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Clinical Study on the Modified Formula of Huang Yuanyu's Gui Fu Ling Wu Decoction for Treating Spleen-Kidney Yang Deficiency Type Diabetic Nephropathy

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Abstract: *Objective:* To evaluate the efficacy of the modified Gui Fu Ling Wu Decoction in treating diabetic nephropathy (DN) of the spleen-kidney Yang deficiency type. *Methods:* A total of 100 DN patients admitted to Changyi Traditional Chinese Medicine Hospital between August 2023 and March 2024 were included in the study. Patients were randomly divided into a control group and a study group, each comprising 50 cases, using a computerized random number generator. The control group received kallikrein treatment, while the study group received a combination of kallikrein and the modified Gui Fu Ling Wu Decoction. Blood glucose control, renal function, and inflammatory markers were assessed before and after treatment in both groups. *Results:* Before treatment, there were no significant differences in blood glucose and renal function indicators between the two groups ($P > 0.05$). After treatment, postprandial blood glucose, fasting blood glucose, 24-hour urinary protein, urinary microalbumin, serum creatinine, serum C-reactive protein (CRP), and interleukin-6 levels significantly decreased in both groups, with the study group showing superior results compared to the control group ($P < 0.05$). *Conclusion:* The combination of Gui Fu Ling Wu Decoction and kallikrein for treating spleen-kidney Yang deficiency type DN significantly improves blood glucose control, enhances renal function, and reduces inflammatory responses.

Keywords: Gui Fu Ling Wu Decoction; Diabetic nephropathy; Renal function; Inflammatory markers

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1. Introduction

With continuous socioeconomic development and evolving lifestyles, diabetic nephropathy (DN) has become more prevalent than glomerulonephritis-related diseases, imposing a greater burden on society than population aging [1]. Clinically, DN manifests as thirst, foamy urine, and lower limb edema. Modern medicine currently lacks

specific treatment protocols, relying primarily on comprehensive symptomatic measures such as blood sugar and lipid control and dietary regulation [2].

As traditional Chinese medicine (TCM) techniques advance and clinical experience accumulates, TCM has demonstrated significant advantages in DN treatment, including confirmed efficacy and fewer side effects [3]. In the *Si Sheng Xin Yuan* (*Four Sacred Sources of the Heart*), Huang Yuanyu proposed the use of Gui Fu Ling Wu Decoction to treat symptoms of "Xiao Ke" (wasting-thirst disorder) [4]. However, clinical research on DN-related applications of this formula remains limited.

To address this gap, a study was conducted on 100 DN patients admitted to Changyi Hospital of Traditional Chinese Medicine between August 2023 and March 2024 to investigate the therapeutic effects of Gui Fu Ling Wu Decoction on spleen-kidney Yang deficiency type DN.

2. Materials and methods

2.1. General information

A total of 100 patients with diabetic nephropathy (DN) admitted to the hospital from August 2023 to March 2024 were included in the study. Patients were randomly divided into a control group and a study group, each comprising 50 cases, using a computer-generated random number generator.

Study group: 26 males and 24 females; age range 46–76 years, mean age (61.58 ± 5.66) years; disease duration 1.2–8.3 years, mean duration (5.15 ± 1.23) years; disease stages: Stage I (13 cases), Stage II (28 cases), Stage III (9 cases).

Control group: 25 males and 25 females; age range 39–79 years, mean age (60.96 ± 5.31) years; disease duration 1.7–8.5 years, mean duration (5.33 ± 1.19) years; disease stages: Stage I (16 cases), Stage II (26 cases), Stage III (8 cases).

The study was approved by the Medical Ethics Committee of Changyi Traditional Chinese Medicine Hospital, and informed consent was obtained from all patients and their families.

2.2. Inclusion criteria

(1) Patients meeting the diagnostic criteria for DN in both traditional Chinese and Western medicine and classified as the spleen-kidney Yang deficiency subtype [5,6].

(2) Aged 18–80 years.

(3) Microalbuminuria (MAU) > 30 mg/L, proteinuria-positive for more than three months.

(4) Complete baseline data available.

2.3. Exclusion criteria

(1) Patients with type 1 diabetes mellitus.

(2) Patients receiving other DN-related treatments outside of the study.

(3) Patients with kidney damage due to other causes.

(4) Patients with severe infections or other organ-related diseases.

(5) Patients with malignant tumors or autoimmune diseases.

(6) Patients with poor compliance.

2.4. Methods

Both groups followed regular routines, engaged in appropriate physical activities, and adhered to a low-sugar, low-fat, low-salt, low-oil, high-quality low-protein diet.

Control group: Treated with kallikrein enteric-coated tablets (National Drug Approval No. H37022253, 120 U per tablet), administered orally at 120 U per dose, three times daily.

Study group: Received the modified Gui Fu Ling Wu Decoction in addition to the control treatment.

Both groups underwent continuous treatment for three months.

2.4.1. Formula of Gui Fu Ling Wu Decoction

(1) Ingredients: *Poria cocos* (15 g), Alismatis rhizoma (15 g), Cinnamon twig (15 g), White peony root (12g), Astragalus (30 g), Glycyrrhizae radix preparata (6 g), Codonopsis (30 g), *Angelica sinensis* (10 g), Earthworm (9 g), *Salvia miltiorrhiza* (20 g), Dry ginger (6 g), Calcined Longgu (30 g, pre-decocted), Calcined oyster (30 g, pre-decocted), Aconite root (6 g, pre-decocted).

(2) Preparation: Decoction prepared with water, reduced to approximately half a cup. Administered warm twice daily, morning and evening.

2.5. Observation indicators

(1) Blood glucose indicators: Fasting blood glucose (FBG) and postprandial 2-hour blood glucose (PBG) levels were measured using a rapid blood glucose meter before treatment and at the end of the three-month treatment period.

(2) Renal function indicators: 24-hour urinary protein quantification, urinary microalbumin, and serum creatinine levels were measured using an automatic biochemical analyzer before treatment and at the end of three months.

(3) Inflammatory indicators: Serum levels of C-reactive protein (CRP) and interleukin-6 (IL-6) were measured using the ELISA method before treatment and at the end of three months.

2.6. Statistical methods

Data analysis was performed using SPSS 19.0 statistical software. Measurement data conforming to the normal distribution, as determined by the Shapiro-Wilk test, were expressed as mean ± standard deviation (SD). Independent sample *t*-tests were used for comparisons between groups. Statistical significance was considered at $P < 0.05$.

3. Results

3.1. Comparison of blood glucose indicators between the two groups

Before treatment, there was no significant difference in blood glucose indicators between the two groups ($P > 0.05$). After treatment, both PBG and FBG levels decreased, with the study group showing significantly lower values than the control group ($P < 0.05$). See **Table 1**.

Table 1. Comparison of blood glucose indicators between the two groups (mean ± SD)

Group	*n*	PBG (mmol/L)		FBG (mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment
Study group	50	9.27 ± 1.34	7.08 ± 0.83*	8.06 ± 1.12	6.04 ± 0.83*
Control group	50	9.34 ± 1.50	7.92 ± 1.27*	8.17 ± 1.30	6.97 ± 0.94*
t		0.246	3.915	0.453	5.244
P		0.806	< 0.001	0.651	< 0.001

*Note: Compared to pre-treatment, $P < 0.05$.

3.2. Comparison of renal function indicators between the two groups

Before treatment, there were no significant differences in renal function indicators between the two groups ($P > 0.05$). After treatment, the levels of 24-hour urinary protein, urinary microalbumin, and serum creatinine decreased, with the study group demonstrating significantly lower levels than the control group ($P < 0.05$). See **Table 2**.

Table 2. Comparison of renal function indicators between the two groups (mean ± SD)

Groups	*n*	24h urine protein (g)		MAU (mg/L)		Serum creatinine (μmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Study group	50	5.09 ± 1.17	3.22 ± 0.89*	320.41 ± 46.51	169.43 ± 33.68*	176.14 ± 29.35	139.36 ± 18.83*
Control group	50	5.16 ± 1.31	4.15 ± 1.02*	331.27 ± 42.28	216.34 ± 35.13*	171.58 ± 28.71	156.47 ± 20.21*
t		0.282	4.858	1.222	6.816	0.785	4.380
P		0.779	< 0.001	0.225	< 0.001	0.434	< 0.001

*Note: Compared to pre-treatment, $P < 0.05$.

3.3. Comparison of inflammatory indicators between the two groups

Before treatment, there were no significant differences in inflammatory indicators between the two groups ($P > 0.05$). After treatment, serum levels of CRP and IL-6 decreased, with the study group showing significantly lower levels than the control group ($P < 0.05$). See **Table 3**.

Table 3. Comparison of inflammatory indicators between the two groups (mean ± SD)

Groups	*n*	CRP (mg/L)		IL-6 (pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment
Study group	50	22.08 ± 3.47	12.21 ± 2.74*	23.31 ± 3.41	11.95 ± 2.83*
Control group	50	21.59 ± 3.62	17.53 ± 2.96*	23.16 ± 3.32	18.84 ± 2.56*
t		0.691	9.326	0.223	12.767
P		0.491	< 0.001	0.824	< 0.001

*Note: Compared to pre-treatment, $P < 0.05$.

4. Discussion

In TCM, DN is often classified under the categories of "wasting-thirst disorder" and "edema." Modern TCM practitioners, inspired by the core concept of "Qi circulation" in Huang Yuanyu's *Si Sheng Xin Yuan*, suggest that when DN progresses to a certain extent, the Qi movement becomes obstructed. This results in the adverse rising of ministerial fire along the gallbladder meridian and descending along the triple burner meridian, leading to symptoms of upper heat and lower cold. Clinically, these manifest as thirst in the upper body and dribbling in the lower body, with coldness in the lower regions being predominant. Treatment should therefore primarily focus on warming the kidney water while supplementing it with clearing heart fire for balance [7].

In this study, the study group received Gui Fu Ling Wu Tang in addition to standard Western medicine treatment. Compared to the control group, the study group demonstrated significant reductions in blood glucose levels, urinary protein, and serum creatinine ($P < 0.05$). Elevated urinary protein, microalbumin, and serum creatinine levels are indicators of impaired glomerular filtration function and are commonly used markers to evaluate kidney function [8]. These results indicate that Gui Fu Ling Wu Tang is effective in improving blood glucose control and kidney function.

The underlying mechanism may be attributed to the herbal composition of Gui Fu Ling Wu Tang. In the formula, *Poria cocos* and Alismatis Rhizoma serve as the primary ingredients, focusing on draining dampness, transforming phlegm, and promoting the elevation and descent of spleen and stomach Qi. Cinnamon twigs and *Polygonum multiflorum* act as secondary ingredients to soothe the liver and nourish the blood while warming yang and dispelling cold. Additionally, Longgu, oyster, aconite root, and dried ginger assist in warming kidney yang and stabilizing kidney essence. Together, these herbs synergize to eliminate dampness, relieve stagnation, and strengthen the spleen and kidney [9].

Modern pharmacological studies support this. For example, *Poria cocos* has been shown to inhibit phosphorylation in glomerular mesangial cells by activating the p38MAPK signaling pathway, thereby reducing blood glucose levels and protecting kidney function [10]. Furthermore, Alismatis Rhizoma contains quercetin, which has been confirmed to enhance insulin efficacy, accelerate glucose metabolism, and lower blood glucose levels [11]. Liu *et al.* [12] found that the combination of *Poria cocos* and Alismatis Rhizoma reduced 24-hour urinary protein and serum creatinine in a rat nephropathy model, potentially by regulating lipid metabolism and renal medulla aquaporins (AQP1 and AQP2), consistent with the results of this study.

IL-6 is closely associated with the pathogenesis of DN. It plays a critical role in immune regulation and inflammation by stimulating the liver and vascular endothelial cells to promote the secretion of CRP. CRP, in turn, induces the production of IL-6, resulting in their high expression during inflammatory responses [13]. In this study, the levels of IL-6 and CRP were significantly lower in the study group treated with Gui Fu Ling Wu Tang compared to the control group, indicating the formula's ability to suppress inflammatory responses. The potential mechanism may be linked to quercetin in Alismatis Rhizoma, which has been proven to possess antioxidant and anti-inflammatory properties by modulating the p38MAPK/NF-κB signaling pathway, thereby reducing inflammatory factor levels and alleviating kidney damage [14]. Moreover, anthraquinone derivatives, such as emodin found in *Polygonum multiflorum*, also exhibit strong anti-inflammatory effects [15].

5. Conclusion

In conclusion, the application of Gui Fu Ling Wu Tang in patients with spleen-kidney yang deficiency-type DN

demonstrates significant therapeutic efficacy. It effectively controls blood glucose, improves kidney function, and reduces inflammatory responses.

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Disclosure statement

The authors declare no conflict of interest.

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