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Retrospective analysis of the overt proteinuria diabetic kidney disease in the treatment of modified Shenzhuo formula for 2 years

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Abstract

The objective of the present study was to evaluate the 2-year effectiveness of modified Shenzhuo formula in the treatment of overt proteinuria diabetic kidney disease (DKD).

Patients diagnosed with type 2 DKD in the clinical research database of Prof Xiaolin Tong (>20,000 data points) with >1-year follow-up were screened for this study. Patients' demographic data, chief complaint, present illness, past history, allergic history, personal history, family history, test results, tongue images, pulse information, and prescription information at 1, 1.5, and 2 years of follow-up were analyzed. EpiData3.1 was used to establish the electronic database of this research and SPSS v20.0 (SPSS Inc, Chicago, IL) was used for performing statistical analyses.

The patients' common main symptoms of overt proteinuria DKD were weak breath and fatigue, numbness of limbs, insomnia, blurred vision, nocturia, edema, low backache, constipation, itchy skin ulcer, and chills. The average 24-hour urinary protein of patients treated with modified Shenzhuo formula was statistically significantly lower than baseline values at 1, 1.5, and 2 years (0.66 g, 95% confidence interval [CI] [−0.95, −0.41]; 1.00 g, 95% CI [−1.67, 0.38]; 1.11 g, 95% CI [−1.79, −0.57]). There are no statistically significant differences between the glomerular filtration rate at the baseline and that after modified Shenzhuo formula intervention. Statistically significant reductions in serum triglyceride and glycosylated hemoglobin values and systolic blood pressure also were recorded. Other indexes, including serum creatinine, blood urea nitrogen, diastolic blood pressure, cholesterol, high-density lipoprotein, and low-density lipoproteins, did not differ between baseline and post-treatment time points.

Modified Shenzhuo formula could reduce 24-hour urinary protein excretion in patients with DKD. The formula maybe had the potential advantages on glomerular filtration rate, creatinine reciprocal, blood lipid levels, etc.

Abbreviations: BP = blood pressure, DKD = diabetic kidney disease, GFR = glomerular filtration rate, HbA1c = glycosylated hemoglobin, LDL = low-density lipoprotein, SCR = serum creatinine, TCM = traditional Chinese medicine, TG = triglyceride, UA = uric acid.

Keywords: diabetic kidney disease, modified Shenzhuo formula, overt proteinuria, retrospective analysis

1. Introduction

Diabetic kidney disease (DKD) is a common chronic complication of diabetes. It usually is progressive, leading to end-stage renal disease, and ultimately to death. According to US Renal Data System, the end-stage renal disease caused by DKD accounts for about 44% of the total in the United States.[1] In Asian countries, the corresponding is about 40% of the total in Japan,[2] 48% in Korea,[3] and 19% in China, and the incidence of DKD in

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HC and JG contributed equally to this study as first authors.

LZ and XT proposed the paper topic; HC and JG finished the study and wrote the paper; XZ, XH, and ZH helped to extract and manage the data; and LZ revised the paper.

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hospitalized diabetic patients has reached 34.7% in China.[4] Chronic, progressive DKD has become a serious threat to people's life and health.

At present, the prevention and treatment of DKD consists of 3 stages. The first is prevention. In persons with abnormal glucose tolerance, lifestyle modification is used to control blood sugar and prevent the development of diabetes and DKD. This measure includes diet, exercise, limited alcohol intake, smoking cessation, and weight control. The second is early treatment. Early treatment of DKD aims at reducing the frequency or delaying the occurrence of macroalbuminuria in patients who have microalbuminuria. Third, prevention or delay of progressive renal dysfunction, with renal transplant therapy, should be considered for the patients with renal failure.[5] However, the effectiveness of the treatment is less than satisfactory in clinic. It is very important to find an effective treatment to reduce the proteinuria for the patients with DKD.

It is reported that the emergency of overt proteinuria predicts the accelerating progression of DKD, so controlling and minimizing proteinuria has been the key point to delay the progression of DKD. Research conducted in recent years has shown advantages that treatment with Chinese medicines can reduce proteinuria and block the progress of DKD.[6–11] There are few high-quality randomized controlled trials conducted in recent years about overt proteinuria DKD treated by traditional Chinese medicine (TCM). It is difficult to conduct randomized controlled trials about overt proteinuria DKD for its clinical features. Li et al[12] achieved 1, and so did Jia et al.[13] But the observation period of most of these researches is $\leq$1 year. Thus, it was very difficult to evaluate whether a long-term intervention with TCM could have more benefits for the patients with overt proteinuria DKD.

By applying modified Shenzhuo formula for the treatment of overt proteinuria of DKD in the long-time clinical work according to the syndrome differentiation in the theory of the TCM combined with the pathological characteristics, Professor Xiaolin Tong has achieved an ideal curative effect.

This research aims to evaluate the long-term intervention effectiveness of modified Shenzhuo formula by analyzing the electronic records of DKD patients with overt proteinuria and to make our experience with the formula widely known to clinicians.

2. Methods

2.1. General data

This research is based on the "Xiaolin Tong Clinical Research Database," which has been established for clinical studies in our institution and includes all of Professor Tong's medical records since 2009. The database is updated after every visit and managed by hospital data manager. The standardized data include demographic data, chief complaint, history of present illness, history of past illness, allergic history, personal history, family history, test indices, tongue images, pulse information, and prescriptions.

2.2. Inclusion and exclusion criteria

Inclusion criteria are as follows: the diagnosis of type 2 diabetes mellitus (T2DM), the diagnosis of overt proteinuria of DKD, and the follow-up period of >1 year with interval between visits $\leq$3 months and >4 visit times per year.

2.3. Exclusion criterion

Exclusion criterion is the following: qualitative measurement of urinary protein but not quantitative measurement.

2.4. Intervention

DKD patients' levels of blood glucose, lipid, and blood pressure (BP) were stabilized by oral medications or insulin injections. All patients were administered a modified Shenzhuo formula (200 mL, bid). The medicines were provided by the Department of Pharmacy, Guang'anmen Hospital. Modified Shenzhuo formula was taken 30 minutes before or after breakfast and supper. Treatment lasted $\geq$1 year. Shenzhuo formula is an empirical compound TCM decoction of Prof Tong. It is composed of *Huang Qi*, *Da Huang*, *Shui Zhi*, *Huang Lian*, *Zhi Mu*, etc. There were associated herbs for the treatment of associated diseases, such as *Huang Lian* and *Zhi Mu* for high blood glucose; *Gegen*, *Dilong*, *Yi Mu Cao*, *Gou Teng*, and *Tianma* for hypertension; *Hong Qu*, *Shan Zha*, and *Heye* for hyperlipidemia; and *Wei Ling Xian*, *Qinpi*, and Bixie for hyperuricemia.

2.5. Measurements

The primary laboratory outcome measurement was 24-hour urinary protein excretion; the secondary outcome measurement was glomerular filtration rate (GFR); the observation measurements were 3 items of renal function (serum creatinine [SCR], blood urea nitrogen, and uric acid [UA]), blood lipids (cholesterol, triglyceride [TG], high-density lipoproteins, and low-density lipoproteins [LDLs]), BP, and glycosylated hemoglobin (HbA1c). These measurements were carried out in a central laboratory in Guang'anmen Hospital. The frequency of each symptom was calculated according to the inquiry information from the 69 visits, summing up the number of times each symptom appears in the 69 visits. Measurements for each patient were recorded at the first visit and 1, 1.5, and 2 years after the first visit. Expected glomerular filtration rate (eGFR) was calculated by Modification of Diet in Renal Disease formula. Adverse events were assessed using vital signs, clinical signs, and symptoms.

2.6. Data extraction and analysis

1. The first 24-hour urinary protein quantitation was taken at the baseline; 2 researchers separately extracted the 0-, 1-, 1.5-, and 2-year records information and filled in the case report forms. The records information included the demographic data, duration of disease, combined diseases, tongue, pulse, the main symptoms of interrogation, change of the main symptoms, test index, formula, dose, etc.

2. Using EpiData3.1 to establish the electronic database of this research, 2 researchers separately recorded data. The third researcher completed the double entry and validation. When the data were not consistent, the case report forms were assessed and errors corrected.

3. Statistical analyses were processed with SPSS v20.0 (SPSS Inc, Chicago, IL). Measurement data were the mean $\pm$ standard deviation ($\overline{X} \pm s$). The 95% confidence interval of mean value difference was used to compare baseline and after intervention change in the abovementioned characteristics. Fitting curve analysis was used to present and predict disease trends.

2.7. Study design figure

The study design figure is shown as Fig. 1.

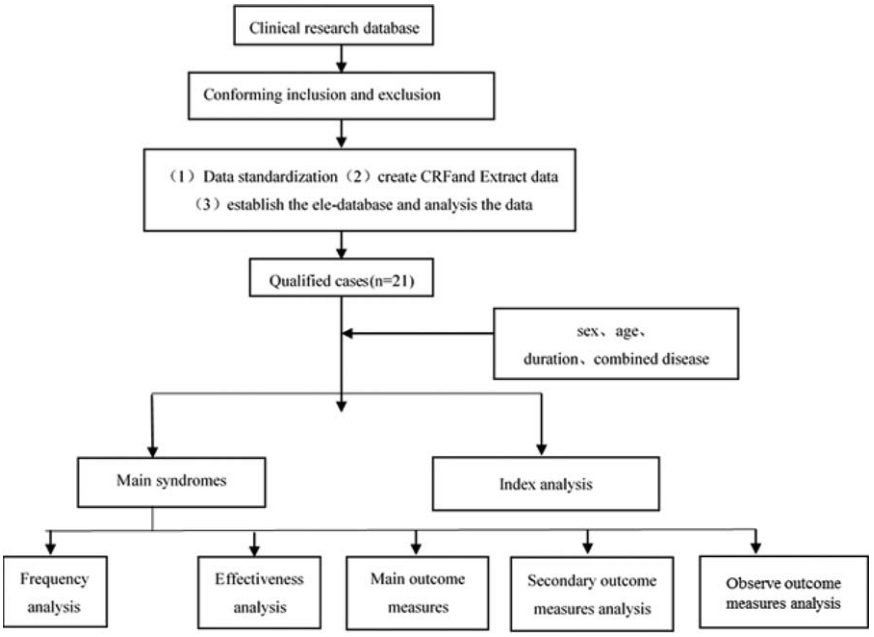

Figure 1. Study design.

2.8. Ethical approval

The present study was a retrospective and small sample study based on the real-world clinical recorded data. It was not a prospective study, and the patients' verbal consent was taken for providing their medical records for analysis and the results of the study. In this study, we have reported only the medical records and statistical results, not including the patients' privacy information, so we think it did not touch on benefits and harms of patients and ethical approval and written patient consent was not necessary.

3. Results

3.1. General information

3.1.1. Demographic and disease duration characteristics. A total of 21 patients with 69 visits with overt proteinuria DKD were included between June 2009 and December 2015 from the Xiaolin Tong Clinical Research Database. All the 21 patients had been followed for >1 year, 13 for >1.5 years, and 11 for >2 years. The average age was 54.3±12.8 years. The maximum age was 79 years and the minimum age was 34 years. The average duration of T2DM was 12±5.5 years, the maximum duration was 22 years, and the minimum duration was 5 years. The average duration of DKD was 2.0±1.5 years. The longest duration was 6 years and the shortest duration was 1 year.

Table 1

Associated diseases.

Associated diseases	Frequency	Percentage
Hypertension	16	76
Hyperlipidemia	12	57
Fatty liver	6	29
Hyperuricemia	5	24
Coronary heart disease	5	24
Cerebral infarction	2	9
Chronic pancreatitis	1	4

3.2. Associated diseases

Diseases associated with DKD are listed in Table 1. As might be expected, the most common diseases were hypertension and hyperlipidemia.

3.3. Main symptoms

3.3.1. Frequency of common symptoms. The patients' 10 most common symptoms are listed in Table 2. The frequency of each symptom was calculated according to the inquiry information from the 69 visits, summing up the number of times each symptom appears in the 69 visits. Data of the top 10 symptoms were extracted and analyzed.

3.4. Effectiveness of top 10 main symptoms

The judgment of effectiveness was based on the baseline. Compared to the baseline, it was recorded as "disappearance" if the symptom disappeared, "better" if there was relief, "no change" if the symptom was at the baseline or not changed

Table 2

Frequency of main symptoms.

Main symptoms	Total	0 y (n=21)	1 y (n=21)	1.5 y (n=13)	2 y (n=11)
Shortness of breath and fatigue	54	17	17	10	6
Numbness of limbs	34	11	12	5	4
Insomnia	33	13	10	5	2
Blurred vision	32	9	10	6	6
Nocturia	32	11	10	7	2
Edema	31	10	11	4	4
Low back pain	25	9	10	3	3
Constipation	21	9	7	2	2
Itch or ulcer of skin	19	5	6	3	4
Chills	18	7	6	3	2

Table 3

Effectiveness of main symptoms.

Main symptoms	Intervention time, y	Disappearance	CR, %	Better	RR, %	No change	nCR, %	Worse	AR, %	IR, %
Shortness of breath and fatigue	1 (n=17)	0	0	12	70	4	24	1	6	70
	1.5 (n=10)	0	0	7	70	3	30	0	0	70
	2 (n=8)	2	25	6	75	0	0	0	0	100
Numbness of limbs	1 (n=12)	0	0	8	66	2	17	2	17	66
	1.5 (n=6)	1	17	3	50	0	0	2	33	67
	2 (n=4)	0	0	1	25	2	50	1	25	75
Insomnia	1 (n=13)	3	23	6	46	3	23	1	8	69
	1.5 (n=7)	2	29	0	0	2	29	3	42	29
	2 (n=4)	2	50	0	0	1	25	1	25	50
Nocturia	1 (n=11)	1	9	6	54	4	36	0	0	63
	1.5 (n=7)	0	0	6	86	1	14	0	0	86
	2 (n=5)	3	60	1	20	1	20	0	0	80
Blurred vision	1 (n=10)	0	0	2	20	7	70	1	10	20
	1.5 (n=6)	0	0	0	0	6	100	0	0	0
	2 (n=6)	0	0	2	33	2	33	2	33	33
Edema	1 (n=11)	2	18	5	46	1	9	3	27	64
	1.5 (n=7)	3	43	2	29	1	14	1	14	72
	2 (n=6)	2	33	2	33	2	33	0	0	66
Low back pain	1 (n=10)	1	10	8	80	0	0	1	10	90
	1.5 (n=6)	3	50	1	16	1	16	1	16	66
	2 (n=5)	2	40	1	20	0	0	2	40	60
Constipation	1 (n=10)	3	30	2	20	2	20	3	30	50
	1.5 (n=4)	2	50	1	25	0	0	1	25	75
	2 (n=4)	2	50	1	25	0	0	1	25	75
Pruritus	1 (n=9)	3	33	1	11	1	11	4	45	44
	1.5 (n=4)	1	25	1	25	0	0	2	50	50
	2 (n=5)	1	20	1	20	1	20	2	40	40
Chills	1 (n=7)	1	14	3	43	3	43	0	0	57
	1.5 (n=4)	1	25	1	25	0	0	2	50	50
	2 (n=4)	2	50	0	0	0	0	2	50	50

AR = aggravated rate, CR = cure rate, IR = improvement rate, nCR = no change rate, RR = relief rate.

significantly, and "worsen" if aggravated. The cure rate was calculated as disappearance frequency/total changed frequency; relief rate was calculated as better frequency/total changed frequency; no change rate was calculated as no changed frequency/total changed frequency; aggravated rate was calculated as worsened frequency/total changed frequency. Improvement rate was calculated as cure rate + relief rate. The results are recorded in Table 3.

3.5. Test indices

The primary laboratory outcome was 24-hour urinary protein excretion. As illustrated in Table 4 and Fig. 2, protein excretion declined significantly from baseline to that at 1-, 1.5-, and 2-year time points. The secondary outcome was GFR. The data in Table 5 and Fig. 3 illustrate that the eGFR did not change significantly over the 2 years of follow-up.

The observation outcomes were 3 items of renal function (SCR, blood urea nitrogen, UA), 4 items of blood lipid (cholesterol, TG, high-density lipoprotein, LDL), BP, and HbA1c. The data are recorded in Table 6.

Table 4

Twenty-four-hour urinary protein excretion quantitation.

Intervention time, y	Samples	Baseline, g/24 h	After, g/24 h	d (95%CI)
1	20	1.58 ± 0.98	0.92 ± 0.75	−0.66 (−0.95, −0.41)
1.5	11	1.85 ± 1.29	0.84 ± 0.48	−1.00 (−1.67, −0.38)
2	11	1.85 ± 1.29	0.74 ± 0.51	−1.11 (−1.79, −0.57)

CI = confidence interval.

3.6. Survival analysis—creatinine reciprocal curve (1/SCR)

The creatinine reciprocal curve was used to predict the prognosis trend of patients. As illustrated in Table 7 and Fig. 4, the slope of creatinine reciprocal curve increases with increased intervention time.

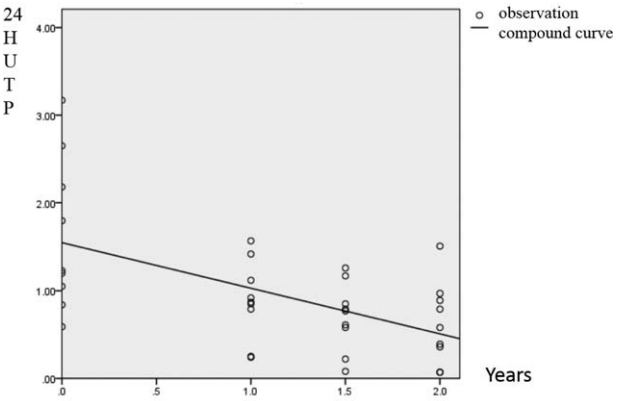

Figure 2. Fit plot of 24-hour urinary protein quantitation. The figure includes data of 9 cases who were screened from the 21 cases whose 24-hour urinary protein quantitation value was fully recorded at baseline, 1, 1.5, and 2 years. GFR = glomerular filtration rate.

Table 5

eGFR.

Intervention time, y	Samples	Baseline, mL/min	After, mL/min	d (95%CI)
1	18	119.6±33.1	121.9±33.1	2.34 (−6.0, 11.1)
1.5	8	127.5±32.3	137.8±37.2	10.4 (−9.3, 31.2)
2	9	111.2±34.9	112.6±34.3	1.5 (−10.9, 13.3)

CI = confidence interval, eGFR = expected glomerular filtration rate.

3.7. Safety

The liver function and routine blood test of all the participants indicated no significant changes after intervention compared with baseline. No discomforts or severe adverse events were reported.

4. Discussion

The major finding of this study was that the 24-hour urinary protein excretion of patients with overt DKD proteinuria was significantly less after the intervention of modified Shenzhuo formula. Moreover, this salutary effect on protein excretion was achieved while a normal GFR was maintained. The study also found that after treatment with modified Shenzhuo formula, many of the patients' main symptoms improved.

The key point in treating overt proteinuria in DKD is reducing the loss of urinary protein, which is still a medical problem. Studies have shown that urinary albumin to creatinine ratio of overt proteinuria of DKD increases 133% in 4 years[14]; thus, urinary protein excretion increases together with the progression of the disease.[15] Effective treatment for the proteinuria of DKD has not been developed. Thus, our finding that Shenzhuo formula seems to decrease the progression DKD, as measured with protein excretion, is a promising development.

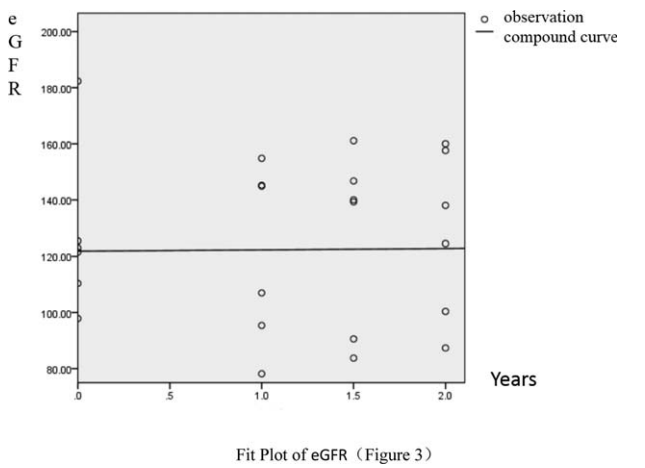

Figure 3. Fit plot of eGFR. The figure includes data of 6 cases who were screened from the 21 cases whose eGFR value was fully recorded at baseline, 1, 1.5, and 2 years. eGFR = expected glomerular filtration rate.

Table 6

Observed outcome measures.

Index	Intervention time, y	Samples	Baseline	After	d (95%CI)
SCR, μmol/L	1	18	76±17.1	74.4±16.2	−2.2 (−7.7, 2.6)
	1.5	9	68.3±16.0	63.6±13.9	−4.6 (−13.6, 2.9)
	2	10	76.7±21.0	74.4±21.9	−2.3 (−7.7, 3.7)
BUN, mmol/L	1	18	6.49±2.14	6.66±2.29	0.2 (−0.6, 0.9)
	1.5	9	5.77±1.30	6.65±2.92	0.9 (−0.6, 2.7)
	2	10	6.71±2.16	7.02±2.78	0.3 (−0.7, 1.5)
UA, mmol/L	1	10	352.3±107.8	313.17±56.9	−39.1 (−88.5, −0.5)
	1.5	5	346.4±120.1	334±141.8	−12.4 (−45.6, 18.9)
	2	6	354.2±109.1	350.9±111.8	−3.3 (−17.7, 11.3)
CHO, mmol/L	1	16	4.95±1.17	4.97±1.15	0.03 (−0.6, 0.7)
	1.5	7	4.51±1.22	4.26±1.12	−0.24 (−1.21, 0.63)
	2	7	4.57±1.28	4.26±1.04	−0.31 (−1.23, 0.61)
TG, mmol/L	1	15	2.37±1.37	1.98±1.11	−0.39 (−1.06, −0.12)
	1.5	6	3.22±1.24	1.67±0.43	−1.55 (−2.31, −0.82)
	2	7	2.97±1.32	1.88±0.70	−1.09 (−1.92, −0.22)
HDL, mmol/L	1	13	1.18±0.26	1.26±0.61	0.08 (−0.09, 0.34)
	1.5	5	1.12±0.24	1.22±0.22	0.10 (−0.09, 0.31)
	2	5	1.08±0.22	1.02±0.19	−0.05 (−0.18, 0.96)
LDL, mmol/L	1	14	3.04±0.89	2.95±1.11	−0.09 (−0.5, 0.4)
	1.5	5	2.36±0.97	2.27±1.07	−0.09 (−0.93, 0.49)
	2	5	2.93±1.22	2.72±1.19	−0.21 (−1.1, 0.68)
HbA1c, %	1	16	7.8±2.03	6.8±2.18	−1 (−1.97, −0.1)
	1.5	8	7.1±1.50	7.1±1.61	0.05 (−0.72, 0.85)
	2	6	7.1±1.54	6.7±1.42	−0.35 (−1.23, 0.58)
SBP, mm Hg	1	20	137±18.67	128±15.08	−9 (−18, −2)
	1.5	11	138±18.34	129±16.40	−9 (−20, 1)
	2	11	140±17.32	126±20.10	−13 (−27, −3)
DBP, mm Hg	1	20	82±11.57	77±10.43	−5 (−11, 1)
	1.5	11	82±17.45	79±10.45	−4 (−10, 3)
	2	11	84±16.98	78±10.78	−5 (−16, 5)

BUN = blood urea nitrogen, CHO = cholesterol, CI = confidence interval, DBP = diastolic blood pressure, HbA1c = glycosylated hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein, SBP = systolic blood pressure, SCR = serum creatinine, TG = triglyceride, UA = uric acid.

Table 7

Creatinine reciprocal.

Intervention time, y	Baseline (n = 7)	1/SCR	After intervention (n = 7)	1/SCR
1	65.67 ± 12.33	0.015227	67.96 ± 15.65	0.014715
1.5	65.67 ± 12.33	0.015227	65.46 ± 14.63	0.015277
2	65.67 ± 12.33	0.015227	64.21 ± 17.14	0.015573

The table includes data of 7 cases who were screened from the 21 cases whose creatinine reciprocal value was fully recorded at baseline, 1, 1.5, and 2 years. SCR = serum creatinine.

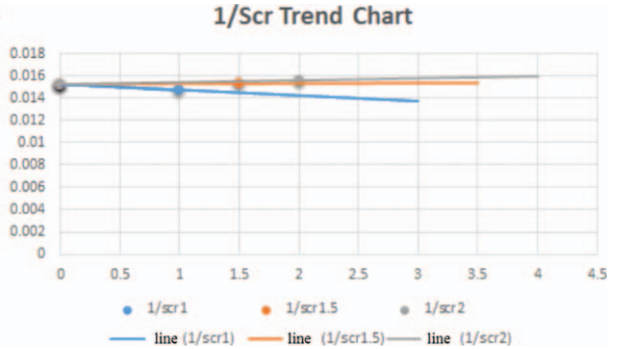

Figure 4. Fit plot of creatinine reciprocal. SCR = serum creatinine.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative has divided chronic kidney disease into 5 stages based on GFR: stage 1, eGFR ≥90 mL/(min 1.73 m^2); stage 2, eGFR 60 to 89 mL/(min 1.73 m^2); stage 3, eGFR 30 to 59 mL/(min 1.73 m^2), stage 4, eGFR 15 to 29 mL/(min 1.73 m^2); and stage 5, eGFR <15 mL/(min 1.73 m^2).[14] Once overt proteinuria is present, there is a progressive reduction in GFR, rate varying widely from patient to patient, with an average decline of approximately 10 mL/(min 1.73 m^2) per year in untreated subjects,[16] and depending on control of promotors of progression such as hypertension and degree of albuminuria and on individual response to treatment, this period is characterized by gradual deterioration of GFR in a linear fashion at a variable rate (average 4.5 mL/[min 1.73 m^2] per year).[17] Our finding that, after the intervention with modified Shenzhuo formula, the GFR did not decline significantly from baseline values may be evidence that this TCM maybe could slow the progressive decline in eGFR and the associated deterioration of renal function.

In this study, the main symptoms of DKD with overt proteinuria were shortness of breath and fatigue, numbness of limbs, insomnia, blurred vision, nocturia, edema, low back pain, constipation, itch or ulcer of skin, and chills. Shortness of breath and fatigue, edema, nocturia, and constipation were well improved. However, not all symptoms improved: blurred vision improved in 66% of patients but worsened in 33%, so was the numbness of limbs; this incomplete response may reflect the reality that diabetic retinopathy often is progressive and has no effective drug treatment. Professor Xiaolin Tong proposes that the core pathogenesis for the symptoms of DKD patients is deficiency of kidney qi and blood stasis of kidney collaterals. The consequences of deficiency of kidney qi are shortness of breath, lack of desire to speak, and fatigue, with shortness of breath and fatigue being the most common. DKD patients with overt proteinuria always have diabetic retinopathy. Since both DKD and diabetic retinopathy are microvascular diseases, they often coexist and are parallel in development; thus, DKD patients often report that they have blurred vision.[18–20] Numbness of the limbs also is a common symptom of long-standing diabetes because of impaired peripheral nerve function. Constipation, loose stools, or alternating constipation and loose stools is a common complaint among diabetics, which is ascribed to impaired gastrointestinal autonomic nerve function.[21,22] The symptom of nocturia is common when long-standing disease leads to impaired kidney collateral and renal tubular dysfunction. Long-standing disease also leads to more deficiency of qi and dysfunction of qi in San Jiao, with accumulation of fluid, or edema.

In this study, the average duration of T2DM was 12.5 years after DKD was recognized. Studies have reported that about 73% of patients with >10 years of T2DM have kidney disease.[23] Thus, these patients must be observed for the possibility of developing DKD. According to Kidney Disease Outcomes Quality Initiative, patients with T2DM should be screened for urinary protein in order to permit early diagnosis and treatment of DKD.[14] This study found that hypertension, hyperlipidemia, fatty liver, hyperuricemia, and coronary artery disease were commonly associated with DKD. Thus, these metabolic disorders are risk factors for DKD,[24–27] and should be comprehensively monitored and treated. The results of the current study show that the modified Shenzhuo formula can lower BP and blood UA, glucose, and lipid concentrations, which may delay the development of DKD.

The various components of modified Shenzhuo formula have various biological effects. *Sheng Huang Qi (raw astragalus)* can boost qi to secure and strict, disinhibit water, and disperse swelling. *Da Huang (rhubarb)* has the effect of expelling stasis to free the channels, free the bowels, and discharge turbidity. *Shui Zhi (leech)* is usually used to supply vacuity and strong body having an advantage that it dispels static blood but does not affect new blood. *Dan Shen (Salvia)* supplies blood and quickens the blood. A combination of the 4 herbs boosts qi and quickens the blood. Studies have reported that total flavonoids of Astragalus, total polysaccharides of Astragalus, and total saponins of Astragalus from *Sheng Huang Qi (raw astragalus)* can improve the clearance of antigen and promote the repair of glomerular basement membrane. Selenium element in *Sheng Huang Qi (raw astragalus)* can protect the charge barrier and mechanical barrier of the basement membrane, thus reducing the permeability of urine protein.[28,29]*Da Huang (rhubarb)* can clean the bowel and relieve the body, which leads to a part of nonprotein nitrogen discharged from intestine; it also restrains the hyperplasia of mesangial cells and renal tubular epithelial cells, thus reducing the compensatory hypertrophy. At the same time, the high coagulation rate and the precarious state of renal failure patients can be improved, with increasing renal blood flow, protecting residual renal function, reducing the occurrence of proteinuria, and delaying the progression of DKD.[30]*Shui Zhi (leech)* contains 17 kinds of amino acids, including 8 kinds of essential amino acids and 14 kinds of elements such as Zn, Mn, Fe, Co, Cr, Se, Mo, and Ni.[31] Gu et al[32] reported that *Shui Zhi (leech)* can ameliorate early kidney hyperdynamic abnormality and protect the kidney of DKD rats by a mechanism that may be associated partly with a downregulation of levels and expression of endothelin-1. *Dan Shen (Salvia)* contains danshensu, labiatenic acid, tanshinone IIa, salvianolic acid A, and other ingredients.[31] Studies have found that *Dan Shen (Salvia)* can lower blood lipids, reduce blood viscosity, dilate blood vessels, inhibit platelet aggregation and nuclear release, have an antithrombotic effect, improve microcirculation, and repair injured vascular endothelial cells. These effects can improve kidney blood flow, protect kidney function, and promote the recovery of kidney function.[32]

Effects on blood lipid, BP, blood sugar, and serum UA can reflect the advantage of individualized treatment and comprehensive regulation TCMs offer. Blood lipid, BP, blood sugar, and serum UA are risk factors for the occurrence and development of DKD. Hypertension can accelerate the progression of the proteinuria of DKD patients and the deterioration of renal function.[33,34] Blood lipid disorders can accelerate blood vessel damage and the procession of DKD. High blood sugar, making the proteins of glomerular basement membrane structural nonenzymatic glycation, will cause the basement membrane barrier defects, resulting in urinary protein to renal damage. According to the Diabetic Nephropathy Prevention Expert Consensus of 2014, the BP target of patients with DKD is 130/80 mm Hg, LDL levels <2.6 mmol/L (<1.86 mmol/L if combined with coronary heart disease), TG <1.5 mmol/L, and Hb A1c value ≤7%. For elderly patients, HbA1c value of 7% to 9% may be allowed.[5] Thus, the key to delay the progression of DKD lies in the comprehensive strict regulation and control. According to individual disease differences, the Shenzhuo formula can be modified to provide accurate treatment for various combined diseases. *Huang Lian (Coptis chinensis)*, *Zhi Mu (Anemarrhenae)*, etc., are associated with Shenzhuo formula for the treatment of high blood glucose; *Gegen (Pueraria)*, *Dilong (Pberetima)*, *Yi Mu Cao (motherwort)*, *Gou Teng (rhynchophylla)*, *Tianma* (*Rhizoma gastrodiae*), etc., for hypertension; *Hong Qu (red rice)* for hyperlipidemia; and *Wei Ling Xian* (*Radix clematidis*), *Qinpi (fraxini)*, and Bixie (*Rhizoma Dioscoreae hypoglaucae*) for hyperuricemia. The addition and subtraction of medications is based not only on the syndrome differentiation theory but also on the >30-year clinic experience of Professor Xiaolin Tong.

5. Limitations

Our study was just a retrospective, small-sample, single-center trial, and has many limitations: first, it is a retrospective study based on real-world data, with the inherent potential for bias and omission of important data. Second, the study is not strictly controlled for therapeutic measures or lifestyle modification that, in addition to modified Shenzhuo formula, might have affected patients' clinical course. Third, the study is not controlled for comparison of patients who received the modified Shenzhuo formula with those who did not. These limitations highlight the need for rigorously controlled, prospective studies of the effects of the modified Shenzhuo formula in the management of DKD. In fact, we are conducting a double-blind, double-simulation, randomized control trial of Shenzhuo formula in the overt proteinuria stage of DKD. The research, which has been registered in the Chinese Clinical Trial Registry, will test the validity and feasibility of using a TCM as an alternative in the treatment of DKD.

Modern medicine advocates the following 5 kinds of preventive and therapeutic measures for DKD: lifestyle modification, control of blood glucose, control of BP, correction of disorders of lipid metabolism, and renal replacement therapy. High-quality studies have shown that strict control of blood glucose, BP, and blood lipids can prevent the emergence of microproteinuria and delay the deterioration of renal function,[35–41] but there is no conclusive evidence that any of these measures significantly reduces the amount of proteinuria in patients with DKD. In the quest for new preventive and treatment measures for DKD, we feel that traditional Chinese medications should be considered. The traditional medications have a rich, 1000-year history in the treatment of diabetes mellitus and DKD and therefore form the basis for future research. The results of this study suggest that Shenzhuo formula, through its effects on blood sugar, BP, and serum lipids, can reduce 24-hour urinary protein excretion, delay the deterioration of renal function, and improve the main symptoms of patients over a long time period. TCM has the potential advantage of targeting multiple facets of the disease and comprehensively improving patients' symptoms and quality of life.[42–46]

6. Conclusions

Modified Shenzhuo formula could reduce 24-hour urinary protein excretion in patients with DKD. The formula maybe had the potential advantages on GFR, creatinine reciprocal, blood lipid levels, etc.

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