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Prospective clinical study of *Kunkui Baoshen* Formula in the treatment of high or extremely high-risk diabetic kidney disease

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Abstract: Objective To compare the clinical efficacy of *Kunkui Baoshen* Formula and *Huangkui* Capsules in patients with high or extremely high-risk diabetic kidney disease (DKD), and to explore the safety of their clinical application. **Methods** This study enrolled high or extremely high - risk DKD patients from the Department of Endocrinology of Jiangsu Province Hospital of Chinese Medicine between February 2021 and August 2023. The patients were randomly divided into a control group and an experimental group (n=157, each). In addition to metabolic control, the control group received *Huangkui* Capsules (5 capsules per dose, 3 times a day, orally), while the experimental group received *Kunkui Baoshen* Formula. Both groups were treated for 3 months. Pre- and post-treatment, changes in urine protein-related indicators [urine albumin-to-creatinine ratio (UACR), urinary microalbumin (Um-Alb), urine retinol-binding protein (U-RBP), urine complement 3, urine α2-macroglobulin (MG)], kidney function-related indicators[serum creatinine (Scr), cystatin C (Cys-C), estimated glomerular filtration rate (eGFR)], and metabolic indicators[fasting blood glucose (FBG), glycated hemoglobin (HbA_{1c}), triglycerides (TG), systolic blood pressure, triglyceride-glucose (TyG) index]were observed. The clinical efficacy of proteinuria reduction, the recent reversal rate of proteinuria, kidney function efficacy, and changes in DKD clinical risk staging were also evaluated, and adverse reactions during treatment were recorded. **Results** Fourteen patients in the experimental group were lost to follow-up or excluded, and 143 patients completed the trial. Seventeen patients in the control group were lost to follow-up or excluded, and 140 patients completed the trial. After treatment, the UACR, Um-Alb, urine complement 3, and U - RBP in the experimental group significantly decreased compared to before treatment (P<0.01), and urine α2 - MG showed a downward trend. The reduction in UACR and Um-Alb was significantly superior to the control group (P<0.01). The total clinical efficacy rate of proteinuria reduction was 83.22%, significantly better than 49.29% in the control group (χ^2=36.523, P<0.01). The proportion of DKD patients with a reduction in UACR greater than 30% reached 58.04%, which was significantly higher than 29.29% in the control group (χ^2=23.763, P<0.01). The decrease in serum creatinine and Cys-C, and the increase in eGFR in the experimental group were significantly better than those in the control group (P<0.01), and the total effective rate of creatinine reduction was 67.83%, significantly better than 48.57% in the control group (χ^2=10.795, P <0.01). The FBG, TG, systolic blood pressure, and TyG index in the experimental group significantly decreased compared to before treatment (P <0.05), with the reduction in TG, systolic blood pressure, and TyG index being superior to the control group (P <0.05). Regarding changes in DKD clinical risk staging, the efficacy rate in the experimental group was higher than in the control group (36.36% *vs* 18.57%, χ^2=11.217, P <0.01). Both groups did not experience any severe adverse reactions during treatment, and there was no significant difference in the incidence of adverse reactions between the experimental group and control group (3.50% *vs* 1.43%, $\chi 2$=0.543, P=0.461). **Conclusion** *Kunkui Baoshen* Formula has certain advantages over *Huangkui* Capsules in reducing proteinuria, protecting kidney function, improving related metabolic factors, and reversing DKD clinical risk staging. It demonstrates significant clinical efficacy and good safety. This has certain implications for clinical practice in treating high or extremely high-risk diabetic kidney disease.

Keywords: *Kunkui Baoshen* Formula; *Huangkui* Capsules; Diabetic kidney disease; High-risk; Urinary microalbumin to creatinine ratio; Estimated glomerular filtration rate; Retinol-binding protein; Albumin

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Diabetic kidney disease (DKD) is the most severe microvascular complication of diabetes, with an incidence that is increasing year by year, and has become the leading cause of end-stage kidney disease (ESKD) [1-2]. DKD has an insidious onset, low awareness rate, high rate of missed diagnosis, and rapid progression. Once it develops to the stage of clinical proteinuria or moderate-to-severe renal insufficiency, it is regarded as a high-risk or very high-risk period with poor reversibility, and the efficacy of Western medicine remains limited. However, in real-world clinical

practice, many DKD patients only present to the hospital when they are found to have massive proteinuria or a substantial decline in renal function [3], at which stage the risk of progression to ESKD is about 14 times that of patients with other kidney diseases [4]. Therefore, the effective treatment of high- and very high-risk DKD patients remains a therapeutic challenge and bottleneck.

Professor YU Jiangyi, a renowned traditional Chinese medicine (TCM) expert of Jiangsu Province, proposed that "dampness and blood stasis obstructing the collaterals, with *Qi* and *Yin* Deficiency" is the central pathogenesis of DKD onset and progression. The *Kunkui Baoshen* Formula was developed by Professor YU Jiangyi based on the aforementioned theoretical insights and years of clinical experience. This optimized formula for DKD treatment has been granted a national invention patent (ZL202211219776.3), and preliminary real-world clinical studies have confirmed the paired use of *Abelmoschi Corolla* (Huangshukuihua, 黄蜀葵花) and *Colquhounia Coccinea var. mollis* (Huobashugen, 火把花根) as principal and minister drugs, effective in the management of DKD [5]. However, there is a lack of clinical efficacy research targeting high- and very high-risk DKD patients. Considering the study population comprised high- or very high-risk DKD patients, and the clinical application of novel nephroprotective agents is restricted, with reference to recent guidelines, *Huang Kui* Capsule was selected as the positive control drug. The therapeutic effect and safety profile of the *Kunkui Baoshen* Formula in high- or very high-risk DKD patients were observed, aiming to provide new evidence for integrative medicine in DKD treatment.

1 Clinical Data

1.1 General Information

This was a randomized controlled trial with a superiority design. The estimated glomerular filtration rate (eGFR) served as the primary endpoint for observation. According to previous real-world research and published literature, the difference in eGFR between the experimental and control groups was 11.2, with a standard deviation of 18.609. Setting a two-sided α =0.05 (one-sided α =0.025), power (1-β) of 0.9, superior boundary at 4, and a 1:1 ratio of sample size in the experimental and control groups, the sample size was calculated using R language according to reference [6], resulting in 141 subjects per group. Allowing for a 10% loss to follow-up or refusal, a minimum of 157 subjects per group was needed, totaling 314 participants.

From February 2021 to August 2023, 314 patients at high or very high risk of DKD progression were recruited from the outpatient department of Jiangsu Provincial Hospital of Chinese Medicine. A randomized number table was used to assign patients into the experimental group and control group, each with 157 cases. During follow-up, 9 cases in the experimental group and 8 in the control group were lost to follow-up due to the epidemic or personal reasons; 3 cases in the experimental group and 7 in the control group were excluded for using other Chinese medicines during the course; 2 cases in each group were excluded for more than 10 days interruption in medication. The final cases were 283 (143 in the experimental group, 140 in the control group), with an overall loss rate of 9.87%. Baseline data, including age, sex, diabetes duration, BMI, blood pressure, fasting blood glucose (FBG), glycated hemoglobin (HbA_{1C}), DKD risk classification, comorbidities, and medication use, were comparable between groups (P>0.05), detailed in **Table 1**. The study was approved by the Ethics Committee of Jiangsu Provincial Hospital of Chinese Medicine (Ethics Approval No. 2021NL-017-02), and all subjects signed informed consent.

Tab.1 Comparison of basic information between the two groups of patients ($\bar{x}\pm s$)

Item	Experimental group (n=143)	Control group (n=140)	t/χ^2 value	P value
Age (years)	55.55±12.55	58.33±12.72	1.835	0.065
Gender [n(%)]			0.032	0.859
Male	108 (75.52)	107 (76.43)		
Female	35 (24.48)	33 (23.57)		
Duration of diabetes (years)	12.59±5.93	14.19±11.56	1.159	0.249
BMI (kg/m²)	24.99±3.21	23.59±3.59	0.672	0.502
SBP (mmHg)	137.04±12.13	128.33±15.17	0.476	0.635
DBP (mmHg)	82.49±12.08	80.73±8.28	0.791	0.431
FBG (mmol/L)	7.88±3.05	7.52±2.90	0.971	0.332
HbA_{1c} (%)	7.69±1.83	7.87±1.54	0.751	0.453
Risk classification [n(%)]			0.021	0.884
High risk	57 (39.86)	57 (40.71)		
Very high risk	86 (60.14)	83 (59.29)		
Complications [n(%)]				
Hypertension	121 (84.62)	108 (77.14)	2.558	0.11
Hyperlipidemia	94 (65.73)	90 (64.29)	0.065	0.798
Hyperuricemia	46 (32.17)	60 (42.86)	3.45	0.063
Coronary heart disease	26 (18.18)	15 (10.71)	3.184	0.074
Cerebral infarction	32 (22.38)	22 (15.71)	2.034	0.154
Medication use [n(%)]				
RASI	63 (44.06)	60 (42.86)	0.041	0.839
SGLT-2i	105 (73.43)	95 (67.86)	1.612	0.203
DPP-4i	70 (48.95)	59 (42.14)	1.322	0.250
GLP-1RA	32 (22.38)	36 (25.71)	0.431	0.511
Insulin	58 (40.56)	60 (42.86)	0.154	0.695

Note: SBP referred to systolic blood pressure; DBP referred to diastolic blood pressure; RASI referred to renin-angiotensin system inhibitor; SGLT-2i referred to sodium-glucose cotransporter 2 inhibitor; DPP-4i referred to dipeptidyl peptidase-4 inhibitor; GLP-1RA referred to glucagon-like peptide-1 receptor agonist.

1.2 Diagnostic Criteria

1.2.1 Western Medicine Diagnostic Criteria for DKD

Referring to the "*Clinical guideline for the prevention and treatment of diabetic kidney disease in China (2021 edition)*" [7] and the "*Expert consensus on the prevention and treatment of diabetic kidney disease with the integrated traditional Chinese and Western medicine (2023 edition)*" [8], the following DKD diagnostic criteria were used: (1) Clear history of diabetes; (2) At least 2 out of 3 urine albumin-to-creatinine ratio (UACR)

measurements ≥30 mg/g, or urinary albumin excretion rate (UAER) ≥30 mg/24h (≥20μg/min), and/or eGFR <60 mL/ (min·1.73m^2) for more than 3 months; (3) Exclusion of non-DKD causes, specifically type 1 diabetes duration <5 years or no diabetic retinopathy, rapid eGFR decline, rapidly increasing proteinuria or nephrotic syndrome, refractory hypertension, active urinary sediment (RBCs, WBCs, casts), symptoms or signs of other systemic diseases, eGFR drop >30% within 2-3 months after angiotensin-converting enzyme inhibitor (ACEI)/ angiotensin receptor blocker (ARB) therapy, renal ultrasound abnormalities. Renal biopsy was recommended if diagnosis remains uncertain.

1.2.2 DKD Clinical Risk Staging Criteria

With reference to the cause-glomerular filtration rate-albuminuria (CGA) staging criteria proposed in the *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease* [9] issued by Kidney Disease: Improving Global Outcomes (KDIGO) in 2022, and the DKD clinical staging risk assessment in the *Expert consensus on the prevention and treatment of diabetic kidney disease with the integrated traditional Chinese and Western medicine (2023 edition)* [8], the risk levels of DKD were classified into low-risk, moderate-risk, high-risk, and very high-risk by combining UACR and eGFR.

1.2.3 TCM Syndrome Differentiation Criteria

The syndrome differentiation criteria for "dampness and blood stasis obstructing the collaterals, with Qi and Yin Deficiency" were formulated with reference to *Staging Syndrome Differentiation Standards, Efficacy Evaluation Protocol and Research on Diabetic Kidney Disease* [10], *Guidelines for diagnosis and treatment of diabetic nephropathy with combinations of diseases and syndromes* [11], and *guiding principles of clinical research of new traditional Chinese medicine in treating diabetes* [12]. (1) Primary Symptoms: Facial and limb edema, turbid urine, limb numbness or pain, fatigue and lassitude. (2) Secondary Symptoms: Sticky stool, dry mouth and throat, heavy sensation in the head and body, soreness and weakness of the waist and knees, blurred vision. Tongue and Pulse Manifestations: Dark red tongue with ecchymoses or petechiae, scanty tongue coating or yellow greasy coating, thready-slippery-rapid pulse or deep-hesitant pulse. A diagnosis of "dampness and blood stasis obstructing the collaterals, with Qi and Yin Deficiency" can be made if any 2 primary symptoms and 2 secondary symptoms mentioned above are present, combined with the corresponding tongue and pulse manifestations.

1.3 Inclusion Criteria

(1) Patients classified as high or very high clinical risk of DKD; (2) Age between 18 and 80 years, any sex; (3) Blood pressure ≤160/100 mmHg; (4) Informed consent and voluntary participation.

1.4 Exclusion Criteria

(1) Recent (<1 month) diabetic ketoacidosis, hyperosmolar hyperglycemic state, or infection; (2) Renovascular hypertension; (3) Undergoing dialysis or in need of immediate dialysis; (4) Recent malignant hypertension, myocardial infarction, or acute cerebrovascular events; (5) Malignant tumors, pregnancy or lactation; (6) Allergy to the study medication.

1.5 Criteria for Dropout and Exclusion

(1) Dropout: Patients who consented and met inclusion criteria but did not complete the prescribed treatment or observation period will be considered dropouts. Telephone follow-up should be performed where possible to ascertain reasons, record last medication intake, and evaluate completed assessments. (2) Exclusion: Subjects not meeting inclusion or meeting exclusion criteria; those not adhering to study medication requirements; those lacking any post-randomization clinical data.

2 Methods

2.1 Treatment Methods

Both groups received basic therapy in accordance with the "*Chinese Guidelines for the Prevention and Treatment of Diabetic Kidney Disease (2021)*" [7], including lifestyle modification, dietary therapy, and control of blood glucose, blood pressure, and blood lipids. The control group additionally received *Huangkui* Capsule (Jiangsu Suchung Pharmaceutical Group, 0.43 g/capsule, approval no. Z19990040), 5 capsules per dose, three times daily, orally after meals. The experimental group additionally received *Kunkui Baoshen* Formula (*Huangshukui* flower 30g, Torch flower root 15g, Astragalus 30g, wine-processed Cornus officinalis 10g), decocted by the hospital pharmacy to a total volume of 400 mL, with 200 mL taken after breakfast and dinner. Both groups were treated continuously for 3 months.

2.2 Observation Indicators and Methods

Before and after treatment, fasting peripheral venous blood and urine were collected in the morning at rest, and tested by the clinical laboratory of Jiangsu Provincial Hospital of Chinese Medicine. Blood specimens for biochemical markers were collected in sterile anticoagulant tubes (5 mL), allowed to clot for 30 minutes at room temperature, centrifuged at 3,000 rpm for 10 minutes at 4°C (radius 10 cm). The supernatant (serum) was aliquoted (200 μL/tube) and stored at -80°C. Automatic biochemical analyzers were used for blood glucose and lipid measurement; Enzyme-linked immunosorbent assay (ELISA) was used for renal function-related indices.

2.2.1 Urinary Protein Indicators

(1) Glomerular damage: UACR, urine microalbumin (Um-Alb); (2) Tubular damage: urine retinol-binding protein (U-RBP), urinary complement 3, urine α2-macroglobulin (MG).

2.2.2 Renal Function Indicators

Serum creatinine (Scr), cystatin C (Cys-C), eGFR.

2.2.3 Glucose and Lipid Metabolism, and Blood Pressure

FBG, HbA_{1C}, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), systolic blood pressure (SBP), diastolic blood pressure (DBP). The triglyceride-glucose (TyG) index was used to assess insulin resistance [13-14]: TyG index =ln[FBG (mg/dL) × TG (mg/dL)/2].

2.3 Clinical Efficacy Evaluation

2.3.1 Urinary Protein Efficacy

The evaluation criteria were formulated with reference to the *Diagnostic, Syndrome Differentiation and Efficacy Evaluation Standards for Diabetic Nephropathy (Trial Protocol)* [15], as well as the definition of UACR reversal in the CREDENCE canagliflozin study [16] and EMPA-REG empagliflozin study [17], and were specified as follows: Short-term remission: UACR decreased by ⩾ 50% or returned to the normal range; Marked effect: UACR decreased by ⩾ 30% but <50%; Effective: UACR decreased but <30%; Ineffective: UACR increased or showed no change. Total effective rate =(short-term remission + marked effect + effective) / total number of cases × 100%. Short-term reversal rate =(short-term remission + marked effect) / total number of cases × 100%.

2.3.2 Efficacy on Renal Function

The evaluation criteria were referenced from *Staging Syndrome Differentiation Standards, Efficacy Evaluation Protocol and Research on Diabetic Kidney Disease* [10], and were specified as follows: Marked Effect: eGFR increased by ⩾20% or serum creatinine decreased by ⩾ 20%; Effective: eGFR increased by 10% to <20% or serum creatinine decreased by 10% to <20%; Stable: eGFR showed no decrease and increased by <10%, or serum creatinine showed no increase and decreased by <10%; Ineffective: eGFR decreased or serum creatinine increased. Total effective rate =(marked effect + effective + stable) / total number of cases × 100%.

2.3.3 Changes in DKD Clinical Risk Staging

The efficacy evaluation criteria for DKD clinical risk staging in this study were formulated with reference to the *Expert Consensus on Integrated Traditional Chinese and Western Medicine Prevention and Treatment of Diabetic Kidney Disease (2023 Edition)* [8] and the *KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease*.

Improved: DKD progressed from high-risk to low-risk or moderate-risk; DKD progressed from very high-risk to low-risk, moderate-risk, or high-risk. Maintained: Patients with high-risk DKD remained in the high-risk stage after treatment; patients with very high-risk DKD showed no significant progression in either A or G staging after treatment (specifically, patients in stages A1–2 did not progress to stage A3, patients in stage G3 did not progress to stages G4–5, and patients in stage G4 did not progress to stage G5). Progressed: DKD progressed from high-risk to very high-risk; patients with very high-risk DKD showed progression in either A or G staging. Effective rate =Improved / Total number of cases × 100%.

2.4 Safety Evaluation

The flowing index were evaluated: liver function [alanine aminotransferase (ALT), aspartate aminotransferase (AST)], routine blood tests (red blood cell count, white blood cell count, neutrophil percentage), sex hormones (screened in young patients, with a focus on inquiring about menstrual history in female patients), and incidence of hypoglycemia before and after treatment. Adverse reactions (such as nausea and vomiting, diarrhea or constipation, dizziness and headache, dry mouth, etc.) also be recorded in detail, including their manifestations, severity, onset time, duration, management measures, and resolution time.

2.5 Statistical Methods

All data were analyzed using SPSS 25.0 software. Continuous variables were assessed for normality by the Shapiro-Wilk test; normally distributed data were shown as $\bar{x}\pm s$, with group comparisons by independent *t*-test and paired *t*-test. Non-normally distributed data were shown as $M(P_{25},P_{75})$, group comparisons were conducted by Wilcoxon rank sum test, and paired changes by paired rank test. Categorical data were expressed as *n*(%) and compared by χ^2 test. A two-sided $P < 0.05$ was considered statistically significant.

3 Results

3.1 Comparison of Urinary Protein–Related Indices Before and After Treatment

Glomerular injury: UACR and Um-Alb in the experimental group significantly decreased versus baseline (P<0.05), with reductions significantly greater than the control group (P<0.01). Tubular injury: Urinary complement 3 and U-RBP in the experimental group significantly decreased (P <0.05), while the control group showed a decreasing trend without statistical significance (P>0.05). No significant between-group differences in the change (Δ) of urine complement 3, U-RBP, or α2-MG after treatment (P >0.05). See **Table 2**.

3.2 Comparison of Renal Function-Related Indices Before and After Treatment

In the experimental group, Scr and Cys-C significantly decreased compared to pretreatment (P <0.05), with greater reductions than the control group (P <0.01); eGFR significantly increased, with a greater rise than in the control group (P <0.01). See **Table 3**.

Tab.2 Comparison of urinary protein-related indicators between the two groups before and after treatment [*M* (P_{25},P_{75})]

Index	Experimental group (*n*=143)	Control group (*n*=140)	*Z* value	*P* value
UACR (mg/g)				
Before treatment	683.50 (302.75,1694.50)	609.50 (382.25,1490.50)	0.332	0.740
After treatment	305.00 (99.25,1186.50)[a]	688.00 (300.00,1550.50)	4.173	<0.001
ΔUACR	-319.00 (-778.00, -105.50)	8.00 (-212.00,307.50)	7.225	<0.001
Um-Alb (mg/L)				
Before treatment	555.50 (206.75,1326.00)	429.5 (272.75,834.00)	0.752	0.452
After treatment	254.00 (95.50,687.00)[a]	434.50 (204.00,858.00)	2.958	0.003
ΔUm-Alb	-230.00 (-622.50, -5.75)	-48.00 (-233.00,198.00)	4.042	<0.001
Urine complement 3 (mg/L)				
Before treatment	0.90 (0.42,4.38)	1.12 (0.26,3.28)	0.605	0.545
After treatment	0.68 (0.34,1.42)[a]	0.97 (0.29,3.18)	1.028	0.304
Δ Urine complement 3	-0.22 (-1.44,0.19)	-0.03 (-1.03,0.36)	0.933	0.351
U-RBP (mg/L)				
Before treatment	1.16 (0.38,4.50)	0.64 (0.32,1.99)	1.522	0.128
After treatment	0.79 (0.28,2.19)[a]	0.53 (0.20,1.74)	1.011	0.312
ΔU-RBP	-0.10 (-0.70,0.08)	-0.02 (-0.37,0.21)	1.622	0.105
α2-MG (mg/L)				
Before treatment	1.40 (0.55,2.60)	1.20 (0.70,2.48)	0.027	0.979
After treatment	1.05 (0.60,2.08)	1.30 (0.85,2.45)	1.171	0.242
Δα2-MG	0 (-0.90,0.62)	0.10 (-0.70,0.90)	0.782	0.434

Note: Compared with before treatment, [a]$P < 0.05$.

Tab.3 Comparison of renal function indicators between the two groups before and after treatment [*M* (P_{25},P_{75})]

Index	Experimental group (*n*=143)	Control group (*n*=140)	*Z*/*t* value	*P* value
Scr (umol/L)				
Before treatment	117.10 (84.53,168.63)	108.90 (84.50,135.00)	1.775	0.076
After treatment	106.20 (78.90,141.00)[a]	113.40 (76.30,138.90)	0.141	0.888
ΔScr	-9.50 (-24.50,2.40)	0.60 (-10.40,12.40)	4.946	<0.001
Cys-C (mg/L, $\bar{x}\pm s$)				
Before treatment	1.96±0.82	1.79±0.72	1.814	0.071
After treatment	1.84±0.73[a]	1.98±0.85[a]	1.349	0.178
ΔCys-C	-0.07±0.34	0.19±0.57	4.161	<0.001
eGFR[mL/ (min·1.73m²)]				
Before treatment	45 (31,64)	48 (36,72)	1.605	0.109
After treatment	49 (36,71)[a]	48 (34,68)[a]	0.856	0.392
ΔeGFR	2 (-3,8)	-1 (-8.5,4)	3.577	<0.001

Note: Compared with before treatment, [a]$P < 0.05$.

3.3 Comparison of Glucose and Lipid Metabolism, and Blood Pressure Indices

Regarding glucose metabolism: FBG in the experimental group decreased (P<0.05), and HbA_{1C} showed a decreasing trend; the control group had a downward trend in FBG and HbA_{1C}, but not statistically significant (P>0.05). There was no significant between-group difference in ΔFBG or ΔHbA_{1C} (P>0.05).

For lipid metabolism: TG in the experimental group decreased significantly (P<0.01), with a greater reduction than the control group (P<0.01); TC, HDL-C, and LDL-C showed no significant changes (P>0.05). No significant changes were observed in the control group for TG, TC, HDL-C, or LDL-C post-treatment (P>0.05). No statistically significant between-group differences in ΔTC or ΔHDL-C were observed (P>0.05).

Blood pressure: SBP in the experimental group decreased (P<0.05), with a greater decline than in the control group (P<0.01); DBP tended to decline without statistical significance (P>0.05). SBP in the control group trended upwards, and DBP downward, both without statistical significance; TyG index in the experimental group decreased significantly (P<0.05), with a greater reduction than the control group (P<0.05). **See Table 4**.

3.4 Efficacy on Urinary Protein, Renal Function, and DKD Clinical Risk Staging

Urinary protein efficacy: In the experimental group, there were 53 cases of short-term remission, 30 marked effect, 36 effective, and 24 ineffective; total efficacy 83.22%. In the control group, 20 short-term remission, 21 marked effect, 28 effective, 71 ineffective; total efficacy 49.29%. Efficacy in the experimental group was significantly higher (χ^2=36.523, P<0.01), with 58.04% (83/143) of DKD patients reaching ⩾ 30% UACR reduction, significantly higher than 29.29% (41/140) in the control (χ^2 =23.763, P<0.01).

Renal function efficacy: In the experimental group, 28 marked effect, 31 effective, 38 stable, 46 ineffective; total efficacy 67.83%. In the control group, 18 significant, 18 effective, 32 stable, 72 ineffective; total efficacy 48.57%. The improvement rate was significantly higher in the experimental group (χ^2 =10.795, P <0.01).

DKD clinical risk staging: Overall efficacy in the experimental group was 36.36% (52/143), significantly higher than the control group (18.57%, 26/140, χ^2 =11.217, P <0.01). In the experimental group, remission rate in the high-risk DKD subgroup was higher than in the very high-risk subgroup [52.63% (30/57) *vs* 25.58% (22/86), χ^2 =10.839, P<0.01]. Both DKD high and very high-risk remission rates in the experimental group were higher than those in the control group [52.63% (30/57) *vs* 29.83% (17/57), χ^2=6.118, P =0.013; 25.58% (22/86) *vs* 10.84% (9/83), χ^2=6.125, P =0.013]. See **Table 5**.

3.5 Safety Evaluation

No significant changes in hepatic function or blood counts were observed post-treatment in either group. Minor gastrointestinal discomfort occurred in 2 control group cases (incidence 1.43%, 2/140); minor gastrointestinal discomfort (n=3) and diarrhea (n=2) occurred in the experimental group (incidence 3.50%, 5/143). No significant difference between groups for adverse events (χ^2=0.543, P=0.461). All adverse events were mild, and no treatment was interrupted.

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

Index	Experimental group (n=143)	Control group (n=140)	Z/t value	P value
FBG (mmol/L)				
Before treatment	7.23 (5.71,9.36)	6.79 (5.68,8.54)	1.099	0.272
After treatment	6.49 (5.57,7.78)[a]	6.82 (5.61,7.70)	0.853	0.394
ΔFBG	-0.47 (-2.86,0.45)	-0.12 (-1.82,1.11)	1.801	0.072
HbA_{1C} (%)				
Before treatment	7.45 (6.44,9.03)	7.50 (6.70,8.75)	0.623	0.534
After treatment	6.95 (6.30,8.13)	7.55 (6.58,8.40)	1.821	0.069
ΔHbA_{1C}	-0.10 (-1.40,0.50)	0 (-1.00,0.58)	0.845	0.398
TC (mmol/L)				
Before treatment	4.90 (3.81,6.29)	4.94 (3.90,5.74)	0.619	0.536
After treatment	5.14 (4.10,5.96)	4.80 (3.82,5.69)	1.447	0.148
ΔTC	0.10 (-1.03,1.02)	-0.19 (-0.81,0.51)	0.841	0.400
TG (mmol/L)				
Before treatment	2.06 (1.46,3.22)	1.89 (1.29,3.02)	0.843	0.399
After treatment	1.73 (1.31,2.97)[a]	1.91 (1.45,2.69)	0.179	0.858
ΔTG	-0.34 (-1.50,0.17)	0 (-0.46,0.60)	2.847	0.004
HDL-C (mmol/L)				
Before treatment	1.26 (1.11,1.43)	1.23 (1.09,1.47)	0.559	0.576
After treatment	1.31 (1.14,1.50)	1.24 (1.06,1.52)	1.38	0.167
ΔHDL-C	-0.03 (-0.21,0.21)	-0.02 (-0.17,0.14)	0.13	0.896
LDL-C (mmol/L)				
Before treatment	2.70 (2.09,3.59)	2.74 (2.06,3.72)	0.083	0.934
After treatment	3.08 (2.41,3.59)	2.61 (2.03,3.33)	2.143	0.032
ΔLDL-C	-0.10 (-0.72,0.64)	-0.12 (-0.58,0.39)	0.208	0.835
SBP (mmHg)				
Before treatment	137.03±21.13	138.89±15.17	0.476	0.635
After treatment	130.00±16.39[a]	142.66±18.06	3.277	0.002
ΔSBP	-12.19±20.48	1.84±10.51	3.14	0.003
DBP (mmHg, $\bar{x}\pm s$)				
Before treatment	82.49±12.08	80.73±8.28	0.791	0.431
After treatment	81.27±11.31	82.2±9.78	0.388	0.699
ΔDBP	-3.35±11.82	-0.8±8.1	0.894	0.376
TyG index ($\bar{x}\pm s$)				
Before treatment	2.31±0.94	1.90±0.78	1.352	0.178
After treatment	1.93±0.74[a]	1.86±0.68	0.861	0.390
ΔTyG index	-0.38±0.86	-0.05±0.66	2.504	0.013

Tab.5 Distribution of DKD clinical risk stage in two groups after treatment [n(%)]

Group	Pre-treatment Stage	Number of Cases	The clinical staging of DKD after treatment			
			Low-risk	Moderate-risk	High-risk	Very High-risk
Experimental Group	Overall	143	8 (19.58)	31 (21.68)	35 (26.57)	69 (32.17)
	DKD High-risk	57	7 (12.28)	23 (40.35)	22 (38.60)	5 (8.77)
	DKD Very High-risk	86	1 (1.16)	8 (9.30)	13 (15.12)	64 (74.42)
Control Group	Overall	140	0	18 (12.86)	36 (22.86)	86 (51.43)
	DKD High-risk	57	0	17 (29.82)	28 (49.12)	12 (21.05)
	DKD Very High-risk	83	0	1 (1.21)	8 (9.64)	74 (89.16)

4 Discussion

The burden of DKD in China is severe, with most patients asymptomatic at early stages and usually presenting at an advanced stage [18]. Multiple RCT studies have shown that on the basis of metabolic control, the use of RASI [19], SGLT-2i [17], finerenone [20], and semaglutide [21] can reduce renal endpoint events, but the incidence of DKD and the End-Stage Kidney Disease (ESKD) caused by it are still on the rise. Recent FIDELITY study [20] indicate that combined maximized RASI, SGLT-2i, and finerenone therapy can reduce UACR by nearly 37% from early to late-stage DKD in Chinese patients, but subgroup analysis reveals limited renal protection in high/very high-risk DKD subgroups [22]. Faced with the potential huge patient population and urgent clinical needs, there are no randomized controlled trials targeting patients with high-risk or very high-risk DKD at home and abroad. This study is an exploratory and innovative clinical study of TCM, aiming to provide options for TCM treatment of patients with high-risk or very high-risk DKD in the future.

This study started in February 2021, focusing on patients with high-risk or very high-risk DKD. Most of these patients have already had moderate to severe renal function decline accompanied by massive proteinuria. Therefore, referring to domestic and international DKD

clinical guidelines and consensuses, this study only included new western kidney-protective drugs as concomitant medications in the analysis, and selected *Huangkui* Capsule as the positive control drug. *Huangkui* Capsule is a TCM patent medicine made from the ethanol extract of *Abelmoschi Corolla*. Previous clinical studies and meta-analyses have shown that *Huangkui* Capsule has significantly better clinical efficacy than RASI in the treatment of DKD with high safety [23-24]. Currently, it has been widely used in clinical treatment of DKD and is recommended by guidelines and expert consensuses [8, 11]. The results of this study showed that in terms of reducing urinary protein, *Kunkui Baoshen* Formula not only significantly reduced the classic indicators of glomerular injury (UACR and Um-Alb) but also effectively improved the indirect clinical indicators of tubular injury (U-RBP and urinary complement 3) [25-28]. The proportion of DKD patients with a UACR reduction of more than 30% reached 58.04%, which was significantly higher than 29.29% in the *Huangkui* Capsule group. In terms of improving renal function, the magnitude of decreases in Scr and Cys-C and the magnitude of increase in eGFR in the *Kunkui Baoshen* Formula group were significantly better than those in the control group. In summary, *Kunkui Baoshen* Formula has a significant "dual-lowering effect" (lowering both proteinuria and creatinine), with remarkable kidney-protective effects and no obvious side effects, which is expected to address the problem of limited drug options for DKD patients with massive proteinuria or severe renal insufficiency in clinical practice. Meanwhile, *Kunkui Baoshen* Formula can also effectively reduce FBG, SBP, TG, and TyG index, comprehensively improving glycolipid toxicity in DKD patients. Among them, the TyG index, as a new indicator for evaluating the degree of insulin resistance, increases with the decrease of eGFR and can be used as one of the important metabolic parameters for the treatment of DKD [29].

Glycotoxicity and lipotoxicity are damp-heat pathogens, which are deeply accumulated in the kidneys, condense to form blood stasis, and damage the renal collaterals. As a result, although there are insufficient external clinical manifestations in the early stage of DKD, the kidneys are already in a hypermetabolic and hyperfiltration state, and microalbuminuria can be seen clinically. With the progression of DKD, dampness and blood stasis bind together, consuming *Qi* and *Yin*, further aggravating renal injury, and leading to massive proteinuria and renal function decline. Therefore, the syndrome of "Dampness and Blood Stasis Obstructing the Collaterals with *Qi* and *Yin* Deficiency" is a common syndrome type in the high-risk or very high-risk stage of DKD, and the fundamental treatment principle is "clearing dampness and harmonizing collaterals, replenishing qi and nourishing yin". This theory, as the main content of the translational application research on TCM prevention and treatment of chronic disease-related renal injury, has won the First Prize of Jiangsu Provincial Science and Technology Progress Award.

Kunkui Baoshen Formula is an optimized fixed formula based on the core pathogenesis of DKD ("Dampness and Blood Stasis Obstructing the Collaterals with *Qi* and *Yin* Deficiency") and the previous research results of the research team. It consists of four TCM herbs: *Abelmoschi Corolla*, *Colquhounia Coccinea var. mollis*. *Radix*, *Astragali Radix*, and processed *Corni Fructus*. Among them, *Abelmoschi Corolla* are used in large doses as the monarch herb to clear away damp-heat, harmonize collaterals and resolve blood stasis. Modern pharmacokinetic and pharmacological studies have shown that *Abelmoschi Corolla* is mainly distributed in the kidneys and liver in animals, with antioxidative stress, anti-inflammatory, and anti-fibrotic effects [30-31]. *Colquhounia Coccinea var. mollis* is a Chinese materia medica with high efficacy and low toxicity, which has a similar mechanism of action to *Abelmoschi Corolla*. It can effectively regulate immunity, improve microcirculation, and resist glomerulosclerosis and tubulointerstitial fibrosis [32-33]. It is selected as the minister herb to assist the monarch herb in clearing heat and activating collaterals. The two herbs work synergistically to reduce urinary protein and improve renal injury. *Astragali Radix* is used as the assistant herb, which is good at replenishing qi and nourishing yin, promoting diuresis and reducing edema, eliminating pathogens without damaging healthy qi. Processed *Corni Fructus* warms and tonifies the liver and kidneys, and together with *Astragali Radix* (both as assistant herbs), they replenish both qi and yin, which is a commonly used herb pair by Zhang Xichun in the treatment of DKD [34]. All herbs combined exert both tonic and purgative effects, treating both the root cause and symptoms, jointly achieving the effects of clearing dampness and harmonizing collaterals, replenishing qi and nourishing yin.

In summary, for patients with high-risk or very high-risk DKD, on the basis of western medicine-based metabolic control, combined use of *Kunkui Baoshen* Formula can significantly increase eGFR, reduce proteinuria, improve various metabolic risk factors that promote DKD progression, and reverse the clinical staging of DKD. Its efficacy is superior to that of *Huangkui* Capsule, and it shows good safety. However, this study has a short observation period and lacks evaluation of long-term efficacy and safety. It is planned to conduct a clinical randomized controlled trial in the future.

Conflict of interest None

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·论　著·

昆葵保肾方治疗高或极高风险糖尿病肾病的前瞻性临床研究

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摘要：目的　对比昆葵保肾方与黄葵胶囊治疗高或极高风险糖尿病肾病（DKD）患者的临床疗效，探讨其临床应用的安全性。**方法**　选取2021年2月至2023年8月江苏省中医院门诊收治高或极高风险DKD患者314例，随机分为对照组和试验组（各157例）。在代谢控制基础上，对照组加用黄葵胶囊（5粒/次，3次/日，口服），试验组加用昆葵保肾方，两组疗程均为3个月。治疗前后观察两组患者尿蛋白相关指标[尿白蛋白/肌酐比值（UACR）、尿微量白蛋白（Um-Alb）、尿视黄醇结合蛋白（U-RBP）、尿补体3、尿α2-巨球蛋白（MG）]、肾功能相关指标[血肌酐、胱抑素C（Cys-C）、估算肾小球滤过率（eGFR）]、代谢指标[空腹血糖（FBG）、糖化血红蛋白（HbA_{1c}）、三酰甘油（TG）、收缩压、三酰甘油-葡萄糖指数（TyG指数）]变化，并评估其尿蛋白临床有效率及近期逆转率、肾功能疗效和DKD临床危险分期变化，记录用药期间不良反应。**结果**　试验组脱落与剔除14例，143例完成试验。对照组脱落与剔除17例，140例完成试验。治疗后，试验组UACR、Um-Alb、尿补体3、U-RBP均较治疗前显著下降（$P<0.01$），尿α2-MG呈下降趋势，UACR、Um-Alb下降幅度显著大于对照组（$P<0.01$）；临床蛋白尿降低总有效率为83.22%，显著优于对照组的49.29%（$\chi^2=36.523$，$P<0.01$），UACR下降幅度超过30%的DKD患者比例达58.04%，显著优于对照组的29.29%（$\chi^2=23.763$，$P<0.01$）。试验组血肌酐、Cys-C下降幅度和eGFR升高幅度显著优于对照组（$P<0.01$），肾功能改善的总有效率为67.83%，显著优于对照组的48.57%（$\chi^2=10.795$，$P<0.01$）。试验组FBG、TG、收缩压、TyG指数均较治疗前显著下降（$P<0.05$），TG、收缩压和TyG指数下降幅度优于对照组（$P<0.05$）。DKD临床危险分期变化中，试验组总有效率高于对照组（36.36% *vs* 18.57%，$\chi^2=11.217$，$P<0.01$）。两组患者在治疗期间均未出现严重不良反应，试验组和对照组不良反应发生率差异无统计学意义（3.50% *vs* 1.43%，$\chi^2=0.543$，$P=0.461$）。**结论**　昆葵保肾方在降低尿蛋白、保护肾功能、改善相关代谢因素和逆转DKD临床危险分期方面较黄葵胶囊有一定的优势，临床疗效显著且安全性良好。

关键词：昆葵保肾方；黄葵胶囊；糖尿病肾脏病；高风险；尿白蛋白/肌酐比值；估算肾小球滤过率；白蛋白
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Prospective clinical study of *Kunkui Baoshen* Formula in the treatment of high or extremely high-risk diabetic kidney disease

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Abstract: Objective　To compare the clinical efficacy of *Kunkui Baoshen* Formula and *Huangkui* Capsules in patients with high or extremely high-risk diabetic kidney disease (DKD), and to explore the safety of their clinical application.

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Methods This study enrolled 314 high or extremely high-risk DKD patients from the Department of Endocrinology of Jiangsu Province Hospital of Chinese Medicine between February 2021 and August 2023. The patients were randomly divided into a control group and an experimental group (n=157, each). In addition to metabolic control, the control group received *Huangkui* Capsules (5 capsules per dose, 3 times a day, orally), while the experimental group received *Kunkui Baoshen* Formula. Both groups were treated for 3 months. Pre- and post-treatment, changes in urine protein-related indicators [urine albumin-to-creatinine ratio (UACR), urinary microalbumin (Um-Alb), urine retinol-binding protein (U-RBP), urine complement 3, urine α2-macroglobulin (MG)], kidney function-related indicators [serum creatinine (Scr), cystatin C (Cys-C), estimated glomerular filtration rate (eGFR)], and metabolic indicators [fasting blood glucose (FBG), glycated hemoglobin (HbA_{1C}), triglycerides (TG), systolic blood pressure, triglyceride-glucose (TyG) index] were observed. The clinical efficacy of proteinuria reduction, the recent reversal rate of proteinuria, kidney function efficacy, and changes in DKD clinical risk staging were also evaluated, and adverse reactions during treatment were recorded. **Results** Fourteen patients in the experimental group were lost to follow-up or excluded, and 143 patients completed the trial. Seventeen patients in the control group were lost to follow-up or excluded, and 140 patients completed the trial. After treatment, the UACR, Um-Alb, urine complement 3, and U-RBP in the experimental group significantly decreased compared to before treatment (P<0.01), and urine α2-MG showed a downward trend. The reduction in UACR and Um-Alb was significantly superior to the control group (P<0.01). The total clinical efficacy rate of proteinuria reduction was 83.22%, significantly better than 49.29% in the control group (χ^2=36.523, P<0.01). The proportion of DKD patients with a reduction in UACR > 30% reached 58.04%, which was significantly higher than 29.29% in the control group (χ^2=23.763, P<0.01). The decrease in serum creatinine and Cys-C, and the increase in eGFR in the experimental group were significantly better than those in the control group (P<0.01), and the total effective rate of creatinine reduction was 67.83%, significantly better than 48.57% in the control group (χ^2=10.795, P<0.01). The FBG, TG, systolic blood pressure, and TyG index in the experimental group significantly decreased compared to before treatment (P<0.05), with the reduction in TG, systolic blood pressure, and TyG index being superior to the control group (P<0.05). Regarding changes in DKD clinical risk staging, the efficacy rate in the experimental group was higher than in the control group (36.36% *vs* 18.57%, χ^2=11.217, P<0.01). Both groups did not experience any severe adverse reactions during treatment, and there was no significant difference in the incidence of adverse reactions between the experimental group and control group (3.50% *vs* 1.43%, χ^2=0.543, P=0.461). **Conclusion** *Kunkui Baoshen* Formula has certain advantages over *Huangkui* Capsules in reducing proteinuria, protecting kidney function, improving related metabolic factors, and reversing DKD clinical risk staging. It demonstrates significant clinical efficacy and good safety.

Keywords: *Kunkui Baoshen* Formula; *Huangkui* Capsules; Diabetic kidney disease; High-risk; Urinary albumin-to-creatinine ratio; Estimated glomerular filtration rate; Albumin

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糖尿病肾病(diabetic kidney disease, DKD)是糖尿病最严重的微血管并发症,其发病率逐年上升,已成为终末期肾病(end-stage kidney disease, ESKD)的首要病因[1-2]。DKD起病隐匿、知晓率低、漏诊率高,进展速度快,一旦发展至临床蛋白尿期或中重度肾功能不全阶段,即被认为是难以逆转的高危或极高危期,西医疗效有限。在现实临床环境中,许多DKD患者只有在检测出大量蛋白尿或发现肾功能中重度下降时才至医院就诊[3],此阶段DKD患者进展为ESKD的风险大约是其他肾脏疾病的14倍[4]。因此,如何有效治疗上述高风险或极高风险的DKD患者,仍然是该病的治疗难点和瓶颈问题。

江苏省名中医余江毅教授提出“湿瘀阻络、气阴两虚”是DKD发生发展的中心环节。昆葵保肾方是余江毅教授基于上述理论,结合多年临床经验,总结优化治疗DKD的经验方,已获国家发明专利

（ZL 2022 1 1219776.3），并通过前期真实世界临床研究证实其君臣药对“黄蜀葵花-火把花根”可有效治疗DKD[5]。但尚缺乏针对高或极高风险DKD患者的临床疗效探索。考虑本研究对象为高或极高风险的DKD患者，新型肾保护西药临床使用受限，参考相关指南，选取黄葵胶囊为阳性对照药物，观察昆葵保肾方对DKD高或极高风险患者的治疗效果和安全性，以期为中医药治疗DKD提供新的循证依据。

1　临床资料

1.1　一般资料　本研究为随机对照试验优效性设计，研究对象的估算肾小球滤过率（estimated glomerular filtration rate，eGFR）为观测的主要结局指标，根据前期真实世界研究结果和既往文献，试验组与对照组的差值为11.2，标准差为18.609，设双侧α=0.05即单侧为0.025，把握度即1-β为0.9，优效界值为4，试验组与对照组样本量比值为1∶1；按参考文献[6]中的方法，采用R语言计算得到试验组样本量为141例，对照组样本量为141例。考虑10%失访以及拒访的情况，最终至少需要试验组157例，对照组157例，总计纳入样本量为314例。

本研究入组2021年2月至2023年8月江苏省中医院门诊收治的DKD进展风险为高或极高风险的患者314例。采用随机数字表法，将入组患者分为试验组和对照组，每组各157例。随访过程中9例试验组和8例对照组患者由于个人原因未能复诊而脱落，3例试验组患者和7例对照组患者因疗程内使用其他中医药而剔除，2例试验组患者和2例对照组患者入组后曾中断干预药物超过10天，因未能连续服药3月而剔除。最终有效病例283例（143例试验组，140例对照组），总脱落率为9.87%。两组患者的年龄、性别、糖尿病病程、身体质量指数（body mass index，BMI）、血压、空腹血糖（fasting blood glucose，FBG）、糖化血红蛋白（glycated hemoglobin，HbA_{1C}）、DKD风险分级、合并症、用药情况等基线资料均衡可比（$P>0.05$），见表1。本研究经江苏省中医院医学伦理委员会审核批准（伦理批件号：2021NL-017-02），所有受试者均签署知情同意书。

表1　两组患者基本资料比较　（$\bar{x}\pm s$）

Tab.1　Comparison of basic information between the two groups of patients　（$\bar{x}\pm s$）

项目	试验组（n=143）	对照组（n=140）	t/χ^2值	P值
年龄（岁）	55.55±12.55	58.33±12.72	1.835	0.065
性别[例（%）]				
男	108（75.52）	107（76.43）	0.032	0.859
女	35（24.48）	33（23.57）		
糖尿病病程（年）	12.59±5.93	14.19±11.56	1.159	0.249
BMI（kg/m^2）	24.99±3.21	25.33±3.59	0.672	0.502
收缩压（mmHg）	137.03±21.13	138.89±15.17	0.476	0.635
舒张压（mmHg）	82.49±12.08	80.73±8.28	0.791	0.431
FBG（mmol/L）	7.88±3.05	7.52±2.90	0.971	0.332
HbA_{1C}（%）	7.69±1.83	7.87±1.54	0.751	0.453
风险分级[例（%）]				
高风险	57（39.86）	57（40.71）	0.021	0.884
极高风险	86（60.14）	83（59.29）		
合并症[例（%）]				
高血压	121（84.62）	108（77.14）	2.558	0.110
高脂血症	94（65.73）	90（64.29）	0.065	0.798
高尿酸血症	46（32.17）	60（42.86）	3.450	0.063
冠心病	26（18.18）	15（10.71）	3.184	0.074
脑梗死	32（22.38）	22（15.71）	2.034	0.154
用药情况[例（%）]				
RASI	63（44.06）	60（42.86）	0.041	0.839
SGLT2i	105（73.43）	95（67.86）	1.612	0.203
DPP-4i	70（48.95）	59（42.14）	1.322	0.250
GLP-1RA	32（22.38）	36（25.71）	0.431	0.511
胰岛素	58（40.56）	60（42.86）	0.154	0.695

注：冠心病指冠状动脉粥样硬化性心脏病；RASI指肾素-血管紧张素系统阻断剂；SGLT-2i指钠-葡萄糖协同转运蛋白2抑制剂；DDP-4i指二肽基肽酶4抑制剂；GLP-1RA指胰高糖素样肽-1受体激动剂。

1.2　诊断标准

1.2.1　DKD西医诊断标准　参照《中国糖尿病肾脏病防治指南（2021年版）》[7]和《糖尿病肾脏病中西医结合防治专家共识（2023版）》[8]，诊断标准如下：（1）明确的糖尿病病史；（2）在3~6个月内的3次检测中至少2次尿白蛋白/肌酐比值（urine albumin-to-creatinine ratio，UACR）≥30 mg/g或尿白蛋白排泄率（urinary albumin excretion rate，UAER）≥30 mg/24 h（≥20 μg/min），和（或）eGFR < 60 mL/（min·1.73 m^2）持续3个月以上；（3）排除非DKD的可能，具体包括：1型糖尿病病程短（<5年）或未合并糖尿病视网膜病变、eGFR迅速下降、尿蛋白迅速增加或出现肾病综合征、顽固性高血压、出现活动性尿沉渣（红细胞、白细胞或细胞管型等）、合并其他系统性疾病的症状或体征、给予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）治疗后2~3个月内eGFR下降>30%、肾脏超声发现异常。临床无法明确诊断时，推荐患者必要时行肾脏穿刺病理检查。

1.2.2　DKD临床危险分期标准　参照2022年改善全球肾脏病预后组织（Kidney Disease：Improving Global Outcomes，KDIGO）颁布的*KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease*[9]中提出的病因-肾小球滤过率-白蛋白尿

(cause-glomerular filtration rate-albuminuria, CGA)分期标准和《糖尿病肾脏病中西医结合防治专家共识(2023版)》[8]中DKD临床分期风险评估,结合UACR与eGFR,将DKD风险程度分为低危、中危、高危和极高危。

1.2.3 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》[10]、《糖尿病肾病病证结合诊疗指南》[11]、《中药新药治疗糖尿病的临床研究指导原则》[12]制定湿瘀阻络、气阴两虚辨证标准。(1)主症:面肢浮肿,尿浊,肢体麻木或疼痛,神疲乏力。(2)次症:大便黏滞,口干咽燥,头身困重,腰膝酸软,视物模糊;舌脉,舌质暗红或有瘀斑,苔少或黄腻,脉细滑数或沉涩。具备以上任意2项主证、2项次证,结合舌脉,即可诊断为湿瘀阻络、气阴两虚证。

1.3 纳入标准 (1)符合DKD临床风险分期为高风险或极高风险。(2)年龄在18周岁至80周岁之间,性别不限;(2)血压≤160/100 mmHg;(4)知情同意,自愿参加本试验。

1.4 排除标准 (1)1个月以内发生过糖尿病酮症酸中毒、高糖高渗综合征或感染等;(2)肾血管性高血压;(3)正在透析治疗或需要立即透析;(4)近期有恶性高血压、心肌梗死、急性脑血管病等危急重症病史;(5)恶性肿瘤、妊娠或哺乳期;(6)对干预药物过敏。

1.5 脱落与剔除标准 (1)脱落标准:经知情同意、并筛选合格进入随机化研究的患者,因故未完成本方案所规定的疗程及观察周期,作为脱落病例。当患者脱落后,采取电话随访方式,尽可能与患者联系,询问理由、记录最后一次服药时间、完成所能完成的评估项目。(2)剔除标准:病例选择不符合纳入标准,或符合排除标准;未按要求使用研究用药;在随机化之后没有任何临床数据。

2 方 法

2.1 治疗方法 两组根据《中国糖尿病肾脏病防治指南(2021年版)》[7]实施常规治疗,包括改善生活方式,饮食治疗,控制血糖、血压、血脂等。对照组在常规治疗的基础上给予黄葵胶囊(江苏苏中药业,规格:0.43 g/粒,国药准字批号:Z19990040),5粒/次,3次/日,饭后口服。试验组在常规治疗的基础上予以昆葵保肾方(黄蜀葵花30 g、火把花根15 g、黄芪30 g、酒萸肉10 g),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。两组均连续治疗3个月。

2.2 观察指标及方法 治疗前后嘱患者空腹,晨起静息状态下采肘正中静脉血和尿液,血尿标本均送至江苏省中医院检验科进行检测。血液检测方法:用无菌抗凝管采集外周静脉血(清晨空腹)5 mL,室温静置30 min使其凝结后,4 ℃条件下3 000 r/min离心10 min(离心半径10 cm),吸取上清液(即血清)200 μL分装于2 mL离心管中,立刻放置于-80 ℃冰箱保存待测,用全自动生化分析仪检测血糖、血脂相关指标,以酶联免疫吸附法检测肾功能相关指标。

2.2.1 尿蛋白指标 (1)肾小球病变:UACR、尿微量白蛋白(urine microalbumin, Um-Alb);(2)肾小管病变:尿视黄醇结合蛋白(urine retinol binding protein, U-RBP)、尿补体3、尿α2-巨球蛋白(macroglobulin, MG)。

2.2.2 肾功能指标 血肌酐、胱抑素C(cystatin C, Cys-C)、eGFR。

2.2.3 糖脂代谢及血压 FBG、HbA_{1C}、总胆固醇(total cholesterol, TC)、三酰甘油(triglycerides, TG)、高密度脂蛋白胆固醇(high density lipoprotein cholesterol, HDL-C)、低密度脂蛋白胆固醇(low density lipoprotein cholesterol, LDL-C)、收缩压、舒张压。采用三酰甘油-葡萄糖(triglyceride-glucose, TyG)指数[13-14]评估胰岛素抵抗水平,TyG指数=ln[FBG(mg/dL)×TG(mg/dL)/2]。

2.3 临床疗效评价

2.3.1 尿蛋白疗效 评定标准参考《糖尿病肾病诊断、辨证分型及疗效评定标准(试行方案)》[15],以及CREDENCE卡格列净研究[16]、EMPA-REG恩格列净研究[17]中对于UACR逆转的定义,具体如下。近期缓解为UACR减少≥50%,或降至正常范围;显效为UACR减少≥30%,但不足50%;有效为UACR减少,但不足30%;无效为UACR上升或无变化。总有效率=(近期缓解+显效+有效)/总例数×100%。近期逆转率=(近期缓解+显效)/总例数×100%。

2.3.2 肾功能疗效 评定标准参考《糖尿病肾脏病分期辨证规范与疗效评定方案及其研究》[10]。显效为eGFR升高≥20%,或血肌酐降低≥20%;有效为eGFR升高10%~<20%,或血肌酐降低10%~<20%;稳定为eGFR无降低且升高<10%,或血肌酐无上升,且降低<10%;无效为eGFR降低或血肌酐上升。总有效率=(显效+有效+稳定)/总例数×100%。

2.3.3 DKD临床危险分期变化 参考《糖尿病肾脏病中西医结合防治专家共识(2023版)》[8]和*KDIGO 2022 Clinical Practice Guideline for Diabetes Manage-*

ment in Chronic Kidney Disease[9]，拟定本研究的DKD临床危险分期疗效评判标准。好转为治疗后DKD由高危好转至低危或中危，DKD由极高危好转至低危、中危或高危；维持为DKD高危患者治疗后仍处于DKD高危分期，DKD极高危患者治疗后A和G分期均未明显进展，具体指A1~2期患者未至A3期，G3期患者未至G4~5期，G4期患者未至G5期；进展为DKD高危进展至DKD极高危；DKD极高危患者A或G分期进展。有效率=好转/总例数×100%。

2.4　安全性评价　评估治疗前后肝功能[丙氨酸转氨酶（alanine aminotransferase，ALT）、天冬氨酸转氨酶（aspartate aminotransferase，AST）]、血常规（红细胞计数、白细胞计数、中性粒细胞百分比）、性激素（对年轻患者筛查，女性患者重点询问月经史）、低血糖发生率等。详细记录不良反应（如恶心呕吐、腹泻或便秘、头晕头痛、口干等）的表现、程度、出现时间、持续时间、处理措施和消除时间等。

2.5　统计学方法　采用SPSS 25.0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；不符合正态分布的，采用$M(P_{25},P_{75})$表示，组间比较用Wilcoxon秩和检验，组内比较采用配对秩和检验。对于分类数据采用例（%）表示，组间比较采用χ^2检验。采用双侧检验，以$P<0.05$作为差异有统计意义。

3　结　果

3.1　两组患者治疗前后尿蛋白相关指标比较　肾小球病变：试验组UACR、Um-Alb均较治疗前显著下降（$P<0.05$），下降幅度显著优于对照组（$P<0.01$）。肾小管病变：试验组尿补体C3、U-RBP均较治疗前显著下降（$P<0.05$）；对照组尿补体C3、U-RBP有下降趋势但差异无统计学意义（$P>0.05$）。两组治疗后的Δ尿补体3、ΔU-RBP、Δα2-MG差异无统计学意义（$P>0.05$）。见表2。

3.2　两组患者治疗前后肾功能相关指标比较　试验组Scr、Cys-C均较治疗前显著下降（$P<0.05$），下降幅度显著大于对照组（$P<0.01$）；eGFR较治疗前显著上升（$P<0.05$），升高幅度显著大于对照组，差异有统计学意义（$P<0.01$）。见表3。

3.3　两组患者治疗前后糖代谢、脂代谢及血压指标比较　糖代谢相关：试验组FBG较治疗前下降（$P<0.05$），HbA_{1C}呈下降趋势；对照组FBG、HbA_{1C}较治疗前呈下降趋势，但差异无统计学意义（$P>0.05$）。ΔFBG、ΔHbA_{1C}组间比较差异无统计学意义（$P>0.05$）。脂代谢相关：试验组TG较治疗前显著下降（$P<0.05$），下降幅度显著优于对照组（$P<0.01$），TC、HDL-C、LDL-C较治疗前变化未见统计学差异（$P>0.05$）。对照组治疗后TG、TC、HDL-C、LDL-C均未见

表2　两组患者治疗前后尿蛋白相关指标比较　[$M(P_{25},P_{75})$]

Tab.2　Comparison of urinary protein-related indicators between the two groups before and after treatment　[$M(P_{25},P_{75})$]

指标	试验组（n=143）	对照组（n=140）	Z值	P值
UACR(mg/g)				
治疗前	683.50(302.75,1 694.50)	609.50(382.25,1 490.50)	0.332	0.740
治疗后	305.00(99.25,1 186.50)[a]	688.00(300.00,1 550.50)	4.173	<0.001
ΔUACR	−319.00(−778.00,−105.50)	8.00(−212.00,307.50)	7.225	<0.001
Um-Alb(mg/L)				
治疗前	555.50(206.75,1 326.00)	429.50(272.75,834.00)	0.752	0.452
治疗后	254.00(95.50,687.00)[a]	434.50(204.00,858.00)	2.958	0.003
ΔUm-Alb	−230.00(−622.50,−5.75)	−48.00(−233.00,198.00)	4.042	<0.001
尿补体3(mg/L)				
治疗前	0.90(0.42,4.38)	1.12(0.26,3.28)	0.605	0.545
治疗后	0.68(0.34,1.42)[a]	0.97(0.29,3.18)	1.028	0.304
Δ尿补体3	−0.22(−1.44,0.19)	−0.03(−1.03,0.36)	0.933	0.351
U-RBP(mg/L)				
治疗前	1.16(0.38,4.50)	0.64(0.32,1.99)	1.522	0.128
治疗后	0.79(0.28,2.19)[a]	0.53(0.20,1.74)	1.011	0.312
ΔU-RBP	−0.10(−0.70,0.08)	−0.02(−0.37,0.21)	1.622	0.105
α2-MG(mg/L)				
治疗前	1.40(0.55,2.60)	1.20(0.70,2.48)	0.027	0.979
治疗后	1.05(0.60,2.08)	1.30(0.85,2.45)	1.171	0.242
Δα2-MG	0(−0.90,0.62)	0.10(−0.70,0.90)	0.782	0.434

注：与治疗前相比，[a]$P<0.05$。

统计学差异（$P>0.05$）。ΔTC、ΔHDL-C组间比较差异均未见明显统计学意义（$P>0.05$）。

血压：试验组收缩压较治疗前下降（$P<0.05$），下降幅度显著优于对照组（$P<0.01$），舒张压呈下降趋势，但差异未见统计学意义（$P>0.05$）；对照组收缩压较治疗前呈上升趋势，舒张压呈下降趋势但差异无统计学意义；试验组TyG指数较治疗前显著下降（$P<0.05$），下降幅度显著由于对照组（$P<0.05$）。结果见表4。

3.4　*尿蛋白和肾功能疗效及DKD临床危险分期变化*　尿蛋白疗效：试验组近期缓解53例，显效30例，有效36例，无效24例，总有效率为83.22%；对照组近期缓解20例，显效21例，有效28例，无效71例，总有效率为49.29%。试验组尿蛋白疗效显著优于对照组（$\chi^2=36.523$，$P<0.01$），UACR下降幅度超过30%的DKD患者比例达58.04%（83/143），显著优于对照组的29.29%（41/140）（$\chi^2=23.763$，$P<0.01$）。

肾功能疗效：试验组显效28例，有效31例，稳定38例，无效46例，总有效率为67.83%；对照组显效18例，有效18例，稳定32例，无效72例，总有效率为48.57%。试验组肾功能改善总有效率显著高于对照组（$\chi^2=10.795$，$P<0.01$）。

DKD临床危险分期变化：试验组总体的有效率为36.36%（52/143），高于对照组的18.57%（26/140），差异有统计学意义（$\chi^2=11.217$，$P<0.01$）。在试验组中DKD高危人群好转率高于极高危人群［52.63%（30/57）*vs* 25.58%（22/86），$\chi^2=10.839$，$P<0.01$］。试验组的DKD高危人群和极高危人群好转率均高于对照组［52.63%（30/57）*vs* 29.83%（17/57），$\chi^2=6.118$，$P=0.013$；25.58%（22/86）*vs* 10.84%（9/83），$\chi^2=6.125$，$P=0.013$］。两组患者治疗前后DKD临床分期分布见表5。

表3　两组患者治疗前后肾功能指标比较　［$M(P_{25},P_{75})$］

Tab.3　Comparison of renal function indicators between the two groups before and after treatment　［$M(P_{25},P_{75})$］

指标	试验组（n=143）	对照组（n=140）	Z/t值	P值
血肌酐（μmol/L）				
治疗前	117.10（84.53，168.63）	108.90（84.50，135.00）	1.775	0.076
治疗后	106.20（78.90，141.00）[a]	113.40（76.30，138.90）	0.141	0.888
Δ血肌酐	−9.50（−24.50，2.40）	0.60（−10.40，12.40）	4.946	<0.001
Cys-C（mg/L，$\bar{x}\pm s$）				
治疗前	1.96±0.82	1.79±0.72	1.814	0.071
治疗后	1.84±0.73[a]	1.98±0.85[a]	1.349	0.178
ΔCys-C	−0.07±0.34	0.19±0.57	4.161	<0.001
eGFR［mL/（min·1.73m^2）］				
治疗前	45（31，64）	48（36，72）	1.605	0.109
治疗后	49（36，71）[a]	48（34，68）[a]	0.856	0.392
ΔeGFR	2（−3，8）	−1（−8，4）	3.577	<0.001

注：与治疗前相比，[a]$P<0.05$。

3.5　*安全性评价*　两组患者治疗后各肝功能、血常规等安全性指标均未出现明显变化，对照组发生轻微胃不适2例，不良反应发生率为1.43%（2/140）；试验组发生轻微胃不适3例，腹泻2例，不良反应发生率为3.50%（5/143）；两组不良反应发生率无明显统计学差异（$\chi^2=0.543$，$P=0.461$）。所有不良反应均症状轻微，未中断治疗。

表4　两组患者治疗前后糖脂代谢及血压相关指标比较　［$M(P_{25},P_{75})$］

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

指标	试验组（n=143）	对照组（n=140）	Z/t值	P值
FBG（mmol/L）				
治疗前	7.23（5.71，9.36）	6.79（5.68，8.54）	1.099	0.272
治疗后	6.49（5.57，7.78）[a]	6.82（5.61，7.70）	0.853	0.394
ΔFBG	−0.47（−2.86，0.45）	−0.12（−1.82，1.11）	1.801	0.072
HbA_{1C}（%）				
治疗前	7.45（6.44，9.03）	7.50（6.70，8.75）	0.623	0.534
治疗后	6.95（6.30，8.13）	7.55（6.58，8.40）	1.821	0.069
ΔHbA_{1C}	−0.10（−1.40，0.50）	0（−1.00，0.58）	0.845	0.398
TC（mmol/L）				
治疗前	4.90（3.81，6.29）	4.94（3.90，5.74）	0.619	0.536
治疗后	5.14（4.10，5.96）	4.80（3.82，5.69）	1.447	0.148
ΔTC	0.10（−1.03，1.02）	−0.19（−0.81，0.51）	0.841	0.400
TG（mmol/L）				
治疗前	2.06（1.46，3.22）	1.89（1.29，3.02）	0.843	0.399
治疗后	1.73（1.31，2.97）[a]	1.91（1.45，2.69）	0.179	0.858
ΔTG	−0.34（−1.50，0.17）	0（−0.46，0.60）	2.847	0.004
HDL-C（mmol/L）				
治疗前	1.26（1.11，1.43）	1.23（1.09，1.47）	0.559	0.576
治疗后	1.31（1.14，1.50）	1.24（1.06，1.52）	1.380	0.167
ΔHDL-C	−0.03（−0.21，0.21）	−0.02（−0.17，0.14）	0.130	0.896
LDL-C（mmol/L）				
治疗前	2.70（2.09，3.59）	2.74（2.06，3.72）	0.083	0.934
治疗后	3.08（2.41，3.59）	2.61（2.03，3.33）	2.143	0.032
ΔLDL-C	−0.10（−0.72，0.64）	−0.12（−0.58，0.39）	0.208	0.835
收缩压（mmHg，$\bar{x}\pm s$）				
治疗前	137.03±21.13	138.89±15.17	0.476	0.635
治疗后	130.00±16.39[a]	142.66±18.06	3.277	0.002
Δ收缩压	−12.19±20.48	1.84±10.51	3.140	0.003
舒张压（mmHg，$\bar{x}\pm s$）				
治疗前	82.49±12.08	80.73±8.28	0.791	0.431
治疗后	81.27±11.31	82.20±9.78	0.388	0.699
Δ舒张压	−3.35±11.82	−0.80±8.10	0.894	0.376
TyG指数（$\bar{x}\pm s$）				
治疗前	2.31±0.94	1.90±0.78	1.352	0.178
治疗后	1.93±0.74[a]	1.86±0.68	0.861	0.390
ΔTyG指数	−0.38±0.86	−0.05±0.66	2.504	0.013

注：与治疗前相比，[a]$P<0.05$。

表5　两组患者治疗后DKD临床风险分期分布　[例(%)]

Tab.5　Distribution of DKD clinical risk stage in two groups after treatment　[n(%)]

分组	治疗前分期	例数	治疗后患者DKD临床分期			
			DKD低危	DKD中危	DKD高危	DKD极高危
试验组	总体	143	8(19.58)	31(21.68)	35(26.57)	69(32.17)
	DKD高危	57	7(12.28)	23(40.35)	22(38.60)	5(8.77)
	DKD极高危	86	1(1.16)	8(9.30)	13(15.12)	64(74.42)
对照组	总体	140	0	18(12.86)	36(22.86)	86(51.43)
	DKD高危	57	0	17(29.82)	28(49.12)	12(21.05)
	DKD极高危	83	0	1(1.21)	8(9.64)	74(89.16)

4　讨　论

我国DKD形势严峻，患者早期多无明显症状，就诊时已处于晚期[18]。多项RCT研究表明在代谢控制基础上，使用RASI[19]、SGLT-2i[17]、非奈利酮[20]及司美格鲁肽[21]等可减少肾脏终点事件，但DKD及其导致的ESKD发病率仍呈上升趋势。近年来，FIDELITY研究结果提示[20]，联合使用最大化的RASI、SGLT-2i和非奈利酮，可降低早期至晚期中国DKD患者UACR近37%，但亚组分析后对于DKD高和极高危患者，联合治疗的肾保护作用仍有限[22]。面对潜在的巨大患者群体和迫切的临床需求，国内外尚无针对高或极高风险DKD患者的随机对照试验。因此，本研究是一个探索性、创新性的中医药临床研究，以期为未来中医药治疗高或极高风险期DKD患者提供选择。

本研究开始于2021年2月，研究对象聚焦于DKD高或极高危患者，此期患者大部分已出现肾功能中重度下降伴大量蛋白尿，因此，参考国内外DKD临床指南和共识，本研究仅将新型保肾西药作为合并用药纳入分析，选用黄葵胶囊作为阳性对照药物。黄葵胶囊是由黄蜀葵花的乙醇提取物制成的一种中成药，既往多项临床研究及荟萃分析表明黄葵胶囊治疗DKD的临床疗效显著优于RASI，且安全性高[23-24]，目前已广泛应用于临床治疗DKD，且被指南和专家共识推荐[8,11]。本研究结果发现，在降低尿蛋白方面，昆葵保肾方既可显著降低肾小球损伤的经典指标UACR、Um-Alb，也可有效改善肾小管损伤的间接临床指标U-RBP和尿补体C3[25-28]，其降低UACR幅度超过30%的DKD患者比例达58.04%，显著优于黄葵胶囊组的29.29%。在改善肾功能方面，昆葵保肾方组血肌酐、Cys-C下降幅度和eGFR升高幅度均显著优于对照组。综上，昆葵保肾方具有显著降低尿蛋白及血肌酐的“双降”功效，保肾作用显著且无明显副作用，有望解决临床大量蛋白尿或严重肾功能不全DKD患者治疗药物选择受限的难题。同时，昆葵保肾方也可有效降低FBG、收缩压、TG、TyG指数，综合改善DKD患者糖脂毒性。其中，TyG指数作为评估胰岛素抵抗程度的新指标，随着eGFR下降而升高，可作为治疗DKD的重要代谢参数之一[29]。

糖毒、脂毒为湿热之邪，深蕴于肾，煎液成瘀，损伤肾络，致DKD早期虽外在临床表现不足，但肾脏已处于高代谢高滤过状态，临床可见微量蛋白尿。随着DKD进展，湿瘀互结，耗伤气阴，进一步加重肾损伤，出现大量蛋白尿和肾功能下降。因此，“湿瘀阻络、气阴两虚”证是DKD高或极高风险期的常见证型，“清利和络，益气养阴”为其治疗大法。该理论作为重大慢病相关肾损伤的中医药防治转化应用研究主要内容已获得江苏省科技进步一等奖。昆葵保肾方是基于DKD“湿瘀阻络，气阴两虚”的核心病机和课题组前期研究结果，最终优化的固定处方，由黄蜀葵花、火把花根、黄芪和酒萸肉四味中药组方而成。其中，重用黄蜀葵花为君药，以清利湿热，和络化瘀。现代药代动力学及药理研究显示，黄蜀葵花在动物体内主要分布于肾脏和肝脏，具有抗氧化应激、抗炎和抗纤维化等作用[30-31]。火把花根是一种高效低毒的中药，与黄蜀葵花作用机制异曲同工，可有效调节免疫、改善微循环及抗肾小球硬化及小管间质纤维化[32-33]，方选其为臣药，助君药清热活络，两者相使为用，共奏降低尿蛋白及改善肾损伤之效。佐以黄芪功善益气养阴、利水消肿，祛邪而不伤正；酒萸肉温补肝肾，与黄芪共为佐药，两者配伍气阴双补，为张锡纯治疗DKD常用药对[34]。诸药合用，补泻同施，标本兼治，共奏清利和络、益气养阴之效。

综上，对于高或极高危DKD患者，在西医药代谢控制基础上，联用昆葵保肾方，可显著提高eGFR，降低蛋白尿，改善多种促DKD进展的代谢危险因素，逆转DKD临床分期，疗效均优于黄葵胶囊，且显示出良好的安全性。但本研究观察时间较短，缺乏远期疗效及安全性的评估，未来拟进行临床随机对照试验

随访后观察，获得长期预后以及肾脏终点事件数据，为临床治疗DKD提供更有力的循证医学证据。

利益冲突　无

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