

# Efficacy of Yishen Tongluo Formula Combined with Sulodexide in the Treatment of Diabetic Nephropathy with Renal Failure

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**Abstract:** *Objective:* To analyze the effect of Yishen Tongluo Formula combined with sulodexide in treating patients with diabetic nephropathy and renal failure. *Methods:* A hundred patients with diabetic nephropathy accompanied by renal failure who were admitted to the hospital for treatment from March 2021 to March 2024 were randomly divided into the control group and the observation group, and were treated with sulodexide therapy and Yishen Tongluo Formula + sulodexide therapy, respectively. The treatment efficacy of the two groups was evaluated. *Results:* After treatment, fasting blood glucose and other levels were lower in the observation group,  $P < 0.05$ ; renal function indexes in the observation group improved, where levels of 24-hour urinary protein, blood urea nitrogen, and blood creatinine were significantly lower than those of the pre-treatment and control group; the effect of microinflammatory state relief was significant, as demonstrated by the significant decrease of interleukin-6 and other indexes,  $P < 0.05$ . *Conclusion:* In the treatment of diabetic nephropathy patients with renal failure, we should pay attention to the protection of renal function, applying sulodexide to improve patients' blood glucose indexes, and at the same time, utilizing Yishen Tongluo Formula to alleviate patients' microinflammatory state and enhance the recovery of renal function.

**Keywords:** Yishen Tongluo Formula; Sulodexide; Diabetic nephropathy; Renal failure; Application

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## 1. Introduction

Prolonged high blood sugar levels in patients can lead to chronic kidney damage and eventually progress to kidney failure. In China, approximately 20% to 25% of diabetic nephropathy patients develop renal failure. This condition is characterized by symptoms such as edema and kidney impairment, significantly reducing patients' quality of life, threatening their safety, and posing challenges to effective treatment<sup>[1]</sup>. Sulodexide, a glycosaminoglycan

comprising low-molecular-weight heparin and dermatan sulfate, is a commonly used drug for diabetic nephropathy. It has demonstrated efficacy in controlling oxidative stress, reducing inflammation, improving vascular function, and lowering blood lipid levels. These mechanisms help alleviate kidney damage. However, the therapeutic outcomes of sulodexide alone fall short of optimal expectations, necessitating improved treatment approaches. In traditional Chinese medicine (TCM), diabetic nephropathy with renal failure is categorized under “drowning poison” and “Guan Ge,” and is attributed to external factors such as the six excesses and overexertion. This condition is considered a deficiency at the root with excessive manifestations <sup>[2]</sup>. Yishen Tongluo Formula offers a TCM-based intervention by tonifying the kidneys, consolidating the root, enhancing energy, promoting blood circulation, improving glucose metabolism, and protecting kidney function. Furthermore, it mitigates oxidative stress, offering complementary benefits when combined with sulodexide. This study explores the synergistic effects of Yishen Tongluo Formula and sulodexide in treating diabetic nephropathy with renal failure, providing valuable insights into optimizing therapeutic strategies for this challenging condition.

## 2. General information and methods

### 2.1. General information

The research subjects selected for this study were 100 patients with diabetic nephropathy with complications of renal failure treated between March 2021 and March 2024. They were randomly divided into the observation group and the control group. In the observation group, there were 31 cases of men and 19 cases of women, with an average age of  $61.23 \pm 1.52$  years, and the average duration of diabetic nephropathy was  $5.63 \pm 0.53$  years. In the control group, there were 32 and 18 cases of men and women, respectively, with a mean age of  $61.28 \pm 1.46$  years and a mean duration of diabetic nephropathy of  $5.59 \pm 0.51$  years. Evaluating the data of both groups, the data were comparable,  $P > 0.05$ .

Inclusion criteria: Patients suffering from diabetic nephropathy combined with renal failure were selected.

Exclusion criteria: Patients who have received hemodialysis therapy; patients with type I diabetes mellitus.

### 2.2. Methodology

#### 2.2.1. Control group methods

Based on the guidelines of the Diabetic Nephropathy Act, the conventional treatment methods were implemented. The patients were instructed to adjust their own dietary structure to a low salt and protein diet, regulating blood lipid levels and correcting acid-base and water-electrolyte imbalance problems. At the same time, patients were instructed to take oral sulodexide (Alpha Weissmann Pharmaceuticals [Italy], approval number: H20080618, specification: 250LSU), one tablet once, twice a day.

#### 2.2.2. Observation group methods

On the basis of the control group’s treatment protocol, the Yishen Tongluo Formula was utilized, and the main components of the formula were *Astragalus*, ripened rhubarb, Cornelian cherry, peony root, diabase, *Angelica sinensis*, danshen, dangshen, earthworm, leech with licorice, etc., and the dosages were 20 g, 15 g, 15 g, 15 g, 15 g, 15 g, 12 g, 9 g, 3 g, and 6 g, respectively. They were decocted with water, to obtain 300 ml of the medicine, and 150 ml was taken twice a day.

### 2.3. Observation indicators

Patients' fasting blood glucose and 2-hour postprandial blood glucose were collected to assess their glucose metabolic status using a blood glucose meter, and their glycosylated hemoglobin level was measured using enzyme-linked immunosorbent assay (ELISA).

When testing the patients' renal function indexes, their blood creatinine and other levels were measured using a fully automatic biochemical detector, and their urine was collected within 24 hours to assess 24-hour urine protein.

To detect patients' microinflammatory state, ELISA assays were utilized to measure patient serum interleukin-6 and other levels.

### 2.4. Statistical analysis

SPSS23.0 was used for data analysis. Count data were tested by  $\chi^2$  test, while measurement data were tested using *t*-test (mean  $\pm$  standard deviation [SD]). If  $P < 0.05$ , the difference between the data was significant.

## 3. Results

### 3.1. Glucose metabolism status

As shown in **Table 1**, after treatment, the observation group had lower levels of fasting blood glucose, 2-hour postprandial blood glucose, and glycosylated hemoglobin ( $P < 0.05$ ).

**Table 1.** Glucose metabolism status of the two groups before and after treatment (mean  $\pm$  SD)

Groups	<i>n</i>	Fasting blood glucose (mmol/L)		2-hour postprandial blood glucose (mmol/L)		Glycosylated hemoglobin (%)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation group	50	10.62 $\pm$ 2.03	5.01 $\pm$ 1.35	12.16 $\pm$ 1.42	6.32 $\pm$ 0.78	9.53 $\pm$ 0.57	7.48 $\pm$ 0.78
Control group	50	10.57 $\pm$ 2.05	8.13 $\pm$ 1.57	12.23 $\pm$ 1.39	9.85 $\pm$ 0.97	9.49 $\pm$ 0.59	8.76 $\pm$ 0.31
<i>t</i>	-	0.227	10.034	0.098	9.534	0.189	8.362
<i>P</i>	-	0.796	0.001	0.921	0.001	0.851	0.009

### 3.2. Renal function indicators

Based on **Table 2**, after treatment, the kidney function indexes of the observation group improved significantly and were better than the control group,  $P < 0.05$ .

**Table 2.** Renal function indexes of the two groups before and after treatment (mean  $\pm$  SD)

Groups	<i>n</i>	24-hour urine protein (g/24h)		Blood urea nitrogen (mmol/L)		Blood creatinine ( $\mu$ mol/L)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation group	50	3.86 $\pm$ 0.56	1.19 $\pm$ 0.14	10.13 $\pm$ 1.32	4.76 $\pm$ 1.57	99.32 $\pm$ 12.14	71.85 $\pm$ 8.62
Control group	50	3.91 $\pm$ 0.52	1.98 $\pm$ 0.29	10.17 $\pm$ 1.28	6.23 $\pm$ 1.59	99.29 $\pm$ 12.16	86.12 $\pm$ 7.16
<i>t</i>	-	1.678	10.241	0.823	8.534	0.752	9.258
<i>P</i>	-	0.124	0.001	0.278	0.007	0.367	0.003

### 3.3. Microinflammatory state

As shown in **Table 3**, after treatment, the microinflammatory state of the observation group improved significantly,  $P < 0.05$ .

**Table 3.** Microinflammatory status of the two groups before and after treatment (mean  $\pm$  SD)

Groups	<i>n</i>	Interleukin-6 (ng/L)		Amyloid (mg/L)		Ultrasensitive C-reactive protein (mg/L)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation group	50	7.42 $\pm$ 1.79	3.81 $\pm$ 0.98*	24.18 $\pm$ 4.72	10.25 $\pm$ 2.31*	7.96 $\pm$ 1.34	4.16 $\pm$ 0.87*
Control group	50	7.39 $\pm$ 1.82	5.16 $\pm$ 1.08*	24.23 $\pm$ 4.68	16.24 $\pm$ 2.47*	7.91 $\pm$ 1.39	5.34 $\pm$ 1.14*
<i>t</i>	-	0.139	10.624	0.048	11.864	0.308	7.524
<i>P</i>	-	0.891	0.001	0.962	0.001	0.758	0.017

Note: Compared with the same group before treatment, \* indicates  $P < 0.05$ .

## 4. Discussion

The etiology of diabetic nephropathy remains unclear, but numerous studies have highlighted its strong correlation with insulin resistance and oxidative stress. Increased insulin resistance elevates glomerular pressure, placing the glomeruli in a state of hyperfiltration. This condition increases urinary protein excretion, decreases tubular reabsorption, and raises urinary protein levels. Prolonged hyperglycemia can weaken the glomerular filtration membrane's charge barrier, reducing protein stability on renal cell surfaces. Additionally, glycosylation product accumulation can stimulate albumin in circulation, increase glycosylation levels of albumin, and heighten albumin filtration, further elevating proteinuria. As diabetic nephropathy progresses, renal function deteriorates, potentially leading to renal failure and a diminished quality of life for patients [3]. Currently, there is no definitive cure for diabetic nephropathy combined with renal failure. Clinical management focuses on addressing glucose and lipid metabolism disorders, controlling proteinuria, and preserving residual renal function.

Sulodexide, a therapeutic agent, has shown promise in diabetic nephropathy management. Initially employed in antithrombotic therapy, modern pharmacological research has revealed its capacity to enhance microcirculation and mitigate inflammatory responses. Sulodexide's antioxidative properties are particularly valuable in diabetic nephropathy treatment, where oxidative stress plays a critical role in disease progression. Diabetic patients typically exhibit reduced antioxidant enzyme activity and increased free radicals, which damage renal tissues, promote glomerulosclerosis, and exacerbate renal dysfunction. Sulodexide suppresses oxidative stress by reducing malondialdehyde levels and enhancing superoxide dismutase activity. Furthermore, it inhibits the expression of cell adhesion factors, helping to control inflammation and oxidative damage. A study has demonstrated that integrating sulodexide with conventional treatments significantly reduced urinary protein levels in diabetic nephropathy patients, underscoring its potential as an adjunctive therapy.

In TCM, diabetic nephropathy is not identified as a distinct disease but is instead categorized under conditions such as thirst disease, edema, and renal elimination as discussed by successive generations of TCM practitioners. Diabetic nephropathy aligns with TCM's classification of thirst disease nephropathy, characterized by a combination of deficiency in essence and excess in pathogenic factors, with the most significant organ damage occurring in the kidneys. Over time, thirst disease depletes yin and qi, leading to qi stagnation and

poor blood circulation. Moreover, the disrupted metabolism of fats and proteins in diabetic patients produces internal pathogenic factors that further obstruct meridians and blood flow<sup>[4]</sup>. Modern pharmacological research highlights the effectiveness of the Yishen Tongluo Formula in addressing these pathologies. Ingredients such as *Astragalus* enhance anti-inflammatory responses, protect renal tubules, and inhibit renal interstitial fibrosis. Other components, including Radix Rehmanniae Praeparata and Cornu Cervi Pantotrichum, improve immunity, reduce platelet aggregation, and optimize blood circulation, while Radix Rhizoma Dioscoreae regulates lipid metabolism and mitigates oxidative damage. Ingredients like *Angelica sinensis* accelerate toxin clearance and support renal tissue repair.

This study revealed improved glycemic control in the observation group post-treatment, likely attributable to the Yishen Tongluo Formula. *Astragalus* tonifies qi and promotes yang, aiding in water excretion to reduce swelling. Radix Rehmanniae Praeparata nourishes yin and fortifies the kidneys<sup>[5]</sup>, while Cornu Cervi Pantotrichum strengthens liver and kidney function. The bark of the Earth (Dixuepi) clears heat, removes dampness, and nourishes yin in the lungs and kidneys, and Radix Codonopsis Pilosulae boosts vital energy by strengthening the middle jiao. Mudanpi activates blood circulation and resolves stasis, supporting meridian health. Combined with sulodexide, which controls oxidative stress and protects the glomerular filtration barrier, this formula enhances overall glycemic regulation and addresses the multifaceted pathology of diabetic nephropathy effectively.

According to modern medical perspectives, patients with diabetes mellitus often experience increased blood viscosity and lipid deposition<sup>[6]</sup>. These deposits, carried through the bloodstream, can accumulate in the kidneys, exacerbating damage to renal tubules and other tissues, and progressively impairing renal function. In this study, the kidney function indices in the observation group significantly improved after treatment. This improvement may be attributed to the primary component, *Astragalus*. Its polysaccharides support the bidirectional regulation of blood glucose, reducing blood sugar levels and correcting renal hyperperfusion. These effects decrease plasma osmolality and slow the thickening of the glomerular basement membrane. Additionally, Rehmanniae Praeparata contains active compounds such as oligosaccharides, which enhance serum insulin levels, improve gut flora, reduce urinary protein excretion, and aid in the recovery of renal function indicators<sup>[7,8]</sup>.

The development of diabetic nephropathy combined with renal failure is closely linked to a microinflammatory state. Elevated interleukin-6 levels promote neutrophil infiltration in the tubular interstitium, increasing the thickness of the glomerular basement membrane and altering glomerular hemodynamics. As renal failure progresses, inflammatory damage intensifies, raising amyloid and ultrasensitive C-reactive protein levels<sup>[9,10]</sup>. This study showed that the microinflammatory state in the observation group improved significantly post-treatment. The improvement may result from the Yishen Tongluo Formula enhancing leukocyte phagocytosis and reducing inflammatory factor levels. The inclusion of sulodexide further contributes by facilitating proteoglycan complex repair and mitigating inflammatory symptoms, thereby improving overall renal function and reducing disease progression.

## 5. Conclusion

In conclusion, when treating patients with diabetic nephropathy and renal failure, the application of Yishen Tongluo Formula and sulodexide can be used to build a combination of traditional Chinese and Western medicine treatment mechanisms. It can control patients' blood glucose, enhance the protection of patients' renal function, improve patients' microinflammatory state, and promote the improvement of patients' quality of life.

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## Disclosure statement

The authors declare no conflict of interest.

## References

- [1] Bu H, Guo L, Xu K, et al., 2024, A Randomized Controlled Clinical Trial of the Renoprotective Effect of Sulodexide Combined with Valsartan in Patients with Type 2 Diabetic Nephropathy. *Journal of Zhengzhou University (Medical Edition)*, 59(02): 260–265.
- [2] Zhang M, Zhang W, Wang A, et al., 2023, Study on the Improvement Effect and Safety of Sulodexide on Multiple Urinary Proteins in Patients with Diabetic Nephropathy. *China Medical Engineering*, 31(02): 1–5.
- [3] Ge J, Fan WX, Ma JY, 2022, Meta-Analysis of the Clinical Efficacy and Safety of Sulodexide Combined with ACEI/ARB Drugs in the Treatment of Diabetic Nephropathy. *Chinese Journal of Integrative Nephrology*, 23(12): 1082–1087.
- [4] Wang J, Ji X, Ji Y, et al., 2022, Efficacy of Yishen Tongluo Formula in the Treatment of Diabetic Nephropathy and its Effects on Glucose Metabolism, Renal Function and Oxidative Stress. *Sichuan Traditional Chinese Medicine*, 40(11): 126–129.
- [5] Dai L, Lin D, 2022, Clinical Analysis of Sulodexide Combined with Tretinoin in the Treatment of Diabetic Nephropathy. *Chinese and Foreign Medical Treatment*, 41(29): 110–113.
- [6] Zhang M, Wang A, Li P, et al., 2022, Effect of Sulodexide on Foot Cell Injury in Patients with Diabetic Nephropathy. *Journal of Xinxiang Medical College*, 39(03): 248–251.
- [7] Ji X, Wang J, Zhang J, 2021, Therapeutic Efficacy of Yishen Tongluo Formula in Treating Vein Stasis Type Diabetic Nephropathy and its Effect on Liver and Kidney Function and CCr. *Sichuan Traditional Chinese Medicine*, 39(11): 146–149.
- [8] Gao X, Wang Y, 2020, Effects of Bailing Capsule Combined with Sulodexide on Vascular Endothelial Function and Oxidative Stress Function Indexes in Elderly Patients with Diabetic Nephropathy. *Drug Evaluation Research*, 43(09): 1864–1867.
- [9] Guo S, Ma L, 2019, Clinical Efficacy Study of Yishen Tongluo Formula in the Treatment of Diabetic Nephropathy Stage III. *Xinjiang Traditional Chinese Medicine*, 37(05): 5–8.
- [10] Zhao H, Zhao Q, Jiao Y, et al., 2018, Efficacy of Sulodexide Combined with Repaglinide in the Treatment of Diabetic Nephropathy and its Effect on Serum Inflammatory Factor Levels. *China Hospital Drug Evaluation and Analysis*, 18(07): 898–900.

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