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Distant Organ Dysfunction in Acute Kidney Injury: A Review

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Abstract

Acute kidney injury (AKI) is common in critically ill patients and associated with increased morbidity and mortality. Dysfunction of other organs is an important cause of poor outcomes from AKI. Ample clinical and epidemiological data show that AKI is associated with distant organ dysfunction in lung, heart, brain, and liver. Recent advancements in basic and clinical research have demonstrated physiologic and molecular mechanisms of distant organ interactions in AKI including leukocyte activation and infiltration, generation of soluble factors like inflammatory cytokines/chemokines, and endothelial injury. Oxidative stress and production of reactive oxygen species (ROS) as well as dysregulation of cell death in distant organs are also important mechanism of AKI-induced distant organ dysfunction. This review will update recent clinical and experimental findings on organ crosstalk in AKI and highlight potential molecular mechanisms and therapeutic targets to improve clinical outcomes during AKI.

Keywords

acute kidney injury (AKI); multi-organ dysfunction; organ crosstalk; lung; cardiorenal syndrome (CRS); reno-cerebral reflex; hepatic dysfunction; microbiota; gut-kidney axis; review

INTRODUCTION

Acute kidney injury (AKI) is a serious medical condition that is associated with significantly increased risks for mortality, hospital length of stay, and healthcare-associated costs.[1] Based on the KDIGO (Kidney Disease Improving Global Outcomes) definition, AKI complicates

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18% of all hospitalized patients, with an associated inhospital mortality of 11%.[2] The incidence of AKI increases to 57% in critically ill patients, with 27% in-hospital mortality.[3] The mortality rate soars to 45–60% when AKI is complicated by other organ dysfunctions, like pneumonia, acute heart failure, or sepsis.[4]

Uremic toxin accumulation, metabolic acidosis, electrolyte imbalances, and fluid overload are the traditionally well-known consequences of AKI that contribute to the high mortality.[5] However, a significant proportion of the AKI-associated mortality cannot be simply explained by loss of kidney functions or by complications occurring during AKI treatment. Instead, AKI-induced multi-organ dysfunction is of particular importance in outcomes of critically ill patients with AKI. 'AKI-induced distant organ crosstalk' describes the phenomenon when AKI leads to dysfunction of other organs including lung, heart, brain, liver, and intestine via aberrant organ-organ communication.[6,7] (Fig 1) Accumulating evidence indicates that interruption of normal immunological balance and generation of inflammatory mediators are important in AKI-induced distant organ crosstalk.[8] Additional mechanisms include increased endothelial injury, cellular apoptosis, and oxidative stress.[9–11]

Organ crosstalk can happen following various types of AKI, but there is no clear data yet whether the etiology of AKI affects the extent of distant organ dysfunction. There is higher chance of distant organ dysfunction with more severe AKI, but even patients with mild to moderate AKI that is not severe enough to require RRT can also experience multi-organ dysfunction.[12] Animal models are useful for discovery and mechanistic studies, but do not fully mimic the complexities of human AKI. In addition, inbred animal strains with relatively limited genetic diversity cannot fully represent human populations with polymorphic genetic backgrounds.[13] Therefore, researchers need caution in extrapolating animal data to humans. In this review, we will briefly update clinical and experimental findings on distant organ effects of AKI and discuss potential molecular and therapeutic targets.

KIDNEY-LUNG INTERACTIONS

Clinical impact

Acute lung injury is one of the most common extra-renal problems in AKI patients. Accumulation of uremic toxins negatively affects lung mechanics and pulmonary gas exchange.[7] Fluid overload can lead to alveolar edema and metabolic acidosis that results in hyperventilation in AKI patients.[7] In clinical settings, respiratory complications from AKI include pulmonary edema, respiratory failure needing mechanical ventilation, longer duration of mechanical ventilation, and slower weaning from mechanical ventilation.[14] Epidemiological studies demonstrate that respiratory failure requiring mechanical ventilation is an important independent risk factor for mortality in AKI patients.[15–17]

Clinical evidence

The underlying pathogenesis of respiratory failure in AKI patients is incompletely understood, but several potential mechanisms have been widely studied. (Fig 2) The effects of AKI on lungs are largely due to pulmonary edema, which can be divided into hydrostatic

or non-hydrostatic forms.[18] Fluid overload, the major cause of hydrostatic edema, occurs because of decreased urine output and dampened cardiac output, and is traditionally recognized as a major cause of lung dysfunction in AKI patients. Fluid overload has been strongly associated with increased mortality in AKI patients accompanying acute lung injury (ALI), and restrictive fluid management improved the lung function and shortened the time that mechanical ventilation is needed in these patients.[19]

Non-hydrostatic pulmonary edema occurs without overt fluid overload. During AKI, the integrity of alveolar-capillary barrier is impaired by uremia, systemic inflammation, and increased oxidative stress, causing fluid accumulation in the lung.[7] Basu *et al.* described this phenomenon as 'nephrogenic pulmonary edema' and this condition cannot be improved simply by resolving uremia and controlling fluid balance with dialysis.[20] Several clinical studies have suggested the role of inflammation in the initiation and progression of lung injury after AKI. Increased inflammatory cytokines, such as interleukin (IL)-6 and/or IL-8 have been associated with prolonged ventilator weaning times[21] and increased mortality[22] in AKI patients with ALI. Non-hydrostatic pulmonary edema has been actively studied in the experimental AKI rather than in the clinical setting which will be further described in the next section.

Laboratory evidence

Extending from these clinical observations, a number of experimental animal studies elucidated the underlying mechanisms of AKI-lung crosstalk, demonstrating increased leukocyte infiltration, increased inflammatory cytokines/chemokine expression, and dysregulation of salt/water transporters with abnormal vascular permeability.[9,23,24] (Fig 3)

Several immune cells are involved in AKI-associated lung injury. Neutrophil infiltration into lung has been found in two different AKI models [bilateral nephrectomy (BNx) and bilateral ischemia-reperfusion injury (IRI) models][23,25] and the release of neutrophil elastase plays a crucial role in the pathogenesis of ALI following AKI.[26] T lymphocyte infiltration into lung also increases during renal IRI and T cell-deficient mice show decreased pulmonary caspase 3 activation, demonstrating the role of T cells in ischemic AKI-induced pulmonary apoptosis.[27] Macrophage infiltration into lung increases pulmonary vascular permeability and interstitial edema in an ischemic AKI model,[28,29] which is attenuated by administration of the vagus nerve-dependent macrophage deactivator CNI-1493.[29]

Inflammatory cytokines/chemokines serve important roles in lung dysfunction during AKI. Based on the clinical finding of increased IL-6 level in acute respiratory distress syndrome (ARDS) patients complicated by AKI,[30] several experimental studies have demonstrated that IL-6 contribute to AKI-induced lung injury.[23,31] Circulating IL-6 induces lung chemokine (C-X-C motif) ligand 1 (CXCL1); in addition, blocking CXCL1 as well as IL-6 can reduce AKI-induced lung injury.[31] A recent mouse study showed that high-dose peritoneal dialysis after AKI significantly lowers serum IL-6 concentration as well as lung inflammation.[32] However, the counter-inflammatory role of IL-6 was demonstrated in another study showing that systemic IL-6 could upregulate splenic IL-10 production as a compensatory anti-inflammatory mechanism in AKI-induced lung injury.[33] Administration of the anti-inflammatory cytokine IL-10 also attenuate pulmonary inflammation.[9] Increased tumor

necrosis factor α (TNF-α) levels and TNF receptor 1 (TNFR1)-dependent pulmonary apoptosis have been observed in a mouse IRI model.[34]

Dysfunctional pulmonary water and salt transporters have been studied as potential mediator of non-hydrostatic pulmonary edema after AKI. In normal conditions, apical sodium channels and basolateral adenosine triphosphatase (ATPase) on pneumocytes actively transport sodium from alveolar space into the pulmonary interstitium.[35] This active transfer of sodium creates an osmotic gradient with consequent water movement in the same direction.[36] In both the ischemic and non-ischemic AKI models, mice show pulmonary septal edema and alveolar hemorrhage in spite of decreased body weight.[9] This finding suggests that dysfunctional pulmonary water transport rather than total body water accumulation is a major culprit for AKI-induced pulmonary edema. Another study found significant decreases in lung mRNA expression of epithelial sodium channel and aquaporin 5, consistent with a decreased level of aquaporin 5 protein, suggesting that the decreased expression of alveolar salt and water transporter cause non-hydrostatic pulmonary edema after AKI.[24] Recently, Yabuuchi *et al.* showed that indoxyl sulfate, a typical oxidative stress-inducing uremic toxin, could play a role in the dysregulation of pulmonary aquaporin 5 in AKI using a rat bilateral nephrectomy model.[37] This study also showed that administration of oral spherical adsorptive carbon beads, AST-120, lowers the level of indoxyl sulfate in serum and lung, restoring pulmonary aquaporin 5 protein expression.

Potential therapeutic targets

Supporting the clinical and experimental findings above, delivery of IL-10 and blocking IL-6, CXCL1, or TNF-α have efficacy on AKI-induced lung injury in animal models, showing their potential as future therapeutic targets.[23,31,34] Administration of atrial natriuretic peptide (ANP), which has anti-inflammatory and natriuretic properties, shows protective effects on the ischemic injured kidney as well as the contralateral kidney, lungs, and heart in a rat IRI model.[38] However, clinical trials on ANP have not shown benefit in AKI.[39,40]

Oxidative stress caused by leukocyte infiltration into lung can lead to tissue damage through systemic inflammatory reaction and active free radical generation.[41,42] A recent study demonstrated the protective potential of prostaglandin E1 (PGE1) on modulation of oxidative stress during renal IRI-induced lung injury in rats.[42] Administration of PGE1 has been found to decrease both IRI-induced kidney injury and IRI-induced remote lung damage through increased antioxidant enzyme activities and decreased leukocyte activities.

Uremic toxins as well as multiple cytokines and toll-like receptor 4 (TLR-4)/high-mobility group box protein B1 (HMGB1) likely participate in distant organ effects of AKI.[43] In the BNx-induced lung injury model, the interaction of TLR-4 with HMGB1 contributes to lung injury induced by AKI and these damages are alleviated in TLR-4-mutant mice or with the use of HMGB1 blockade.[44] An *in vitro* study showed that hemofiltration using surface-treated polyacrylonitrile (AN69ST) membrane could adsorb HMGB1[45] and another *ex vivo* study in human cells showed that continuous hemofiltration using a cellulose triacetate membrane could remove various cytokines as well as HMGB1.[46] Removal of cytokines and

uremic toxins with CRRT using a novel membrane is a promising approach to treat distant organ injury in AKI.

KIDNEY-HEART INTERACTIONS

Clinical impact

The interaction between kidney and heart is often found in patients and primary disorder of one of these organs often results in secondary dysfunction of the other organ. The term, "cardiorenal syndrome (CRS)", has been increasingly used to explain this relationship, and a working definition/classification of CRS was established in 2008 by Ronco *et al.*.[47] (Box 1) These complex interactions between kidney and heart contribute to the worse outcomes from dual organ dysfunction compared to single organ dysfunction. Although the hemodynamic mechanisms in acute cardiac decompensation that leads to AKI are well described, less is known about the effect of AKI on heart.

Box 1

Classification of cardiorenal syndromes

CRS General Definition

A complex pathophysiological disorder of the heart and the kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ[47]

Types of CRS

- **CRS Type 1** (Acute cardiorenal syndrome)
  - Description: Abrupt worsening of cardiac function leading to AKI
  - Examples: Acute coronary syndrome, acute decompensated heart failure
- **CRS Type 2** (Chronic cardiorenal syndrome)
  - Description: Chronic abnormalities in cardiac function causing progressive and permanent CKD
  - Examples: chronic heart failure, ischemic heart disease, hypertension
- **CRS Type 3** (Acute renocardiac syndrome)
  - Description: Abrupt worsening of renal function causing acute cardiac disorder
  - Examples: Postsurgery AKI, acute glomerulonephritis, rhabdomyolysis
- **CRS Type 4** (Chronic renocardiac syndrome)

- Description: CKD contributing to decreased cardiac function, cardiac hypertrophy, fibrosis, and/or increased risk of adverse cardiovascular events
- Examples: Cardiac hypertrophy/fibrosis in CKD

- **CRS Type 5** (Secondary cardiorenal syndrome)
  - Description: Systemic condition causing both acute cardiac and kidney injury and dysfunction
  - Examples: sepsis, diabetes mellitus

Note: Based on the information presented in Ronco *et al.*.[47]; Abbreviations: CRS, Cardiorenal Syndrome; AKI, acute kidney injury; CKD, chronic kidney injury

Clinical evidence

CRS can occur following any forms of AKI, but only a limited number of studies have studied cardiovascular outcomes of AKI patients, making the exact estimation for the incidence and outcome of AKI-induced CRS unclear. In one multicenter AKI cohort study, cardiovascular failure was found in 60% of AKI patients in ICU.[48] Another study showed that cardiovascular-related deaths were the second most common cause of death after sepsis in AKI patients.[15] Long-term cardiovascular effects of AKI have also been observed: postoperative AKI was found to be associated with increased 5-year risk of myocardial infarction and heart failure as well as increased all-cause mortality.[49] In another study, patients who recovered from dialysis-requiring AKI had higher long-term risks of coronary events and all-cause mortality regardless of subsequent progression to chronic kidney disease (CKD), showing the independent association of AKI with long-term cardiovascular risk.[50] More detailed clinical studies are required to elucidate the exact risk and impact of AKI-induced CRS.

Laboratory evidence

AKI causes cardiac dysfunction through many possible mechanisms. (Fig 4) Fluid overload attenuates myocardial performance and induces maladaptive myocardial remodeling.[49] Accumulation of uremic toxins leads to cardiovascular toxicity and can increase risk for myocardial ischemia by compromising coronary vasoreactivity.[51] Protein-bound uremic toxins (PBUTs) have deleterious effect on many vital organs including kidney, heart and blood vessels and are poorly removed by current dialysis approaches. Indoxyl sulfate and *p*-cresyl sulfate, the most well-known PBUTs, have been shown to induce vascular inflammation, endothelial dysfunction, and vascular calcification.[52] Metabolic acidosis also affect the myocardial contractility and electrolyte imbalances like hyper/hypokalemia trigger life-threatening arrhythmia.[53]

Beside these classically-known mechanisms, there are other important factors with direct and immediate impact on heart, including systemic immune response, activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), and increased oxidative stress.[54,55] A rat AKI study showed that renal IRI, but not bilateral

nephrectomy results in a significant increase in myocardial apoptosis, indicating that systemic inflammation after IRI as opposed to uremia itself has more important role in the myocardial injury following AKI.[56] This study also showed the association of ischemic AKI with cardiac injury based on increased myeloperoxidase activity and abnormal echocardiographic findings - increased left ventricular end diastolic/end systolic diameter, relaxation time, and decreased fractional shortening. This was observed to be accompanied by increased systemic and cardiac tissue levels of TNF-α and IL-1 and increased cardiac intercellular adhesion molecule 1 (ICAM-1) expression. In the same study, TNF-α blocker significantly decreased cardiomyocyte apoptosis, implying the role of TNF-α in AKI-induced cardiac damage. Based on the myocardial depressant effect of TNF-α, there have been large multicenter trials about the effect of anti-TNF-α therapies (Etanercept) on congestive heart failure (CHF), but there is still no clear evidence of clinical benefit and some studies even showed worsening CHF.[57]

Neuroendocrine activation also underlies the pathophysiology of AKI-induced CRS. During AKI, SNS is activated and leads to norepinephrine overflow.[53] Activation of SNS alters myocardial function by disrupting myocardial calcium homeostasis, increasing myocardial oxygen demand, and inducing apoptosis/hypertrophy of cardiac myocytes through adrenergic receptor stimulation.[51] Activated SNS stimulates β1-adrenergic receptors in the juxtaglomerular apparatus of the kidney, which leads to decreased renal blood flow and activation of RAAS.[58] Dysfunctional RAAS activation induces angiotensin II release, increasing systemic vascular resistance. Angiotensin II itself contributes to cardiac myocyte hypertrophy and apoptosis.[59,60]

Potential therapeutic targets

The immunomodulatory role of heme oxygenase 1 (HO-1) in AKI has been widely studied.[61] Lack of HO-1 increases the susceptibility to renal IRI and renal IRI in HO-1-knockout mice increases both IL-6 and its downstream signaling effector pSTAT3 in injured kidney as well as in heart and lung.[62] Based on its cyto-protective effects in AKI animal models, HO-1 induction is considered a promising therapeutic target in AKI.

A recent study found that dysfunction of cardiac mitochondria could play an important role in the pathogenesis of cardiac damage induced by AKI.[63] This study showed that renal IRI induces fragmentation of mitochondria in a fission-dominant manner through dynamin-related protein 1 (Drp1) activation, which is followed by cardiomyocyte apoptosis in the heart. The use of a Drp1 inhibitor, Mdivi-1, induces a significant decrease in mitochondrial fragmentation and cardiomyocyte apoptosis as well as improvement in cardiac function. These data suggest that preservation of normal mitochondrial dynamics could be a potential therapeutic target in AKI-induced heart dysfunction.

KIDNEY-BRAIN INTERACTIONS

Clinical impact

AKI-induced uremic toxins are well known to cause neurological complications including irritability, attention deficit, hyperreflexia, decreased mental status, seizures, and even death.

[54] The severity of neurologic impairment is more closely associated with the rate at which kidney function decreases than the level of azotemia itself.[64] Therefore, uremic symptoms are usually more severe and advance more rapidly in AKI patients than in patients with CKD.[65]

Several clinical studies have identified long-term neurological effects of AKI.[66,67] One nationwide population study showed that patients who survive dialysis-requiring AKI have higher risk and higher severity of stroke events compared to the control group after the adjustment of progression to consequent CKD or end stage renal disease (ESRD), and the impact is almost similar to that of diabetes.[66] Another cohort study showed that among elderly patients who require ICU care during hospitalization, patients with dialysis-requiring AKI has a long-term risk of dementia even after the adjustment of other dementia-related risk factors (Hazard Ratio, 1.70).[67]

Laboratory evidence

The pathophysiology of neurologic complications after AKI is associated with the accumulation of neurotoxic metabolites that cause disturbances to the blood-brain barrier and an imbalance in cellular water transport.[11,68] The central nervous system is generally considered to be an immune-privileged site due to blood-brain barrier, but AKI can lead to disruption of the blood-brain barrier, resulting in cerebral edema as well as infiltration of neuro-toxic metabolites into brain. The short-term effects of AKI on mouse brain include increases of soluble inflammatory proteins (such as keratinocyte-derived chemokine and granulocyte-colony stimulating factor) and increased cellular inflammation, with glial fibrillary acidic protein in astrocytes.[69] Post-AKI brain histology shows increased microglial cells and pyknotic neuronal cells in the hippocampus. Another study showed the significant increase of TLR-4 in the hippocampus and striatum following renal IRI, suggesting a role for TLR-4 in AKI-induced neuronal injury.[70] In an animal behavioral study, uremic mice showed decreased central dopamine turnover in the striatum, mesencephalon, and hypothalamus, which was correlated with the impairment of motor activity.[71]

Potential therapeutic targets

A novel reflex pathway between injured kidney and the brain has been recently described, called ‘reno-cerebral reflex’.[72] In this study, Cao et al showed that ischemic AKI could co-activate the intrarenal and intracerebral RAAS, oxidative stress and sympathetic activity, promoting ongoing inflammation in both organs. The authors also found that blocking of renal afferent sympathetic activity, central blockade of angiotensin II, or prevention of sympathetic activation could lower the AKI-induced systemic oxidative stress and inflammation. Intervention with RAAS inhibitors, sympatholytic drugs, or renal nerve ablation could be new therapeutic approaches targeting reno-cerebral crosstalk.

KIDNEY-LIVER INTERACTIONS

Clinical impact/evidence

Traditionally, hepatorenal syndrome denotes decrease in kidney function secondary to liver disease. For example, hepatic veno-occlusive disease often leads to reduced kidney function.

The efficacy of defibrotide for the treatment of sinusoidal obstruction syndrome, a life-threatening complication following stem cell transplantation shows that treating liver dysfunction can directly lead to improvement of renal function.[73] However, the clinical significance of AKI on liver is less well defined.[8] Liver dysfunction can be observed in critically-ill AKI patients and hepatic failure increases the in-hospital mortality among these patient groups.[74] Several clinical studies have found development of hepatic dysfunction in AKI patients who had alterations in protein synthesis, inflammatory responses, and metabolism of lipid, protein, and drugs.[8,75,76] During AKI, there are changes not only in renal drug metabolism, but also in non-renal metabolism, which can have considerable influence on clinical outcomes due to under- or over-dosing and related toxicity problems. The mechanisms by which AKI impacts liver drug metabolism remains unclear, but the interaction is felt to be related to uremic toxins, inflammatory cytokines, activated leucocytes, and other neuro-humoral factors.[8] Drug dosing needs to be carefully monitored in the AKI patients with hepatic dysfunction.

Laboratory evidence

An experimental study showed that AKI promotes oxidative stress, inflammation, apoptosis, and tissue damage in hepatocytes while increasing vascular permeability and leukocyte infiltration into liver.[77] Recently, Lee and colleagues demonstrated that renal IRI induces peptidyl arginine deiminase 4 (PAD-4) in the liver. Hepatic injury and inflammation in PAD-4 deficient mice were found to be significantly attenuated after renal IRI compared to wild-type (WT) mice, implying that the extra-renal PAD-4 contributes to the distant organ damage after AKI.[78] Lee et al also suggested that systemic increase of TNF-α, IL-17A, and IL-6 predispose to liver and small intestine injury after ischemic or non-ischemic AKI.[79] Furthermore, AKI-induced damaging changes in the liver and intestine are partly induced by direct activation of small intestine Paneth cells, which release granules containing IL-17A into the intestinal lumen.[80]

Potential therapeutic targets

Several groups have studied the therapeutic effect of antioxidants in AKI-induced liver damage, targeting activated oxidative stress. Administration of glutathione significantly ameliorates the structural and enzymatic changes in the liver after AKI.[77] Another study investigated the effects of vitamin E on AKI-induced liver damage, showing that vitamin E administration alleviates the increase of plasma aspartate transaminase (AST) and alanine transaminase (ALT) level while preserving glutathione activity.[81] Administration of thymoquinone, a main constituent of *Nigella sativa* that has anti-oxidant and anti-inflammatory effect, before renal IRI improves renal and hepatic function and increases antioxidant enzyme activity in both organs.[82] This was observed to be accompanied by a decrease of CYP3A1 and spermidine/spermine-N_1-acetyl-transferase gene expression in liver, implying less oxidative stress following thymoquinone treatment.

Isoflurane, a well-known volatile anesthetic, shows protective effects on ischemic and non-ischemic AKI-induced hepatic and intestinal injury via induction of the sphingosine kinase 1 (SK-1)/sphingosine-1-phosphate pathway.[83,84] Through induction of SK-1 in small intestine, isoflurane ameliorates hepatic and intestinal pro-inflammatory cytokine production and

vascular permeability as well as intestinal apoptosis. Given the high incidence of postoperative-AKI, it is possible that using isoflurane may improve the outcome of postoperative AKI-induced distant organ damage by its protective action on liver and intestine as well as less effects on systemic blood pressure/renal blood flow.

KIDNEY-INTESTINAL MICROBIOTA INTERACTIONS

Clinical impact/evidence

Recent clinical and experimental studies have shown the bidirectional relationship between intestinal microbiota and kidney diseases, but most of them have been limited to the interaction of intestinal microbiota with development and progression of CKD/ESRD.[85,86] Despite the limited data available on AKI-gut microbiome interactions, accumulating clinical data about the immunomodulatory role of gut microbiome in CKD patients implicates the possible role of intestinal microbiota in the patients with AKI-induced distant organ dysfunction.[87]

Laboratory evidence/Potential therapeutic targets

The significance of normal gut microbiota on experimental AKI was initially demonstrated by using germ-free mice that lacked any exposure to symbiotic microorganisms and parasites.[88] In ischemic AKI, these mice showed worse functional/structural renal damage and enhanced inflammation compared to the control mice. Unexpectedly, they had higher NKT cells in the kidney. Reconstitution of germ-free mice using WT gut microbiota (conventionalization) was found to alleviate their increased susceptibility to AKI. In the analysis of baseline levels of kidney cytokines, the germ-free mice had higher interferon-γ (IFN-γ) and lower IL-4 level compared to the WT mice, which suggests that germ-free mice are more prone to a T_H1 type response, similar to that seen in autoimmune disease. This finding implicates a potential immunomodulatory role of gut microbiota in the development of kidney diseases.

During fermentation, gut microbiota generate various metabolites, including multiple uremic retention molecules and short chain fatty acids (SCFAs). SCFAs, the fermentation end products from complex polysaccharides, are mostly comprised of acetate, propionate, and butyrate.[89] Accumulating evidences suggest that SCFAs regulate inflammation, energy metabolism, and blood pressure, which affects kidney function through the gut-kidney axis.[89] Uremic toxins (e.g. indoles, ammonia, and trimethylamine N-oxide) generated by the gut microbiota, are felt to have a detrimental effect on kidney function.[90]

Restoring the balance of the gut microbiome has received a lot of attention as a potential therapeutic target for kidney disorders. These interventions include (1) reducing harmful uremic toxins by restricting the intake of uremic toxin precursors (lowering protein intake)[91] or by enhancing the disposal of the toxins (adsorbent therapy)[92] and (2) supplementing a more balanced gut microbiome using pre-/pro-/syn-biotics.[93,94].

Several studies have examined the effects of SCFAs on AKI using ischemia- and gentamicin-induced AKI models.[95,96] Administration of the three main SCFAs had protective effect in ischemic AKI by decreasing local and systemic inflammation, oxidative

stress, inflammatory cell infiltration, and apoptosis in injured kidney. Administration of acetate, one of the main SCFAs, could also modulate epigenetic modifications in ischemic-injured kidney tissue, by inhibiting the activity of histone deacetylase and reversing the decreased global DNA methylation status.[95] Given the therapeutic potential of SCFAs on AKI outcome, more studies are necessary to elucidate the detailed mechanisms and effects of SCFAs on AKI.

CONCLUSION

AKI induces systemic and organ-specific hemodynamic-, humoral-, and immunologic imbalances, which helps explain why patients are not just dying with AKI, but from AKI.[18] Based on the current findings about different pathways linking kidney injury with distant organs, therapeutic strategies that targeting just a single molecule are less likely to succeed in reducing the AKI-induced distant organ dysfunctions. (Table 1) Understanding the complex interactions between kidney and distant organs should lead to new diagnostics and therapies to improve outcomes in patients with AKI.

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Acronym

AKI	Acute kidney injury
ROS	Reactive oxygen species
KDIGO	Kidney Disease Improving Global Outcomes
CRRT	Continuous renal replacement therapy
ICU	Intensive care unit
ALI	Acute lung injury
IL	Interleukin
BNx	Bilateral nephrectomy
IRI	Ischemia-reperfusion injury
ARDS	Acute respiratory distress syndrome
CXCL1	Chemokine (C-X-C motif) ligand 1
TNF-α	Tumor necrosis factor alpha
TNFR1	Tumor necrosis factor receptor 1
ANP	Atrial natriuretic peptide
PGE1	Prostaglandin E1

TLR-4	Toll-like receptor 4
HMGB1	High-mobility group box protein B1
CRS	Cardiorenal syndrome
CKD	Chronic kidney disease
PBUT	Protein-bound uremic toxin
SNS	Sympathetic nervous system
RAAS	Renin-angiotensin-aldosterone system
ICAM-1	Intercellular adhesion molecule-1
CHF	Congestive heart failure
ANG II	Angiotensin II
HO-1	Heme oxygenase-1
Drp1	Dynamin-related protein 1
ESRD	End stage renal disease
PAD-4	Peptidyl arginine deiminase-4
AST	Aspartate transaminase
ALT	Alanine transaminase
SK-1	Sphingosine kinase-1
WT	Wild-type
SCFA	Short chain fatty acids

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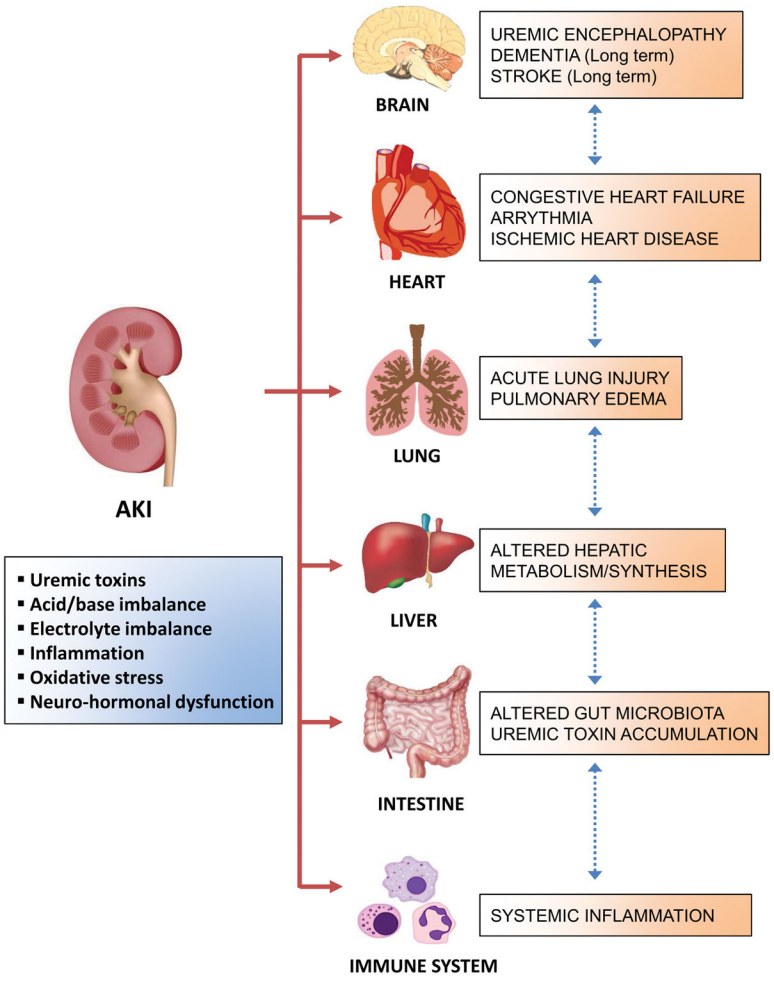

Figure 1. The impact of acute kidney injury (AKI) on distant organs

Acute kidney injury (AKI) causes hemodynamic-, humoral-, and immunologic changes, which leads to dysfunction of distant organs including lung, heart, brain, liver, intestine and immune system. Abbreviations: AKI, acute kidney injury.

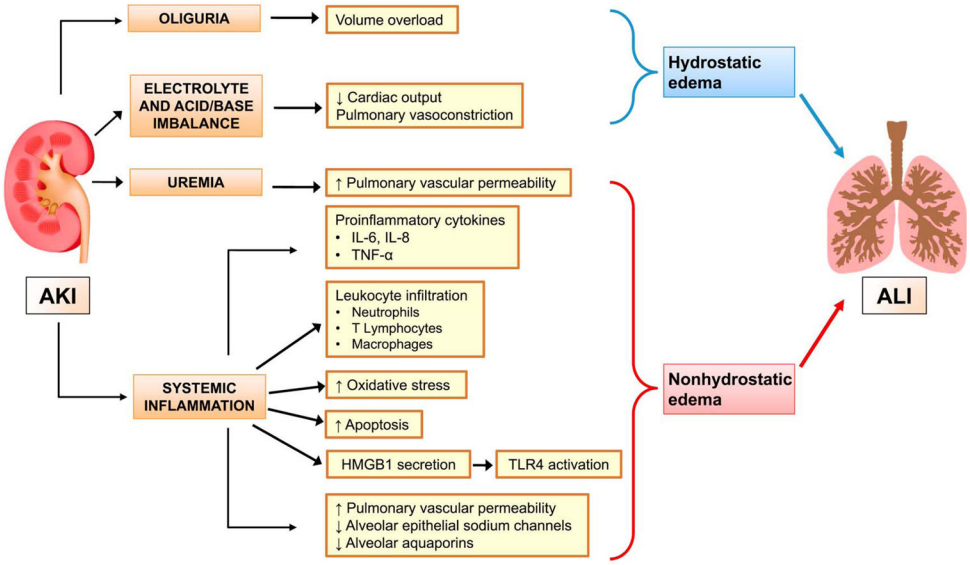

Figure 2. Mechanisms of acute lung injury (ALI) during acute kidney injury (AKI)

Acute kidney injury (AKI) can facilitate development of acute lung injury (ALI) through different mechanisms - volume overload, impairment of cardiac function, systemic inflammation, oxidative stress, increased pulmonary vascular permeability and impaired alveolar fluid clearance. Abbreviations: AKI, acute kidney injury; ALI, acute lung injury; IL, interleukin; TNF-α, tumor necrosis factor alpha; HMGB1, high-mobility group box protein B1; TLR-4, toll-like receptor 4.

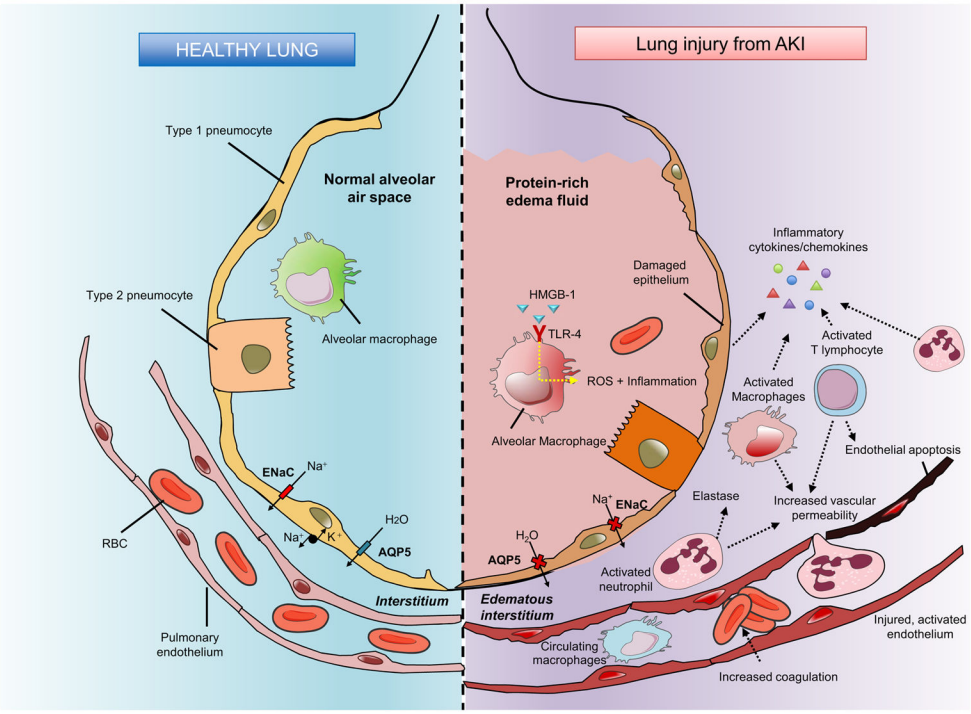

Figure 3. Cascade of lung changes after acute kidney injury (AKI)

Following acute kidney injury (AKI), various inflammatory events occur in the alveolar and pulmonary interstitial spaces. Activated endothelium and increased vascular permeability allow leukocytes to transmigrate into pulmonary interstitium. Infiltrated leukocytes aggravate lung injury through inflammatory cytokine/chemokine secretion, increased oxidative stress and cell damage/apoptosis. Epithelial sodium channel and aquaporin 5 expressions are also downregulated following AKI. Protein-rich fluid accumulation in the alveolar space, alveolar hemorrhage and edematous pulmonary interstitial space are observed in acute lung injury (ALI) following AKI. Abbreviations: AKI, acute kidney injury; Na, sodium, H_2O, dihydrogen oxide; AQP, aquaporin; ENaC, epithelial sodium channel; RBC, red blood cell; HMGB-1, high-mobility group box protein B1; TLR-4 - Toll-like receptor 4; ROS, reactive oxygen species. Based on information in Ware & Matthay[97]

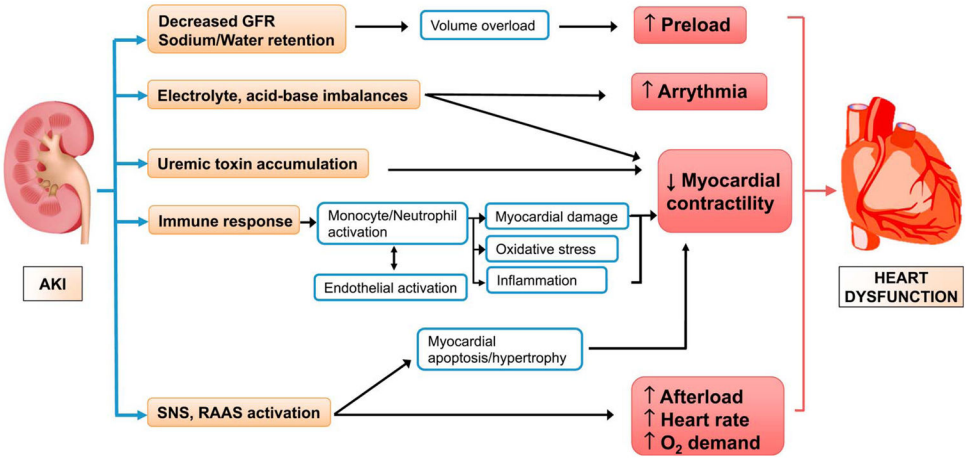

Figure 4. Pathophysiology of acute kidney injury (AKI)-induced cardiorenal syndrome

Acute kidney injury (AKI) triggers cardiac dysfunction through various pathophysiological mechanisms, including volume overload, electrolyte and acid-based imbalances, accumulation of uremic toxins, enhanced immune response and activation of sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS). Abbreviations: AKI, acute kidney injury; GFR, glomerular filtration rate; SNS, sympathetic nervous system; RAAS, renin–angiotensin–aldosterone system.

Table 1

Possible therapeutic targets against AKI-induced distant organ injury

Organ	Intervention	Subject	Effects	Reference
Lung	Blocking of CXCL1	Mouse	↓ Lung neutrophil	31
	Blocking of TNF-α	Mouse	↓ Pulmonary apoptosis	34
	Administration of IL-10	Mouse	Improved lung architecture, ↑ Lung neutrophil	9
	Blocking neutrophil elastase	Mouse	↓ Lung inflammation, Survival	26
	Administration of CNI-1493	Mouse	↓ Pulmonary vascular permeability	29
	Administration of ANP	Rat	↓ Pulmonary edema, Inflammatory cytokine in the lung	38
		Human	No significant benefit	39,40
	Administration of PGE1	Rat	↓ Antioxidant stress in lung, Improved lung architecture	42
	Hemofiltration using novel membrane	Human (*Ex vivo*)	Efficient removal of systemic cytokines and HMGB1	46
Heart	Blocking of TNF-α	Rat	↓ Cardiomyocyte apoptosis	56
		Human	No significant benefit	57
	Mitochondrial fission protein (Drp1) inhibition	Mouse	↓ Cardiomyocyte apoptosis, ↑ Cardiac function	63
Brain	Inhibition of reno-cerebral reflex using RAAS inhibitors, sympatholytic drugs, or renal nerve ablation	Mouse	↓ Cerebral inflammation, Down-regulation of cerebral/renal RAAS	72
Liver	Administration of glutathione	Rat	Improved liver architecture, ALT	77
	Administration of vitamin E	Mouse	↓ AST and ALT, Improved hepatic oxidant/ antioxidant balance	81
	Administration of thymoquinone	Rat	↓ Hepatic oxidative stress	82
	Use of Isoflurane	Mouse	↓ ALT, Improved hepatic architecture	83,84
Intestine	Use of Isoflurane	Mouse	↓ Intestinal apoptosis, Improved intestinal villi architecture	83,84
	Supplementation with SCFA	Mouse	Modulation of inflammatory process, oxidative stress, & apoptosis in kidney after IRI	95
		Rat	↑ Renal antioxidant enzyme activity, ↑ Renal prohibitin protein expression	96

Abbreviations: AKI, Acute kidney injury; CXCL1, Chemokine (C-X-C motif) ligand 1; TNF-α, Tumor necrosis factor α; IL, Interleukin; ANP, Atrial natriuretic peptide; PGE1, Prostaglandin E1; HMGB1, High-mobility group box protein B1; Drp1, Dynamin-related protein 1; RAAS, Renin-angiotensin-aldosterone system; ALT, Alanine transaminase; AST, Aspartate transaminase; SCFA, Short chain fatty acids; IRI, Ischemia-reperfusion injury