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REVIEW

Research on TCM Comprehensive Treatment of DKD Based on Pathophysiological Mechanism

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Abstract: Diabetic kidney disease (DKD) is the predominant etiology of end-stage renal disease (ESRD). Despite rigorous therapeutic interventions aimed at managing hyperglycemia, regulating blood pressure, and employing renin-angiotensin system inhibitors, the incidence of DKD remains high. Recent investigations have indicated a shift in the disease spectrum of DKD accompanied by significant advancements in the development of novel therapeutic options. Nevertheless, in addition to agents such as renin-angiotensin system inhibitors (RASi), sodium-glucose cotransporter-2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1RA), and mineralocorticoid receptor antagonists (MRA), there is currently no optimal strategy in contemporary medicine to effectively mitigate the progression of DKD. The application of TCM in the management of DKD has demonstrated its potential in delaying disease progression and enhancing patient quality of life, thereby playing a crucial role in the prevention and treatment of this condition. Clinical evidence supports its efficacy and safety profile. This article aimed to explore the TCM approach to DKD, focusing on aspects such as etiology, pathogenesis, syndrome differentiation, and comprehensive treatment, while also analyzing the latest research developments in the pathophysiology of DKD.

Keywords: DKD, ERSD, pathophysiology, TCM

Literature Retrieval Strategy and Method

Retrieval Strategy

CNKI, Wanfang, VIP, PubMed, Cochrane Library, and Web of Science databases were searched systematically for randomized controlled trials (RCTs) of TCM in the treatment of obesity until January 3, 2025. The search terms included "diabetic kidney disease", "traditional Chinese medicine", "decoction", "acupuncture", "moxibustion", "electroacupuncture", "clinical research", "clinical observation" and "random". The search strategy followed the PICOS principle and adopted a combination of subject and free words. Simultaneously, the relevant meta-analysis and review literature were traced to supplement the literature.

Inclusion Criteria

This study was a randomized controlled trial (RCT). Patients with a definite diagnosis of Diabetic kidney disease (DKD) were included in the study, regardless of sex, age, or race. ③ Intervention measures: The control group could be a blank group without treatment, TCM, acupuncture, western medicine, placebo, or another effective treatment method. We believe that another effective treatment method includes emollient, incense, diet control, music therapy, meditation, and yoga, which includes the comprehensive treatment of TCM, including decoction, acupuncture, moxibustion, Chinese patent medicine, pills, Western medicine, and any combination of two or more. There was no limit to the duration of the treatment. The main outcome indicators were blood glucose levels, inflammation, and renal function.

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Exclusion Criteria

① Conference papers. Non-Chinese and English literature. Literature with incomplete data. ④ Repeatedly published literature, excluding conference papers or those published later.

Literature Screening and Data Extraction

Endnote 20 software was used for literature review. Two researchers independently searched the literature and screened and extracted data. When they disagreed, a third researcher was consulted. Data extraction included the title, author, year of publication, number of trials, actual number of cases included, interventions, outcome measures, and course of treatment.

Quality Evaluation

The Cochrane Bias Risk Assessment Tool was used to assess the risk of bias of the included articles. The evaluation included seven aspects: the generation of random sequences, allocation concealment, blinding of investigators and subjects, blinding of outcome indicators, completeness of outcome data, reporting bias, and other biases. Each item is judged as "low risk", "high risk", or "unclear". However, because this article is a literature review, it is difficult to evaluate the quality completely using the systematic review method.

Introduction

Diabetes has emerged as a significant global health crisis, with morbidity and mortality largely attributable to complications that affect various organ systems, particularly the kidneys.[1] DKD is a chronic and progressive condition that ultimately leads to renal failure and represents the foremost cause of renal replacement therapy on a global scale.[2] DKD is characterized by alterations in renal structure and function, with notable structural changes including mesangial expansion, thickening of the glomerular and tubular basement membranes, and glomerulosclerosis.[3] Clinically, DKD manifests as a syndrome marked by persistent proteinuria, hypertension, consistently low glomerular filtration rate (GFR), and increased risk of cardiovascular mortality. According to the International Diabetes Federation, as of 2014, approximately 380 million individuals worldwide are affected by diabetes, constituting 8.3% of the global population, with type 2 diabetes accounting for 30–47% of end-stage renal disease (ESRD) cases. In the United States, it is estimated that approximately 54.4% of individuals with type 1 diabetes will ultimately require renal replacement therapy (RRT).[4]

Proteinuria is one of the most distinctive clinical indicators of DKD. Historically, particularly in the context of type 1 diabetes, the clinical progression of DKD was thought to commence with early glomerular hyperfiltration, followed by the emergence of microalbuminuria and subsequent decline in GFR.[5] However, recent investigations involving patients with type 2 diabetes have revealed that many individuals with DKD do not exhibit the conventional sequential changes described previously. Consequently, our understanding of the natural history of DKD is evolving. Albuminuria is now perceived as an active and deteriorating condition rather than merely a subsequent manifestation of DKD.[6] The onset of significant proteinuria is frequently associated with a reduction in the GFR and can advance to ESRD.[4]

Compared to other diabetic complications, the incidence of DKD has remained relatively stable over the past three decades.[7] Current therapeutic strategies for DKD primarily involve the management of blood pressure and stringent glycemic control, often utilizing angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), which have demonstrated modest efficacy in delaying the onset and progression of renal impairment.[8] Nevertheless, contemporary medical approaches to DKD remain in the early stages of investigation and their therapeutic outcomes are still deemed unsatisfactory.[9] In contrast, TCM has shown promise in the treatment of DKD, demonstrating both efficacy and a favorable safety profile.[10]

This review aimed to examine the comprehensive management of DKD through the lens of TCM, taking into account the multifactorial pathophysiological mechanisms underlying the condition.

Epidemiology

Diabetes mellitus affects approximately 30.3 million individuals in the United States, representing 9.4% of the population.[11] In China, the prevalence is even higher, with approximately 149 million individuals diagnosed, accounting

for 10.9% of the population.[12] Globally, an estimated 450 million people live with diabetes.[13] Although the incidence of chronic kidney disease (CKD) in the United States has declined in recent years, it has remained significantly high. The total number of DKD patients has increased in tandem with the increasing number of individuals diagnosed with diabetes. Notably, the number of adults aged ≥ 18 years who progressed to ESRD due to diabetes increased from over 40,000 in 2000 to more than 50,000 in 2014.[14] In China, the incidence and prevalence of DKD have increased dramatically over the past decade, with DKD identified as the leading cause of CKD, accounting for 26.96% of cases according to the 2015 report from the China Kidney Disease Network.[15]

While advancements in diabetes management have contributed to a reduction in the proportion of individuals with diabetes who develop CKD within a given timeframe,[7,16,17] the improved prognosis for these patients[18,19] and the rising incidence of both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM)[20] have resulted in a continued increase in CKD prevalence.[21] Among approximately 400 million individuals with T2DM globally,[21] it is estimated that nearly half will exhibit symptoms of CKD.[22] Approximately 20% of adult patients with T2DM have an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m², and between 30% and 50% demonstrate elevated urinary albumin excretion. The incidence of CKD in T1DM differs from that in T2DM, with estimates suggesting that approximately one-third of T1DM patients develop chronic renal failure during their lifetime.[23,24] This discrepancy is primarily attributed to the generally younger age and lower blood glucose levels of T1DM patients at diagnosis, who tend to be healthier and experience fewer complications than their T2DM counterparts. Consequently, renal manifestations in T1DM may more accurately reflect DKD, whereas CKD in T2DM is influenced by additional factors, such as aging, vascular disease, insulin resistance, and obesity.

The incidence, clinical presentation, and progression of CKD among patients with diabetes exhibit considerable variability across different countries and populations.[22] For instance, African Americans, Middle Easterners, Hispanics, Asians, and Polynesians with diabetes have higher rates of elevated urinary albumin/creatinine ratios (ACR) than Europeans.[25] Vulnerable and minority populations are disproportionately affected by chronic renal failure, which may exacerbate health disparities. The underlying causes of these disparities are multifaceted,[26] encompassing economic, social, and educational disadvantages as well as issues related to access to and acceptance of treatment, achievement of treatment goals, screening rates, early management of complications, dietary and lifestyle factors, smoking, obesity, genetic predispositions, and developmental processes. Additionally, a notable characteristic of high-risk populations is the younger age of onset of T2DM, which may correlate with a more aggressive disease course, including accelerated loss of pancreatic beta cells and increased renal and cardiovascular complications.[27]

The cumulative risk of developing ESRD due to diabetes varies significantly across countries and populations, ranging from less than 1% to as high as 13%.[25] This variation is partially attributable to the competing risks of premature mortality, as many individuals with chronic kidney disease may die before progressing to ESRD.[26,27] Furthermore, most individuals with diabetes currently reside in developing nations,[20] where access to RRT programs is limited for those who develop ESRD. Nevertheless, the prevalence of diabetes remains unparalleled, establishing it as the leading cause of ESRD. In the United States, over half of the patients undergoing RRT programs are diagnosed with diabetes.[28]

Diagnosis

The diagnosis of DKD is predicated on the assessment of the estimated Glomerular Filtration Rate (eGFR) and albuminuria, alongside clinical indicators such as the duration of diabetes and the presence of diabetic retinopathy.[29,30] Clinically, an increase in the Albumin-to-Creatinine Ratio (ACR) exceeding 30 mg/G or a decline in eGFR below 60 mL/min/1.73 m² is indicative of DKD.[31] It is recommended that patients undergo annual screening for DKD starting five years post-diagnosis, with all individuals diagnosed with T2DM screened annually from the time of diagnosis. In cases in which albuminuria is present, the concomitant occurrence of diabetic retinopathy serves as a strong indicator of DKD. The ACR test, conducted on a spot urine sample, preferably collected in the morning, is the preferred method for assessing albuminuria.[30,32] eGFR is derived from serum creatinine levels; although the Chronic Kidney Disease – Epidemiology Prognosis Initiative equation is recognized for its accuracy, particularly when eGFR values are within or near the normal range, the Renal Disease Diet Adjustment Equation[30] is the one most frequently reported by clinical laboratories. Confirmation of albuminuria or a low eGFR necessitates two abnormal measurements taken at least three

months apart. In instances where atypical features of DKD are observed, alternative etiologies of renal disease should be explored. Atypical features may include a sudden onset of low eGFR or a rapid decline in eGFR, a sudden increase in albuminuria, symptoms indicative of nephrotic syndrome, refractory hypertension, other systemic diseases, and a decrease in eGFR exceeding 30% within two–three months of the initiation of renin-angiotensin system inhibitors.[31]

Pathophysiological Mechanisms

Effect of Hyperglycemia on Renal Structure

Hyperglycemia is a significant contributor to the onset and progression of DKD, which causes structural damage to the kidneys through various mechanisms. At the glomerular level, hyperglycemia induces mesangial cell proliferation, accumulation of extracellular matrix (ECM), and thickening of basement membrane. In a rat model of type 1 diabetes, persistent hyperglycemia was shown to enlarge the glomerular mesangial area, enhance the expression of ECM components such as collagen and fibronectin, and markedly increase the thickness of the glomerular basement membrane.[33] These alterations can result in impaired glomerular filtration function, proteinuria, and other symptoms.

Additionally, elevated blood glucose levels can adversely affect renal tubules. Acute hyperglycemia is associated with renal tubular injury through inhibition of mitochondrial autophagy. In experimental studies involving rats, acute hyperglycemic conditions resulted in notable morphological and functional alterations in the renal tubular epithelial cells, including cellular swelling, disorganization of epithelial cell architecture, and mitochondrial swelling. Concurrently, there is an increase in urinary biomarkers such as microalbumin, β2-microglobulin, and cystatin C.[34] The underlying mechanism suggests that acute hyperglycemia may exacerbate mitochondrial damage and renal tubular dysfunction by inhibiting the AMPK/mTOR signaling pathway, leading to a decreased LC3-II/LC3-I ratio and elevation in the expression of P62 and BNIP3L/Nix.

The Mechanism of Inflammatory Reaction in DKD

The inflammatory response is pivotal in the pathogenesis of DKD and is characterized by the activation of various inflammatory cells and signaling pathways.[35] The Toll-like receptor 4 (TLR4) signaling pathway is particularly significant in both the initiation and perpetuation of inflammation associated with DKD. Upon activation, TLR4 stimulates the expression of downstream inflammatory mediators, including tumor necrosis factor-alpha (TNF-α) and monocyte chemoattractant protein-1 (MCP-1). These mediators subsequently facilitate the recruitment of inflammatory cells into renal tissue, resulting in tissue damage. Notably, upregulation of TLR4 expression, along with elevated levels of associated inflammatory factors,[35] has been documented in patients with DKD, as well as in relevant animal models.

Furthermore, the activation of the NLRP3 inflammasome is a critical component of the inflammatory response in DKD. Hyperglycemia and hyperlipidemia can trigger the activation of the NLRP3 inflammasome, leading to the activation of caspase-1. This process promotes the maturation and secretion of inflammatory cytokines, including interleukin-1β (IL-1β) and IL-18, thereby exacerbating the inflammatory response and contributing to renal injury.[36] Inhibition of NLRP3 inflammasome activity has been demonstrated to reduce renal inflammation and proteinuria as well as enhance renal function in murine models of diabetes.[37]

Oxidative Stress and Fibrosis in DKD

Oxidative stress and fibrosis are critical pathological mechanisms involved in the advancement of DKD.[1,38] In the context of hyperglycemia, there is increased production of reactive oxygen species (ROS) within the renal system, which surpasses the body's antioxidant defense capabilities, resulting in oxidative stress-related damage. Numerous studies have indicated that patients with DKD and relevant animal models exhibit elevated levels of ROS in renal tissues, diminished activity of antioxidant enzymes such as superoxide dismutase (SOD), and increased concentrations of lipid peroxidation products, including malondialdehyde (MDA).[39] Oxidative stress is implicated in the development of renal fibrosis through various mechanisms, including activation of the transforming growth factor-β (TGF-β) signaling pathway, which facilitates the synthesis and deposition of ECM components.

The TGF-β/Smad signaling pathway is particularly significant during fibrosis.[40] Hyperglycemia-induced oxidative stress can activate TGF-β, which leads to the phosphorylation and nuclear translocation of Smad proteins upon binding to its receptor. This translocation regulates the expression of genes associated with ECM synthesis, thereby promoting the production of components, such as collagen and fibronectin, ultimately resulting in renal fibrosis.[15] Furthermore, other cytokines, including platelet-derived growth factor (PDGF) and connective tissue growth factor (CTGF), contribute to the fibrotic processes associated with DKD. These cytokines interact with TGF-β to enhance ECM accumulation and disrupt renal structural integrity.[41]

Effect of TCM on Pathophysiology of DKD

TCM has a significant influence on the pathophysiology of DKD (DKD). Inflammatory injury is a critical contributor to DKD progression. Key signaling pathways, including nuclear factor-κB (NF-κB), mitogen-activated protein kinase (MAPK), and NOD-like receptor protein 3, are integral to renal inflammatory injury associated with DKD, with the NF-κB pathway being particularly pivotal. The network of inflammatory factors activated through these pathways interconnects various signaling mechanisms, thereby exacerbating renal inflammatory damage. Numerous compounds derived from TCM, including individual herbs and their active constituents, have been shown to modulate the expression of essential molecules within these signaling pathways, such as transforming growth factor-β-activated kinase 1, NF-κB, and p38MAPK. This multitarget therapeutic approach has the potential to mitigate renal inflammatory injury in DKD.[42]

Furthermore, TCM has the capacity to regulate the intestinal microbiota. Research indicates that patients with DKD often exhibit dysbiosis, characterized by alterations in the populations of Lactobacillus, Streptococcus, and Clostridium, which manifest as elevated levels of uremic solutes and reduced concentrations of short-chain fatty acids. Various TCM modalities, including prescriptions, tablets, granules, capsules, and decoctions, possess distinct advantages for addressing microbiota imbalances in the treatment of DKD. By modulating the intestinal microbiota and its metabolites, TCM can influence related signaling pathways and improve the pathophysiological condition of the kidneys, thereby offering a novel therapeutic avenue for the management of DKD.[43]

Molecular Mechanism of TCM Intervention in DKD

The intervention in DKD is characterized by a well-defined molecular mechanism. For instance, in vitro studies utilizing astragaloside IV demonstrated that its addition to rat mesangial cells (RMCs) cultured under high glucose conditions resulted in dose-dependent downregulation of miR-192 expression and subsequent inhibition of RMC proliferation. In vivo experiments involving a DKD rat model revealed that treatment with astragaloside IV led to a reduction in the mRNA and protein levels of miR-192, TGF-β1, Smad3, alpha-smooth muscle actin (alpha-SMA), and type I collagen (col1) within the renal tissue, while simultaneously increasing the expression of Smad7. These findings suggest that astragaloside IV may exert its therapeutic effects in DKD by inhibiting mesangial cell proliferation and renal fibrosis through the TGF-β1/Smad/miR-192 signaling pathway.[44]

Similarly, Jinqi Jiangtang granules (JLD) exert their effects by activating the AMPK/PGC-1α pathway. In db/db mice, JLD has been shown to significantly enhances renal function, mitigates podocyte injury, ameliorates mitochondrial dysfunction, and inhibits apoptosis. In vitro investigations indicated that JLD can prevent mitochondrial fission and apoptosis in podocytes exposed to high glucose levels, enhance AMPK phosphorylation, and promote the expression of peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), thereby improving both apoptosis and mitochondrial homeostasis. These findings provide a theoretical foundation for the clinical management of DKD.[45]

Standardization of DKD in TCM

DKD is a term used in contemporary medicine, specifically referring to a condition characterized by excessive thirst associated with kidney dysfunction, as outlined in the "Guidelines for the Diagnosis and Treatment of Diabetic Kidney Diseases with Integrated Traditional Chinese and Western Medicine".[46] The text "Zheng Zhi Zhun Sheng · Xiao" states, "Thirsty and then there is a number of paste for the next elimination", indicating a historical understanding of the condition. The "Sheng Ji Zong Lu" describes Xiaoke Nephropathy,[47] which is named based on clinical manifestations such as edema resulting from kidney qi deficiency and impaired qi transformation, as well as turbid urine due to the

kidney's inability to properly seal and store fluids. The "Medical Compendium" documents symptoms such as polydipsia, polyuria, and turbid urine, which are attributed to kidney water deficiency and abnormal steaming, collectively referred to as "kidney elimination".[48]

In modern Chinese medicine, DKD is classified according to the severity of renal impairment, the progression of the disease, and associated clinical signs and symptoms into categories such as "urine turbidity", "edema", "consumptive disease", and "Guange". Nanzheng[49] standardized the TCM terminology for DKD as "consumptive thirst involving kidney" in his publication "Diabetes Nephropathy Research", emphasizing that DKD arises from the fundamental etiology of diabetes, with the kidneys being the primary site of pathology. This nomenclature maintains the traditional characteristics of TCM while aligning with the essential features of modern medical terminology, thereby achieving a degree of standardization. The formal inclusion of the term "consumptive thirst involving kidney" in the 2010 edition of the "Terminology of Traditional Chinese Medicine, Internal Medicine", facilitates further research and discourse in the field of TCM.[50]

Basic Characteristics of the Included Literature

Thirteen articles[51–53] were included with the following characteristics (see Table 1).

Study on the Treatment of DKD with TCM

Hu et al[54] conducted an RCT to evaluate the efficacy of a modified Yangyin Qingre Decoction in elderly patients with DKD characterized by yin deficiency as well as its impact on inflammatory markers, specifically C-reactive protein (CRP) and interleukin-6 (IL-6). The study involved 65 elderly participants diagnosed with yin deficiency-type DKD, who were randomly assigned to either a TCM group (n = 33) or a Western medicine group (n = 32). The Western medicine group received standard symptomatic treatment, while the TCM group received the modified Yangyin Qingre Decoction in conjunction with conventional treatment. The researchers compared the therapeutic outcomes, TCM syndrome scores,

Table 1 Basic Characteristics of the Included Literature

Included in the Study	N cases		Interventions	
	Test Group	Control Group	Test Group	Control Group
Lv Yanli[51]	47	47	On the basis of the control group, Shenan Decoction was added.	Conventional treatment measures
Zhao Huiye[52]	40	40	On the basis of the control group, Jianpi Yishen Jiangzhuo Decoction was added.	Conventional treatment measures
Hu Yali[54]	33	32	The control group was treated with Yangyin Qingre Decoction.	Conventional treatment measures
Peng Bin[55]	59	56	The control group was treated with Jianpi Anshen Decoction.	Conventional treatment measures
Jiang Jian[56]	39	38	On the basis of the control group, Ziyishen prescription was added.	Conventional treatment measures
Zhou Shumei[57]	55	55	The control group was treated with traditional Chinese medicine acupoint application.	Conventional treatment measures
Liu Liang[58]	6	6/6/6/6/6	Acupuncture for regulate spleen and stomach	They were intervened according to different control groups.
Chen Jia[59]	10	12/11	"Acupoint matching with specimen" electroacupuncture	They were intervened according to different control groups.
Wang Kunxiu[60]	11	10/12/11/11	"Acupoint matching with specimen" electroacupuncture	They were intervened according to different control groups.
Wu Weili[61]	46	46	The control group was treated with acupuncture on this basis.	Qishen Tongluo Huayu Recipe
Kong Linglong[62]	30	30	The control group was treated with Jianpi Yishen Huoxue Decoction combined with warm acupuncture.	Conventional treatment measures
Wang Yuehua[63]	66	66	The control group was treated with Buyang Huanwu Decoction combined with Shenqi Dihuang Decoction.	Conventional treatment measures
Zhang Huijie[53]	28	28/28	Routine treatment plus Zishen Jiangtang Decoction combined with warm acupuncture	They were intervened according to different control groups.

inflammatory markers (CRP, IL-6, and tumor necrosis factor-α [TNF-α]), and renal function indicators (serum creatinine [SCr], blood urea nitrogen [BUN], and cystatin C [Cys-C]) between the two groups. The findings of this study suggest that the Yangyin Qingre Decoction significantly reduces inflammatory responses in elderly patients with yin deficiency-type DKD, alleviates associated symptoms, and effectively enhances renal function, demonstrating a notable therapeutic benefit.

Yanli et al[51] conducted an RCT to investigate the effects of Shenanfang on urinary microalbumin (m-UALB), microinflammatory states, and insulin resistance in patients with early stage DKD. The study involved 94 patients with DKD who were randomly assigned to either an observation group or a control group, with 47 participants in each group. The control group received standard therapeutic interventions, whereas the observation group was administered Shenanfang in conjunction with conventional therapy. The researchers assessed various parameters, including TCM syndrome scores; urinary protein levels (m-UALB and urinary albumin/urinary creatinine ratio [UACR]); serum inflammatory markers (such as IL-6, IL-22, and IL-1β); insulin resistance indicators (including fasting insulin [FIN] and fasting blood glucose [FBG]); and renal function metrics (SCr and BUN). The findings of this study suggest that Shenanfang significantly alleviated urinary protein levels and insulin resistance in patients with early DKD while also inhibiting the production of inflammatory mediators, thereby demonstrating its clinical relevance.

Zhao et al[52] conducted an RCT to evaluate the clinical efficacy of the Jianpi Yishen Jiangzhuo Decoction in the management of DKD and its impact on the microinflammatory state of affected patients. The study involved 80 patients diagnosed with DKD, who were randomly assigned to two groups: the control group, consisting of 40 patients receiving standard Western medical treatment, and the treatment group, comprising 40 patients who received Jianpi Yishen Jiangzhuo Decoction in addition to conventional treatment. After a treatment period of 12 weeks, the outcomes of both groups were assessed. Researchers compared various parameters, including blood glucose levels (fasting plasma glucose [FPG], 2-hour postprandial plasma glucose [2 hPG], and HbA1c), inflammatory markers (high-sensitivity C-reactive protein [hs-CRP], interleukin-8 [IL-8], IL-6, and TNF-α), and renal function indicators (SCr). Additionally, changes in BUN, urinary albumin excretion rate (UAER), and TCM symptom scores were analyzed. The findings of the study indicated that the Jianpi Yishen Jiangzhuo Decoction demonstrated significant clinical efficacy in treating DKD, effectively ameliorating the microinflammatory state of patients, enhancing renal function, alleviating TCM-related symptoms, and consequently slowing disease progression, while also being deemed safe and reliable.

Peng Bin et al[55] conducted an RCT to assess the efficacy of Jianpi Anshen Decoction in treating DKD characterized by deficiencies in both qi and yin, as well as its potential to delay the progression of renal fibrosis. This study involved 115 patients diagnosed with DKD, with 56 individuals assigned to the control group receiving standard Western medical interventions. These interventions included hypoglycemic, hypotensive, and lipid-lowering treatments along with dietary modifications and appropriate exercise regimens. Patients in the control group were administered benazepril tablets orally at a dosage of 5–10 mg per administration, once daily, with gradual increases based on clinical response. The observation group comprised 59 patients who received a combination of standard Western medicine and the Jianpi Anshen Decoction. Both groups were treated for 14 d. This study compared clinical symptom scores; blood glucose levels (including fasting plasma glucose and HbA1c); renal function indicators (such as urinary microprotein, blood urea nitrogen, and serum creatinine); and renal fibrosis biomarkers (including TGF-β1, TSP-1, and TIMP-1) before and after the treatment period. The findings of this study suggest that the Jianpi Anshen Decoction is effective in treating DKD associated with qi and yin deficiencies. Furthermore, the combination of Jianpi Anshen Decoction with Western medicine demonstrated superior efficacy, significantly reducing urinary albumin levels and serum concentrations of TGF-β1, TSP-1, and TIMP-1, thereby delaying renal fibrosis progression and preserving residual renal function. These results warrant consideration in clinical practice.

Jiang Jian et al[56] conducted an RCT to evaluate the clinical efficacy of Ziyishen Fang in treating proteinuria in patients diagnosed with stage IV type 2 DKD. Additionally, this study aimed to investigate the underlying mechanisms of Ziyishen Fang's therapeutic effects on type 2 DKD through the application of network pharmacology and molecular docking techniques. A total of 86 patients with stage IV type 2 DKD were enrolled in the study, which involved random assignment to either a treatment group or a control group. The researchers monitored the changes in symptom scores, laboratory indices, and overall disease efficacy. Concurrently, the mechanisms by which Ziyishen Fang exerts its effects

were explored using network pharmacology and molecular docking. The findings of this study indicate that the Ziyishen Prescription is effective in reducing proteinuria, preserving renal function, and enhancing insulin sensitivity. The proposed mechanisms of action may involve the modulation of the AGE-RAGE and PI3K-Akt signaling pathways, targeting key therapeutic proteins such as HIF1A, CASP3, PPARG, EGFR, and CCND1.

The mechanisms of TCM in the treatment of DKD are summarized in Table 2.

Study on Acupuncture and Moxibustion Treatment of DKD

Zhou Shumei et al[57] conducted an RCT to evaluate the effectiveness of acupoint application of TCM as an adjunctive treatment for elderly patients with DKD characterized by deficiencies in both qi and yin accompanied by blood stasis. The study involved 110 elderly individuals diagnosed with type 2 DKD at stages III and IV who were randomly assigned to either a control group or an observation group, with 55 participants in each group. The control group received losartan potassium tablets in conjunction with standard therapy, whereas the observation group received acupoint application of TCM alongside standard therapy. After an 8-week treatment period, various outcomes were assessed, including blood glucose levels, renal function, symptom scores related to qi and yin deficiency with blood stasis syndrome, and overall clinical efficacy. The findings of this study suggest that the application of TCM at acupoints, when combined with conventional Western medical treatment, can significantly reduce blood glucose levels, enhance renal function, and alleviate the symptoms associated with TCM syndrome in elderly patients with DKD.

Liang et al[58] conducted a series of animal experiments to investigate the impact of "regulating spleen and stomach acupuncture" on the gene expression of podocyte marker proteins, specifically podocalyxin (PCX), CD2-associated protein (CD2AP), nephrin, and desmin, in podocytes of rats with type 2 DKD. This study aimed to elucidate the mechanisms underlying these effects. In this study, a total of 70 healthy male Sprague-Dawley (SD) rats were randomly assigned to either a model group (n = 52) or a control group (n = 18). Following an 8-week regimen of high-fat and high-sugar diet, the model group rats were administered a low dose of streptozotocin (30 mg/kg) via intraperitoneal injection to induce a type 2 DKD model. Based on blood glucose levels and qualitative assessment of urinary protein, 36 rats were further randomized into various acupuncture and model groups for intervention durations of 4, 8, and 12 weeks, with each group comprising six rats. The control group was divided into subgroups at 4, 8, and 12 weeks. The acupuncture group underwent treatment using the "regulating spleen and stomach acupuncture method", whereas the model and control groups received equivalent handling without acupuncture intervention. Following the respective intervention periods, 24-hour urinary protein levels were measured, and histological examination of the renal tissue was performed using hematoxylin and eosin staining under a light microscope. Additionally, fluorescence quantitative PCR was used to assess the mRNA expression levels of PCX, CD2AP, nephrin, and desmin. The findings of this study indicate that acupuncture aimed at regulating the spleen and stomach significantly reduces 24-hour urinary protein levels in rats with type 2 DKD. Furthermore, it decreased the levels of desmin protein and gene expression as well as the expression of PCX, CD2AP, and nephrin in podocytes, thereby ameliorating podocyte injury in this model. This intervention also

Table 2 The Mechanism of TCM in Treating DKD

Treatment	Mechanism of Action	References
Nourishing Yin and Clearing Heat Decoction	Alleviate the inflammation reaction of the elderly DKD patients with yin deficiency type, relieve the symptoms of the DKD patients, and effectively improve the renal function of the DKD patients.	[54]
Shen'an Prescription	It can effectively improve the symptoms of urinary protein and insulin resistance in patients with early DKD, and inhibit the production of inflammatory mediators.	[51]
Jianpi Yishen Jiangzhuo Recipe	It can effectively improve the micro-inflammatory state of DKD patients and improve renal function.	[52]
Jianpi Anshen Decoction combined with Benazepril	Decrease the content of urinary albumin, decrease the levels of serum TGF-β1, TSP-1 and TIMP-1, delay the process of renal fibrosis, and protect the residual renal function.	[55]
Ziyishen Prescription	It can reduce proteinuria, protect renal function and improve insulin resistance. Its potential mechanism may be involved in the regulation of AGE-RAGE signaling pathway, PI3K-Akt signaling pathway and other pathways by acting on key therapeutic targets such as HIF1A, CASP3, PPARG, EGFR and CCND1.	[56]

resulted in a reduction in glomerular basement membrane thickening, suggesting a potential mechanism for delaying the progression of diabetic kidney disease, which may be associated with the observed decrease in urinary protein content.

Chen Jia et al[59] conducted an animal study to investigate the protective effects of "specimen matching acupoint" electroacupuncture on oxidative stress-induced injury to renal mitochondria in DKD rats, specifically through the modulation of the silent information regulator 1 (SIRT1)/peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) signaling pathway. Wistar rats were randomly assigned to three groups: normal (n = 10), model (n = 12), and electroacupuncture (n = 11). The DKD model was established by administering a high-glucose and high-fat diet for six weeks, in conjunction with streptozotocin injections. The electroacupuncture treatment involved the application of needles at the "Zusanli", "Guanyuan", "Fenglong", and "Zhongwan" acupoints for 15 minutes per session, conducted every other day over a period of eight weeks. Various parameters were measured, including body weight, fasting blood glucose (FBG), 24-hour urine protein excretion, HbA1c, Scr, and BUN. Serum triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels were quantified using an automated biochemical analyzer. The activities of SOD, reduced glutathione (GSH), and catalase (CAT) in renal tissues were assessed using xanthine oxidation, dithio-dinitrobenzoic acid, and ammonium molybdate methods, respectively. Additionally, malondialdehyde (MDA) content in renal tissue was measured using the thiobarbituric acid sodium method. Histopathological alterations in the kidneys were evaluated using hematoxylin-eosin (HE) staining, periodic acid-Schiff (PAS) staining, and Masson staining, while the ultrastructure of the renal tissue was examined using transmission electron microscopy. The mRNA and protein expression levels of SIRT1 and PGC-1α in the renal tissue were analyzed using fluorescence quantitative PCR and Western blot techniques. The expression of α-smooth muscle actin (α-SMA) was assessed by immunohistochemistry, and the levels of collagen type I (Col I), collagen type IV (Col IV), and fibronectin (FN) were determined by immunofluorescence staining. The findings of this study suggest that "specimen matching acupoint" electroacupuncture may mitigate renal oxidative stress and mitochondrial dysfunction by activating the SIRT1/PGC-1α signaling pathway, thereby improving renal fibrosis in DKD rats.

Wang Kunxiu[60] conducted an animal study to investigate the impact of electroacupuncture (EA) at designated " specimen-matching points" on the expression of forkhead transcription factor O1 (FoxO1) and peroxisome PGC-1α in the kidneys of rats with DKD. This study aimed to elucidate the protective effects of EA on renal function in rats with DKD and to explore the underlying mechanisms. Male Wistar rats were randomly assigned to five groups: normal (n = 10), model (n = 12), an electroacupuncture group (n = 11), an electroacupuncture + inhibitor (n = 11), and inhibitor (n = 11). The DKD model was established by intraperitoneal administration of streptozotocin following a 6-week regimen of a high-sugar and high-fat diet. Following successful model establishment, the electroacupuncture and electroacupuncture + inhibitor groups received EA treatment at the acupoints "Zusanli", "Guanyuan", "Fenglong", and "Zhongwan" for 15 minutes per session. Additionally, the electroacupuncture + inhibitor and inhibitor groups were administered the FoxO1-targeted inhibitor AS1842856 orally every other day for 8 weeks. Various parameters were measured, including body weight, blood glucose levels, serum creatinine (Scr), blood urea nitrogen (BUN), urinary albumin (ALB), SOD, MDA, and ROS. Changes in the renal subcellular structure were examined using transmission electron microscopy, while protein expression levels in renal tissue were assessed via Western blot analysis. The findings of this study suggest that electroacupuncture may confer renal protection by upregulating the expression of FoxO1 and PGC-1α in rats with DKD, thereby mitigating the oxidative stress response associated with the condition.

The mechanisms of action of acupuncture and moxibustion in the treatment of DKD are summarized in Table 3.

Comprehensive Treatment of DKD with TCM

Weili et al[61] conducted an RCT to evaluate the clinical efficacy of Qishen Tongluo Huayu Decoction in conjunction with acupuncture for the treatment of early DKD. The study involved 92 patients diagnosed with early DKD, who were randomly assigned to either the study or control group, with 46 participants in each group. Both groups received standard Western medical treatment aimed at managing blood pressure, blood lipid levels, and blood glucose levels. The control group was administered Qishen Tongluo Huayu Decoction, while the study group received acupuncture in addition to the treatment provided to the control group over a period of 8 weeks. Following the treatment period, the clinical efficacy of both groups was assessed, and various TCM syndrome scores, including symptoms such as thirst, soreness and coldness

Table 3 The Mechanism of Acupuncture and Moxibustion in the Treatment of DKD

Treatment	Mechanism of Action	References
Acupoint application of TCM combined with losartan potassium	Can effectively inhibit the blood sugar level of the elderly DKD patients and improve the renal function of the patients.	[57]
Acupuncture for regulate spleen and stomach	It can reduce the content of 24 H urinary protein in type 2 DKD rats, and reduce the level of desmin protein and gene expression through the level of PCX, CD2AP, nephrin protein and gene expression in podocyte of type 2 DKD rats, so as to improve the podocyte injury of type 2 DKD rats, alleviate the thickening of glomerular basement membrane, and delay the progress of DKD.	[58]
Specimen with acupoint electroacupuncture	Reduce renal oxidative stress and mitochondrial dysfunction by activating SIRT1/PGC-1α signaling pathway, and improve renal fibrosis in DKD rats.	[59]
Specimen with acupoint electroacupuncture	By up-regulating the expression of FoxO1 and PGC-1α in the kidney of DKD rats, it can reduce the oxidative stress response of the kidney of DKD rats and protect the kidney.	[60]

in the waist and knees, turbid urine, limb edema, fatigue, and feverish palms and soles were measured before and after the intervention. Additionally, changes in FPG, 2hPG, Scr, BUN, and urinary albumin excretion rate (UAER) were evaluated. The study further compared the serum levels of chitinase 3-like protein 1 (CHI3L1) and suppressor of cytokine signaling 3 (SOCS3) between the two groups pre- and post-treatment. The findings of this study indicate that the combination of Qishen Tongluo Huayu Decoction and acupuncture significantly enhanced the clinical manifestations and symptoms in patients with early DKD, effectively regulated blood glucose levels, improved renal function, and modulated the serum levels of CHI3L1 and SOCS3, demonstrating a notable therapeutic effect.

Kong Linglong et al[62] conducted an RCT to evaluate the clinical efficacy of a self-formulated prescription combined with warm acupuncture in treating patients with DKD characterized by spleen and kidney qi deficiency and blood stasis. The study involved 60 patients with DKD, who were randomly assigned to either a control group or a treatment group, with 30 participants in each group. The control group received standard Western medical treatment, which included oral irbesartan, while the treatment group was administered a TCM decoction, Jianpi Yishen Huoxue Fang, along with warm acupuncture, in addition to the control group's treatment. Both groups underwent treatment for two courses, each lasting four weeks. After treatment, the researchers compared various renal function indicators, including SCr, BUN, 24-hour urinary protein, TC, TG, fasting blood glucose (FBG), HbA1c, CysC, tissue inhibitor of metalloproteinases-1 (TIMP-1), transforming growth factor-beta 1 (TGF-β1), and collagen IV (CIV) between the two groups. The findings of this study suggest that the combination of the self-formulated Jianpi Yishen Huoxue Decoction and warm acupuncture may effectively mitigate diabetic kidney injury, reduce urinary protein levels, slow the progression of renal fibrosis, and consequently enhance the quality of life of patients.

Wang Yuehua[63] conducted an RCT to evaluate the clinical efficacy of Buyang Huanwu Decoction in conjunction with Shenqi Dihuang Decoction for patients with stage III–IV DKD characterized by deficiencies in both qi and yin, as well as collateral obstruction. The study involved 132 DKD patients who met the specified inclusion criteria and were subsequently divided into control and Chinese medicine groups, with 66 participants in each cohort. The control group received standard Western medical treatment supplemented with Engelijing Tablets, while the Chinese medicine group was administered Buyang Huanwu Decoction and Shenqi Dihuang Decoction in addition to the control treatment. Both the groups underwent treatment for 12 weeks. Clinical efficacy was assessed and comparisons were made regarding TCM syndrome scores and the Diabetes-Specific Quality of Life Scale (DQOL) between the two groups before and after the intervention. Additionally, various indicators related to glucose and lipid metabolism, renal function, renal tubular injury, inflammatory factor expression, and incidence of adverse reactions were evaluated. The findings of this study indicate that the combination of Buyang Huanwu Decoction and Shenqi Dihuang Decoction is effective in treating DKD, as it significantly reduces urinary protein excretion, regulates glucose and lipid metabolism, inhibits inflammatory factor expression, ameliorates kidney injury, delays the progression of DKD, and demonstrates a favorable safety profile.

Zhang et al[53] investigated the therapeutic efficacy of warming acupuncture in conjunction with Zishen Jiangtang Fang in patients diagnosed with DKD characterized by spleen-kidney yang deficiency syndrome. This study assessed its effect

on serum nitric oxide (NO), endothelial nitric oxide synthase (eNOS), and renal artery hemodynamics. A total of 84 patients meeting the inclusion criteria were randomly assigned to three groups: a control group, TCM treatment group, and combined acupuncture and medicine group, with 28 participants in each cohort. The control group received standard treatment alongside Shenyang Wenyang capsules, whereas the TCM group received conventional treatment with Zishenjiangtang decoction. The combined acupuncture and medicine group received the same conventional treatment supplemented with Zishenjiangtang decoction and warming acupuncture applied to the back shu points (Pishu, Sanjiaoshu, Shenshu, and Bladder Shu) over a duration of four weeks. Biochemical parameters, including urine and serum indicators, 24-hour urine protein, HbA1c, CysC, β2-microglobulin (β2-MG), TC, and TG levels, were compared across the three groups before and after treatment. Additionally, changes in the maximum systolic velocity (Vsmax), minimum diastolic velocity (Vdmin), and resistance index (RI) in various segments of the renal aorta (MRA), renal segmental artery (SRA), and interlobar artery (IRA) of the left kidney were analyzed, along with differences in NO and eNOS levels and overall clinical efficacy. The findings of this study indicate that the combination of warming acupuncture and Zishen Jiangtang Fang significantly enhanced renal function, decreased proteinuria, lowered blood lipid levels, elevated NO and eNOS concentrations, improved renal hemodynamics, alleviated renal ischemia and hypoxia, and ultimately enhanced therapeutic outcomes and prognoses in patients with DKD associated with spleen-kidney yang deficiency syndrome.

The mechanism of action of TCM in the comprehensive treatment of DKD is summarized as follows, as shown in Table 4.

Controversies and Challenges in the Treatment of DKD with TCM

Safety of TCM in Treating DKD

The safety profile of TCM for the management of DKD has garnered considerable scholarly interest. While the majority of studies indicate that TCM interventions are generally safe, some studies have raised concerns regarding potential adverse reactions. For instance, a clinical trial assessing the efficacy of tripterygium glycosides (TWHF) in reducing proteinuria among DKD patients randomized 124 participants to receive either valsartan monotherapy or a combination of TWHF and valsartan. The findings revealed that the TWHF group experienced a more pronounced decrease in proteinuria; however, the incidence of adverse reactions was notably higher than that in the control group, thereby underscoring the need for vigilance regarding the safety of TWHF despite its effectiveness in proteinuria reduction.[64]

Conversely, several investigations have demonstrated that the integration of TCM with Western medicine in the treatment of DKD does not elevate the risk of adverse reactions. A systematic review and meta-analysis encompassing 66 RCTs indicated that the occurrence of adverse reactions in patients receiving TCM decoctions in conjunction with Western medicine was not significantly different from that in the control group. This suggests that when utilized

Table 4 The Mechanism of Action of DKD Treated by TCM

Treatment	Mechanism of Action	References
Qishen Tongluo Huayu Recipe combined with acupuncture	Can obviously improve the clinical signs and symptoms of DKD patients, effectively regulate the blood sugar of the patients, improve the renal function of the patients, and regulate the levels of serum CHI3L1 and SOCS3.	[61]
Jianpi Yishen Huoxue Recipe Combined with Moxibustion	It can reduce diabetic kidney injury, reduce urinary protein and delay the progress of renal fibrosis.	[62]
Buyang Huanwu Decoction combined with Shenqi Dihuang Decoction	It can effectively reduce the excretion of urinary protein in patients with DKD, regulate the disorder of glucose and lipid metabolism, inhibit the expression of inflammatory factors, improve kidney injury and delay the progress of DKD.	[63]
Warming Acupuncture and Moxibustion Combined with Nourishing Kidney and Lowering Blood Sugar Prescription	It can effectively improve renal function, reduce proteinuria, reduce blood lipids, increase the levels of NO and eNOS, improve renal hemodynamics in patients with DKD, and improve renal ischemia and hypoxia.	[53]

judiciously, the combination of TCM and Western medicine may offer a safer therapeutic approach in the management of DKD.[65]

Scientific Verification of Curative Effect of TCM on DKD

The effectiveness of TCM in the management of DKD has been substantiated in several studies; however, further rigorous scientific validation is necessary. Some systematic reviews and meta-analyses have provided evidence supporting the efficacy of TCM. For instance, a comprehensive meta-analysis encompassing 44 randomized controlled trials indicated that the combination of TCM with conventional Western medicine significantly reduced 24-hour urinary protein levels, improved renal function markers, such as serum creatinine and blood urea nitrogen, and demonstrated benefits in lowering glycosylated hemoglobin, fasting blood glucose, and enhancing lipid profiles. These findings suggest that the integration of TCM with Western medicine may have a substantial impact on DKD.[66]

Nonetheless, many existing studies are hindered by limitations, such as small sample sizes and suboptimal research designs, which compromise the reliability of their conclusions. Future research should focus on conducting larger, multicenter, high-quality, randomized controlled trials that employ rigorous research methodologies and scientifically sound evaluation metrics. This approach is essential to further substantiate the efficacy of TCM in treating DKD and to establish a robust scientific foundation for its clinical application.

Standardization of TCM Treatment of DKD

The urgent need for the standardization of TCM for the treatment of DKD is evident. Currently, clinical practice lacks a unified standard for the diagnosis of TCM syndromes, resulting in variability in syndrome differentiation among practitioners for the same patient. This inconsistency ultimately undermines the uniformity of the treatment approaches. For instance, the classification methods and standards for TCM syndrome differentiation in patients with DKD vary across studies, complicating clinical research and broader application of TCM.

Moreover, challenges persist in quality control of TCM. Factors such as geographical origin, harvesting season, and processing method can significantly influence the quality and therapeutic efficacy of TCM. Variations in active ingredient content across different batches may lead to inconsistencies in treatment outcomes. Therefore, it is imperative to establish a standardized quality framework for TCM encompassing the cultivation, harvesting, processing, and preparation stages to ensure both efficacy and safety in the treatment of DKD. Additionally, the development of standardized TCM diagnostic and treatment protocols, along with clarification of diagnostic criteria and corresponding therapeutic strategies for various syndromes, will enhance the standardization and reproducibility of TCM interventions.

Summary

Research Trend of DKD Treated by TCM

Future research on the treatment of DKD using TCM is anticipated to reveal diverse trends. First, investigations of the mechanisms underlying the action of TCM are expected to become increasingly sophisticated. Advances in molecular biology, cell biology, and related technologies will facilitate the elucidation of targets and signaling pathways associated with TCM compounds, individual herbs, and their active constituents at both cellular and molecular levels. For instance, a thorough examination of the mechanisms by which TCM influences mitochondrial function, the gut microbiota, and autophagy will provide a theoretical foundation for the development of more effective therapeutic agents.

Second, the application of multi-omics technologies is likely to become more prevalent in TCM research. By integrating genomics, transcriptomics, proteomics, and metabolomics, researchers can conduct comprehensive and systematic analyses of the overall effects and mechanisms of TCM in the treatment of DKD, thereby identifying novel biomarkers and therapeutic targets. Furthermore, it is essential to emphasize the synergy between clinical and basic research with a focus on addressing clinical challenges. By elucidating the mechanisms of TCM efficacy through foundational research, these findings can be translated into clinical practice, thereby enhancing the precision and effectiveness of TCM interventions.

Potential Breakthrough in Treatment of DKD with TCM

TCM is anticipated to yield significant advancements in DKD management. Given the critical factors involved in the pathophysiology of DKD, including oxidative stress, inflammation, and apoptosis, TCM may offer more effective interventions by modulating associated signaling pathways. For instance, certain TCM formulations exhibiting antioxidant and anti-inflammatory properties can mitigate renal damage and slow disease progression by inhibiting oxidative stress-related mediators and modulating inflammatory signaling pathways.

Furthermore, as research deepens the understanding of the interplay between intestinal microbiota and DKD, TCM demonstrates distinct advantages in the regulation of the gut microbiota. This presents the potential for the development of novel therapeutic strategies aimed at modulating intestinal microbiota. Such approaches may represent a promising avenue for treating DKD by restoring the balance of the gut flora, enhancing intestinal barrier integrity, and decreasing the production of uremic toxins. Additionally, the integration of contemporary scientific advancements, such as nanotechnology and gene editing, could facilitate the creation of innovative TCM formulations, thereby improving drug targeting and bioavailability and ultimately leading to new breakthroughs in the treatment of DKD.

The Future Role of TCM in the Management of DKD

TCM is expected to play a significant and multifaceted role in the management of DKD. In the context of comprehensive treatment, TCM can be integrated with conventional Western medical approaches to create a synergistic effect and enhance therapeutic outcomes while mitigating the adverse effects associated with Western pharmacotherapy. For instance, in conjunction with the regulation of blood glucose and blood pressure, TCM may further safeguard renal function and impede DKD progression by enhancing renal microcirculation, diminishing inflammatory responses, and modulating immune function.

Regarding disease prevention, TCM offers the advantage of "preventive treatment of disease". For individuals diagnosed with pre-diabetes or early stage DKD, TCM can facilitate a tailored approach through constitutional identification and syndrome differentiation. This comprehensive intervention may include TCM therapies, dietary modifications, and exercise recommendations, all of which aim to improve the body's metabolic status and to prevent or delay the onset and progression of DKD. Furthermore, TCM plays a distinctive role in alleviating symptoms and enhancing the quality of life of patients, addressing issues such as fatigue, edema, and musculoskeletal discomfort, thereby significantly contributing to the long-term management of DKD.

Abbreviations

DKD, diabetic kidney disease; ESRD, end-stage renal disease; RCT, randomized controlled trials; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; ACR, albumin/creatinine ratio; RRT, renal replacement therapy; RAAS, renin-angiotensin-aldosterone system; JGA, juxtaglomerular apparatus; ATP, adenosine triphosphate; RPF, renal plasma flow; MRI, Magnetic Resonance Imaging; ECM, extracellular matrix; HIFla, hypoxia-inducible factor la; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; SCr, serum creatinine; BUN, blood urea nitrogen; Cys-C, cystatin-C; m-UALB, urinary microalbumin; UACR, urinary albumin/urinary creatinine; FBG, fasting blood glucose; 2 hPG, 2 H postprandial plasma glucose; hs-CRP, high-sensitivity C-reactive protein; UAER, urinary albumin excretion rate; PCX, podocyte marker protein; CD2AP, CD2-related protein; SIRT1, silent information regulation factor 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1α; 24-h up, 24-hour urine protein; TG, serum triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SOD, superoxide dismutase; GSH, glutathione; CAT, catalase; MDA, malondialdehyde; HE, hematoxylin-eosin; PAS, periodic acid Schiff; α-SMA, α-smooth muscle actin; Col I, collagen I; FN, fibronectin; CHI3L1, chitinase 3-like protein 1; SOCS3, suppressor of cytokine signal transduction 3; β2-MG, β2-microglobulin; MRA, middle segmental artery; SRA, renal segmental artery; IRA, interlobar artery.

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The authors declare that they have no affiliation with, or involvement in, any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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