Review

Discovery Medicine 2026; 38(204): 31–45
https://doi.org/10.24976/Discov.Med.202638204.3

Clinical Review of Renal Fibrosis Mechanisms and Intervention Windows in the Transition from Acute Kidney Injury to Chronic Kidney Disease

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Submitted: 21 November 2025 Revised: 11 December 2025 Accepted: 24 December 2025 Published: 20 January 2026

The transition from acute kidney injury (AKI) to chronic kidney disease (CKD) represents a continuously evolving pathological process in which renal interstitial fibrosis serves as the central nexus. This review synthesizes current evidence and delineates the major pathogenic axes that drive fibrosis, including amplification of the NOD-like receptor family pyrin domain containing 3 (NLRP3)–Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF-κB)/Signal Transducer and Activator of Transcription 3 (STAT3) inflammatory cascade, sustained activation of the renin–angiotensin system (RAS), maladaptive tubular epithelial repair with G2/M cell-cycle arrest, endothelial injury and microvascular rarefaction leading to hypoxia-inducible factor (HIF) signaling, mitochondrial dysfunction with impaired autophagy, cellular senescence with a senescence-associated secretory phenotype (SASP), multiple programmed cell-death pathways, and epigenetic alterations involving DNA methylation, histone modifications, and miR-21/29/200 networks. A key innovative finding of this review is the identification of temporally defined intervention windows in the AKI–CKD continuum. Early intervention targets inflammation and oxidative stress suppression; the intermediate phase focuses on transforming growth factor-β (TGF-β) and RAS-mediated fibrogenesis, while promoting adaptive repair; the late phase aims to restore tissue homeostasis through anti-senescence and regenerative strategies. This approach shifts from generalized treatment strategies to personalized, stage-specific therapies in renal fibrosis. Representative interventions—including ACE inhibitor (ACEI)/angiotensin receptor blocker (ARB) therapy, Roxadustat, mesenchymal stem cells and extracellular vesicles, and senolytic regimens—are discussed with regard to their mechanisms and optimal timing. Barriers to clinical translation, such as patient heterogeneity, lack of reliable biomarkers for early fibrosis detection, and discrepancies between preclinical models and clinical endpoints, are also highlighted. The integration of predictive modeling, multi-omics, and spatial transcriptomics is essential for refining individualized intervention windows, advancing precision strategies to prevent or attenuate AKI–CKD progression.

Keywords: acute kidney injury; chronic kidney disease; renal interstitial fibrosis; inflammatory signaling; RAS activation

Introduction

Acute kidney injury (AKI) is a clinical syndrome characterized by a rapid decline in renal excretory function over a short period due to diverse etiologies, ultimately resulting in structural and functional alterations of the kidney. Its incidence continues to rise, affecting an estimated 13.3 million individuals worldwide each year and contributing to approximately 1.7 million deaths [1]. AKI has been increasingly recognized as an independent risk factor for the subsequent development of chronic kidney disease (CKD). The likelihood of progression from AKI to CKD is strongly associated with the severity and recurrence of AKI episodes. Approximately 30–70% of patients eventually develop CKD or end-stage renal disease (ESRD) following an episode of AKI [2]. Severity staging based on serum creatinine levels (stages 1–3) correlates directly with long-term outcomes, and evidence indicates that each additional AKI episode nearly doubles the risk of progressing to CKD stage 4 [3].

The transition from AKI to CKD is a multifactorial and dynamic pathological process involving multiple cell types and interconnected molecular pathways. Tubular epithelial cells, interstitial cells, endothelial cells, and immune cells engage in reciprocal signaling, resulting in excessive extracellular matrix deposition, microvascular rarefaction, persistent hypoxia, and activation of epithelial–stromal interactions, collectively driving renal fibrosis [4]. Fibrosis

is not only a characteristic feature of advanced CKD but also a pivotal pathological determinant in the AKI–CKD continuum. Early events—including G2/M cell-cycle arrest, mitochondrial injury, metabolic reprogramming, partial epithelial-to-mesenchymal transition (partial epithelial-to-mesenchymal transition (EMT)), and sustained activation of signaling pathways such as Wingless/Integrated (Wnt)/β-catenin, transforming growth factor-β (TGF-β), Hippo/Yes-associated protein (YAP), and Notch—can promote a pro-fibrotic state and compromise the kidney's regenerative capacity [5].

These observations underscore the importance of therapeutic timing. The period between 7 and 90 days after AKI onset—referred to as the "subacute phase" or "acute kidney disease (AKD)"—has been proposed as a critical window during which the structural and functional trajectory of the injured kidney may be redirected [1]. Interventions that facilitate adaptive repair and suppress pro-fibrotic signaling during this phase may prevent or attenuate progression to CKD.

In this context, the present review synthesizes recent clinical and mechanistic findings to delineate the core cellular and molecular drivers of renal fibrosis during the AKI–CKD transition, evaluate potential biomarkers capable of identifying early and reversible stages of injury, and highlight time-specific therapeutic strategies. These include renin-angiotensin-aldosterone system (RAAS) modulation, anti-inflammatory and antioxidant approaches, anti-fibrotic agents, and emerging interventions, such as senescent cell clearance and cell-based therapies. By summarizing current evidence and limitations, this review aims to inform the development of future therapeutic interventions and guide the design of clinical trials targeting the AKI–CKD continuum.

Mechanistic Insights Into Renal Fibrosis During AKI–CKD Transition

The transition from AKI to CKD is not driven by a single mechanism in isolation, but rather is a dynamic process centered around the "injury-inflammation-impaired repair-fibrosis" axis. These mechanisms are sequentially activated over time, interlinked, and form amplification loops. A systematic overview of the temporal characteristics of each core mechanism, the associated key molecules, and the corresponding intervention windows is listed in Table 1, offering a comprehensive framework for subsequent mechanistic discussions.

Inflammatory Injury

Inflammatory responses are a central contributor to AKI and its transition to CKD. During acute renal injury, damaged renal tubular epithelial cells and vascular endothelial cells secrete numerous cytokines and Kidney International chemokines. These factors induce the infiltration of neutrophils, macrophages, and lymphocytes [6]. These inflammatory cells release pro-inflammatory mediators, such as interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and transforming growth factor-α (TGF-α), which further amplify local inflammatory responses and tissue damage. Shankar *et al*. [7] demonstrated that elevated levels of tumor necrosis factor-α receptor 2 (TNF-αR2) and IL-6 in renal tissue are positively correlated with CKD incidence, suggesting that persistent inflammation is a key factor promoting chronic renal structural remodeling.

The NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome forms a positive feedback loop with nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and signal transducer and activator of transcription 3 (STAT3), amplifying signaling during both the initiation of AKI and the maintenance phase of AKI-to-CKD transition. In canonical pathways, Toll-like receptors (TLRs) and pro-inflammatory cytokines activate NF-κB, upregulating transcription of NLRP3 and pro-interleukin-1β (pro-IL-1β)/pro-interleukin-18 (pro-IL-18), while secondary signals such as mitochondrial reactive oxygen species (ROS) trigger NLRP3 activation and release of mature IL-1β/IL-18. These cytokines, in turn, feedback to activate NF-κB, further enhancing NLRP3 expression and forming an IL-1β–NF-κB–NLRP3 positive loop [8,9]. STAT3 can be activated by IL-6 and mediates NLRP3 mitochondrial localization and assembly, whereas NLRP3 activation and mitochondrial dysfunction maintain STAT3 signaling, constituting an additional positive circuit [10,11]. In the kidney, NLRP3-mediated pyroptotic release of damage-associated molecular patterns (DAMPs) and pro-inflammatory mediators amplifies oxidative stress and TGF-β signaling via NF-κB, coupling inflammation with pro-fibrotic pathways and driving irreversible AKI-to-CKD progression [12,13].

Damaged renal tubular epithelial cells are not only targets of inflammatory signals but also important amplifiers. Studies have shown that injured epithelial cells can induce the expression of monocyte chemoattractant protein-1 (MCP-1) and regulated upon activation, normal T cell expressed and secreted (RANTES) via TGF-β signaling. These factors bind to C-C chemokine receptor type 2 (CCR2) and C-C chemokine receptor type 5 (CCR5) receptors, respectively, promoting the recruitment of monocytes/macrophages and dendritic cells to the injury site [14, 15]. Additionally, renal tubular epithelial cells can produce macrophage colony-stimulating factor, which enhances the proliferation and activation of macrophages [16].

Macrophages exert dual roles in the AKI-to-CKD transition. In the early stage, classically activated macrophages (M1) predominate, secreting pro-inflammatory factors such as IL-1, IL-6, and TNF-α to exacerbate tissue damage. During the repair phase, macrophages gradually polarize to alternatively activated macrophages (M2), releasing growth factors like TGF-β

Table 1. Mechanisms and Intervention Windows in the Transition from AKI to CKD.

Time phase	Core mechanism	Key molecules/Pathways	Mechanism interactions (Feedforward/Feedback effects)	Corresponding intervention window (Section 3)
Early (Injury Immediate-72 h)	Inflammatory Injury RAS Activation	TNF-α, IL-6, MCP-1, Ang II, AT1R, NF-κB	(1) Tubular/Endothelial injury initiates inflammation; pro-inflammatory mediators (e.g., IL-6) induce excessive RAS expression. (2) Ang II amplifies inflammation through NF-κB, forming a positive feedback loop of "inflammation-RAS".	Early Intervention Window: Anti-inflammatory, Antioxidant, Inhibition of Overactive RAS
Mid (72 h–2 weeks)	Tubular Repair Defects, Renal Ischemia-Hypoxia, Mitochondrial Dysfunction	p53/p21, G2/M Arrest, HIF-1α, VEGF, PGC-1α, ROS	(1) Persistent inflammation/hypoxia induces tubular DNA damage, triggering G2/M arrest. (2) ROS from mitochondrial injury exacerbates G2/M arrest and endothelial injury, leading to vascular rarefaction. (3) Hypoxia-induced HIF-1α initially promotes repair; continuous activation triggers fibrosis via TGF-β.	Mid Intervention Window: Release G2/M arrest, Improve Mitochondrial Function, Target TGF-β Anti-fibrosis
Late (Post-2 weeks)	Cellular Senescence, Epigenetic Regulation	SASP, p16Ink4α, miR-21/29, DNA Methylation, Histone Modifications	(1) Chronic G2/M arrest and ROS induce cellular senescence; SASP factors sustain chronic inflammation. (2) Epigenetic modifications (e.g., upregulation of miR-21) lock in fibrotic gene expression, suppress repair-related genes (e.g., Klotho).	Late Intervention Window: Clearance of Senescent Cells, Epigenetic Regulation, Promote Tissue Regeneration

RAS, renin–angiotensin system; TNF-α, tumor necrosis factor-α; IL-6, Interleukin-6; MCP-1, monocyte chemoattractant protein-1; Ang II, angiotensin II; AT1R, Ang II binds to type 1 receptor; NF-κB, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; HIF-1α, Hypoxia-Inducible Factor 1 Alpha; VEGF, Vascular Endothelial Growth Factor; PGC-1α, Peroxisome proliferator-activated receptor gamma coactivator 1α; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; TGF-β, Transforming Growth Factor Beta.

and vascular endothelial growth factor (VEGF) to participate in tissue repair and fibrosis formation [15,17]. Sustained activation of M2 macrophages can promote renal fibrosis by inducing epithelial-mesenchymal transition (EMT) and collagen deposition. Animal studies have shown that M1 macrophages dominate in the early stage of the unilateral ureteral obstruction (UUO) model, followed by polarization to M2 macrophages that secrete TGF-β and induce interstitial fibrosis. Specific depletion of M2 macrophages significantly inhibits EMT and improves renal fibrosis [17]. Furthermore, c-Jun N-terminal kinase (JNK) signaling positively regulates M2 macrophage polarization and migration, suggesting that JNK inhibitors may serve as a novel strategy to block fibrosis [18].

Beyond macrophages, the complement system and adaptive immune responses also contribute to inflammation-mediated persistent injury. Complement components 3a and 5a (C3a, C5a) can activate endothelial cells and induce their transdifferentiation into fibroblasts, promoting renal interstitial fibrosis. In contrast, C1 inhibitor, which blocks the classical and lectin complement pathways, alleviates fibrosis in ischemia-reperfusion injury models [19]. In an ischemic AKI model using aged mice, excessive proliferation of intrarenal immune cells and sustained elevation of pro-inflammatory cytokines similarly accelerate fibrotic changes in CKD [20].

Renin–Angiotensin System (RAS) Activation

Excessive activation of the renin–angiotensin system (RAS) is recognized as one of the key molecular mechanisms underlying the transition from AKI to CKD. In the early stage of AKI, renal tubular necrosis and ischemia-reperfusion injury can induce overexpression of intrarenal RAS, leading to increased levels of angiotensin II (Ang II) [21]. Ang II binds to type 1 receptor (AT1R), causing selective constriction of efferent arterioles, increased intraglomerular pressure, and hyperfiltration. These effects subsequently trigger glomerulosclerosis and renovascular hypertension [22,23]. Meanwhile, AT1R signaling can activate pathways such as NF-κB, mitogen-activated protein kinase/extracellular signal–regulated kinase 1/2 (MAPK/ERK1/2), and TGF-β/suppressor of mothers against decapentaplegic (SMAD). This activation promotes oxidative stress and inflammatory responses, enhances fibroblast activation, and increases extracellular matrix deposition, ultimately resulting in renal tubulointerstitial fibrosis [23–25].

In addition to Ang II, aldosterone plays a key role in post-AKI fibrotic processes. It induces reactive oxygen species (ROS) production, upregulates epidermal growth factor receptor (EGFR) and AT1R expression, and activates NF-κB and activator protein-1 (AP-1) signaling pathways. These actions promote epithelial cell phenotypic transformation and the expression of profibrotic factors, such as TGF-β, connective tissue growth factor (CTGF), and plasminogen activator inhibitor-1 (PAI-1), accelerating tissue remodeling and scar formation [26].

Both animal experiments and clinical studies have confirmed that RAS blockade effectively slows renal fibrosis and functional deterioration after AKI. Rodríguez-Romo *et al*. [27] found that administration of losartan before renal blood flow restoration in ischemia-reperfusion models increases hypoxia-inducible factor-1α (HIF-1α) activity and VEGF expression, thereby improving renal perfusion and reducing hypoxia and fibrosis. Similarly, treatment with angiotensin receptor antagonists after AKI significantly reduces interstitial fibrosis and mortality in IRI mice [27,28]. Clinical studies have also shown that angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) drugs decrease the risk of AKI progression to CKD and disease progression in CKD patients [29,30]. A cohort study by Chou *et al*. [31] revealed that RAS inhibitor use during the recovery phase of post-cardiac surgery AKI significantly reduces the incidence of secondary CKD (26.6% vs 42.2%, $p = 0.005$).

Tubular Epithelial Repair Defects and Cell Cycle Arrest

After AKI, the kidney typically achieves tissue regeneration through dedifferentiation, proliferation, metabolic regulation of renal tubular epithelial cells, and inflammatory resolution. Impaired repair leads to changes, such as renal tubular atrophy, persistent inflammation, and ECM deposition, driving the progression from AKI to CKD [32]. Among these, G2/M phase arrest of renal tubular epithelial cells is recognized as a key event underlying repair failure.

Under severe ischemia, toxic exposure, or persistent inflammatory stimulation, renal tubular cells undergo DNA damage, which activates the ataxia-telangiectasia mutated (ATM)/ATM and Rad3-related (ATR) pathway. This pathway subsequently triggers G2/M phase arrest via the tumor protein p53 (p53)/cyclin-dependent kinase inhibitor 1A (p21) axis and further activates JNK signaling to promote the expression of profibrotic factors, such as TGF-β1 and CTGF [33,34]. This process forms a positive feedback loop where TGF-β1 itself can continuously induce G2/M phase arrest, further amplifying fibrotic signals [35]. The proportion of renal tubular epithelial cells undergoing G2/M phase arrest is closely correlated with the degree of fibrosis [36]. Experimental induction of G2/M arrest exacerbates renal fibrosis, while blocking this process significantly alleviates interstitial hyperplasia [33]. Furthermore, DNA damage markers, such as checkpoint kinase 1/checkpoint kinase 2 (Chk1/Chk2) (downstream of ATM/ATR) and phosphorylated histone H2AX (γ-H2AX), are significantly elevated in IRI, UUO, as well as aristolochic acid-induced renal injury, and are closely associated with the fibrotic process [37,38].

Metabolic abnormalities also contribute to this process. In the early stage of AKI, renal tubules switch from fatty acid oxidation to glycolysis to maintain energy sup-

ply. However, lactic acid accumulation can activate fibroblasts, promoting chronic inflammation and interstitial deposition [39]. When metabolic disorders coexist with G2/M phase arrest, the fibrotic process is further enhanced [40]. Moreover, metabolic remodeling of renal tubular cells and cell cycle arrest are interconnected. After AKI, cells switch from β-oxidation of fatty acids to glycolysis to meet the energy demand in the early stage of regeneration. Excessive lactic acid deposition, however, can activate fibroblasts, promote chronic inflammation and ECM production, thereby facilitating the transition from AKI to CKD [39]. If G2/M phase arrest occurs simultaneously, renal tubular epithelial cells will persist in abnormal metabolism and persistent injury response, leading to further worsening of fibrosis. Alleviating G2/M arrest and improving DNA damage response (DDR) have emerged as potential therapeutic strategies. Experimental studies have shown that p53 inhibitors, JNK inhibitors, or ATM inhibitors can reduce G2/M arrest and the expression of related profibrotic factors, thereby inhibiting renal fibrosis [35]. Simultaneously inhibiting NF-κB activation can also alleviate oxidative damage and cellular senescence [41].

Renal Tissue Ischemia and Hypoxia

Ischemia and hypoxia are recognized as key drivers of the progression from AKI to CKD. When AKI occurs, the renal microcirculation is first impaired, characterized by endothelial cell dysfunction, enhanced vasoconstriction, and decreased peritubular capillary density. This impairment leads to persistent hypoperfusion in the renal cortex and outer medulla [42]. Endothelial cell damage not only reduces nitric oxide (NO) synthesis, causes abnormal permeability, and exacerbates edema but also promotes the adhesion and infiltration of inflammatory cells. Under poor repair conditions, endothelial cells can even lose their intrinsic markers, acquire a fibroblast phenotype, migrate to the interstitium, and directly participate in fibrosis formation [19,31,43]. Vascular rarefaction caused by persistent ischemia further impairs renal oxygen supply, progressing to a chronic hypoxia and forming an irreversible vicious cycle [32].

Hypoxia not only damages endothelial cells but also directly affects highly energy-dependent renal tubular epithelial cells (TECs). Under an insufficient oxygen supply, mitochondrial dysfunction occurs, reactive oxygen species (ROS) production increases, and further loss of endothelial cells and peritubular capillaries is induced, perpetuating microcirculatory disorders [44]. Hypoxia can also upregulate miR-493 and inhibit the cell cycle regulatory protein stathmin-1 (STMN-1), inducing G2/M phase arrest and promoting the release of inflammatory cytokines, thereby aggravating the fibrotic microenvironment [45].

Hypoxia-inducible factors (HIFs) are key molecules coordinating this process. Under hypoxic conditions, HIF-1/2α escape the prolyl hydroxylase domain (PHD)–von Hippel–Lindau (VHL) degradation pathway, translocate to the nucleus, and activate the expression of downstream genes such as VEGF, erythropoietin (EPO), and glucose transporter 1 (GLUT1) [46]. Although HIFs exert certain protective effects in the early stage, sustained activation may promote fibrosis via pathways, such as TGF-β, NF-κB, or p53-G2/M arrest [47]. In addition, under hypoxic states, HIF-1α promotes the accumulation and activation of forkhead box O3 (FoxO3), while tubule-specific deletion of Hif-1α reduces hypoxia-induced FoxO3 activation, leading to exacerbated kidney injury and interstitial fibrosis following ischemia–reperfusion [48]. In recent years, HIF-PHD inhibitors such as Roxadustat have shown potential in improving hypoxia-related renal injury. By regulating HIF stability, they alleviate mitochondrial damage, inhibit inflammation and apoptosis, and promote angiogenesis via the HIF-1α/VEGFA/VEGFR1 pathway, ultimately reducing the fibrotic burden [49].

Mitochondrial Dysfunction and Autophagy Regulation

Mitochondria are the core organelles for cellular aerobic respiration and energy metabolism, and are also highly prone to damage. As a high-energy-consuming organ, the kidney's renal tubular epithelial cells are most vulnerable to mitochondrial damage during AKI [50]. This damage is characterized by reduced mitochondrial number, abnormal morphology, and decreased adenosine triphosphate (ATP) production, leading to cellular dysfunction and structural changes that ultimately drive the progression from AKI to CKD [51,52]. Peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) is a key factor regulating mitochondrial biogenesis. During AKI, PGC-1α expression is significantly downregulated, inhibiting mitochondrial generation and exacerbating renal tubular hypoxia and persistent injury [53]. Research has shown that activating PGC-1α can improve mitochondrial function and integrity, thereby alleviating renal interstitial fibrosis [54].

Typical features of mitochondrial dysfunction include increased ROS production, calcium overload, and cytochrome c release. Damaged mitochondria release molecules, such as ROS, DNA, and cardiolipin, which can activate NLR family pyrin domain containing (NLRP) receptors, upregulate pro-inflammatory factors, induce oxidative stress, inflammation, apoptosis, as well as endothelial injury, and promote persistent renal damage [52]. Nephrotoxic factors such as cisplatin can accelerate AKI and CKD progression by increasing mitochondrial ROS and disrupting the electron transport chain. Mitochondria-specific superoxide dismutase mimetics can mitigate such damage, indicating the critical role of mitochondrial oxidative stress in disease progression [55].

Autophagy is an important mechanism of cellular stress response that maintains cellular homeostasis by degrading damaged proteins and organelles. During the AKI-

to-CKD transition, autophagy exerts a bidirectional regulatory effect: moderate autophagy can clear damaged mitochondria and oxidized proteins, reduce ROS accumulation and cellular injury, and delay fibrosis [56,57]. Excessive or abnormal autophagy, however, may exacerbate renal injury and fibrosis.

Cellular Senescence and Death Regulation

AKI-induced renal injury can trigger senescence in renal tubular cells and interstitial cells, characterized by the senescence-associated secretory phenotype (SASP). Through secreting profibrotic factors such as TGF-β and IL-6, SASP promotes the sustained activation of inflammatory and fibrotic signals, accelerating the transition from AKI to CKD [58]. The expression of anti-senescence factors such as α-Klotho decreases after injury, which can enhance oxidative stress and inflammatory responses, block cellular repair, and further exacerbate senescence and tissue fibrosis [59]. Activation of the Notch signaling pathway can also promote renal tubular epithelial cell proliferation and interstitial fibrosis by upregulating senescence markers, such as p16Ink4α and p21 [60].

At the level of cell death, the imbalance between apoptosis and necroptosis induced by AKI is an important mechanism in tissue remodeling and renal fibrosis. Necroptosis is mainly mediated by the RIP1/RIP3/MLKL pathway. Its activation can enhance inflammasome activation and aggravate renal tubular injury, while blocking this pathway can significantly alleviate AKI and delay progression to CKD [61]. Additionally, ferroptosis, a form of cell death dependent on iron and lipid peroxidation, also plays a key role in renal tubular injury. The protective effect of GPX4 can inhibit iron-dependent cell death, thereby reducing fibrosis [62].

Interventional strategies targeting cellular senescence have shown potential therapeutic value. Senolytic drug combinations, such as dasatinib and quercetin, can selectively eliminate senescent cells, reduce SASP factor secretion, and thus inhibit the fibrotic process, providing an intervention window for the AKI-to-CKD transition [63]. Overall, senescence and regulated cell death pathways collectively shape the fibrotic microenvironment after renal injury, emerging as important targets for delaying or blocking the progression from AKI to CKD.

Epigenetic Regulation

Epigenetic modifications regulate the expression of fibrotic genes by influencing chromatin conformation without altering the DNA sequence, and they play a pivotal role in the transition from AKI to CKD [64]. DNA methylation, histone acetylation/deacetylation, and miRNA regulation collectively participate in the activation of inflammatory and fibrotic programs [65]. Increased levels of histone methylation and acetylation have been observed in UUO, IRI, and CKD, which are closely associated with the activation of inflammatory and fibrotic genes [64]. Dynamic changes in histone acetylation are not only correlated with the severity of AKI injury but also affect cellular adaptation to hypoxia and oxidative stress [66]. These findings suggest that chromatin accessibility is an important basis for the sustained expression of fibrotic genes. Protective genes such as Klotho undergo aberrant methylation after severe AKI, and their silencing promotes fibrosis and CKD progression. Demethylation treatment can reverse fibrosis in IRI models [67]. Furthermore, ten-eleven translocation methylcytosine dioxygenase 3 (TET3)-mediated demethylation can reverse Rasal1 methylation and suppress renal fibrosis [68], further supporting its value as a potential therapeutic target.

Multiple miRNAs are involved in epithelial-mesenchymal transition (EMT) and extracellular matrix (ECM) deposition. For instance, miR-21 promotes interstitial fibrosis following IRI and UUO [69]; the miR-29 family inhibits the expression of collagen and fibronectin, and is regarded as a typical anti-fibrotic molecule; miR-200 regulates the EMT process. Additionally, miR-192 and miR-382 have been shown to exert pathogenic or protective roles in TGF-β-related fibrotic pathways [70]. These miRNA changes reflect the elaborate epigenetic hierarchy of fibrotic gene transcriptional regulation.

In models of renal fibrosis and chronic kidney disease, studies and reviews have indicated that long non-coding RNAs (lncRNAs) can serve as molecular bridges, linking DNA methylation, histone acetylation/methylation, RNA methylation, and other non-coding RNA-mediated regulatory mechanisms. Through this crosstalk, lncRNAs enable multilayered regulation of fibrosis- and inflammation-related genes, including those involved in extracellular matrix (ECM) remodeling, TGF-β signaling, and cell cycle control [71]. *In vivo* experiments using folic acid-induced renal fibrosis models have demonstrated that combined treatment with the DNA methyltransferase inhibitor 5-aza-2′-deoxycytidine (5-Aza-dC) and the histone deacetylase inhibitor trichostatin A (TSA) can effectively reverse aberrant ECM and epithelial–mesenchymal transition (EMT) gene expression and ameliorate tissue fibrosis [72]. These findings suggest that future epigenetic therapeutic strategies for AKI-to-CKD transition should transition beyond single-mechanism interventions toward multi-layered epigenetic reprogramming, aiming to restore protective gene expression while suppressing pro-fibrotic and pro-inflammatory networks.

Core Signaling Hubs: Integration of Multi-Pathway Networks in AKI–CKD Transition

During the AKI-to-CKD transition, disparate injury signals converge through core hubs such as TGF-β, NF-κB, and p53, amplifying the cascade from injury to fibrosis. These hubs integrate upstream stimuli, including inflammation, hemodynamic dysregulation, and metabolic stress, and their interplay drives irreversible fibrosis. TGF-β1 acti-

vates ECM gene expression via canonical Smad2/3-Smad4 signaling and non-Smad pathways (e.g., ROS, MAPK, Janus kinase [JAK]/STAT), intersecting with inflammatory, metabolic, and oxidative stress pathways to promote fibroblast activation, EMT, and microvascular rarefaction [73,74]. NF-κB acts as an amplifier of inflammation and oxidative stress, reinforcing immune cell infiltration and ROS production in a vicious cycle that perpetuates tubular-interstitial injury and fibrosis [75,76]. p53, a central regulator of DNA damage response, is activated by hypoxia, metabolic dysregulation, or oxidative stress. The p53–Smad3 complex drives transcription of pro-fibrotic genes (e.g., plasminogen activator inhibitor-1 [PAI-1], connective tissue growth factor [CTGF]), induces G2/M cell cycle arrest, and promotes SASP in tubular epithelial cells, reducing regenerative potential and enhancing ECM accumulation [76,77]. Thus, in AKI-to-CKD progression, diverse injury mechanisms—ischemia, inflammation, metabolic/oxidative stress, and immune activation—do not act in isolation but converge through TGF-β1, NF-κB, and p53 hubs, forming an integrated network that leads to irreversible fibrosis and renal function loss. This network perspective explains the limited efficacy of single-target interventions and supports multi-target, multi-node therapeutic strategies.

Collectively, these sections delineate the central mechanisms of AKI-to-CKD transition along a logical chain of "inflammation initiation–RAS activation–repair impairment–fibrosis consolidation" and highlight core signaling hubs as integrative nodes linking upstream insults to downstream fibrotic outcomes, providing theoretical grounding for future multi-target interventions.

Therapeutic Intervention Windows and Strategies

Early Intervention Window: Anti-Inflammatory & Anti-Oxidative Phase

The therapeutic goal in the early stage of AKI is to alleviate excessive inflammatory responses and oxidative stress and protect the functions of renal tubular epithelial cells and vascular endothelial cells. Typical strategies include the use of drugs that scavenge free radicals and inhibit inflammatory pathways. Ligustrazine can scavenge excessive ROS, exert significant anti-inflammatory and antioxidant effects, and protect endothelial cells by stabilizing mitochondrial function and regulating autophagy [78], thereby effectively preventing AKI. Ligustrazine injections have been used as adjunctive therapy for chronic kidney disease in parts of China and have been shown to attenuate renal interstitial fibrosis in animal models [79,80], suggesting potential to delay the progression from acute kidney injury to chronic kidney disease. Pachymic acid A can also significantly reduce the levels of inflammatory factors such as TNF-α and IL-6 in acutely injured renal tissue, and enhance cellular protection by activating the nuclear factor erythroid 2–related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) antioxidant pathway [81]. Additionally, melatonin is well-known for its endogenous antioxidant and immunomodulatory effects, which can downregulate NF-κB and NLRP3 inflammasome signaling, thereby reducing the expression of pro-inflammatory proteins [82]. In rat models, melatonin, pachymic acid A, and their combination have been shown to significantly reduce elevated serum creatinine and blood urea nitrogen levels, protect renal tubular epithelial cells (TECs), improve renal fibrosis and podocyte injury, and alleviate renal tubular dilation, interstitial inflammatory infiltration, and collagen deposition [83]. Therefore, the combination of melatonin and pachymic acid A is a promising therapeutic regimen for preventing the transition from AKI to CKD.

Epigenetic regulation, such as targeting histone deacetylases (HDACs), has emerged as a promising strategy in the early phase of AKI, capable of reducing apoptosis, suppressing inflammation, and promoting tubular autophagy and proliferation, thereby mitigating acute injury and potentially preventing progression to CKD. In murine I/R and folic acid-induced AKI models, the selective class IIa HDAC inhibitor 2-(4-(Dimethylamino)phenyl)-N-(1,3-thiazol-2-yl)acetamide (TMP269) significantly improved renal function, decreased apoptosis, and enhanced H3 acetylation and autophagy markers, indicating that increased histone acetylation facilitates repair [84]. Similarly, the pan-HDAC inhibitor Trichostatin A (TSA) has been shown to expand regulatory T cells and attenuate inflammatory responses in I/R-AKI, supporting HDAC inhibitors' immunomodulatory and anti-inflammatory roles [85]. Moreover, antagonism of miR-155 (AntagomiR-155) reduces renal TNF-α and IL-6 levels, upregulates suppressor of cytokine signaling 1 (SOCS1), inhibits apoptosis and necrotic pathways, and markedly improves renal function and histological injury [86,87].

Targeting mitochondrial damage and oxidative stress, which are common in AKI, the use of regimens focusing on mitochondrial protection and activation of endogenous antioxidant pathways is of great importance. For example, the senolytic combination of dasatinib + quercetin can eliminate senescent cells and indirectly improve the cellular oxidative microenvironment. Studies have reported that this combination can selectively clear Inhibitor of cyclin-dependent kinase 4a (p16^INK4a)-positive renal senescent cells, reduce fibrosis, and improve renal function [5]. Additionally, drugs emphasizing the activation of antioxidant pathways such as Nrf2 are under exploration.

The role of the gut-kidney axis in AKI-CKD progression has attracted increasing attention. Regulating gut microbiota can affect immune responses and fibrotic pathways through its metabolites (e.g., short-chain fatty acids). Several animal studies have shown that depletion of gut microbiota with broad-spectrum antibiotics can significantly al-

ter the intrarenal immune environment: for instance, Emal *et al*. [88] found that antibiotic treatment reduced markers of mature macrophages in mouse kidneys and significantly alleviated ischemia-reperfusion injury; a study by Yang *et al*. [89] also demonstrated that oral antibiotics reduced T helper 1 (Th1) and T helper 17 (Th17) cell responses and increased regulatory T cells, similarly mitigating renal ischemia/reperfusion injury. However, current research results on microbiota intervention are inconsistent, and there are significant differences in drug types, doses, and administration durations among different studies. More experiments are needed to determine the optimal antibiotic type, dose, and duration for preventing the transition from AKI to CKD [90].

Intermediate Window: Anti-Fibrotic & Pro-Repair Phase

The therapeutic focus at this stage is to inhibit profibrotic pathways and promote tissue repair. Core mechanisms include blocking TGF-β/Smad signaling, reducing extracellular matrix (ECM) remodeling, and facilitating normal tissue regeneration. Blocking the renin-angiotensin-aldosterone system (RAAS) is a classic antifibrotic strategy, which reduces the production of fibrotic factors by inhibiting the Ang II–TGF-β axis [91]. Commonly used drugs include ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). RAAS inhibitors such as ACEIs/ARBs are not recommended in the acute phase of AKI to avoid exacerbating hemodynamic injury, but long-term administration during the recovery phase can yield benefits. Meta-analyses have shown that continued use of ACEIs/ARBs after AKI recovery significantly reduces the risks of all-cause mortality, recurrent AKI, and CKD progression [30]. Correspondingly, therapeutic intervention requires close monitoring of hyperkalemia and hypotension risks, with dosage adjustments as needed.

Addressing DNA methylation abnormalities, inhibition of DNA methyltransferases (e.g., 5-aza-2′-deoxycytidine/5-Aza) or DNMT1 knockdown can reverse hypermethylation of the Klotho promoter, restore Klotho transcription and protein expression, and ameliorate renal injury outcomes. Preclinical studies have demonstrated that low-dose 5-Aza upregulates Klotho and exerts renal protective effects [92–94]. Selective class IIa HDAC inhibitors (e.g., MC1568, TMP269) have further shown efficacy in renal injury and fibrosis models by inhibiting TGF-β/Smad3 signaling, preserving Smad7 and Klotho expression, and reducing ECM synthesis. Partial HDAC subtype inhibition restores Smad7 transcription, thereby enhancing suppression of TGF-β/Smad signaling and attenuating fibrosis [95,96]. miR-155 also interacts with anti-inflammatory molecules such as SOCS1, and its sustained dysregulation may drive chronic inflammation and fibrosis. Intervention targeting miR-155 (or upregulating SOCS1) during chronic or compensatory phases has been shown in animal models to reduce inflammation and fibrosis-related signaling, highlighting its potential as a long-term therapeutic strategy to block AKI-to-CKD transition [97].

Experimental studies have further demonstrated that exogenous antithrombin III can effectively alleviate renal injury after IRI and delay post-AKI renal fibrosis in mice by inhibiting fibrogenesis and inflammatory processes [98]. Antithrombin III also promotes endothelial cell release of prostacyclin, a potent vasodilator that improves renal microcirculation and reduces hypoxia [99]. As a HIF stabilizer, Roxadustat significantly mitigates renal interstitial fibrosis in ischemia/reperfusion AKI models. Its mechanism may involve enhancing renal tubular regeneration, inhibiting ferroptosis and inflammation via Protein kinase B (Akt)/Glycogen synthase kinase-3 beta (GSK-3β)-mediated Nrf2 pathway activation, thereby reducing fibrin deposition [100]. Lactoferrin has also been confirmed to inhibit early post-AKI fibrosis: in a vicine-induced AKI-CKD model, lactoferrin administration restored renal function and further alleviated fibrosis by inducing autophagy and inhibiting epithelial cell apoptosis [101].

Huaier, a polypore fungus parasitic on locust trees, has been shown to attenuate kidney injury and fibrosis. The mechanism by which Huaier extract delays the transition from AKI to CKD remains unclear, but research suggest that it may mitigate AKI by inhibiting apoptosis and upregulating miR-1271, thereby reducing Glucose-regulated protein 78 and C/EBP homologous protein (CHOP) expression [102].

The recombinant human serum albumin-thioredoxin fusion protein (HSA-Trx) is a long-acting fusion protein of human serum albumin and thioredoxin-1. It significantly alleviates renal tubular dilation, reduces the mRNA expression of Kidney injury molecule-1 (KIM-1) in renal tissue, and exerts anti-renal fibrosis effects. These effects may be associated with inhibiting renal tubular G2/M phase arrest and apoptosis, and mitigating the decline in endogenous thioredoxin-1 levels [81]. HSA-Trx can also reduce renal oxidative stress and inflammatory responses [103]. The anti-TNF biological agent etanercept exerts anti-inflammatory and anti-fibrotic effects during the AKI-to-CKD transition by blocking TNF released by immune cells. It can effectively prevent post-AKI renal fibrosis, reducing renal fibrosis by an average of approximately 25% [104]. Protease-activated receptor-1 (PAR-1) is a key profibrotic factor in the kidney. PAR-1 activation leads to ECM deposition in the renal interstitium and induces epithelial-mesenchymal transition. The PAR-1 antagonist vorapaxar has anti-fibrotic potential: it significantly alleviates renal injury and reduces capillary loss and the expression of vascular endothelial cell adhesion molecules during the AKI-to-CKD transition [105].

Exosomes are extracellular vesicles with a diameter of 40–160 nm, which exert regulatory effects mainly

through their contents. They possess regenerative, anti-inflammatory, and anti-fibrotic capabilities, with biological activity not significantly associated with their source. Macrophage-derived exosomes can reduce macrophage infiltration and improve mitophagy, thereby delaying the AKI-to-CKD transition [106]. Red blood cell-derived exosomes loaded with KIM-1 have also been shown to retard the AKI-CKD process. Adipose-derived mesenchymal stem cells promote renal tubular regeneration and alleviate AKI injury and post-AKI renal fibrosis via exosomes [107]. This provides a novel therapeutic model for the transition from AKI to CKD.

Late Intervention Window: Regeneration & Anti-Senescence Strategies

In the late stage of the AKI-CKD progression, tissue fibrosis is prominent and the self-repair capacity of renal tubules is limited. As a result, eliminating senescent cells and improving metabolic status have emerged as potential therapeutic approaches. The classic senolytic strategy involves the use of drug combinations capable of clearing senescent cells: for example, the dasatinib + quercetin combination has been confirmed to selectively eliminate p16^INK4a-positive senescent cells, thereby reducing fibrosis and protecting renal function [108]. Animal studies indicate that late-phase application of senolytics improves fibrosis outcomes; however, efficacy is highly dependent on dosing window and model type, requiring careful consideration of safety and timing [63]. Restoration of cellular energy and Nicotinamide adenine dinucleotide (NAD^+) metabolism (e.g., supplementation with Nicotinamide mononucleotide [NMN] or Nicotinamide riboside [NR]) suppresses DNA damage responses, reduces tubular cell senescence markers, and alleviates post-ischemic fibrosis, as validated in Unilateral ischemia-reperfusion injury (uIRI) and interstitial fibrosis animal and cellular models, highlighting the feasibility of metabolic regeneration strategies for late-stage repair [109]. Locus-specific epigenome editing can target demethylation or "unsilencing" of key protective genes; for instance, dCas9-TET3CD-mediated targeting of Rasal1 or Klotho promoters restores gene expression and markedly reduces renal fibrosis, demonstrating the potential of reversible, site-specific epigenetic interventions in late-stage fibrosis [110].

Based on these mechanistic insights, a rational combinatorial approach involves: an initial short-term, intermittent senolytic "clearance" to remove SASP sources and reduce inflammatory and pro-fibrotic stimuli; followed by or concurrent administration of NAD^+ precursors or other metabolic/repair-supportive agents to enhance DNA repair and regenerative capacity of residual cells; ultimately combined with locus-specific epigenetic interventions (or small-molecule DNA methyltransferase inhibitor (DNMTi)/Histone deacetylase inhibitor (HDACi), miRNA-based anti-fibrotic therapies) to reverse established fibrotic gene silencing and resolve persistent ECM deposition. This "clear–support–reprogram" framework has been partially validated in animal and conceptual studies, yet optimal timing, dosing, sequence, and long-term safety require systematic evaluation in AKI-to-CKD animal models and preclinical research [63,109].

Collectively, this chapter establishes a temporally stratified intervention framework for AKI-to-CKD progression: early anti-inflammatory and antioxidant therapy, mid-phase anti-fibrotic and reparative strategies, and late-phase anti-senescence and regenerative interventions. The core innovation lies in integrating epigenetic modulation with conventional pharmacotherapy, proposing a "signaling-hub targeting plus epigenetic reprogramming" synergistic strategy. Current challenges include insufficient temporal precision (reliance on traditional markers fails to capture mechanistic transitions), low drug delivery efficiency (limited penetration through fibrotic barriers), and overlooked inter-individual variability (lack of etiology-stratified approaches). Future efforts should focus on developing mechanism-guided biomarker panels, designing intelligent, responsive drug delivery systems, and conducting etiology-stratified adaptive clinical studies to achieve precise "cause–mechanism–intervention" matching and accelerate translation from basic research to clinical application.

Clinical Challenges and Future Directions

Differences in the etiologies of AKI (ischemia, toxicity, infection, surgery-related, etc.) and patient baselines (age, pre-existing CKD, comorbidities) underlie significant heterogeneity in pathological processes and repair capacities. Thus, the efficacy of the same intervention often varies across patients with AKI of different etiologies, making it difficult to guide clinical practice with a single time window or uniform regimen. Studies have pointed out that due to inconsistent endpoint definitions and follow-up time windows, research findings on AKI-to-CKD progression are highly heterogeneous, limiting the generalizability of evidence [111]. Currently, biomarkers used for AKI risk stratification and early injury detection (e.g., urinary KIM-1, Neutrophil gelatinase-associated lipocalin [NGAL], Tissue inhibitor of metalloproteinases-2 [TIMP-2]×Insulin-like growth factor-binding protein 7 [IGFBP7]) have been applied in the early diagnosis of AKI. However, their performance in identifying "early fibrosis" or predicting long-term progression to CKD remains inadequate and inconsistent across different cohorts. Existing systematic reviews indicate that while several biomarkers are valuable for short-term prognosis, there is a lack of widely accepted long-term fibrosis predictors that can directly guide "intervention windows" in clinical decision-making [112].

Common animal models (unilateral ureteral obstruction, ischemia-reperfusion, drug toxicity, etc.) can reveal molecular pathways but differ significantly from human

AKI in terms of etiological complexity, immune responses, renal scale, and comorbidities. This has led to the failure of many targeted strategies effective in animals to replicate efficacy in human clinical trials. Reviews emphasize the need to interpret animal data cautiously and develop models with greater human relevance [113].

Clinical studies vary greatly in the selection of outcomes (e.g., definition of "recovery" or "CKD progression") and observation windows (30 days, 90 days, 1 year, etc.). This causes result heterogeneity, reduces the comparability of different intervention effects, and hinders the development of evidence-based guidelines [111]. Integrating clinical variables, laboratory indicators, and urine/blood biomarkers with machine learning can significantly improve the prediction accuracy of adverse outcomes, including long-term CKD and End-stage kidney disease (ESKD). Systematic reviews have shown that machine learning-based prediction models outperform traditional scoring systems in AKI outcome prediction; the next step requires rigorous external validation and prospective clinical deployment [114]. Recent studies demonstrate that spatial transcriptomics can reveal the enrichment and interaction of specific cell populations (e.g., activated fibroblasts, senescent epithelial cells) at fibrotic sites, providing molecular evidence for time-sequential interventions [115]. Integrating single-cell/spatial transcriptomics, metabolomics, epigenomics, and proteomics can dissect the spatiotemporal progression of fibrosis at the level of cell types and tissue microenvironments, identifying early, reversible pathological nodes and druggable targets. Given that AKI-to-CKD progression is a long-term process, multi-center, large-sample, long-term follow-up randomized controlled trials are needed to verify the long-term benefits and safety of time-sequential interventions (e.g., ACEI/ARB use during recovery, early anti-inflammatory/mitochondrial-targeted therapy, late-stage senolytics). Simultaneously, establishing an open multi-omics-clinical database will support the validation of prediction models and biomarkers [116].

The marked heterogeneity among patients and etiologies implies that individuals differ fundamentally in injury type, inflammatory response intensity, fibrosis progression, and regenerative capacity, making fixed intervention timelines insufficiently applicable across the AKI population. To enable precise and tailored therapeutic strategies, future studies must prioritize AKI phenotyping and endotyping. Such stratification could integrate multi-dimensional characteristics, including injury etiology (ischemic, toxic, or infection/inflammation-driven), immune-metabolic status, cellular senescence burden, fibrosis activity, and markers of recoverability, thereby defining subgroups with predictable structural and functional trajectories. Crucially, these phenotypes and endotypes can be directly linked to "personalized intervention windows". For instance, an inflammation-dominant endotype may benefit most from early anti-inflammatory therapy; a mitochondrial dysfunction endotype could preferentially respond to early metabolic or mitochondria-targeted interventions; whereas endotypes with high senescence burden or active fibrosis may require late-phase strategies such as senolytics or epigenetic reprogramming. Advancing stratification research will not only improve comparability and success rates in clinical trials but also provide the foundation for an actionable "time + biology window" therapeutic framework, ultimately shifting AKI-to-CKD management toward a truly individualized, predictable, and controllable precision medicine approach.

Conclusion

The transition from acute kidney injury to chronic kidney disease is a dynamic, multifactorial process. In this process, inflammation, microvascular rarefaction, epithelial-mesenchymal transition, senescence, metabolic reprogramming, and epigenetic dysregulation collectively shape the trajectory of renal repair versus fibrosis. Despite significant progress in describing the cellular and molecular landscape of this transition, the clinical translation of these mechanistic insights remains challenging.

From early anti-inflammatory and antioxidant strategies to intermediate anti-fibrotic and pro-repair approaches, and finally to late-stage regenerative and anti-senescence therapies, the identification of intervention windows provides a temporal framework for precision treatment. However, the heterogeneity of AKI etiologies, the lack of reliable biomarkers for early fibrosis, and the limited translational relevance of traditional animal models continue to hinder the identification of optimal treatment timings and patient stratification.

Future research needs to integrate multi-omics, spatial transcriptomics, and machine learning-based prediction models to capture patient-specific disease trajectories and define personalized intervention windows. These approaches, combined with refined preclinical models and well-designed longitudinal clinical trials, are crucial for translating mechanistic discoveries into effective, personalized strategies to prevent CKD progression after AKI.

Availability of Data and Materials

Not applicable.

Author Contributions

XY and SK conceived the study and defined the overall research framework and intellectual content. SK supervised the entire review process and coordinated contributions from all authors. LF performed the systematic literature search and selection of relevant publications. LM, LT, LH, and YM contributed to data extraction, interpretation of the literature, and thematic synthesis of evidence. LH and YM were responsible for methodological appraisal and

qualitative analysis of the included studies. the included studies. TL and LZ made contributions to the organization of the extracted data and the interpretation of the research, and drafted the first draft of the manuscript. LZ, together with XY and SK, critically revised the manuscript for important intellectual content. All authors participated in the critical revision of the manuscript, provided critical feedback, and contributed to refining the scientific arguments and interpretation. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

The work was supported by the National Natural Science Foundation of China (NSFC) Project, Grant No. 82174366.

Conflict of Interest

The authors declare no conflict of interest.

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