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A prospective cohort study on *Qiling Hushen* Formula in the treatment of type 2 diabetic kidney disease

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Abstract: Objective To observe the clinical efficacy and safety of *Qiling Hushen* Formula on proteinuria and renal function in patients with type 2 diabetic kidney disease (T2DKD) of dampness-stasis obstructing collaterals syndrome. Methods A total of 380 T2DKD patients admitted to the Department of Endocrinology, Jiangsu Provincial Hospital of Chinese Medicine from August 2022 to August 2025 were enrolled. They were divided into the Chinese medicine group and the control group according to whether *Qiling Hushen* Formula was taken, with 190 cases in each group. The control group was given simple basic western medicine treatment, while the Chinese medicine group was given *Qiling Hushen* Formula on the basis of control group. The course of treatment for both groups was 12 weeks. Changes in urinary albumin- to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), glucose and lipid metabolism indicators cholesterol (LDL - C) and total score of Chinese medicine syndromes were observed in the two groups of T2DKD patients before and after treatment, and the occurrence of adverse event reactions and conduct statistics were recorded. Results During the clinical study, 25 patients in the Chinese medicine group dropped out or were excluded and 165 cases completed the trial. In the control group, 26 patients dropped out or were excluded and 164 cases completed the trial. After treatment, the UACR level of T2DKD patients in both groups was significantly lower than that before treatment (P<0.05), and the decreasing range in the Chinese medicine group was significantly better than that in the control group (P<0.01). There was no significant difference in UACR of patients in stage A2 of the control group before and after treatment (P>0.05), while the UACR of patients in stage A2 of the Chinese medicine group was significantly decreased after treatment compared to before treatment (P<0.01). After treatment, the UACR of patients in stage A3 of both groups was significantly lower than that before treatment (P<0.05), and the decreasing range in the Chinese medicine group was still significantly better than that in the control group (P<0.01). According to the subgroup analysis of eGFR level by GA stage, there was no significant difference in eGFR between before and after treatment and between the two groups in both the control group and the Chinese medicine group (P>0.05). After treatment, HbA1C in both groups was lower than that before treatment (P<0.05) ; TC and LDL-C in the Chinese medicine group after treatment were lower than those before treatment (P<0.05), while there was no statistically significant difference between the two groups (P>0.05). The total score of Chinese medicine syndromes in both groups decreased after treatment, and the total score in the Chinese medicine group was significantly lower than that in the control group (11.6±3.6 *vs* 17.2±6.2, t=9.991, P<0.01). The total incidence of adverse reactions was 5.45% (9/165) in the Chinese medicine group and 3.05% (5/164) in the control group, and there was no statistically significant difference between the two groups (χ^2=1.168, P=0.280). Conclusion Compared with simple basic western medicine treatment, *Qiling Hushen* Formula combined with basic western medicine treatment was confirmed to significantly reduce the UACR level proteinuria of T2DKD patients and effectively improve clinical symptoms with good safety.

Keywords: Type 2 diabetes mellitus; Diabetic kidney disease; *Qiling Hushen* Formula; Proteinuria; Urinary albumin- to-creatinine ratio; Estimated glomerular filtration rate
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Type 2 diabetic kidney disease (T2DKD) is a common microvascular complication of type 2 diabetes mellitus and the leading cause of end-stage kidney disease [1]. A meta-analysis has shown that the prevalence of T2DKD among Chinese patients with type 2 diabetes is 21.8% [2]. Owing to the continuously increasing incidence of type 2 diabetes, the number of patients with T2DKD has also been rising annually, posing a serious threat to the health of the Chinese population and imposing a heavy socioeconomic burden. Therefore, early prevention of T2DKD and delay of disease progression are of critical importance. The main clinical manifestations of T2DKD include persistent elevation of urinary protein and a decline in estimated glomerular filtration rate (eGFR) [3]. Currently, conventional Western medical interventions for T2DKD include intensive glycemic control, blood pressure management, lipid regulation, and early use of renin-angiotensin-aldosterone system (RAAS) inhibitors, sodium-dependent glucose transporters 2 inhibitors (SGLT2i), mineralocorticoid receptor antagonists (MRA), and glucagon-like peptide-1 receptor agonists (GLP-1RA), which have achieved certain clinical benefits [1].

In recent years, multiple studies have confirmed that angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) can reduce urinary protein and delay the progression of DKD in patients with T2DKD [4-5]; however, their clinical application is limited by renal function and serum potassium levels. The addition

of MRA to RAAS inhibitors can effectively reduce proteinuria levels in patients with chronic kidney disease, but it may increase the risk of hyperkalemia and acute kidney injury [6]. SGLT2i can reduce the risk of T2DKD progression, but they are often associated with increased risks of genitourinary tract infections, lower-limb amputation, and ketoacidosis, and are not recommended for T2DKD patients with eGFR <45 mL/(min·1.73 m²) [7]. Compared with SGLT2i, GLP-1RA can be used in patients with lower eGFR, but their gastrointestinal adverse reactions may reduce medication adherence [7]. Therefore, how to effectively delay the progression of T2DKD remains a therapeutic challenge and a bottleneck issue in clinical practice.

In recent years, traditional Chinese medicine (TCM) has demonstrated significant clinical efficacy and unique advantages in reducing proteinuria, delaying renal function decline, improving clinical symptoms, and regulating glucose and lipid metabolism in patients with T2DKD [8-9]. According to TCM theory, "dampness and blood stasis obstructing the collaterals" is considered the main pathogenesis of T2DKD [10-11]. Based on this theory and combined with years of practical experience, our research group developed the *Qiling Hushen* Formula, which is purported to have the effects of "drain dampness and resolve stasis to free the collateral vessels" Preliminary clinical studies have shown that this formula can reduce urinary protein in T2DKD [12], and basic research has suggested that it can lower urinary protein levels and improve glomerular hyperfiltration in a mouse model of DKD [13]. The present trial was designed to further evaluate the clinical efficacy and safety of the *Qiling Hushen* Formula on proteinuria and renal function impairment in patients with T2DKD using a prospective cohort study, with the aim of providing new evidence-based support for TCM treatment of T2DKD. The report is as follows.

1 Subjects and Methods

1.1 Sample Size Estimation

The primary outcome measure of this study was the reduction in the natural logarithm-transformed urinary albumin-to-creatinine ratio (UACR). Based on preliminary experimental data and the literature [12], the mean difference in the reduction of log-transformed UACR between the TCM group and the control group was Δ=0.87, with a pooled standard deviation σ=1.09. A two-sided α=0.05, power 1-β=0.9, superiority margin=0.3, and a 1:1 group sample size ratio was set. Sample size calculation was performed using R software, yielding 138 cases required per group. Considering a 10% dropout rate, at least 152 cases per group were ultimately needed, totaling 304 cases. The present study enrolled 380 patients (190 in the TCM group and 190 in the control group), maintaining a 1:1 group ratio.

1.2 General Information

A total of 380 patients with T2DKD admitted to the Department of Endocrinology at Jiangsu Provincial Hospital of Chinese Medicine from August 2022 to August 2025 were enrolled in this study.

Diagnostic criteria:

(1) Western medical diagnostic criteria for DKD: according to the *Chinese Guidelines for the Prevention and Treatment of Diabetic Kidney Disease (2021 Edition)* [7], the diagnosis of T2DKD was established when diabetes was identified as the cause of kidney damage and other causes of chronic kidney disease were excluded, with at least two out of three measurements over a period of 3–6 months showing UACR ≥30 mg/g or urinary protein excretion rate ≥30 mg/24 h, and/or eGFR <60 mL/(min·1.73 m²) persisting for more than 3 months.

(2) TCM syndrome differentiation criteria: based on the *Staging and Syndrome Differentiation Criteria for Diabetic Kidney Disease and Its Therapeutic Efficacy Evaluation Scheme and Research* [14] and the *Guiding Principles for Clinical Research of New Chinese Medicines for the Treatment of Diabetes* [15], the syndrome of dampness and blood stasis obstructing collaterals was defined. The primary symptoms included facial and limb edema, fatigue and weakness, soreness and weakness of the waist and knees, and abdominal distension and fullness; secondary symptoms included dry mouth and throat, numbness of the extremities, heat in the palms and soles, and turbid frothy urine; tongue and pulse manifestations included a dark tongue or with ecchymosis, a thin white or white greasy coating, and a deep, slow, or fine, hesitant pulse. The diagnosis of dampness and blood stasis obstructing collaterals was established when at least two primary and two secondary symptoms were present, in combination with the tongue and pulse findings.

Inclusion criteria:

(1) meeting the Western medical diagnostic criteria for T2DKD;

(2) aged 25–75 years, regardless of gender;

(3) UACR between 30 and 3,500 mg/g;

(4) eGFR ≥15 mL/(min·1.73 m²);

(5) providing informed consent and voluntarily participating in this trial.

Exclusion criteria:

(1) occurrence of acute diabetic complications within 1 month, such as diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, or a history of severe liver disease, acute heart failure, acute cerebrovascular disease, or end-stage malignant tumors;

(2) use of glucocorticoids, immunosuppressants, or Tripterygium wilfordii preparations within 3 months;

(3) pregnancy or lactation;

(4) psychiatric disorders or other conditions rendering the patient unable to cooperate;

(5) other conditions judged medically inappropriate for inclusion in this clinical study.

Withdrawal criteria:

(1) voluntary request by the patient to withdraw from the study;

(2) loss to follow-up.

Exclusion criteria for analysis:

(1) failure to meet inclusion criteria or meeting exclusion criteria;

(2) failure to take medication as required or incomplete treatment;

(3) concurrent participation in other clinical studies during the treatment period;

(4) occurrence of serious adverse events during treatment, with assessment indicating that continuation of treatment was not appropriate;

(5) occurrence of cardiovascular or cerebrovascular events or severe infections during treatment;

(6) use of medications during treatment that were medically judged to potentially interfere with the results of this study.

Patients were divided into a TCM group and a control group based on whether they received the *Qiling Hushen* Formula, with 190 cases in each group. Additionally, patients were staged according to eGFR into G stages: G1 [≥30 mL/(min·1.73 m²)], G2 [60–<90 mL/(min·1.73 m²)], G3 [30–<60 mL/(min·1.73 m²)], and G4 [15–<30 mL/(min·1.73 m²)]. According to UACR, patients were staged into A2 (30–300 mg/g) and A3 (>300–3,500 mg/g). The above GA staging referred to the *KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease* [3]. During follow-up, 7 patients in the TCM group and 16 in the control group were excluded because they used other TCM compound formulas during the treatment course; 4 patients in the TCM group were excluded for not taking the TCM formula as required; 14 patients in the TCM group and 10 in the control group dropped out due to failure to return for follow-up for personal reasons. Ultimately, 329 valid cases were included (165 in the TCM group and 164 in the control group), with a total dropout rate of 13.4%. Compared with the control group, fewer patients in the TCM group used SGLT2i (P<0.05). No statistically significant difference was observed between the two groups in terms of age, gender, duration of diabetes, blood pressure, body mass index (BMI), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), UACR, eGFR, comorbidities, other medication use, or GA staging **(Table 1).** The study protocol was approved by the Ethics Committee of Jiangsu Provincial Hospital of Traditional Chinese Medicine (approval No.: 2018NL-108-02).

1.3 Treatment Protocols

1.3.1 Control Group

Based on the *Chinese Guidelines for the Prevention and Treatment of Diabetic Kidney Disease (2021 Edition)* [7], the control group received standard care, including lifestyle modification and control of blood glucose, blood pressure, and blood lipids. Glycemic management: according to eGFR levels, glucose-lowering regimens with good renal safety recommended by the guidelines, including GLP-1RA, linagliptin, and insulin, were selected. Individualized HbA1c targets were set, with FBG ≤7.0 mmol/L, 2-hour postprandial blood glucose ≤10.0 mmol/L, and HbA1c ≤7.0%. Blood pressure management: ACEI/ARB medications were used at tolerable doses to maintain blood pressure below 130/80 mmHg, with regular monitoring of serum potassium and creatinine to maximize renal protection while controlling risks. Cardiovascular risk prevention: atorvastatin ± ezetimibe was selected to maintain TC ≤4.5 mmol/L and LDL-C ≤2.5 mmol/L. Basic symptomatic interventions: high-quality low-protein diet, smoking cessation and alcohol restriction, correction of renal anemia and calcium-phosphorus metabolic disorders, and avoidance of nephrotoxic drugs.

Tab.1 Comparison of general data between two groups [$M(P_{25},P_{75})$]

Indicator	Control group (n=164)	TCM group (n=165)	Z/χ^2 value	P value
Age(year)	61.0 (50.0, 69.0)	58.0 (46.0, 68.0)	1.568	0.117
Gender[case(%)]				
Male	117 (71.3)	107 (64.8)	1.596	0.207
Female	47 (28.7)	58 (35.2)		
Duration(year)	10.0 (5.0, 14.7)	9.0 (5.0, 15.0)	0.238	0.812
BMI(kg/m²)	24.1±2.8	23.9±2.6	0.496	0.621
SBP(mmHg)	136.0 (128.0, 139.7)	135.8 (126.5, 145.5)	0.577	0.564
DBP(mmHg)	80.0 (75.0, 88.0)	80.9 (74.0, 85.0)	0.087	0.931
FBG(mmol/L)	7.3 (5.9, 8.8)	7.2 (5.8, 8.7)	0.343	0.731
HbA_{1C}(%)	8.0 (7.0, 9.6)	7.7 (6.8, 8.9)	1.744	0.081
TC(mmol/L)	4.5 (3.8, 5.5)	4.6 (3.8, 5.5)	0.755	0.450
LDL-C(mmol/L)	2.6 (2.1, 3.1)	2.7 (2.0, 3.3)	1.173	0.241
UACR(mg/g)	285.0 (93.5, 731.2)	360.0 (138.5, 884.0)	1.919	0.055
eGFR[mL/(min·1.73m²)]	67.0 (51.2, 93.0)	74.1 (51.0, 101.0)	1.113	0.266
Comorbidities [n (%)]				
Hypertension	113 (68.9)	119 (72.1)	0.410	0.522
Hyperlipidemia	60 (36.6)	71 (43.0)	1.426	0.232
Hyperuricemia	31 (18.9)	39 (23.6)	1.100	0.294
CHD	20 (12.2)	25 (15.2)	0.609	0.435
Cerebral infarction	31 (18.9)	31 (18.8)	0.001	0.979
Combination drug use [n (%)]				
Insulin	89 (54.3)	92 (55.8)	0.074	0.786
Insulin secretagogues	40 (24.4)	55 (33.3)	3.203	0.074
SGLT2i	51 (31.1)	15 (9.1)	24.839	<0.01
DPP-4	59 (36.0)	56 (33.9)	0.150	0.699
GLP-1RA	36 (22.0)	33 (20.0)	0.189	0.664
ACEI/ARB	80 (48.8)	82 (49.7)	0.028	0.868
Statins	63 (38.4)	64 (38.8)	0.005	0.945
Antiplatelet drugs	51 (31.1)	36 (21.8)	3.641	0.056
G Stage [n (%)]				
G1	48 (29.3)	60 (36.4)	3.645	0.302
G2	57 (34.7)	50 (30.3)		
G3	48 (29.3)	39 (23.6)		
G4	11 (6.7)	16 (9.7)		
A Stage [n (%)]				
A2	84 (51.2)	74 (44.8)	1.337	0.248
A3	80 (48.8)	91 (55.2)		

1.3.2 TCM Group

In addition to the same treatment as the control group, the TCM group received the *Qiling Hushen* Formula, composed of *Astragali Radix* (Huangqi,黄芪)20 g, *Poria* (Fuling,茯苓)20 g, *Paeoniae Radix Rubra* (Chishao,赤

芍)10 g, *Achyranthis Bidentatae Radix* (Niuxi,牛膝)10 g, *Corni Fructus* (Shanzhuyu, 山茱萸)15 g, *Dioscoreae Rhizoma* (Shanyao, 山药)15 g, *Imperatae Rhizoma* (Baimaogen, 白茅根)20 g, *Lonicerae Japonicae Flos* (Jinyinhua, 金银花)10 g, *Luffae Fructus Retinervus* (Sigualuo,丝瓜络)15 g, *Plantaginis Semen* (Cheqianzi,车前子)10 g. The formula was uniformly decocted by the Chinese pharmacy of Jiangsu Provincial Hospital of Traditional Chinese Medicine to a volume of 400 mL, with 200 mL administered orally after breakfast and dinner each day. Treatment was continued until the end of follow-up (12 weeks after enrollment).

1.4 Observational Indices

1.4.1 Primary Outcome Measures

(1) Urinary protein: comparison of UACR between the two groups in all T2DKD patients and in the A2 and A3 stage subgroups.

(2) Renal function: comparison of eGFR between the two groups in all T2DKD patients and in the G2, G3, and G4 stage subgroups.

1.4.2 Secondary Outcome Measures

(1) Glucose and lipid metabolic parameters: FBG, HbA1c, TC, and LDL-C.

(2) Quantified Chinese medicine syndrome scores: according to the *Staging and Syndrome Differentiation Criteria for Diabetic Kidney Disease and Its Therapeutic Efficacy Evaluation Scheme and Research* [14] and the *Technical Guiding Principles for Clinical Research of New Chinese Medicines for Diabetic Kidney Disease (2020 Edition)*, a Chinese medicine syndrome score table was used for quantification. Primary symptoms were graded as none (0 points), mild (2 points), moderate (4 points), or severe (6 points) according to severity; secondary symptoms were graded as none (0 points), mild (1 point), moderate (2 points), or severe (3 points).

1.4.3 Safety Indicators

Routine blood tests, liver function tests, and electrocardiographic examinations were performed, and the incidence of adverse reactions was evaluated.

1.5 Statistical Methods

Statistical analysis was performed using SPSS 27.0 software. For continuous variables, normality was assessed using the Shapiro-Wilk test. Normally distributed data were expressed as $\bar{x} \pm s$, with comparisons between groups performed using independent-sample *t*-tests and within-group comparisons using paired-sample *t*-tests. Non-normally distributed data were expressed as $M(P_{25},P_{75})$, with comparisons between groups performed using the Wilcoxon rank-sum test and within-group comparisons using the paired rank-sum test. Categorical data were expressed as cases (percentages) and compared using the chi-square test. Ordinal data were compared using the rank-sum test. A *P*-value of <0.05 was considered statistically significant.

2 Results

2.1 Comparison of UACR

Before treatment, there was no statistically significant difference in UACR between the control group and the TCM group among all T2DKD patients ($P>0.05$). After treatment, UACR decreased significantly in both groups compared with baseline ($P<0.05$), and the reduction in the TCM group was significantly greater than that in the control group ($P<0.01$). Subgroup analysis showed that before treatment, there was no statistically significant difference in UACR between the control group and the TCM group in both the A2 and A3 stage subgroups ($P>0.05$). In the control group, UACR in A2 stage patients showed no significant difference before and after treatment ($P>0.05$), whereas in the TCM group, UACR in A2 stage patients decreased significantly after treatment compared with baseline ($P<0.01$). In both groups, UACR in A3 stage patients decreased significantly after treatment compared with baseline ($P<0.01$), and the reduction in the TCM group was significantly greater than that in the control group ($P<0.01$). See **Table 2**.

Tab.2 Comparison of UACR before and after treatment in the two groups and each subgroup [mg/g, $M(P_{25},P_{75})$]

Stage	Control group	TCM group	*Z* value	*P* value
All patients (Control group, *n*=164; TCM group, *n* =165)				
Before treatment	285.0(93.5, 731.2)	360.0(138.5, 884.0)	1.919	0.055
After treatment	274.5 (85.5, 624.7)[a]	190.0 (58.5, 523.5)[a]	1.751	0.080
D-value	20.0(−41.2, 92.5)	102.0(36.0, 374.5)	6.927	<0.001
A2 (Control group, *n* =84; TCM group, *n* =74)				
Before treatment	107.0(56.5, 166.0)	129.0(84.5, 173.0)	1.692	0.091
After treatment	94.5(48.2, 163.7)	57.5(33.7, 114.2)[a]	2.845	0.004
D-value	11.0(−46.5, 32.0)	52.0(22.7, 94.0)	5.147	<0.001
A3 (Control group, *n* =80; TCM group, *n* =91)				
Before treatment	740.5 (463.7, 1,056.5)	848.0 (470.0, 1,690.0)	0.952	0.341
After treatment	621.5 (352.5, 1,129.5)[a]	455.0 (238.0, 1,103.0)[a]	2.337	0.019
D-value	61.0(−34.0, 187.0)	327.0(119.0, 649.0)	5.661	<0.001

Note: Compared with before treatment in same group, [a]*P*<0.05.

2.2 Comparison of Renal Function

Before treatment, there was no statistically significant difference in eGFR between the control group and the TCM group ($P>0.05$). No statistically significant differences were observed in eGFR within either group before and after treatment, nor between the two groups after treatment ($P>0.05$). Subgroup analysis showed that before treatment, there was no statistically significant difference in eGFR between the control group and the TCM group in the G2, G3, and G4 stage subgroups ($P>0.05$). In the TCM group, eGFR in G3 stage T2DKD patients showed an increasing trend after treatment compared with baseline, but the difference was not statistically significant ($P>0.05$). See **Table 3**.

2.3 Comparison of Glucose and Lipid Metabolic Parameters

Before treatment, there was no statistically significant difference in glucose and lipid metabolic parameters between the control group and the TCM group (P>0.05). After treatment, FBG in both groups showed a decreasing trend compared with baseline, but the difference was not significant (P>0.05); HbA1c in both groups decreased significantly compared with baseline (P<0.05), and there was no significant difference in ΔFBG or ΔHbA1c between the two groups (P>0.05). In the TCM group, TC and LDL-C showed statistically significant differences before and after treatment (P<0.05), and the between-group difference in ΔTC was statistically significant (P<0.05). See **Table 4.**

2.4 Changes in Total Chinese Medicine Syndrome Scores

There was no significant difference in total Chinese medicine syndrome scores between the two groups before treatment (P>0.05). After treatment, within-group comparisons and between-group comparisons both showed statistically significant differences (P<0.01), and the total Chinese medicine syndrome score in the TCM group was significantly lower than that in the control group after treatment (P<0.01). See **Table 5.**

2.5 Safety Evaluation

During the treatment period, 5 cases of gastrointestinal reactions and 4 cases of abnormal liver function occurred in the TCM group; in the control group, there were 2 cases of gastrointestinal reactions, 1 case of abnormal liver function, and 2 cases of leukopenia. No rash, pruritus, or electrocardiographic abnormalities were observed in either group. The overall incidence of adverse reactions was 5.45% (9/165) in the TCM group and 3.05% (5/164) in the control group (χ^2=1.168, P=0.280). All adverse reactions improved after symptomatic treatment, and no other serious adverse reactions occurred.

Tab.3 Comparison of eGFR before and after treatment in the two groups and each subgroup[mL/(min·1.73m^2), $M(P_{25},P_{75})$]

Stage	Control group	TCM group	*Z* value	*P* value
All patients (Control group, *n* =164; TCM group, *n* =165)				
Before treatment	67.0(51.2, 93.0)	74.1(51.0, 101.0)	1.113	0.266
After treatment	71.0(50.0, 91.0)	75.0(50.5, 100.2)	1.087	0.277
D-value	0(-5.0, 5.0)	1.0(-5.0, 5.0)	0.352	0.725
G2 (Control group, *n* =57; TCM group, *n* =50)				
Before treatment	71.0(64.0, 82.0)	74.0(67.7, 80.0)	0.531	0.595
After treatment	75.0(63.0, 81.0)	74.2(64.0, 80.0)	0.134	0.893
D-value	0(-8.5, 5.5)	0(-5.0, 6.5)	0.153	0.878
G3 (Control group, *n* =48; TCM group, *n* =39)				
Before treatment	47.5(39.2, 54.0)	46.0(38.0, 53.0)	0.286	0.775
After treatment	47.5(38.5, 59.0)	49.0(37.0, 55.0)	0.423	0.672
D-value	0(-8.6, 3.0)	-3.0(-7.0, 5.0)	0.543	0.587
G4 (Control group, *n* =11; TCM group, *n* =16)				
Before treatment	24.0(19.0, 26.0)	24.5(21.2, 28.0)	0.942	0.368
After treatment	22.0(19.0, 32.0)	24.5(22.0, 29.0)	0.670	0.503
D-value	0(-5.0, 2.0)	-0.5(-2.7, 2.0)	0.224	0.823

Tab.4 Comparison of glucose and lipid metabolism indicators before and after treatment in two groups [$M(P_{25},P_{75})$]

Indicators	Control group (*n*=164)	TCM group (*n*=165)	*Z* value	*P* value
FBG(mmol/L)				
Before treatment	7.3(5.9, 8.8)	7.2(5.8, 8.7)	0.343	0.731
After treatment	7.0(5.9, 8.3)	6.7(5.9, 7.7)	1.184	0.237
D-value	0(-1.2, 1.7)	0.1(-0.8, 1.6)	1.124	0.261
HbA_{1c}(%)				
Before treatment	8.0(7.0, 9.6)	7.7(6.8, 8.9)	1.744	0.081
After treatment	7.3(6.6, 8.4)[a]	7.2(6.6, 8.0)[a]	0.717	0.473
D-value	0.4(-0.1, 1.4)	0.3(-0.2, 1.2)	0.753	0.452
TC(mmol/L)				
Before treatment	4.5(3.8, 5.5)	4.6(3.8, 5.5)	0.755	0.450
After treatment	4.5(3.8, 5.2)	4.4(3.8, 5.3)[a]	0.505	0.614
D-value	-0.1(-0.5, 0.5)	0.1(-0.2, 0.6)	2.186	0.029
LDL-C(mmol/L)				
Before treatment	2.6(2.1, 3.1)	2.7(2.0, 3.3)	1.173	0.241
After treatment	2.5(2.0, 3.1)	2.5(2.1, 3.2)[a]	0.590	0.555
D-value	0(-0.3, 0.4)	0.1(-0.2, 0.4)	1.484	0.138

Note: Compared with before treatment in same group, [a]P<0.05.

Tab.5 Comparison of total Chinese medicine syndrome scores before and after treatment in two groups (point, $\bar{x} \pm s$)

Group	Before treatment	After treatment	D-value
Control group(*n*=164)	19.9±5.1	17.2±6.2[a]	2.6±7.2
TCM group(*n*=165)	20.3±4.5	11.6±3.6[a]	8.7±4.8[b]
***t* value**	0.754	10.026	9.046
***P* value**	0.451	<0.001	<0.001

Note: Compared with before treatment in same group, [a]P<0.05.

3 Discussion

The development and progression of T2DKD result from the interplay of multiple pathophysiological mechanisms, including hyperglycemia-related metabolic abnormalities, hemodynamic alterations, inflammatory responses, oxidative stress, and genetic susceptibility [16-17]. The core pathological mechanisms primarily involve the formation of advanced glycation end-products, activation of protein kinase C, and aberrant activation of the RAAS, which collectively lead to disruption of the glomerular filtration barrier, thickening of the glomerular basement membrane, glomerulosclerosis, and tubulointerstitial fibrosis [18]. Patients with T2DKD are often asymptomatic in the early stages; once persistent massive proteinuria emerges, the disease tends to progress irreversibly toward end-stage renal failure. Therefore, early intervention in the development and progression of T2DKD is of great significance for improving the survival rate and quality of life of patients with diabetes mellitus.

In TCM, T2DKD falls under the categories of "edema (shuizhong, 水肿)" "consumptive disease (xulao, 虚劳)" and "difficulty in urination and defecation (guange, 关格)" [19]. The *Shengji Zonglu* (General Medical Collection of Royal Benevolence, 圣济总录) states: "Excessive consumption of water in diabetes, over time leads to leakage of lipid-rich substances, depletion of body fluids, which descend to the bladder, mix with the turbid urine, and are discharged as cloudy urine, hence it is called diabetes with white turbid urine." In TCM theory, both glucose and lipid toxins are considered dampness-heat

pathogens. They first impair the spleen (pi-earth), leading to dysfunction of the spleen in transportation and transformation. Over time, they accumulate in the kidney, obstructing the flow of qi. This results in qi not circulating blood, leading to poor blood circulation. Over time, this can lead to blood stasis. Dampness, heat, stasis, and toxin become mutually entangled, resulting in obstruction of the kidney collaterals, loss of the kidney's storing function, loosening of the essence gate, and leakage of subtle essences, manifesting as proteinuria. Over time, dampness, heat, stasis, and toxin consume the kidney qi, leading to kidney deficiency and collateral damage, which further aggravates renal injury. This indicates that dampness, heat, stasis, and toxin are not only pathological products but also causative factors, running through the entire course of the disease [11]. Professor An Xiaofei, targeting the fundamental pathogenesis of dampness and stasis obstructing collaterals in T2DKD, has proposed the therapeutic principle of " drain dampness and resolve stasis to free the collateral vessels" on the basis of strengthening the spleen and tonifying the kidney, attending to both deficiency and excess and addressing both the root and the branch, and formulated the *Qiling Hushen* Formula accordingly [12]. In this formula, Huangqi is heavily dosed to replenish qi, strengthen the spleen, raise yang, and promote diuresis, while Fuling strengthens the spleen, promotes diuresis, and drains dampness; these two herbs serve as the sovereign drugs. Chishao invigorates blood and resolves stasis, and Niuxi tonifies the kidney, invigorates blood, and promotes diuresis; these are the minister drugs. Shanyao tonifies the spleen and kidney, replenishes qi and nourishes yin; Shanzhuyu tonifies the liver and kidney; Baimaogen clears heat, cools blood, and promotes diuresis; these serve as assistant drugs. Jinyinhua clears heat and detoxifies; Sigualuo unblocks the meridians and collaterals; and Cheqianzi promotes diuresis and treats strangury; these are the messenger drugs. The entire formula achieves the effects of draining dampness, resolving stasis, unblocking collaterals, and tonifying the kidney. Previous clinical practice has demonstrated that the *Qiling Hushen* Formula has a definite effect in reducing proteinuria in T2DKD patients with the syndrome of dampness and stasis obstructing collaterals, and can significantly improve patients' clinical symptoms [12]. However, large-scale evidence-based medical data are still lacking regarding its efficacy in improving proteinuria and renal function impairment in T2DKD patients.

Based on previous clinical observations, the present study aimed to expand the clinical sample size and optimize the inclusion criteria. A total of 329 T2DKD patients who completed follow-up were included (165 in the TCM group and 164 in the control group). The results of the present study demonstrated that the reduction in UACR in the TCM group, both in A2 and A3 stage patients, was statistically significant compared with the control group patients at the same stages. Meanwhile, TC and LDL-C levels in the TCM group were significantly reduced after treatment compared with baseline. The total TCM syndrome scores in both groups decreased significantly after treatment. These findings indicate that adding the *Qiling Hushen* Formula to conventional Western medical treatment offers advantages in reducing proteinuria and alleviating clinical symptoms in patients with T2DKD.

The *Qiling Hushen* Formula effectively reduced proteinuria across various T2DKD subgroups, but no significant improvement in eGFR was observed. A comprehensive analysis suggests the following possible reasons: (1) Previous studies have shown a certain time lag between the reduction of proteinuria and the improvement of eGFR in the treatment of kidney disease; it may take 3 to 6 months or even longer of sustained proteinuria reduction before a significant increase in eGFR can be observed [20]. The relatively short follow-up duration in the present study (12 weeks) may have been insufficient to detect the beneficial effect of the *Qiling Hushen* Formula on eGFR in T2DKD patients. (2) Renal function in patients with G2 and G3 stage T2DKD is relatively stable and declines slowly, making it difficult to observe significant changes in eGFR over a short period of intervention. In the present study, the proportion of G3 and G4 stage patients in the TCM group (55/165, 33.3%) was relatively low, which may have limited the accuracy of assessing the potential improvement of eGFR by the *Qiling Hushen* Formula in patients with moderate to advanced renal impairment. Future studies could prolong the follow-up period, increase the relative sample size of G3 and G4 stage patients, and further control confounding factors such as concomitant medications, in order to conduct in-depth investigations into the clinical efficacy of the *Qiling Hushen* Formula in delaying the progression of renal function in T2DKD patients.

In conclusion, this prospective cohort study indicates that the addition of the *Qiling Hushen* Formula to conventional Western medical treatment can significantly reduce proteinuria levels, alleviate clinical symptoms, and improve quality of life in patients with T2DKD, with a favorable safety profile. Future multicenter randomized controlled trials with renal endpoint events as the primary efficacy measures and long-term follow-up are planned to provide more comprehensive efficacy data and more robust evidence-based support for the treatment of T2DKD with the *Qiling Hushen* Formula, thereby offering a more solid clinical research foundation for leveraging the characteristics and advantages of Chinese medicine in the management of T2DKD.

Conflict of Interest None

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·论　著·

芪苓护肾方治疗2型糖尿病肾病的前瞻性队列研究

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摘要：目的　观察芪苓护肾方对2型糖尿病肾病（T2DKD）湿瘀阻络证患者蛋白尿和肾功能损伤的临床疗效及安全性。**方法**　选取2022年8月至2025年8月江苏省中医院内分泌科收治的T2DKD患者380例，根据是否服用芪苓护肾方分为中药组与对照组，每组190例。对照组给予单纯西医基础治疗，中药组在对照组基础上给予芪苓护肾方，两组疗程均为12周。观察两组T2DKD患者治疗前后尿白蛋白/肌酐比值（UACR）、估算肾小球滤过率（eGFR）、糖脂代谢指标[包括空腹血糖（FBG）、糖化血红蛋白（HbA_{1c}）、总胆固醇（TC）、低密度脂蛋白胆固醇（LDL-C）]和中医证候总积分的变化情况，并统计不良反应发生情况。**结果**　在临床研究期间中药组患者脱落与剔除25例，165例完成试验；对照组脱落与剔除26例，164例完成试验。两组T2DKD患者治疗后UACR水平较治疗前均有明显下降（$P<0.05$），中药组下降幅度显著优于对照组（$P<0.01$）。对照组A2期患者治疗前后UACR差异无统计学意义（$P>0.05$），而中药组A2期患者治疗后UACR较治疗前显著下降（$P<0.01$）。两组A3期患者治疗后UACR均较治疗前明显下降（$P<0.05$），但中药组下降幅度显著优于对照组（$P<0.01$）。对照组和中药组eGFR在治疗前后比较及组间比较差异均无统计学意义（$P>0.05$）。两组治疗后HbA_{1c}较治疗前均下降（$P<0.05$），中药组治疗后TC、LDL-C较治疗前下降（$P<0.05$），但组间比较差异均无统计学意义（$P>0.05$）。两组中医证候总积分治疗后较治疗前均有下降（$P<0.05$），且治疗后中药组显著低于对照组（11.6±3.6 *vs* 17.2±6.2，$t=9.991$，$P<0.01$）。中药组和对照组的不良反应总发生率分别为5.45%（9/165）和3.05%（5/164），两组比较差异无统计学意义（$\chi^2=1.168$，$P=0.280$）。**结论**　与单纯西医基础治疗相比，芪苓护肾方联合西医基础治疗可以显著降低T2DKD患者UACR，且安全性良好。

关键词：2型糖尿病；糖尿病肾病；芪苓护肾方；蛋白尿；尿白蛋白/肌酐比值；估算肾小球滤过率
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A prospective cohort study on *Qiling Hushen* Formula in the treatment of type 2 diabetic kidney disease

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Abstract: Objective　To observe the clinical efficacy and safety of *Qiling Hushen* Formula on proteinuria and renal function in patients with type 2 diabetic kidney disease (T2DKD) of dampness-stasis obstructing collaterals syndrome. **Methods**　A total of 380 T2DKD patients admitted to the Department of Endocrinology, Jiangsu Provincial Hospital of Chinese Medicine from August 2022 to August 2025 were enrolled. They were divided into the Chinese medicine group and the control group according to whether *Qiling Hushen* Formula was taken, with 190 cases in each group. The control group was given simple basic western medicine treatment, while the Chinese medicine group was given *Qiling Hushen* Formula on the basis of control group. The course of treatment for both groups was 12 weeks. Changes in urinary albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), glucose and lipid metabolism indicators

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including fasting blood glucose (FBG), glycosylated hemoglobin (HbA_{1C}), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and total score of Chinese medicine syndromes were observed in the two groups of T2DKD patients before and after treatment, and the occurrence of adverse event reactions and conduct statistics were recorded. **Results** During the clinical study, 25 patients in the Chinese medicine group dropped out or were excluded and 165 cases completed the trial. In the control group, 26 patients dropped out or were excluded and 164 cases completed the trial. After treatment, the UACR level of T2DKD patients in both groups was significantly lower than that before treatment ($P<0.05$), and the decreasing range in the Chinese medicine group was significantly better than that in the control group ($P<0.01$). There was no significant difference in UACR of patients in stage A2 of the control group before and after treatment ($P>0.05$), while the UACR of patients in stage A2 of the Chinese medicine group was significantly decreased after treatment compared to before treatment ($P<0.01$). After treatment, the UACR of patients in stage A3 of both groups was significantly lower than that before treatment ($P<0.05$), and the decreasing range in the Chinese medicine group was still significantly better than that in the control group ($P<0.01$). According to the subgroup analysis of eGFR level by GA stage, there was no significant difference in eGFR between before and after treatment and between the two groups in both the control group and the Chinese medicine group ($P>0.05$). After treatment, HbA_{1C} in both groups was lower than that before treatment ($P<0.05$); TC and LDL-C in the Chinese medicine group after treatment were lower than those before treatment ($P<0.05$), while there was no statistically significant difference between the two groups ($P>0.05$). The total score of Chinese medicine syndromes in both groups decreased after treatment, and the total score in the Chinese medicine group was significantly lower than that in the control group (11.6±3.6 *vs* 17.2±6.2, $t=9.991$, $P<0.01$). The total incidence of adverse reactions was 5.45%(9/165) in the Chinese medicine group and 3.05%(5/164) in the control group, and there was no statistically significant difference between the two groups ($\chi^2=1.168$, $P=0.280$). **Conclusion** Compared with simple basic western medicine treatment, *Qiling Hushen* Formula combined with basic western medicine treatment was confirmed to significantly reduce the UACR level proteinuria of T2DKD patients and effectively improve clinical symptoms with good safety.

Keywords: Type 2 diabetes mellitus; Diabetic kidney disease; *Qiling Hushen* Formula; Proteinuria; Urinary albumin-to-creatinine ratio; Estimated glomerular filtration rate

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2型糖尿病肾病(type 2 diabetic kidney diseases, T2DKD)是2型糖尿病常见的微血管并发症,也是导致终末期肾病的首要原因[1]。荟萃分析表明,我国2型糖尿病患者T2DKD患病率为21.8%[2],由于2型糖尿病发病率持续升高,T2DKD患病人数也逐年攀升,严重威胁我国居民健康,并造成沉重的社会经济负担。因此,早期预防T2DKD并延缓疾病进展至关重要。T2DKD主要临床表现为持续性尿蛋白升高及估算肾小球滤过率(estimated glomerular filtration rate, eGFR)下降[3]。目前,西医治疗T2DKD的主要干预措施包括强化控制血糖、血压、血脂及早期使用肾素-血管紧张素-醛固酮系统(renin angiotensin aldosterone system, RAAS)抑制剂、钠-葡萄糖协同转运蛋白2抑制剂(sodium-dependent glucose transporters 2 inhibitor, SGLT2i)、盐皮质激素受体拮抗剂(mineralocorticoid receptor antagonist, MRA)、胰高糖素样肽-1受体激动剂(glucagon-like peptide-1 receptor agonist, GLP-1RA)等,取得了一定临床获益[1]。

近年多项研究证实,血管紧张素转化酶抑制剂(angiotensin converting enzyme inhibitor, ACEI)或血管紧张素受体拮抗剂(angiotensin receptor blocker, ARB)可减少T2DKD患者尿蛋白、延缓DKD进展[4-5],但临床应用受患者肾功能和血钾水平限制。在RAAS抑制剂基础上加用MRA可有效降低慢性肾脏病患者蛋白尿水平,但易导致高钾血症和急性肾损伤[6]。SGLT2i可降低T2DKD进展风险,但常增加泌尿生殖系统感染、下肢截肢及酮症酸中毒等风险,且不建议eGFR<45 mL/(min·1.73 m^2)的T2DKD患者使用[7]。与SGLT2i相比,GLP-1RA可在eGFR更低的患者中使用,但其胃肠道反应会降低患者用药依从性[7]。因此,如何有效延缓T2DKD的进展仍是该病的治疗难点和瓶颈问题。

近年来,中医药在降低T2DKD患者蛋白尿以及延缓肾功能减退、改善临床症状、调节糖脂代谢等方面取得显著临床疗效,并有独特优势[8-9]。中医理论认为"湿瘀阻络"为T2DKD的主要病机[10-11],基于上述理论并结合多年实践经验,本课题组拟定了具有"利湿化瘀通络"功效的芪苓护肾方,初步临床研究

显示其对T2DKD尿蛋白有降低作用[12]，基础研究提示该方可降低DKD小鼠模型尿蛋白水平并改善肾小球高滤过状态[13]。本试验拟采用前瞻性队列研究进一步评价芪苓护肾方对T2DKD患者蛋白尿及肾功能损伤的临床疗效和安全性，以期为中医药治疗T2DKD提供新的循证依据，现报道如下。

1　资料与方法

1.1　样本量估算　本研究以尿白蛋白/肌酐比值（urinary albumin-to-creatinine ratio，UACR）经自然对数转换后的下降幅度为主要结局指标。根据前期实验数据和文献[12]，中药组与对照组转换后UACR下降幅度的均值差Δ=0.87，合并标准差σ=1.09；设双侧α=0.05、把握度1−β=0.9，优效界值=0.3，组间样本量比值为1∶1。采用R软件计算样本量每组需138例。考虑10%失访等情况，最终每组至少需152例，总计需要纳入样本量为304例。本研究纳入380例患者（中药组190例，对照组190例），组间比例1∶1。

1.2　一般资料　本研究入组2022年8月至2025年8月江苏省中医院内分泌科收治的T2DKD患者380例。

诊断标准：（1）DKD西医诊断标准，符合《中国糖尿病肾脏病防治指南（2021年版）》中T2DKD的诊断标准[7]。明确糖尿病作为肾损害的病因并排除其他原因引起慢性肾脏病的情况下，在3~6个月内的3次检测中至少2次UACR≥30 mg/g或尿蛋白排泄率≥30 mg/24 h，和（或）eGFR<60 mL/（min·1.73 m^2）持续3个月以上。（2）中医辨证标准，参照《糖尿病肾脏病分期辨证规范与疗效评定方案及其研究》[14]及《中药新药治疗糖尿病的临床研究指导原则》[15]拟定湿瘀阻络证辨证标准。主症为面浮肢肿，倦怠乏力，腰膝酸软，脘腹胀满；次症为口干咽燥，肢体麻木，手足心热，尿多浊沫；舌脉为舌质暗或有瘀斑，苔薄白或白腻，脉沉缓或细涩。具备主症和次症各2项及以上，结合舌脉即可明确湿瘀阻络证。

纳入标准：（1）符合T2DKD西医诊断标准；（2）年龄25~75岁，性别不限；（3）UACR为30~3 500 mg/g；（4）eGFR≥15 mL/（min·1.73 m^2）；（5）对本试验知情同意，并自愿参加。

排除标准：（1）1个月内发生过糖尿病急性并发症，如糖尿病酮症酸中毒、高糖高渗综合征，或有严重肝病、急性心力衰竭、急性脑血管病或终末期恶性肿瘤等病史；（2）3个月内有糖皮质激素、免疫抑制剂或雷公藤制剂使用史；（3）处于妊娠、哺乳期；（4）患有精神病或其他情况不能合作；（5）经医学判断不适合纳入本临床研究的其他情况。

脱落标准：（1）患者自行要求退出研究；（2）失访病例。剔除标准：（1）不符合纳入标准或符合排除标准；（2）未按要求用药或未完成治疗；（3）治疗期间同时参加其他临床研究；（4）治疗期间出现严重不良事件，经评估不宜继续治疗；（5）治疗期间发生心脑血管事件或严重感染等重大疾病；（6）治疗期间使用医学判定可能干扰本研究结果的药物。

根据患者是否接受服用芪苓护肾方分为中药组和对照组，每组各190例。另根据患者的eGFR进行G分期，即G1期[≥30 mL/（min·1.73 m^2）]、G2期[60~<90 mL/（min·1.73 m^2）]、G3期[30~<60 mL/（min·1.73 m^2）]和G4期[15~<30 mL/（min·1.73 m^2）]；根据患者的UACR进行A分期，即A2期（30~300 mg/g）、A3期（>300~3 500 mg/g）。以上GA分期参考*KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease*分期标准[3]。随访过程中7例中药组和16例对照组患者因疗程内使用其他中药复方而剔除，4例中药组患者因未按要求服用中药而剔除，14例中药组和10例对照组患者由于个人原因未能复诊而脱落，最终有效病例329例（中药组165例，对照组164例），总脱落率为13.4%。与对照组相比，中药组患者使用SGLT2i人数较少，组间比较差异有统计学意义（P<0.05）。两组患者的年龄、性别、糖尿病病程、血压、身体质量指数（body mass index，BMI）、低密度脂蛋白胆固醇（low-density lipoprotein cholesterol，LDL-C）、总胆固醇（total cholesterol，TC）、空腹血糖（fasting blood glucose，FBG）、糖化血红蛋白（glycated hemoglobin，HbA_{1C}）、UACR、eGFR、合并症、其他用药情况及GA分期等一般资料差异均无统计学意义（表1）。本研究方案已通过江苏省中医院伦理委员会批准（批件号：2018NL-108-02）。

1.3　*治疗方法*

1.3.1　对照组　根据《中国糖尿病肾脏病防治指南（2021年版）》[7]给予基础治疗，包括改善生活方式、控制血糖、血压、血脂等。血糖管理：根据eGFR水平，选择GLP-1RA、利格列汀、胰岛素等指南推荐的肾脏安全性较好的降糖方案，个体化设定HbA_{1C}控制目标，控制FBG≤7.0 mmol/L，餐后2 h血糖≤10.0 mmol/L，HbA_{1C}≤7.0%。血压管理：使用可耐受剂量的ACEI/ARB类药物，血压控制在130/80mmHg以下，定期监测血钾、肌酐，在可控风险下最大化肾脏保护获益。心血管风险防控：选择阿托伐他汀±依折麦布，控制TC≤4.5 mmol/L，LDL-C≤2.5 mmol/L。基础对症干预：

表 1　两组患者一般资料比较　[$M(P_{25}, P_{75})$]

Tab.1　Comparison of general data between two groups of patients　[$M(P_{25}, P_{75})$]

项目	对照组(n=164)	中药组(n=165)	$Z/\chi^2/t$ 值	P 值
年龄(岁)	61.0(50.0, 69.0)	58.0(46.0, 68.0)	1.568	0.117
性别[例(%)]				
男	117(71.3)	107(64.8)	1.596	0.207
女	47(28.7)	58(35.2)		
病程(年)	10.0(5.0, 14.7)	9.0(5.0, 15.0)	0.238	0.812
BMI(kg/m^2, $\bar{x}\pm s$)	24.1±2.8	23.9±2.6	0.496	0.621
收缩压(mmHg)	136.0(128.0, 139.7)	135.8(126.5, 145.5)	0.577	0.564
舒张压(mmHg)	80.0(75.0, 88.0)	80.9(74.0, 85.0)	0.087	0.931
FBG(mmol/L)	7.3(5.9, 8.8)	7.2(5.8, 8.7)	0.343	0.731
HbA_{1C}(%)	8.0(7.0, 9.6)	7.7(6.8, 8.9)	1.744	0.081
TC(mmol/L)	4.5(3.8, 5.5)	4.6(3.8, 5.5)	0.755	0.450
LDL-C(mmol/L)	2.6(2.1, 3.1)	2.7(2.0, 3.3)	1.173	0.241
UACR(mg/g)	285.0(93.5, 731.2)	360.0(138.5, 884.0)	1.919	0.055
eGFR[mL/(min·1.73 m^2)]	67.0(51.2, 93.0)	74.1(51.0, 101.0)	1.113	0.266
合并症[例(%)]				
高血压	113(68.9)	119(72.1)	0.410	0.522
高脂血症	60(36.6)	71(43.0)	1.426	0.232
高尿酸血症	31(18.9)	39(23.6)	1.100	0.294
冠状动脉粥样硬化性心脏病	20(12.2)	25(15.2)	0.609	0.435
脑梗死	31(18.9)	31(18.8)	0.001	0.979
合并用药[例(%)]				
胰岛素	89(54.3)	92(55.8)	0.074	0.786
胰岛素促泌剂	40(24.4)	55(33.3)	3.203	0.074
SGLT2i	51(31.1)	15(9.1)	24.839	<0.001
二肽基肽酶-4抑制剂	59(36.0)	56(33.9)	0.150	0.699
GLP-1RA	36(22.0)	33(20.0)	0.189	0.664
ACEI或ARB	80(48.8)	82(49.7)	0.028	0.868
他汀类调脂药	63(38.4)	64(38.8)	0.005	0.945
抗血小板药物	51(31.1)	36(21.8)	3.641	0.056
G分期[例(%)]				
G1期	48(29.3)	60(36.4)	0.848	0.397
G2期	57(34.7)	50(30.3)		
G3期	48(29.3)	39(23.6)		
G4期	11(6.7)	16(9.7)		
A分期[例(%)]				
A2期	84(51.2)	74(44.8)	1.155	0.248
A3期	80(48.8)	91(55.2)		

优质低蛋白饮食，戒烟限酒、纠正肾性贫血、钙磷代谢紊乱、规避各类肾毒性药物。

1.3.2　中药组　在对照组治疗基础上给予芪苓护肾方(黄芪20 g，茯苓20 g，赤芍10 g，牛膝10 g，山茱萸15 g，山药15 g，白茅根20 g，金银花10 g，丝瓜络15 g，车前子10 g)治疗，由江苏省中医院中药房统一煎取至400 mL，每次200 mL，早晚饭后各1次，持续用药至随访终点(入组后12周)。

1.4　观察指标

1.4.1　主要观察指标　(1) 尿蛋白：两组T2DKD所有患者和A2期、A3期亚组患者UACR比较。(2) 肾功能：两组T2DKD所有患者和G2期、G3期、G4期亚组患者eGFR比较。

1.4.2　次要观察指标　(1) 糖脂代谢指标：FBG、HbA_{1C}、TC及LDL-C。(2) 中医证候量化积分：参照《糖尿病肾脏病分期辨证规范与疗效评定方案及其研究》[14]和《中药新药用于糖尿病肾脏疾病临床研究技术指导原则(2020版)》，应用中医证候积分表进行量化，主症按程度分为无(0分)、轻(2分)、中(4分)、重(6分)，次症按程度分为无(0分)、轻(1分)、中(2

分)、重(3分)。

1.4.3　安全性指标　进行血常规、肝功能及心电图检查,评价不良反应发生率。

1.5　统计学方法　采用SPSS 27.0软件进行统计分析。对于连续性变量,通过Shapiro-Wilk检验是否符合正态分布,符合正态分布的采用$\bar{x}\pm s$表示,组间比较采用独立样本t检验,组内比较采用配对样本t检验;不符合正态分布采用$M(P_{25},P_{75})$进行描述,两组间比较采用Wilcoxon秩和检验,组内比较用配对秩和检验。计数资料以例(%)表示,组间比较采用χ^2检验。等级资料比较采用秩和检验。P<0.05为差异有统计学意义。

2　结　果

2.1　两组患者及A2、A3期亚组患者治疗前后UACR比较　治疗前对照组和中药组T2DKD患者UACR差异无统计学意义(P>0.05)。治疗后两组患者UACR较治疗前均明显下降(P<0.05),中药组下降幅度显著大于对照组(P<0.01)。亚组分析显示,治疗前对照组和中药组A2期、A3期T2DKD患者UACR差异无统计学意义(P>0.05)。对照组A2期患者治疗前后UACR差异无统计学意义(P>0.05),中药组A2期患者治疗后UACR较治疗前显著下降(P<0.01)。两组A3期患者治疗后UACR较治疗前均下降(P<0.01),且中药组患者UACR下降幅度显著大于对照组(P<0.01)。见表2。

2.2　两组患者治疗前后肾功能比较　治疗前对照组和中药组患者eGFR差异无统计学意义(P>0.05)。两组患者治疗前后eGFR组内比较及治疗后组间比较差异均无统计学意义(P>0.05)。亚组分析显示,治疗前对照组和中药组G2期、G3期及G4期患者eGFR差异均无统计学意义(P>0.05),其中中药组G3期T2DKD患者治疗后eGFR较治疗前有上升趋势,但差异无统计学意义(P>0.05)。见表3。

2.3　两组T2DKD患者治疗前后的糖脂代谢指标比较　治疗前对照组和中药组T2DKD患者糖脂代谢指标差异无统计学意义(P>0.05)。治疗后两组T2DKD患者FBG较治疗前呈下降趋势,但差异无统计学意义(P>0.05);两组患者HbA_{1C}较治疗前明显下降(P<0.05),ΔFBG、ΔHbA_{1C}组间比较差异无统计学意义(P>0.05)。中药组患者治疗前后TC、LDL-C差异有统计学意义(P<0.05),ΔTC组间比较差异有统计学意义(P<0.05);对照组治疗后TC、LDL-C均未见统计学差异(P>0.05)。见表4。

2.4　两组患者治疗前后中医证候总积分变化情况　两组T2DKD患者中医证候总积分治疗前比较差异无统计学意义(P>0.05),治疗后组内比较及组间比较差异均有统计学意义(P<0.01),且中药组治疗后中医证候总积分较对照组降低更明显(P<0.01)。见表5。

2.5　安全性评价　治疗期间中药组发生胃肠道反应5例,肝功能异常4例;对照组发生胃肠道反应2例,肝功能异常1例,白细胞减少2例。两组均未见皮疹、瘙痒或心电图异常。中药组和对照组的不良反应总发生率分别为5.45%(9/165)和3.05%(5/164),两组比较差异无统计学意义(χ^2=1.168, P=0.280)。所有不良反应均在对症治疗后改善,未发生其他严重不良反应。

表2　两组所有患者及各亚组治疗前后UACR比较　[mg/g,$M(P_{25},P_{75})$]

Tab.2　Comparison of UACR before and after treatment in all patients of the two groups and each subgroup　[mg/g,$M(P_{25},P_{75})$]

分层	对照组	中药组	Z值	P值
组内所有患者				
治疗前UACR	285.0(93.5, 731.2)	360.0(138.5, 884.0)	1.919	0.055
治疗后UACR	274.5(85.5, 624.7)[a]	190.0(58.5, 523.5)[a]	1.751	0.080
ΔUACR	20.0(−41.2, 92.5)	102.0(36.0, 374.5)	6.927	<0.001
A2期				
治疗前UACR	107.0(56.5, 166.0)	129.0(84.5, 173.0)	1.692	0.091
治疗后UACR	94.5(48.2, 163.7)	57.5(33.7, 114.2)[a]	2.845	0.004
ΔUACR	11.0(−46.5, 32.0)	52.0(22.7, 94.0)	5.147	<0.001
A3期				
治疗前UACR	740.5(463.7, 1 056.5)	848.0(470.0, 1 690.0)	0.952	0.341
治疗后UACR	621.5(352.5, 1 129.5)[a]	455.0(238.0, 1 103.0)[a]	2.337	0.019
ΔUACR	61.0(−34.0, 187.0)	327.0(119.0, 649.0)	5.661	<0.001

注:与同组治疗前相比,[a]P<0.05。组内所有患者对照组n=164,中药组n=165;A2期对照组n=84,中药组n=74;A3期对照组n=80,中药组n=91。

表3　两组所有患者及各亚组治疗前后eGFR比较　[mL/(min·1.73 m^2), $M(P_{25}, P_{75})$]

Tab.3　Comparison of eGFR before and after treatment in all patients of the two groups and each subgroup [mL/(min·1.73 m^2), $M(P_{25}, P_{75})$]

分层	对照组	中药组	Z值	P值
组内所有患者				
治疗前eGFR	67.0(51.2,93.0)	74.1(51.0,101.0)	1.113	0.266
治疗后eGFR	71.0(50.0,91.0)	75.0(50.5,100.2)	1.087	0.277
ΔeGFR	0(−5.0,5.0)	1.0(−5.0,5.0)	0.352	0.725
G2期				
治疗前eGFR	71.0(64.0,82.0)	74.0(67.7,80.0)	0.531	0.595
治疗后eGFR	75.0(63.0,81.0)	74.2(64.0,80.0)	0.134	0.893
ΔeGFR	0(−8.5,5.5)	0(−5.0,6.5)	0.153	0.878
G3期				
治疗前eGFR	47.5(39.2,54.0)	46.0(38.0,53.0)	0.286	0.775
治疗后eGFR	47.5(38.5,59.0)	49.0(37.0,55.0)	0.423	0.672
ΔeGFR	0(−8.6,3.0)	−3.0(−7.0,5.0)	0.543	0.587
G4期				
治疗前eGFR	24.0(19.0,26.0)	24.5(21.2,28.0)	0.942	0.368
治疗后eGFR	22.0(19.0,32.0)	24.5(22.0,29.0)	0.670	0.503
ΔeGFR	0(−5.0,2.0)	−0.5(−2.7,2.0)	0.224	0.823

注：组内所有患者对照组n=164，中药组n=165；G2期对照组n=57，中药组n=50；G3期对照组n=48，中药组n=39；G4期对照组n=11，中药组n=16。

表4　两组治疗前后糖脂代谢指标比较　[$M(P_{25}, P_{75})$]

Tab.4　Comparison of glucose and lipid metabolism indicators before and after treatment in two groups　[$M(P_{25}, P_{75})$]

指标	对照组(n=164)	中药组(n=165)	Z值	P值
FBG(mmol/L)				
治疗前	7.3(5.9, 8.8)	7.2(5.8, 8.7)	0.343	0.731
治疗后	7.0(5.9, 8.3)	6.7(5.9, 7.7)	1.184	0.237
ΔFBG	0(−1.2, 1.7)	0.1(−0.8, 1.6)	1.124	0.261
HbA_{1c}(%)				
治疗前	8.0(7.0, 9.6)	7.7(6.8, 8.9)	1.744	0.081
治疗后	7.3(6.6, 8.4)[a]	7.2(6.6, 8.0)[a]	0.717	0.473
ΔHbA_{1c}	0.4(−0.1, 1.4)	0.3(−0.2, 1.2)	0.753	0.452
TC(mmol/L)				
治疗前	4.5(3.8, 5.5)	4.6(3.8, 5.5)	0.755	0.450
治疗后	4.5(3.8, 5.2)	4.4(3.8, 5.3)[a]	0.505	0.614
ΔTC	−0.1(−0.5, 0.5)	0.1(−0.2, 0.6)	2.186	0.029
LDL-C(mmol/L)				
治疗前	2.6(2.1, 3.1)	2.7(2.0, 3.3)	1.173	0.241
治疗后	2.5(2.0, 3.1)	2.5(2.1, 3.2)[a]	0.590	0.555
ΔLDL-C	0(−0.3, 0.4)	0.1(−0.2, 0.4)	1.484	0.138

注：与本组治疗前相比，[a]P<0.05。

表5　两组患者治疗前后中医证候总积分比较　(分, $\bar{x}\pm s$)

Tab.5　Comparison of total Chinese medicine syndrome scores before and after treatment in two groups of patients　(point, $\bar{x}\pm s$)

组别	治疗前	治疗后	差值
对照组(n=164)	19.9±5.1	17.2±6.2[a]	2.6±7.2
中药组(n=165)	20.3±4.5	11.6±3.6[a]	8.7±4.8
t值	0.766	9.991	8.916
P值	0.444	<0.001	<0.001

注：与治疗前相比，[a]P<0.05。

3　讨　论

T2DKD发生发展是多种病理机制交互作用的结果，包括高血糖相关代谢异常、血流动力学改变、炎症反应、氧化应激及遗传易感性等因素[16-17]，核心病理机制主要包括终末糖基化终产物形成、蛋白激酶C激活以及RAAS异常激活，从而导致肾小球滤过屏障破坏、肾小球基底膜增厚、肾小球硬化及肾小管间质纤维化[18]。T2DKD患者早期多无明显症状，一旦出现持续性大量蛋白尿，病情往往不可逆转，直至终末期肾衰竭。因此，早期干预T2DKD发生发展对提高糖尿病患者生存率，改善其生活质量具有重要意义。

中医学将T2DKD归于“水肿”“虚劳”“关格”[19]。《圣济总录》曰“消渴饮水过多，久则渗漏脂膏，脱耗精液，下流胞中，与水液混浊，随小便利下膏凝，故谓之消渴小便白浊也。”体内糖毒、脂毒均为湿热之邪，先损脾土，脾失健运，久蕴于肾，阻碍气机，气不行血，血行不畅，日久成瘀，湿热瘀毒互结，致肾络闭阻，肾失封藏，精关失固，精微外泄，则见蛋白尿。病久湿热瘀毒耗伤肾气，导致肾虚络损，加重肾脏损伤，由此可见湿热瘀毒既是病理产物，又为致病因素，贯穿本病始终[11]。安晓飞教授针对T2DKD湿瘀阻络基本病机，在健脾补肾的基础上，提出“利湿化瘀通络”治法，虚实兼顾、标本兼治，拟定了芪苓护肾方[12]。方中重用黄芪益气健脾，升阳利水，茯苓健脾利水渗湿，共为君药；赤芍活血化瘀，牛膝益肾活血，兼以利水，为臣药；山药补脾益肾，益气养阴，酒萸肉补益肝肾，白茅根清热凉血利尿，同为佐药；金银花清热解毒，丝瓜络通经活络，车前子利水通淋，共为使药。全方共奏利湿化瘀、通络补肾之效。前期临

床实践表明，芪苓护肾方对降低T2DKD湿瘀阻络证患者的尿蛋白有确切疗效，并可显著改善患者临床症状[12]，但针对改善T2DKD患者蛋白尿和肾功能损伤的临床疗效，尚缺乏大样本循证医学依据。

在既往临床观察的基础上，本研究旨在通过扩大临床样本量并优化入组标准，完成随访的T2DKD患者共329例（中药组165例，对照组164例）。本研究结果发现，中药组T2DKD患者A2期和A3期治疗后UACR下降程度与对照组同分期患者相比差异有统计学意义，同时中药组T2DKD患者TC、LDL-C指标较治疗前也明显降低。两组T2DKD患者治疗后中医证候总积分均明显降低。上述结果表明，在西医常规治疗基础上联合芪苓护肾方治疗T2DKD具有降低尿蛋白及缓解临床症状等优势。

芪苓护肾方可有效降低T2DKD各亚组患者蛋白尿，但未能观察到其对患者eGFR有明显改善作用，综合分析可能存在以下原因：（1）既往研究显示肾脏疾病治疗过程尿蛋白降低与eGFR改善之间存在一定滞后性，尿蛋白持续降低3~6个月甚至更长时间才可能观察到eGFR显著升高[20]，本研究随访时间相对较短（12周），可能不足以观察到芪苓护肾方对T2DKD患者eGFR的改善作用。（2）G2和G3期T2DKD患者肾功能相对稳定且下降较为缓慢，干预措施难以在短期内观察到eGFR显著变化。本研究中G3和G4期患者占中药组总入组患者的比例（55/165，33.3%）相对较低，难以准确评估芪苓护肾方对T2DKD中晚期肾功能受损患者eGFR的潜在改善作用。未来研究可通过延长随访时间，增加G3期和G4期患者相对样本量，进一步控制合并用药等混杂因素，深入研究芪苓护肾方延缓T2DKD患者肾功能进展的临床疗效。

综上所述，本前瞻性队列研究表明，在西医常规治疗基础上联用芪苓护肾方可显著降低T2DKD患者蛋白尿水平，缓解患者临床症状并提高其生活质量，同时具有良好的安全性。未来拟开展多中心临床随机对照研究，以肾脏终点事件为主要疗效指标进行长期随访，旨在为芪苓护肾方治疗T2DKD提供更完整的疗效、更充分的循证医学依据，为发挥中医药治疗T2DKD的特色和优势提供更扎实的临床研究证据。

利益冲突 无

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