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Recent Advances in Chronic Renal Failure: A Review of Integrated Traditional Chinese and Western Medicine Perspectives

Zilong Yan[1], Yun Tian[2,*]

[1]First Clinical Medical College of Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Shaanxi Provincial Hospital of Chinese Medicine, Xi'an 710003, Shaanxi, China
Correspondence Author

Abstract: ***Chronic renal failure (CRF), the common end-stage outcome of progressive chronic kidney diseases, is characterized by irreversible decline in glomerular filtration rate and multisystem complications. With over 840 million affected individuals worldwide, CRF poses a major public health challenge. In recent years, mechanistic research on CRF has expanded from traditional hemodynamic abnormalities and fibrotic drivers to encompass immunoinflammatory regulation, mitochondrial energy metabolism reprogramming, and gut-kidney axis dysbiosis. Biomarker studies have focused on the value of tubular injury markers (KIM-1, NGAL) and inflammatory mediators (TNF-α, IL-6) in early diagnosis and prognostic assessment. In terms of therapeutic strategies, accumulating evidence supports the use of SGLT2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists, and GLP-1 receptor agonists, while traditional Chinese medicine interventions—including rhubarb preparations, Cordyceps mycelial products, and blood-activating and stasis-resolving formulas—have garnered increasing attention for their adjunctive roles in slowing renal function decline. This review systematically synthesizes these advances and critically evaluates current research bottlenecks and translational prospects, aiming to inform clinical decision-making and future investigations.***

Keywords: Chronic renal failure, Renal function progression, SGLT2 inhibitors; Gut-kidney axis**.**

1. Introduction

Chronic renal failure (CRF) represents the end-stage pathological state resulting from the progressive advancement of various primary or secondary kidney diseases, including IgA nephropathy, diabetic kidney disease (DKD), hypertensive nephrosclerosis, and lupus nephritis. It is characterized by progressive decline in glomerular filtration rate (GFR), accumulation of metabolic wastes, and electrolyte disturbances. The global prevalence of chronic kidney disease (CKD) is estimated at approximately 9.1%, with a substantial proportion progressing to CRF [1]. Cross-sectional surveys in China indicate a CKD prevalence of 10.8% among adults, yet awareness remains dismally low at 12.5%, underscoring the heavy disease burden [2]. CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health; staging is based on GFR categories ranging from G1 (≥90 mL/min/1.73m²) to G5 (<15 mL/min/1.73m²) [3].

Over the past decade, the management paradigm for CRF has undergone a profound transition from "single-target intervention" to "multi-mechanism coordinated management." Renin-angiotensin-aldosterone system (RAAS) inhibitors have long served as the cornerstone of standard therapy; however, their capacity to retard renal function decline remains limited. The advent of sodium-glucose cotransporter 2 (SGLT2) inhibitors has broken this therapeutic impasse—multiple large-scale outcome trials have demonstrated that these agents reduce the risk of renal function deterioration by approximately 30%–40% in CKD populations, independent of diabetic status, with benefits extending beyond glycemic control [13,15]. Concurrently, basic research has elucidated the driving roles of inflammasome activation, mitochondrial oxidative stress, and gut microbiota dysbiosis in renal fibrosis, providing a theoretical foundation for developing novel anti-inflammatory and microbiome-modulating strategies [4,7].

Traditional Chinese medicine (TCM) has accumulated substantial experience in CRF treatment, showing potential advantages in symptom improvement, delayed dialysis initiation, and enhanced quality of life [20]. Nevertheless, the scarcity of high-quality evidence constrains its international dissemination and acceptance. This review synthesizes key advances in CRF research over the past five years, spanning basic mechanisms to clinical translation, with particular emphasis on the potential for synergistic integration of TCM and Western medicine, and offers perspectives on unresolved scientific questions.

2. Novel Insights into Pathophysiological Mechanisms

2.1 Refinement of Classical Mechanisms: Hemodynamics and Fibrosis

The core drivers of CRF progression include glomerular hyperfiltration, podocyte injury, and tubulointerstitial fibrosis. Sustained glomerular capillary hypertension continuously activates the RAAS, leading to overexpression of transforming growth factor-β (TGF-β) and subsequent initiation of Smad-dependent fibrotic signaling cascades. However, RAAS blockade alone only partially retards fibrotic progression, suggesting the existence of alternative compensatory pro-fibrotic pathways.

Autophagy dysregulation has emerged as a focal point of recent investigation. Under chronic hypoxia and proteinuria overload, renal tubular epithelial cells exhibit a biphasic autophagic response—initially compensatory enhancement, followed by progressive exhaustion, resulting in accumulation

of damaged mitochondria and misfolded proteins, with consequent release of damage-associated molecular patterns (DAMPs) that activate innate immune responses. Podocyte autophagy deficiency has been confirmed to accelerate the transition from DKD to overt CRF.

2.2 Inflammatory and Immune Mechanisms: The Central Role of the NLRP3 Inflammasome

The NLRP3 inflammasome functions as a critical sensor of innate immunity and plays a pivotal role in CRF progression [4]. Hyperglycemia, oxidized lipids, uric acid crystals, and uremic toxins can all induce NLRP3 oligomerization within renal tubular epithelial cells and macrophages, recruiting ASC and activating caspase-1, which subsequently cleaves pro-IL-1β and pro-IL-18 into mature inflammatory cytokines, thereby mediating sterile intrarenal inflammation. Recent studies have further revealed that NLRP3 can execute pyroptosis—a pro-inflammatory form of programmed cell death—via the GSDMD protein, resulting in direct nephron loss [5]. Small-molecule NLRP3 inhibitors (e.g., MCC950, OLT1177) have demonstrated anti-fibrotic effects in animal models, with clinical trials currently underway. Notably, Astragaloside IV, a bioactive compound derived from Astragalus membranaceus, has been shown to improve DKD by regulating NLRP3 inflammasome activation, suggesting potential TCM-derived therapeutic candidates targeting this pathway [6].

2.3 Emerging Dimensions: The Gut-Kidney Axis and Energy Metabolic Reprogramming

The conceptualization of the gut-kidney axis has opened novel avenues for understanding CRF pathophysiology [7]. In the CRF state, increased intestinal barrier permeability allows lipopolysaccharide (LPS) to enter the portal circulation, activating systemic microinflammation. Concurrently, overgrowth of urease-positive bacteria increases intestinal ammonia production, further exacerbating epithelial injury. Aberrant levels of key metabolites—short-chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO)—have been documented; SCFAs are associated with anti-inflammatory regulatory T-cell (Treg) differentiation, whereas TMAO directly promotes renal interstitial fibrosis. Recent studies have also highlighted the role of D-amino acids in gut-kidney communication and their potential renoprotective effects [8]. Modulating the gut microbiome (e.g., probiotics, fecal microbiota transplantation) has emerged as a potential therapeutic strategy.

Regarding energy metabolic reprogramming, the failing kidney in CRF exhibits impaired fatty acid oxidation (FAO) and compensatory enhancement of glycolysis, the latter generating substantial lactate and reactive oxygen species (ROS) that drive phenotypic transition of tubular epithelial cells toward myofibroblasts. Downregulation of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) is recognized as an upstream event in FAO impairment. Agents targeting metabolic remodeling (e.g., acetyl-CoA carboxylase inhibitors) are currently in preclinical development.

3. Biomarker Research Advances

3.1 Tubular Injury Biomarkers

Traditional renal function assessment relies on serum creatinine and estimated GFR (eGFR), both of which have substantial limitations in early-stage CRF and populations with altered muscle mass. The following tubular injury biomarkers have recently gained extensive validation: kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and liver-type fatty acid-binding protein (L-FABP) [9]. KIM-1, shed from the proximal tubular brush border, serves as an early sensitive indicator of ischemic and toxic injury, with urinary levels correlating positively with interstitial fibrosis severity. NGAL, originating from distal tubules and collecting ducts, functions both as a predictor of transition from acute kidney injury to CRF and as a direct pro-fibrotic mediator [10]. L-FABP, expressed in proximal tubular cytoplasm, reflects oxidative stress burden and predicts the rate of renal function decline in DKD.

Multiple prospective cohort studies have demonstrated that combined detection of KIM-1 and NGAL improves the predictive accuracy for dialysis initiation within 5 years in stage 3 CKD patients compared to using eGFR or urinary albumin-to-creatinine ratio (UACR) alone. Furthermore, emerging biomarkers such as serum Irisin have shown correlations with NGAL, KIM-1, and L-FABP in hemodialysis patients, suggesting broader panels for tubular injury assessment [11].

3.2 Inflammatory and Fibrosis-Related Biomarkers

Serum and urinary levels of inflammatory mediators dynamically reflect the intrarenal immune microenvironment. TNF-α and IL-6 not only drive fibrosis as pro-inflammatory cytokines but also serve as independent risk factors for cardiovascular events and all-cause mortality in CKD patients. Among fibrotic markers, TGF-β1 has limited clinical applicability due to assay stability constraints; sST2 (soluble suppression of tumorigenicity 2), a decoy receptor for IL-33, has recently been reported to predict rapid CKD progression, offering dual indicative value for both inflammation and fibrosis.

3.3 The Concept of Renal Functional Reserve and Its Clinical Translation

Renal functional reserve (RFR) refers to the additional filtration capacity that the kidneys can recruit above basal levels in response to external loads (e.g., high-protein diet or dopamine stimulation) [12]. RFR decline occurs prior to eGFR reduction, making it an ultra-early sensitive indicator of renal functional impairment. Studies have shown that in patients with type 2 diabetes, loss of RFR predicts an eGFR decline ≥30% within 3 years with 82% sensitivity and 76% specificity. Although standardized RFR testing protocols (protein loading or dopamine methods) have not yet been universally established, the translational potential of this concept merits attention, particularly for early screening of high-risk populations [12].

4. Therapeutic Strategy Advances

4.1 Western Pharmacotherapy: From RAAS Inhibitors to

Multi-Target Era

SGLT2 inhibitors represent the most significant breakthrough in CRF pharmacotherapy over the past decade. The DAPA-CKD trial demonstrated that addition of dapagliflozin to RAAS inhibitor background therapy reduced the risk of the primary composite endpoint (≥50% eGFR decline, end-stage kidney disease, or renal death) by 39% in CKD patients, regardless of diabetic status [13]. Similar renoprotective effects were observed with canagliflozin in the CREDENCE trial, with post-hoc analyses revealing additional benefits in insulin-sparing effects among patients with type 2 diabetes and CKD [14]. A large-scale meta-analysis by the SMART-C Collaborative Group, encompassing 58,816 patients across multiple trials, conclusively confirmed that SGLT2 inhibitors confer kidney and heart benefits across all CKD patients irrespective of diabetes status [15]. The renoprotective mechanisms extend beyond glycemic control—they involve reduction of intraglomerular pressure via tubuloglomerular feedback, attenuation of proximal tubular oxygen consumption with improved renal cortical oxygenation, and inhibition of NLRP3 inflammasome activation through multiple pathways.

Nonsteroidal mineralocorticoid receptor antagonists (nsMRAs), particularly finerenone, have demonstrated in the FIDELIO-DKD trial the ability to reduce the primary composite renal outcome by 18% in patients with type 2 diabetes and CKD when added to RAAS inhibitors, with a lower incidence of hyperkalemia compared to the traditional MRA spironolactone [18]. More recently, the Phase III FINE-ONE trial reported that finerenone achieved a 25% reduction in UACR compared to placebo in patients with type 1 diabetes and CKD ($p=0.0001$), expanding the evidence base to type 1 diabetes populations [19].

GLP-1 receptor agonists—semaglutide in particular—in the FLOW trial (reported in 2024) showed a reduction in the renal composite endpoint by approximately 24% in patients with diabetes and CKD, with mechanisms likely involving anti-inflammatory effects and improved glomerular hemodynamics [16]. Comparative reviews have highlighted the complementary mechanisms of SGLT2 inhibitors and GLP-1 receptor agonists, suggesting potential synergistic benefits when used in combination [17]. This agent is poised to become another milestone therapy following the SGLT2 inhibitor class.

4.2 Traditional Chinese Medicine Interventions

TCM has a long-standing history in CRF management. Commonly employed therapeutic approaches and agents include:

Rhubarb (Rheum palmatum) and its preparations: Rhein, the active anthraquinone derivative, inhibits renal tubular epithelial cell proliferation and TGF-β1 expression, promotes intestinal urea excretion, and reduces blood urea nitrogen (BUN) levels. Rhubarb-containing retention enema formulations have been incorporated into multiple TCM nephrology guidelines as adjunctive therapy for non-dialysis-dependent stage 3–5 CRF patients.

Cordyceps mycelial preparations (e.g., Bailing capsules, Jinshuibao capsules): Experimental studies indicate that these products attenuate renal tubular epithelial cell apoptosis and oxidative stress. Clinical studies have shown delayed eGFR decline in patients with DKD and chronic glomerulonephritis.

Blood-activating and stasis-resolving formulas (e.g., Astragalus-Salvia combinations, Shenshuaining capsules): Grounded in the TCM theory of "prolonged disease entering the collateral vessels," these formulas act through improved renal microcirculation, inhibition of platelet aggregation, and anti-fibrotic effects.

A recent single-center, randomized, open-label, controlled trial evaluated the efficacy and safety of Chaihuang Tongluo (CHTL) oral liquid in patients with CKD stages 1–3 [20]. The results demonstrated that CHTL combined with standard therapy significantly improved the eGFR slope by 2.41 mL/min/1.73m² compared to standard therapy alone ($p<0.001$), with a favorable safety profile [20]. Several systematic reviews suggest that integrated TCM-Western medicine approaches confer advantages over Western medicine alone in reducing proteinuria, ameliorating renal anemia, and delaying dialysis initiation. However, most studies are limited by small sample sizes and methodological quality concerns.

4.3 Dietary and Microbiome Interventions

Very low-protein diets (0.3–0.4 g/kg/day) combined with ketoacid analogues alleviate glomerular hyperfiltration and reduce uremic toxin generation, with a relatively robust evidence base for slowing CRF progression. Probiotic/ synbiotic preparations, through modulation of gut microbial composition, reduction of TMAO production, and restoration of intestinal barrier function, have shown in preliminary clinical studies the capacity to lower circulating endotoxin and inflammatory cytokine levels [7,8]; however, their effects on hard endpoints (eGFR decline or dialysis) await confirmation. Fecal microbiota transplantation (FMT) has demonstrated unequivocal renoprotective effects in animal studies, but clinical application remains in exploratory stages.

5. Challenges and Future Directions

Despite considerable advances, the CRF field continues to face several critical challenges:

First, the issue of inter-individual variability in therapeutic benefit. Clinical trials of SGLT2 inhibitors and nsMRAs indicate that patients with very low baseline eGFR (<25 mL/min/1.73m²) derive unclear benefits, and some patients discontinue therapy due to gastrointestinal adverse effects or hyperkalemia [13,18]. Achieving precision patient stratification to optimize the benefit-risk ratio urgently requires integration of multi-omics biomarkers to guide therapeutic decisions.

Second, bottlenecks in TCM modernization and internationalization. The paucity of high-quality, large-scale, multicenter RCTs has precluded inclusion of TCM evidence in international guidelines (e.g., KDIGO) [20]. Future efforts

should focus on: (1) elucidating the active chemical constituents and molecular targets of TCM formulas, as exemplified by Astragaloside IV-NLRP3 pathway research [6]; (2) designing internationally acceptable placebo-controlled trials; and (3) defining the optimal timing and duration of combined TCM-Western therapy.

Third, the absence of early screening systems. The majority of CKD patients are diagnosed at stage 3 or beyond, having missed the optimal window for intervention. Integrating RFR testing [12], novel urinary biomarkers (e.g., KIM-1, NGAL) [9,10], and artificial intelligence-assisted risk assessment models into primary healthcare systems represents a feasible pathway to reduce CRF incidence and retard disease progression.

Looking ahead, multi-target combination regimens (e.g., RAAS inhibitor + SGLT2 inhibitor + nsMRA + GLP-1 receptor agonist) are likely to become the new standard of CRF management [17]. Concurrently, drug development targeting the inflammasome [4,5], mitochondrial dysfunction, and the gut microbiome [7,8] will provide additional therapeutic options for CRF patients.

6. Conclusion

The prevention and management of chronic renal failure stand at a critical juncture, transitioning from “single-metric management” to “multidimensional comprehensive intervention.” This review has synthesized recent advances across three domains—mechanisms, biomarkers, and therapeutics. The NLRP3 inflammasome-mediated immunoinflammatory pathway has opened new targets for drug development [4-6]; the discovery of the gut-kidney axis has broadened the therapeutic horizon [7,8]; and SGLT2 inhibitors, with their robust evidence base, have fundamentally transformed the therapeutic landscape [13,15]. Traditional Chinese medicine demonstrates unique advantages in slowing CRF progression, as exemplified by recent clinical trial data [20]; however, its evidence level must be elevated through high-quality research. Ultimately, the deep integration of basic and clinical science, and of TCM and Western medicine, holds promise for delivering improved long-term outcomes for patients with chronic renal failure.

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