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Recent Update on Acute Kidney Injury-to-Chronic Kidney Disease Transition

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Acute kidney injury (AKI) is characterized by an abrupt decline of excretory kidney function. The incidence of AKI has increased in the past decades. Patients diagnosed with AKI often undergo diverse clinical trajectories, such as early or late recovery, relapses, and even a potential transition from AKI to chronic kidney disease (CKD). Although recent clinical studies have demonstrated a strong association between AKI and progression of CKD, our understanding of the complex relationship between AKI and CKD is still evolving. No cohort study has succeeded in painting a comprehensive picture of these multi-faceted pathways. To address this lack of understanding, the idea of acute kidney disease (AKD) has recently been proposed. This presents a new perspective to pinpoint a period of heightened vulnerability following AKI, during which a patient could witness a substantial decline in glomerular filtration rate, ultimately leading to CKD transition. Although AKI is included in a range of kidney conditions collectively known as AKD, spanning from mild and self-limiting to severe and persistent, AKD can also occur without a rapid onset usually seen in AKI, such as when kidney dysfunction slowly evolves. In the present review, we summarize the most recent findings about AKD, explore the current state of biomarker discovery related to AKD, discuss the latest insights into pathophysiological underpinnings of AKI to CKD transition, and reflect on therapeutic challenges and opportunities that lie ahead.

Key Words: Acute kidney injury, renal insufficiency, chronic, kidney disease

INTRODUCTION

Acute kidney injury (AKI) occurs frequently, particularly during critical illness situations. Many studies have revealed that its incidence rate is increasing, contributing to substantial morbidity and mortality.[1] Worldwide, AKI is responsible for nearly 2 million deaths annually. Although progress has been made in understanding AKI in humans, causes for the drastic decrease in kidney function for numerous patients with acute injuries are not yet fully understood. Furthermore, emerging evidence have indicated that a considerable proportion of AKI survivors do not regain normal kidney function.[2] AKI is an independent risk factor for chronic kidney disease (CKD), end stage kidney disease (ESKD), and death.[3] A meta-analysis has indicated that patients with AKI have significantly higher risks of developing CKD, ESKD, and mortality (approximately 9, 3, and 2 times, respectively) compared to individuals without AKI.[3] As CKD and ESKD are also considerable public health concerns with severe human and economic impacts, it is vital to explore and grasp the transition process from AKI to CKD. Gaining insight into this transition will enable the development of more effective approaches to address repercussions of these health issues.

AKI is a condition marked by a rapid decrease in kidney function. It is diagnosed based on increased serum creatinine levels and reduced urine output that typically last no longer than 7 days.[2,4] The Risk, Injury, Failure, Loss, and End-stage renal disease (RIFLE) classification system, Acute Kidney Injury Network, and The Kidney Disease: Improving Global Outcomes (KDIGO) currently provide standardized approaches to evaluate the incidence and outcomes of AKI. The relationship

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between AKI and CKD or ESKD has been examined based on the severity of AKI as determined by these classification systems, taking into account changes in serum creatinine and urine output. Chawla, et al.[5] demonstrated the development of multivariate prediction models to identify patients at risk of progressing to advanced CKD during their hospital stay after surviving AKI. The study found that the severity of AKI is a robust predictor of CKD progression, with three significant prediction models showing good accuracy in identifying at-risk patients. In addition to the severity of AKI, the duration and frequency of AKI episode can also affect outcomes.[6] Data from approximately 220000 patients in the Veterans Health Administration Database were analyzed to examine AKI recovery pattern and subsequent risk of CKD.[7] That study categorized the recovery time of AKI into less than 2 days, 2–10 days, and over 10 days, and found that corresponding risks of developing CKD were 1.5, 1.6, and 2.97 times higher, respectively, compared to patients without AKI. On the other hand, Thakar, et al.[8] analyzed the risk of developing CKD stage 4 based on the number of AKI episodes during hospitalization among 4082 diabetic patients. Compared to patients without any AKI episodes, those with three AKI episodes had 3.56 times higher risk of developing CKD stage 4, while patients with two episodes had 2.02 times higher risk. They demonstrated that the frequency of AKI episodes represents a major cumulative risk for the progression of CKD in diabetic patients.[8] These findings emphasize that not only AKI severity, but also recovery patterns such as duration and frequency, as reflected in various AKI trajectories, ultimately influence long-term kidney health and the progression from AKI to CKD.

On the other hand, CKD is an important risk factor for the development and detection of AKI. Experimental findings support clinical observations and the reciprocal relationship between AKI and CKD.[9-11] Consequently, it is reasonable to view AKI and CKD as interconnected syndromes rather than distinct disease entities. These two conditions share common risk factors, such as age, genetic factors, diabetes, hypertension, and metabolic syndrome. They are organically linked through disease modifiers, such as AKI severity, CKD stage, and proteinuria. Ultimately, they manifest in hard outcomes, such as cardiovascular events, kidney outcomes, and mortality, forming a continuous disease spectrum. Furthermore, both AKI and CKD are independent risk factors for cardiovascular morbidity and reduced life expectancy.[12] As a result, a comprehensive examination of the AKI-CKD relationship holds substantial clinical and public health importance. Therefore, the importance of defining the concept of acute kidney disease (AKD) as a transition stage between AKI and CKD, or as a separate disease entity, is gaining attention.[13-16] Recently, a discussion on this topic took place at the KDIGO consensus conference in 2020.[17] The purpose of this review was to provide recent updates on the clinical significance of AKD, including the transition from AKI to CKD, and explore the related mechanistic insights and therapeutic approaches.

DEFINING THE SPECTRUM: AKD

The KDIGO definition of CKD is based on both functional and structural abnormalities, whereas AKI is defined solely based on serum creatinine levels and urine output without considering the duration of AKI, recovery, or markers of kidney damage.[18] CKD is defined based on markers of kidney damage or a decrease in the glomerular filtration rate (GFR) for 3 months or more, which is then categorized based on the cause, GFR, and albuminuria criteria. However, these abnormalities in kidney function can occur within a period of less than 3 months, which might leave some patient groups unable to satisfy existing definitions of AKI or CKD. Thus, it becomes necessary to establish an entity for the disorder status known as AKD.[17] Defining and staging AKD in terms of both time and state are essential for understanding the disease, accurately assessing its incidence, prevalence, and impact on health, and establishing appropriate care models based on its severity. "kidney disease (KD)" is a comprehensive term proposed to describe a variety of abnormalities affecting health that present abnormalities in kidney function and/or structure. Therefore, AKD and CKD can be distinguished based on disease duration. They can be harmoniously integrated under the umbrella term of KD.

AKD is currently defined as kidney functional or structural impairment lasting for a period of less than 3 months, as shown in Fig. 1. There are several considerations to note. Firstly, AKI is a subset of AKD, and AKD can occur with or without AKI.[18] If a patient's kidney function decline is confirmed within less than 3 months and does not deteriorate rapidly enough to meet the diagnostic criteria for AKI within the initial 7 days, this clinical scenario could be characterized as AKD without AKI. AKD encompasses a spectrum of kidney conditions, ranging from mild and self-limiting to severe and persistent, and it can also develop gradually, unlike the rapid onset typically seen in AKI. Also, the definition of AKI includes the criteria for functional abnormalities (an increase in the rate of serum creatinine or a decrease in urine output measured over an interval of 6 hours to 7 days).[2] The definition of AKI does not include the criteria related to markers of kidney damage, such as abnormalities in urine sediment or proteinuria. It does not include situations where kidney function deteriorates less severely or progresses less rapidly than AKI. To address these discrepancies and harmonize definitions over time, some AKI criteria can be incorporated into the definition of AKD and existing CKD criteria can be smoothly intertwined. Therefore, the three diseases, AKI, AKD, and CKD, can be viewed as a conceptual model on a continuum of time.

Despite the lack of comprehensive data on the incidence and prognosis of AKD, the clinical significance of AKD has gradually emerged from recent studies utilizing the AKD concept. James

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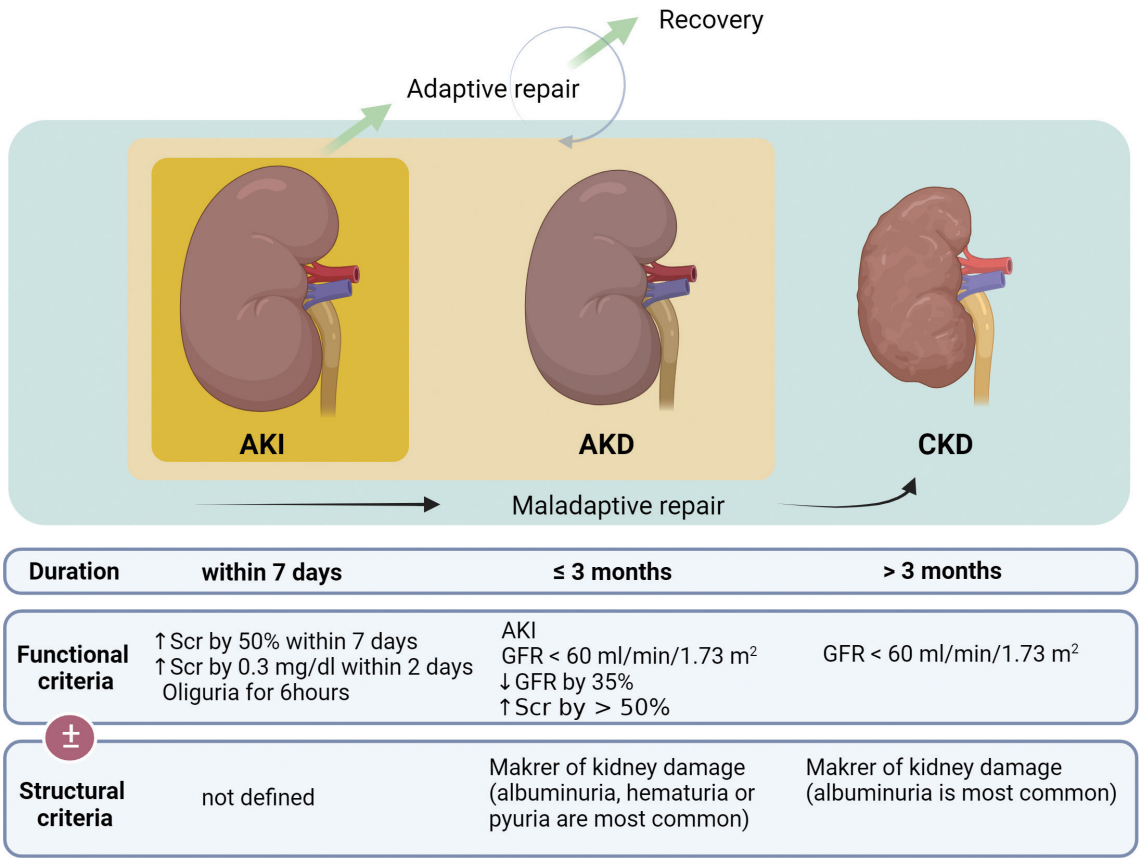

Fig. 1. Proposed conceptual model and definitions of a kidney disease: acute kidney injury (AKI), acute kidney disease (AKD), and chronic kidney disease (CKD).[17] The AKI definition, characterized by functional abnormalities such as an increase in serum creatinine rate or decrease in urine output within 7 days, does not encompass kidney damage markers, such as abnormalities in urine sediment or proteinuria, nor does it cover instances of less severe or slower kidney function deterioration. This figure illustrates the harmonization of these diseases' definitions, integrating specific AKI criteria into the AKD definition and seamlessly intertwining existing CKD criteria, thereby presenting AKI, AKD, and CKD as interconnected points on a time continuum. Scr, serum creatinine; GFR, glomerular filtration rate.

and his colleagues[19] divided their cohort into CKD, AKI, AKD without AKI, and combinations of these conditions using a large administrative population database. They found that AKD without AKI was about three times more common than AKI in patients without previous CKD. Similar to AKI, AKD without AKI increased the risk of mortality and progression to CKD. The combination of AKD and CKD resulted in the highest risk of progression to kidney failure, while the combination of CKD and AKI posed the greatest risk of death.[19] Meanwhile, See and his colleagues[20] investigated epidemiological characteristics and long-term outcomes of AKD in a retrospective research cohort of adult patients who were admitted for more than 24 hours in a medical institution from 2012 to 2016. Their study subjects were patients who had survived 30 days with baseline estimated GFR ≥60 mL/min/1.73 m^2. They analyzed the risk of major adverse kidney events, CKD, kidney failure, and death in 36118 patients with follow-up data. They found that patients with AKD and AKI had relatively higher risks of major adverse kidney events (MAKE), CKD, kidney failure, and death. Patients with AKD without AKI also had higher risks of MAKEs, CKD, kidney failure, and death. Nonetheless, according to the results of a recent research by Orieux and his colleagues,[21] the risk factor for the transition to CKD in the case of AKI occurring in the intensive care unit (ICU) was more due to the trajectory of non-recovery from AKI than the disease of AKD itself. This was a 5-year follow-up observational study to evaluate the progression of kidney disease and risk factors for CKD in patients with AKI occurring in the ICU. It was conducted on 232 patients, of whom 47% progressed to AKD on day 7 after AKI, and 28% recovered. Among patients with CKD, 70% showed a linear trajectory. The cumulative incidence of CKD at 5-year follow-up was 30%. In multivariate analysis, the risk of CKD in AKD patients was higher for 6 months after AKI; however, the risk decreased after 6 months. The risk of transitioning to CKD was related to a lack of kidney recovery. These results demonstrate that the course of kidney disease after AKI occurring in the ICU is diverse, and that the "lack of kidney recovery" rather than AKD per se is related to the risk of CKD.[21] Other studies on AKD published so far have focused primarily on AKD along with AKI in cohorts associated with cardiovascular disease. They included all inpatients and patients in various clinical areas (intensive care, post-operative care, liver disease, etc.).[22-27] These

reported studies were all retrospective, with outcomes mainly limited to mortality and incidence of CKD. Their follow-up periods ranged from 3 months to 10 years. Most of these studies have consistently found that risks of both mortality and onset of CKD are increased in the presence of AKD. These studies have confirmed the burden and poor prognosis of AKD and indicated the need to prioritize clinical interventions and research strategies to mitigate these risks.

Both AKI and AKD can occur not only in inpatients, including intensive care patients, but also in community settings. Literature defining community-acquired AKI is becoming increasingly available. Community-acquired AKD, which can have potential long-term impacts, is often largely undetected if the entity of the disease is not properly recognized.[28,29] In the past, AKI was traditionally regarded as a distinct event that would either resolve or stabilize into a new state within 3 months. However, current AKI management emphasizes early phase of AKI rather than post-AKI period, irrespective of complete restoration of kidney function.[30] Multiple AKI events can occur during the course of the disease within an individual. Patients may still have abnormalities in kidney function and/or structure after AKI recovery, meeting the criteria for AKD.[8] The KDIGO working group has stated that the proposed 7-day arbitrary time-based AKI duration definition by the Acute Disease Quality Initiative (ADQI) requires additional consideration. Specific criteria for AKI duration and recovery are expected to be clarified in the next AKI guideline update.[16] Until then, there will continue to be some uncertainty regarding the suitable nomenclature for patients after AKI onset. However, it is crucial to primarily understand the clinical concept of AKD and the nature of the disease with potentially poor prognosis in the management of kidney diseases related to the integrated and systematic transition from AKI to CKD.

CHALLENGES FOR IDENTIFYING BIOMARKERS FOR AKI-TO-CKD TRANSITION

Several factors, including the intensity, duration, and frequency of AKI episodes, patient's age, pre-existing CKD, and additional health conditions, are known to increase the risk of AKI-to-CKD transition. However, currently available biomarkers for AKI have shown limited efficacy in predicting AKD, although their combinations with clinical parameters may prove valuable. There is a pressing need for the development of novel biomarkers capable of accurately predicting AKI-to-CKD transition.[31-34] Initiatives such as the CKD Biomarker Consortium funded by the National Institutes of Health (NIH)-National Institute of Diabetes and Digestive and Kidney Diseases are working towards the discovery of biomarkers. They aim to pinpoint which patients with CKD will experience accelerated progression and identify biomarkers that can assist in monitoring the disease's progression. Increased concentrations of urinary and serum biomarkers, such as kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), liver fatty acid-binding protein, interleukin-18, and tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 (TIMP-2×IGFBP7), indicate the presence of sustained tubular injury, which may serve as indicators for identifying individuals at risk of CKD development.[34-39] Indeed, KIM-1 has been demonstrated to be a predictor of both AKI and CKD progression in patients with type 1 diabetes.[40] Also, in a study involving 692 patients, a TIMP-2×IGFBP7 value greater than 2.0 at the time of admission was associated with either mortality or the requirement for dialysis during a 9-month period.[41] Urinary angiotensinogen associated with increased severity of AKI and mortality has been found to be a potential prognostic marker due to the role of renin-angiotensin-aldosterone system in activating CKD progression.[42] Exploration of other biomarker approaches may also be valuable. In the Chronic Renal Insufficiency study, individuals identified as rapid progressors displayed distinct DNA methylation patterns across several genes associated with inflammation or fibrosis, such as transforming growth factor-β (TGF-β).[43] The key indicator of progression is the onset of fibrosis. However, there is no qualified biomarker to measure continued injury or intrarenal fibrosis. This limits the detection of dysfunctional repair and the potential efficacy of treatments that target these pathways. Other options for measuring interstitial fibrosis, such as non-invasive imaging techniques, represent an ongoing challenge. For example, kidney hypoxia has been evaluated in post-AKI patients and in those with progressive CKD using blood oxygen level-dependent magnetic resonance imaging (MRI).[44] Elastography techniques, which can assess tissue stiffness, have been innovated using MRI or ultrasound imaging. These methods have been implemented in preclinical models to study kidney fibrosis.[45,46] These innovative methods for non-invasive assessment of kidney fibrosis have drawn considerable interest from the NIH. They hold potential to significantly advance diagnostics, particularly in identifying individuals at risk of CKD following an AKI episode.

Biomarkers of kidney damage might be present before functional abnormalities in AKI, AKD, and CKD. Recently, the ADQI has proposed a staging system for AKI, which includes biomarkers of kidney damage. Research is ongoing to validate specific markers for this purpose.[39] Some biomarkers used in AKI, such as NGAL and KIM-1, along with albuminuria, hematuria, and imaging findings used in CKD, might be useful for further stratifying AKD based on the underlying cause (Table 1). Outcomes of future research in this area are eagerly anticipated. Successful outcomes of these studies could provide opportunities to develop strategies for preserving kidney function and preventing AKI-to-CKD transition.

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Table 1. Candidate AKI Biomarkers

Biomarker	Sample source	Stress marker*	Structural damage marker	Functional marker	Potential clinical applications and remarks
Kidney injury molecule-1 (KIM-1)	Urine		V		Prediction, diagnosis, and assessment of AKI severity; various factors, such as Ischemia and sepsis, may impact tubular KIM-1 expression
Neutrophil gelatinase-associated lipocalin (NGAL)	Urine, plasma		V		Diagnosis and assessment of AKI severity; plasma NGAL levels can be modulated by malignancy, inflammation, and hypertension
Liver-type fatty acid-binding protein (L-FABP)	Urine, plasma		V		Diagnosis of AKI
Interleukin-18	Urine		V		Prediction and diagnosis of AKI; no reliable cut-off value
Tissue metalloproteinase-2 and insulin-like growth factor binding protein-7 (TIMP-2×IGFBP7)	Urine	V			Prediction, diagnosis, and assessment of AKI severity; proteinuria can disrupt quantification
N-acetyl-β-D-glucosaminidase (NAG)	Urine		V		Diagnosis of AKI
Angiotensinogen	Urine		V		Association with AKI severity and potential prognostic marker
Cystatin-C	Plasma			V	Diagnosis and assessment of AKI severity; can be influenced by thyroid dysfunction and high glucocorticoid therapy

AKI, acute kidney injury.
*Stress markers indicate cellular stress, which can either resolve or progress to damage.

AKI-TO-CKD TRANSITION: RECENT MECHANISTIC INSIGHTS

While our understanding of the mechanisms driving AKI-to-CKD transition in humans remains incomplete, decades of experimental data have indicated that such transition may stem from an inappropriate cellular reaction or incorrect healing process, commonly referred to as a maladaptive repair process.[47-53] Although no animal model can fully represent the transition from AKI to CKD, the majority of models have utilized ischemia reperfusion in rats or mice, coupled with histological or biochemical indicators of fibrosis and other easily measurable functional end points in rats, but not in mice. The rate and intensity of fibrosis can be affected by diminished kidney mass or dietary changes. Such strategies may shed light on unique mechanisms that propel the progression from AKI to CKD. Models involving nephrotoxins and unilateral ureteral obstruction (UUO) have also been introduced, again with fibrosis being the primary outcome.[54]

Following an injury, the kidneys will initiate healing mechanisms, which include transforming into a dedifferentiation, adapting to stressful conditions, changing metabolic activities, infiltration of inflammatory cells, production of extracellular matrix (ECM), and hypertrophy of remnant nephrons.[47,55,56] These processes reciprocally support one another and necessitate the synchrony of various cell types in wounded kidneys. When effective, these carefully coordinated healing mechanisms enable injured kidneys to achieve a new state of equilibrium and recover from the damage, a phenomenon referred to as adaptive repair.[56] The regenerative capacity of the kidney is believed to account for the rapid restoration of normal or near-normal kidney function in young and mildly injured patients shortly after AKI regardless of the underlying cause.[49] Nonetheless, these same mechanisms and signaling pathways can become misguided or dysfunctional if they are either too much, inadequate, prolonged, or incorrectly directed, leading to kidney dysfunction and scarring, a condition known as maladaptive repair.[51] Maladaptive repair can occur in tubular, vascular, and interstitial compartments after AKI, leading to an increased risk of interstitial fibrosis. Specific mechanisms related to this encompass a substantial body of experimental evidence related to tubular cell cycle arrest, epigenetic regulation, mitochondrial dysfunction, capillary rarefaction, and various other factors (Fig. 2).[53]

Activation of DNA damage response signaling plays a vital role in facilitating the reparative process in kidney proximal epithelial cells after AKI.[47] In cases where complete repair is not achieved, proximal tubules experience cell cycle arrest at the G2/M phase, which is likely to be a protective mechanism aiming for preserving genomic stability.[57] However, if this cell cycle arrest at G2/M persists, it can induce a profibrotic secretory phenotype, leading to fibrosis and irreversible damage. Yang, et al.[58] have demonstrated a causal relationship between

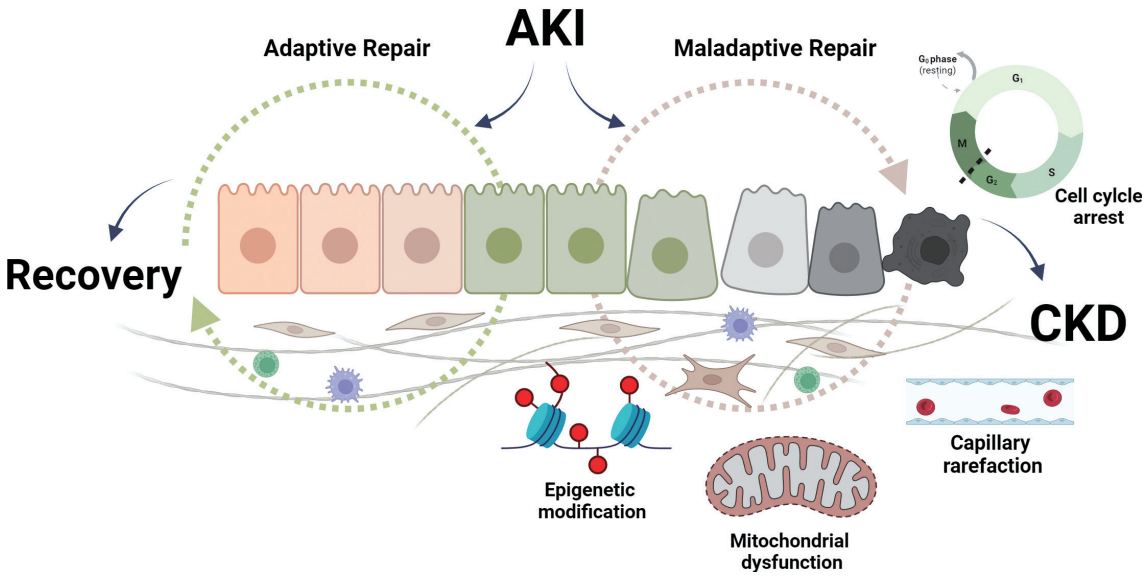

Fig. 2. Illustration of the mechanistic insights into the transitions from AKI to CKD. Following AKI, healing mechanisms, such as cell dedifferentiation, stress adaptation, and inflammation, are activated. If well-coordinated, this leads to adaptive repair and kidney recovery, particularly in young or mildly injured patients. However, if these processes are excessive or misdirected, they result in maladaptive repair, causing kidney dysfunction and scarring, and increasing the risk of fibrosis. This involves complex factors, including cell cycle arrest, epigenetic modifications, mitochondrial dysfunction, capillary rarefaction, and various other factors. AKI, acute kidney injury; CKD, chronic kidney disease.

cell cycle arrest and fibrosis in models of toxic nephropathy and obstructive nephropathy. After AKI, abnormal repair processes can lead to atrophy of kidney tubular epithelial cells (TECs) and acquisition of a pro-fibrotic phenotype. G2/M-arrested TECs can activate c-jun NH2-terminal kinase signaling pathway, resulting in the production of pro-fibrotic cytokines such as TGF-β, ultimately promoting the progression of fibrotic changes and mediating the AKI-to-CKD transition. Overall, while favorable cell cycle events can contribute to tissue repair, cell cycle arrest plays a crucial role in determining the progression of injury. Dysregulated and inefficient repair of kidney tubules, known as maladaptive repair, is associated with persistent inflammation, ECM deposition, and the development of a pro-fibrotic and senescent state in TECs. In fact, dedifferentiated TECs can acquire pro-fibrotic characteristics and contribute to CKD progression. Targeting the mitotic cell cycle is a promising approach in the pursuit of innovative strategies for the prevention of AKI-to-CKD transition.[58]

The study of epigenetic modifications in the kidney after AKI is an emerging and rapidly advancing area.[59,60] There exist various mechanisms through which alterations in the epigenome can impact subsequent regulation of proinflammatory and anti-inflammatory genes. Studies on CKD patients have already associated DNA methylation and histone modifications with their roles in contributing to CKD transition.[59] Furthermore, AKI has been linked to changes in DNA methylation and histone modifications, resulting in dysregulated transcription of genes involved in kidney injury.[60-62] The progress in epigenetic assessment technologies in the kidney is facilitating the exploration of models that elucidate the transition from AKI to CKD. Epigenetic modulation, exemplified by utilization of histone deacetylase inhibitors or p300/CBP-associated factor (PCAF), a histone acetyltransferase, has emerged as a promising approach in this pursuit, supported by relevant research findings.[61] PCAF participates in numerous cellular processes, including differentiation, proliferation, apoptosis, and response to cellular damage, by regulating activities of various genes and proteins through acetylation of either histones or transcription factors. We have investigated the pathogenic role of PCAF and its potential as a novel therapeutic target in the progression of kidney tubulointerstitial fibrosis induced by UUO, which serves as an animal model for AKI-to-CKD transition.[62] Administration of garcinol, a PCAF inhibitor, can reverse elevated kidney expression of total PCAF and histone 3 lysine 9 acetylation induced by UUO. PCAF inhibition can also lead to reductions in positive areas of trichrome staining, α-smooth muscle actin, and collagen content. Additionally, garcinol administration can result in decreased mRNA levels of TGF-β, matrix metalloproteinase (MMP)-2, MMP-9, and fibronectin. Furthermore, garcinol can suppress nuclear factor-κB (NF-κB) and pro-inflammatory cytokines, such as tumor necrosis factor-α and IL-6, while preserving nuclear expression of nuclear factor erythroid-derived 2-like factor 2 (Nrf2) and levels of Nrf2-dependent antioxidants, including heme oxygenase-1, catalase, superoxide dismutase 1, and NAD(P)H:quinone oxidoreductase 1.[63,64] These findings suggest that inhibiting the excessive activity of PCAF can alleviate kidney fibrosis by restoring imbalanced inflammatory signaling and antioxidant response by modulating NF-κB and Nrf2. These approaches have potential to partially uncover mechanisms by which maladaptive kidneys may undergo per-

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sistent transcriptional changes that can make patients susceptible to CKD transition after AKI.

Mitochondrial dysfunction in proximal tubules has been implicated in increased susceptibility to injury and fibrotic process.[65] Recent studies have put forward the idea that damage of mitochondrial function in early AKI plays a critical role in causing tubular injury and persistent kidney insufficiency.[65-67] Perturbation of mitochondrial homeostasis, disruptions in bioenergetics, and interplay of organelle stress collectively contribute to the transition from AKI to CKD. Significant emphasis has been placed on preserving mitochondrial biogenesis and maintaining mitochondrial integrity during processes of injury and repair.[68] Furthermore, Chung, et al.[69] recently introduced a hypothesis that the release of mitochondria DNA (mtDNA) during AKI can trigger immune responses and injury progression. They demonstrated that mitochondrial transcription factor A is depleted in fibrotic kidneys of both human and murine subjects, providing additional insights into its impact on mitochondria and subsequent translocation of mtDNA into the cytosol. The mtDNA in turn can activate the cGAS-stimulator of interferon genes (STING) pathway, leading to induction of a pro-inflammatory state and development of kidney fibrosis. Similarly, Maekawa, et al.[70] used a cisplatin-induced AKI model to demonstrate that mtDNA dislocation facilitated by Bcl-2-associated X can induce mitochondrial membrane permeabilization and trigger the STING pathway and subsequent process. Deleting or inhibiting STING pathway can ameliorate AKI and inflammation.

Proximal tubule cells rely on ATP produced by the mitochondrial respiratory chain to support reabsorption of filtrate through activity of Na-K-ATPase. As a result, these cells are highly dependent on oxygen. Insufficient oxygen supply during AKI can result in mitochondrial dysfunction, abnormal production of reactive oxygen species, and inflammation.[71-73] Inflammation and dysfunction of endothelial cells can contribute to the reduction in peritubular capillary density, exacerbating tissue hypoxia and perpetuating this detrimental cycle. The so-called "capillary rarefaction" phenomenon occurs during the early stages of AKI. It can lead to kidney hypoxia, probably induced by decreased expression of vascular factors such as vascular endothelial growth factor (VEGF) in tubular cells. It can also be associated with pericyte detachment. Hypoxia not only results in injury of TECs, potentially hindering re-differentiation of regenerating tubular cells, but also triggers the activation of fibroblasts and initiates inflammatory responses. These processes collectively play pivotal roles in the development of tubulointerstitial fibrosis.[74] Hypoxia-inducible factors (HIFs), a family of crucial transcription factors that can evade degradation under hypoxic conditions, play a significant role in orchestrating various downstream pathways, such as VEGF, and erythropoietin upregulations in kidneys.[75] Under hypoxic conditions in AKI, activation of HIF occurs. It is generally considered an essential process for adaptive responses to hypoxia.[76] Recently, Li, et al.[77] revealed that under hypoxia, HIF-1a can bind to Forkhead box O3 (FoxO3), a stress-responsive transcription factor known to upregulate autophagy after UUO, subsequently suppressing prolyl hydroxylation and degradation of FoxO3 by the ubiquitin-proteasome system. The removal of FoxO3 from tubular cells can lead to increased interstitial fibrosis after ischemia-reperfusion Injury, with a decrease in autophagy and more severe oxidative damage. These findings suggest a renoprotective role of FoxO3 after AKI.[77]

THERAPEUTIC CONSIDERATIONS

Comprehending the timeline of specific progression events and maladaptive repair processes in human and animal models of AKI could potentially provide the rationale for targeted treatments at specific points in the course of AKI.[47] For instance, the onset of capillary loss and myofibroblast activation may occur very early in AKI, while persistent fibrotic signals resulting from maladaptive tubular repair may be amenable to interventions at both initial and later stages.[58,78-80] To date, preclinical research studies focusing on recovery from AKI have rarely examined its impacts on long-term function and progression. There is a significant lack of information across different models to determine whether specific damages can induce distinct maladaptive repair responses to influence the progression post-AKI. Nonetheless, given the similarity of the progression after AKI to characteristics found in other CKD models, it is plausible to think that targeting known progression pathways in CKD (e.g., antifibrotic treatments, inhibition of hypoxia, or RAAS inhibition) has beneficial effects on the post-AKI scenario.[81-83] However, for studies aiming to comprehend the relative factors contributing to AKI-to-CKD transition, an essential aspect to consider carefully is to what extent early interventions can mediate the degree of initial injury.[84] This can make it difficult to distinguish the protective effect against AKI from those against consequences of the initial injury.

The conventional clinical approach for improving outcomes in AKI has primarily focused on prevention and early intervention. However, the rising population of AKI survivors and patients now being identified with the newly established AKD calls for appropriate post-acute care, a paradigm that has not been clearly defined yet. Currently, many of these patients experience varying degrees of kidney function recovery, often with little to no systematic follow-up care for their kidneys. Therefore, it is of significant importance to clinically identify and monitor patients situated in this AKI-to-CKD transitional timeline and ensure that no further kidney injury occurs.

CONCLUSION

The interconnected relationship between AKI and CKD pres-

ents a substantial public health challenge due to their high prevalence and economic impact. The term of AKD has been introduced to describe the post-AKI phase of continued kidney damage lasting from 7 to 90 days. Factors influencing the spectrum of AKI-to-AKD-to-CKD transition include the type of kidney injury, pre-existing chronic conditions, and genetic factors. Understanding of the maladaptive repair pathways contributing to CKD highlights the potential for targeted interventions to disrupt this complex progression. Currently, there is a significant lack of clinical data concerning the epidemiology of AKD. Given this, we anticipate that future research adhering to the formal definition of AKD will address these constraints. By incorporating diverse populations and applying varied observational timeframes for AKD identification, these forthcoming studies hold the potential to enhance generalizability of our understanding of the AKD entity.

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AUTHOR CONTRIBUTIONS

Conceptualization: Eun Sil Koh and Sungjin Chung. Data curation: Eun Sil Koh. Formal analysis: Eun Sil Koh. Funding acquisition: Eun Sil Koh and Sungjin Chung. Investigation: Sungjin Chung. Resources: Eun Sil Koh and Sungjin Chung. Supervision: Sungjin Chung. Visualization: Eun Sil Koh and Sungjin Chung. Writing—original draft: Eun Sil Koh. Writing—review & editing: Eun Sil Koh and Sungjin Chung. Approval of final manuscript: Eun Sil Koh and Sungjin Chung.

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