kidney. Urine angiotensinogen, which is a surrogate of intra-renal RAS activity and other novel biomarkers, such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1 may provide timely diagnosis and allow for early intervention to improve patient outcomes of AKI-CKD continuum.[52] Excitingly, a working group of the 15th Acute Dialysis Quality Initiative

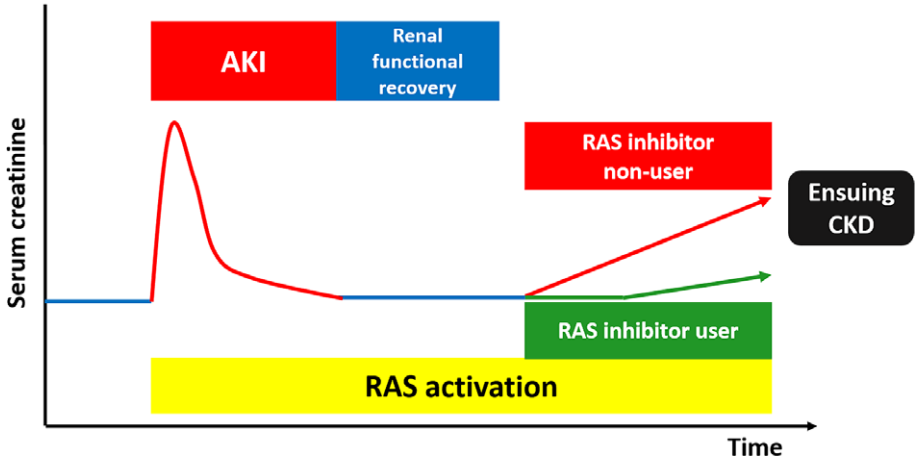

Fig. 1 Scheme summary for renin-angiotensin system (RAS) activation after acute kidney injury (AKI) and the effect of RAS inhibitor on AKI-chronic kidney disease (CKD) transition.

conference has initiated the consensus-building process to address concerns related to the opportunities, methodological requirements and barriers for longitudinal follow-up of patients with AKI.[57] Although there is no faithful therapeutic approach at present, RAS inhibitors have the potential and are readily available to block AKI-CKD transition, at least partially. Randomized controlled clinical trial should be initiated to prove the beneficial effect of RAS blockade.

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DISCLOSURE

We have no conflict of interest to report.

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