OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2022.XX.XX

Research Article
Efficacy and Safety of *Tripterygium wilfordii* Polyglycosides Versus Valsartan in Management of Diabetic Nephropathy

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Abstract

Background and Objective: Valsartan is recommended to prevent the progression of diabetic nephropathy but is insufficient for the management of proteinuria. The objectives of the study were to evaluate the effectiveness and safety profile of *Tripterygium wilfordii* polyglycosides against valsartan in diabetic nephropathy patients. **Materials and Methods:** Patients with at least 1 month history of urinary protein excretion of >3 g/day and serum creatinine <1.5 mg dL^{-1} have received 160 mg/day valsartan for 24 weeks (VS cohort, n = 127) or 60 mg/day *Tripterygium wilfordii* polyglycosides plus 160 mg/day valsartan for 24 weeks (TV cohort, n = 158) or 120 mg/day for 12 weeks followed by 60 mg/day for 12 weeks *Tripterygium wilfordii* polyglycosides (TP cohort, n = 165). **Results:** Patients of the TP cohort had a significant percentage reduction of urinary protein excretion than those of VS cohort (18.06±7.57 vs. 16.09±6.48%, p = 0.043, q = 3.419). Patients of TP (p<0.0001, q = 31.772) and TV (p<0.0001, q = 9.457) cohorts had significant percentage elevation in serum albumin levels than those of VS cohort. Patients of the VS cohort have reported dizziness, that of the TV cohort have reported dizziness and that of the TP cohort have reported liver function abnormalities and hyperkalemia. **Conclusion:** A total of 160 mg/day valsartan plus 60 mg/day of *Tripterygium wilfordii* polyglycosides for 24 weeks is recommending in the management of diabetic nephropathy in case of a large amount of proteinuria.

Key words: Diabetic nephropathy, hyperkalemia, proteinuria, valsartan, serum albumin, *Tripterygium wilfordii* polyglycosides, serum creatinine

Citation: Wang, Y.Y., Y.L. Cheng and J.L. Zhang, 2022. Efficacy and safety of *Tripterygium wilfordii* polyglycosides versus valsartan in management of diabetic nephropathy. Int. J. Pharmacol., 18: XX-XX.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

One of the microvascular complications of diabetes is diabetic nephropathy[1]. Diabetic nephropathy is characterized by albuminuria, renal injuries and hypertension and later-stage renal failure[2]. Approximately 22-41% of Chinese patients with type 2 diabetes may develop diabetic nephropathy[3], which leads to damage to the physical and mental health of diabetic patients and increases the economic burden on patients' heads[4]. In China, diabetic nephropathy is the most common cause of end-stage renal diseases[2]. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are recommended to reduce proteinuria and to prevent the progression of diabetic nephropathy in type 2 diabetes patients[5]. These are insufficient for the management of proteinuria in diabetic nephropathy and controversial for patients with serum creatinine >3 mg dL^{-1} [6]. Therefore, new potential effective drug therapies are needed for the management of diabetic nephropathy.

Polyglycosides extracted from *Tripterygium wilfordii* Hook. F (*Tripterygium wilfordii* polyglycosides) are reported effective in kidney diseases and diabetic nephropathy[7] for management of pathological indicators during 3-6 months of treatment[8]. However, *Tripterygium wilfordii* Hook F. is reported to have multi-organ toxicity such as myelosuppression and infertility[6]. Also, severe adverse effects are reported after 3 months of consecutive intervention of *Tripterygium wilfordii* polyglycosides[8].

The objectives of the non-randomized retrospective study were to evaluate the effects of 120 mg/day of *Tripterygium wilfordii* polyglycosides for 12 weeks followed by 60 mg/day of *Tripterygium wilfordii* polyglycosides for 12 weeks and 160 mg/day valsartan plus 60 mg/day of *Tripterygium wilfordii* polyglycosides for 24 weeks against those of 160 mg/day valsartan for 24 weeks regarding urinary protein excretion per day, serum albumin level, blood glucose level, serum potassium level and unwanted adverse effects in Chinese diabetic nephropathic patients.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Nephrology, Third People's Hospital of Wuxi, China from 11January, 2012-14 July, 2020.

Ethics approval and consent to participate: The designed protocol (February 18, 2021) was approved by the affiliated Hospital of Jiangnan University review board. The study reporting adheres to the law of China and the v2008 Declarations of Helsinki. An informed consent form was signed by all participating patients regarding pathology, interventions and publication of anonymized information of patients in the form of the article during the period of treatments.

Inclusion criteria: A total of 465 diabetic patients with an age range of 30-70 years, a large amount of proteinuria (urinary protein excretion of more than 3 g/day) with a history of at least 1 month and serum creatinine less than 1.5 mg dL^{-1} were included in the analysis.

Exclusion criteria: Type 1 diabetic and non-diabetic patients with kidney diseases, patients with severe infection(s), patients with immune deficiency, patients with white blood cell count less than 3.0×10^9 L^{-1}, patients with liver disease(s) or liver dysfunction(s) (serum alanine aminotransferase level $\geq$3-folds of normal), female patient with pregnancies and patients with allergies to valsartan or *Tripterygium wilfordii* polyglycosides were excluded from the analysis. Also, patients with incomplete interventions were excluded from the analysis.

Sample size calculation: The study was assumed that at least 15±5% of patients would be reduced proteinuria after 24 weeks of interventions. The sample size was calculated on this assumption, two-sided type-I error ($\alpha = 0.05$) and type-II error, $\beta = 0.2$ (80% power) with 95% of confidence interval. The sample size (minimum number of patients required in each cohort) was 105[6].

Cohorts: A total of 127 patients have received 160 mg/day valsartan (Beijing Novartis Pharmaceutical Co. LTD, Beijing, China) for 24 weeks (VS cohort). A total of 158 patients have received 20 mg *Tripterygium wilfordii* polyglycosides (Shanghai Fudan Fuhua Pharmaceutical Co., Ltd., Shanghai, China) three times a day plus 160 mg/day valsartan for 24 weeks (TV cohort). A total of 165 patients have received 40 mg *Tripterygium wilfordii* polyglycosides three times a day for 12 weeks followed by 20 mg *Tripterygium wilfordii* polyglycosides 3 times a day for 12 weeks (TP cohort). Besides these treatments, patients have also received oral hypoglycemic agent (s) or insulin, antihypertensive (s) and/or diuretic (s) as prescribed by a physician (s).

Demographics, clinical and laboratory parameters: Demographics (sex, age, ethnicity, body mass index and

history of type-2 diabetes), clinical (diastolic blood pressure and systolic blood pressure) and laboratory (urinary protein excretion/day, serum creatinine, estimated glomerular filtration rate, serum albumin, fasting blood glucose, glycosylated haemoglobin, total cholesterol, triglycerides, serum alanine aminotransferase level, serum potassium and white blood cell count) parameters at the start of interventions were retrospectively collected and analyzed.

Outcome measures: Data regarding clinical and laboratory parameters after 24 weeks of interventions and side effects (for example, liver function abnormalities, leukopenia and/or amenorrhea) during 24 weeks of interventions were retrospectively collected and analyzed.

Estimated glomerular filtration rate: It was calculated as per the Chronic kidney disease epidemiology collaboration Eq. 1[9]:

$$\text{Estimated glomerular filtration rate} = 175 \times \text{serum creatinine}^{-1.154} \times \text{Age}^{-0.203} \times 0.742 \text{ (if female)} \quad (1)$$

Liver function abnormalities: A 3-fold or more increase in serum alanine aminotransferase level above the upper limit of the normal range (35 IU L^{-1}) was considered as abnormalities in the liver functions[6].

Leukopenia: Leukocyte counts less than 3000 L^{-1} was considered leukopenia[6].

Amenorrhea: Altered menstruation was considered a menstrual disorder or amenorrhea[6].

Hyperkalemia: Serum potassium level increased by 50% and/or above 5.50 mEq L^{-1} was considered as hyperkalemia[10].

Statistical analysis: SPSS 26.0 IBM Corporation, Armonk, NY, USA was used for statistical analysis purposes. Quantitative variables are presented as Mean±Standard Deviation (SD) and qualitative variables are presented as frequency (%). One-way analysis of variance (ANOVA) was used for quantitative variables and the Chi-square test of Independence was used for qualitative variables. Univariate following multivariate analysis was performed for evaluation of the effect of the demographics, clinical and laboratory parameters of before interventions on urinary protein excretion after 24 weeks of interventions. The Tukey test (considering critical value (q)>3.32 as significant) was used for *post hoc* analysis. All results were considered significant if $p<0.05$.

RESULTS

Study population: During the study period, a total of 473 patients with type 2 diabetes were diagnosed with diabetic nephropathy (urinary protein excretion >3 g/day with a history of at least one month and serum creatinine <1.5 mg dL^{-1}) at the department of nephrology of the parent hospital and the department of the medicine of referring hospitals. Among them one patient with severe infection(s), one patient with immune deficiency, two patients with white blood cell count less than 3.0×10^9 L^{-1}, one patient with liver dysfunction(s), one female patient with pregnancy and two patients with known allergies to valsartan and/or *Tripterygium wilfordii* polyglycosides. Therefore, these patients were not put on valsartan and/or *Tripterygium wilfordii* polyglycosides. A total of 465 diabetic nephropathy patients were put on valsartan and/or *Tripterygium wilfordii* polyglycosides. Also, 15 patients were reported with incomplete interventions. Therefore, data of these patients (n = 15) were excluded from the analysis. Data regarding demographics, clinical and laboratory parameters of a total of 450 patients before interventions and 24 weeks after interventions were retrospectively collected and analyzed. The flow diagram of the management of diabetic nephropathy is reported in Fig. 1.

Demographics, clinical and laboratory parameters: Participants at age of 48-50 (mean) years with a large amount of proteinuria were included in the study and patients with other glomerular diseases, such as membranous nephropathy and monoclonal gammopathy of renal significance were excluded from the analysis. Before interventions, there were no significant differences for male: Female ratio, age, ethnicity, body mass index, history of type-2 diabetes, diastolic blood pressure, systolic pressure, urinary protein excretion/day, serum creatinine, estimated glomerular filtration rate, serum albumin levels, fasting blood glucose levels, glycosylated haemoglobin levels, total cholesterol levels, triglycerides levels and serum potassium levels of patients among cohorts ($p>0.05$ for all). The details of demographics, clinical and laboratory parameters before interventions of the included patients are reported in Table 1.

Outcome measures

Urinary protein excretion: After 24 weeks of interventions, patients of VS (4.33±0.46 vs. 3.61±0.23 g/day/patient, $p<0.0001$, $q = 22.138$), TV (4.29±0.38 vs. 3.51±0.21 g/day/patient, $p<0.0001$, $q = 27.499$) and TP (4.21±0.46 vs.

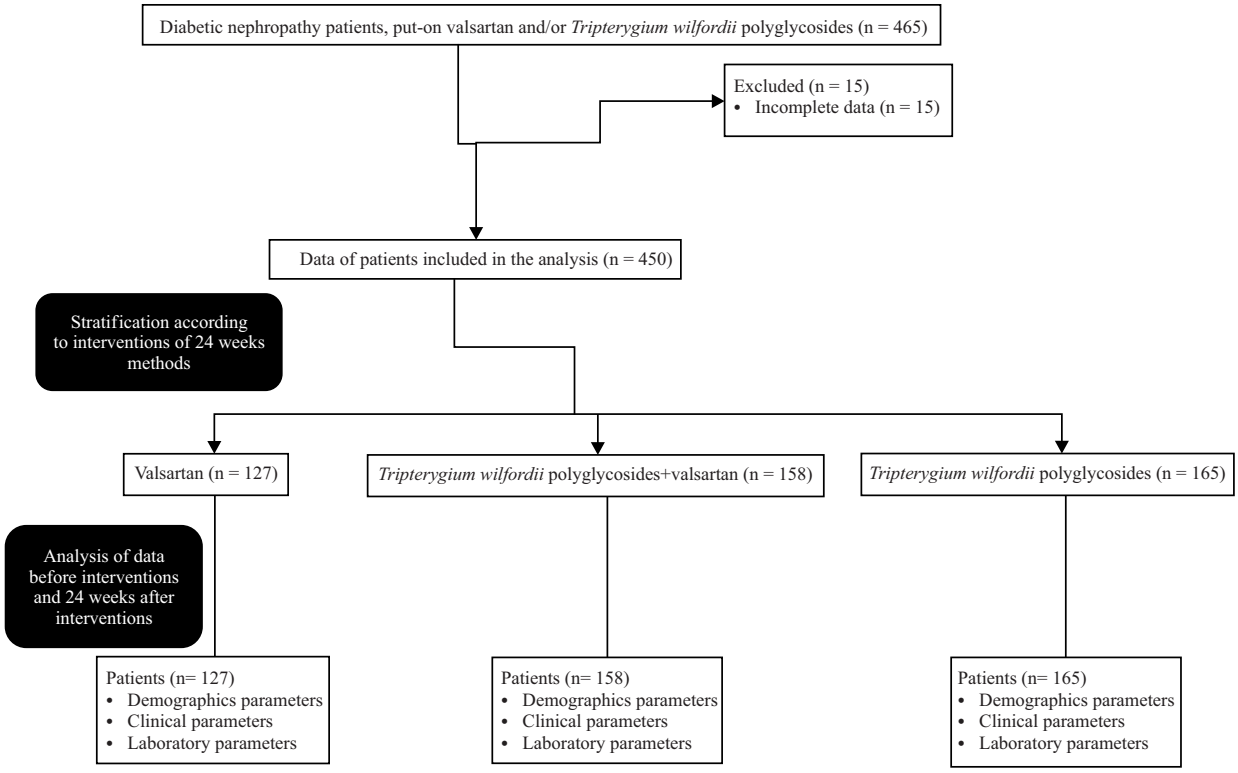

Fig. 1: Flow diagram of the management of diabetic nephropathy

3.42±0.14 g/day/patient, p<0.0001, q = 27.154) cohorts were reported reduction in urinary protein excretion per day (Fig. 2a). After 24 weeks of interventions, patients of TP cohort had significant percentage reduction of urinary protein excretion than those VS cohort (18.06±7.57% vs. 16.09±6.48%, p = 0.043, q = 3.419). The details of percentage reduction of urinary protein excretion per day are reported in Fig. 2b.

Serum albumin level: After 24 weeks of interventions patients of TV (34.32±4.77 vs. 36.91±3.62 g L^{-1} per patient, p<0.0001, q = 7.839) and TP (33.50±3.92 vs. 41.19±3.39 g L^{-1} per patient, p<0.0001, q = 26.418) cohorts were recorded elevation in serum albumin level (Fig. 3a). After 24 weeks of interventions, patients of TP (23.88±11.29 vs. 1.75±1.93%, p<0.0001, q = 31.772) and TV (8.40±7.88 vs. 1.75±1.93%, p<0.0001, q = 9.457) cohorts had significant percentage elevation in serum albumin levels than those of VS cohort. Also, after 24 weeks of interventions, patients of the TP cohort had a significant percentage elevation in serum albumin levels than those of the TV cohort (p<0.0001, q = 23.569). The details of percentage elevation in serum albumin levels are reported in Fig. 3b.

Fasting blood glucose: After 24 weeks of interventions patients VS, TV and TP cohorts were not successful to reduce fasting blood glucose as compared to the values of before interventions (p>0.05 for all) but after 24 weeks of interventions, fasting blood glucose of patients of the TP cohort had a significantly lower value than those of patients of VS cohort (139.4±12.57 vs. 142.89±10.98 mg dL^{-1} per patient, p = 0.032, q = 3.604) (Table 2).

Serum potassium level: After 24 weeks of interventions, there was an elevation in serum potassium levels (mild hyperkalemia) of patients of VS, TV and TP cohort (p<0.05 for all) as compared to before interventions but at 24 weeks after interventions, there were no significant differences for serum potassium levels of patients among cohorts (p = 0.298). The details of serum potassium level are reported in Fig. 4.

After 24 weeks of interventions, there were no significant changes in body mass index, diastolic pressure, systolic pressure, serum creatinine levels, estimated glomerular filtration rate, glycosylated haemoglobin levels, total cholesterol levels and triglycerides levels of patients within and among cohorts (p>0.05 for all). The details of clinical and laboratory parameters after 24 weeks of interventions of the included patients are reported in Table 2.

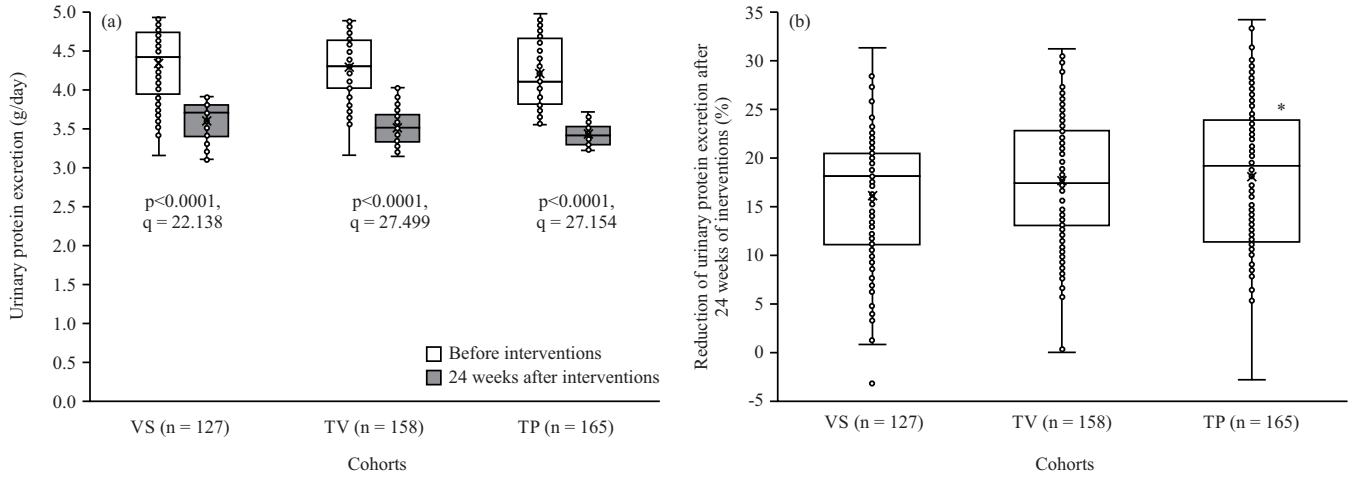

Fig. 2(a-b): Urinary protein excretion per day in different groups, (a) Before interventions and 24 weeks after of interventions values and (b) Percentage reduction of urinary protein excretion

*Significant higher value than that of the VS cohort. VS cohort: Patients have received 160 mg/day valsartan for 24 weeks, TV cohort: Patients have received 20 mg *Tripterygium wilfordii* polyglycosides 3 times in a day plus 160 mg/day valsartan for 24 weeks, TP cohort: Patients have received 40 mg *Tripterygium wilfordii* polyglycosides 3 times in a day for 12 weeks followed by 20 mg *Tripterygium wilfordii* polyglycosides 3 times for 12 weeks

Table 1: Demographics, clinical and laboratory parameters of the included patients before interventions

	Cohorts			
	VS	TV	TP	
Parameters/ Interventions	Valsartan	*Tripterygium wilfordii* polyglycosides+valsartan	*Tripterygium wilfordii* polyglycosides	Comparisons
Patients put on intervention(s)	127	158	165	p-value
Sex				
Male	85 (67)	101 (64)	105 (64)	0.819
Female	42 (33)	57 (36)	60 (36)	
Age (years)				
Minimum	30	31	31	0.564
Maximum	70	69	70	
Mean±SD	49.12±12.15	48.56±13.11	50.08±13.25	
Ethnicity				
China mainland residential Han Chinese	112 (88)	141 (89)	144 (88)	0.976
Mongolian	11 (9)	12 (7)	13 (8)	
Tibetan	3 (2)	3 (2)	4 (2)	
Uighur Muslims	1 (1)	1 (1)	2 (1)	
North American residential Han Chinese	0 (0)	1 (1)	2 (1)	
Body mass index (kg m^{2-1})	24.52±2.25	25.01±2.45	24.89±2.58	0.225
History of type 2 diabetes (years)	10.15±3.14	10.82±4.12	10.56±4.57	0.381
Diastolic pressure (mmHg)	84.94±4.65	85.71±3.82	84.64±5.01	0.093
Systolic pressure (mmHg)	136.72±7.69	136.54±6.47	135.61±5.69	0.286
Urinary protein excretion (g/day)	4.33±0.46	4.29±0.38	4.21±0.46	0.067
Serum creatinine (mg dL^{-1})	1.01±1.00	0.99±0.09	1.00±0.09	0.095
Estimated glomerular filtration rate (mL/min/1.73 m^2)	96.10±9.91	94.89±11.25	96.92±12.61	0.276
Serum albumin (g L^{-1})	34.52±3.93	34.32±4.77	33.50±3.92	0.086
Fasting blood glucose (mg dL^{-1})	142.79±11.19	142.10±11.49	140.18±13.30	0.154
Glycosylated hemoglobin (% HbA1C)	7.30±0.51	7.27±0.57	7.21±0.54	0.384
Total cholesterol (mg dL^{-1})	267.10±21.07	269.46±20.34	270.44±19.21	0.365
Triglycerides (mg dL^{-1})	186.96±16.81	191.27±18.66	188.38±19.07	0.124
Serum potassium (mEq L^{-1})	4.03±0.25	3.98±0.23	3.99±0.22	0.211

Quantitative variables are presented as Mean±Standard Deviation (SD) and qualitative variables are presented as frequency (%). One-way ANOVA was performed for quantitative variables and the Chi-square test of independence was performed for qualitative variables. A p<0.05 was considered significant. VS cohort: Patients have received 160 mg/day valsartan for 24 weeks, TV cohort: Patients have received 20 mg *Tripterygium wilfordii* polyglycosides 3 times in a day plus 160 mg/day valsartan for 24 weeks, TP cohort: Patients have received 40 mg *Tripterygium wilfordii* polyglycosides 3 times in a day for 12 weeks followed by 20 mg *Tripterygium wilfordii* polyglycosides 3 times for 12 weeks

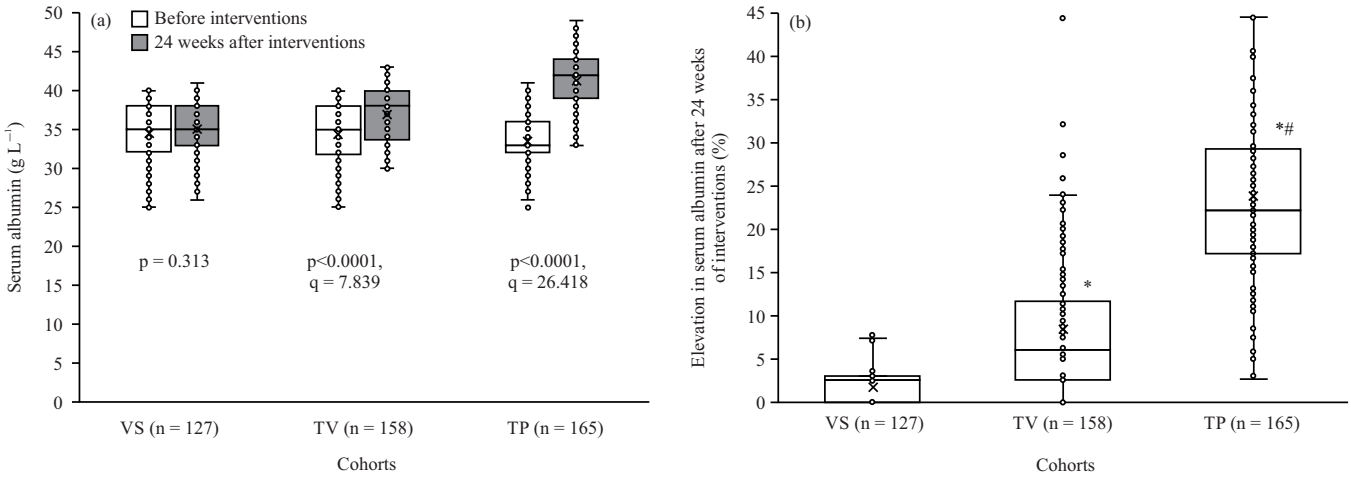

Fig. 3(a-b): Serum albumin levels of different groups, (a) Before interventions and 24 weeks after of interventions values and (b) Percentage elevation in serum albumin after 24 weeks of interventions

*Significantly higher than VS cohort. #Significantly higher than the TV cohort. VS cohort: Patients have received 160 mg/day valsartan for 24 weeks, TV cohort: Patients have received 20 mg *Tripterygium wilfordii* polyglycosides 3 times in a day plus 160 mg/day valsartan for 24 weeks, TP cohort: Patients have received 40 mg *Tripterygium wilfordii* polyglycosides 3 times in a day for 12 weeks followed by 20 mg *Tripterygium wilfordii* polyglycosides 3 times for 12 weeks

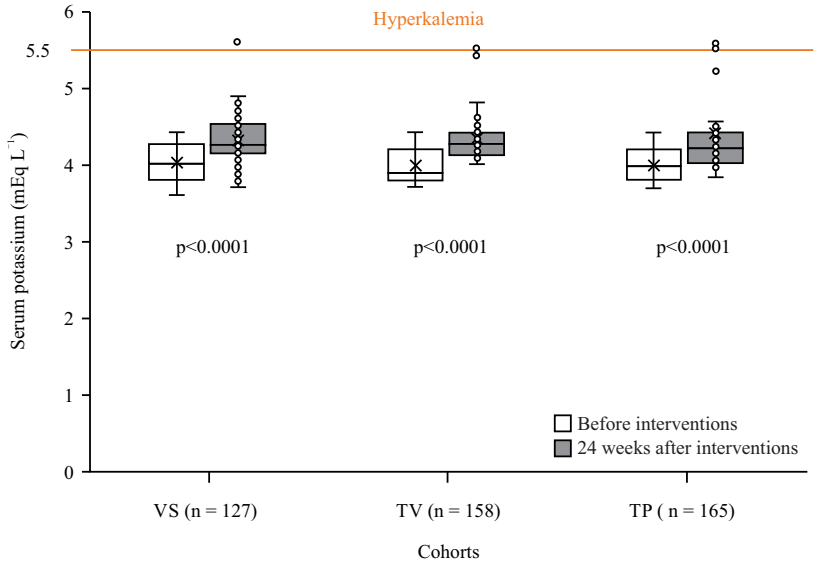

Fig. 4: Serum potassium levels. Serum potassium level increased by 50% and/or above 5.50 mEq L^{-1} was considered as hyperkalemia

A p-values indicated in the figure are for serum potassium levels between before intervention and 24 weeks after intervention. VS cohort: Patients have received 160 mg/day valsartan for 24 weeks, TV cohort: Patients have received 20 mg *Tripterygium wilfordii* polyglycosides 3 times in a day plus 160 mg/day valsartan for 24 weeks, TP cohort: Patients have received 40 mg *Tripterygium wilfordii* polyglycosides 3 times in a day for 12 weeks followed by 20 mg *Tripterygium wilfordii* polyglycosides 3 times for 12 weeks

Effects of parameters on urinary protein excretion: The demographics, clinical and laboratory parameters of before interventions of the included patients were not independent parameters for significant reduction of urinary protein excretion (Table 3, p>0.05 for all). The reason for the significant decrease in urinary protein excretion was due to treatment interventions for the management of diabetic nephropathy themselves.

Table 2: Clinical and laboratory parameters of the included patients after 24 weeks of interventions

Parameter/ Interventions	Cohorts: VS Valsartan	Cohorts: TV *Tripterygium wilfordii* polyglycosides+valsartan	Cohorts: TP *Tripterygium wilfordii* polyglycosides	Comparisons: p-value	Comparisons: q-value VS vs. TV	Comparisons: q-value VS vs. TP	Comparisons: q-value TV vs. TP
Patients put on intervention(s)	127	158	165				
Body mass index (kg m^{2-1})	24.32±2.11	24.97±2.31	24.75±2.45	0.060	N/A	N/A	N/A
Diastolic pressure (mmHg)	84.83±4.46	85.61±3.69	84.47±4.69	0.054	N/A	N/A	N/A
Systolic pressure (mmHg)	136.57±7.49	136.49±6.41	135.56±5.61	0.311	N/A	N/A	N/A
Serum creatinine (mg dL^{-1})	1.01±0.09	0.99±0.09	1.00±0.09	0.092	N/A	N/A	N/A
Estimated glomerular filtration rate (mL min^{-1} 1.73 m^{2-1})	96.22±9.73	95.11±10.91	97.12±12.32	0.270	N/A	N/A	N/A
Fasting blood glucose (mg dL^{-1})	142.89±10.98	141.67±11.01	139.40±12.57	0.032	1.247	3.604	2.487
Glycosylated hemoglobin (% HbA1C)	7.30±0.49	7.25±0.55	7.17±0.49	0.071	N/A	N/A	N/A
Total cholesterol (mg dL^{-1})	266.93±20.90	269.22±20.05	270.12±18.91	0.386	N/A	N/A	N/A
Triglycerides (mg dL^{-1})	186.91±16.80	191.22±18.65	188.21±18.92	0.118	N/A	N/A	N/A
Serum potassium (mEq L^{-1})	4.33±0.28	4.35±0.36	4.41±0.56	0.298	N/A	N/A	N/A

Quantitative variables are presented as Mean±Standard Deviation (SD) and qualitative variables are presented as frequency (%). One-way ANOVA was performed for statistical analysis. The Tukey test was used for *post hoc* analysis. All results were considered significant if $p<0.05$ and $q>3.32$. N/A: Not applicable. VS cohort: Patients have received 160 mg/day valsartan for 24 weeks, TV cohort: Patients have received 20 mg *Tripterygium wilfordii* polyglycosides 3 times in a day plus 160 mg/day valsartan for 24 weeks, TP cohort: Patients have received 40 mg *Tripterygium wilfordii* polyglycosides 3 times in a day for 12 weeks followed by 20 mg *Tripterygium wilfordii* polyglycosides 3 times for 12 weeks

Table 3: Effects of the demographics, clinical and laboratory parameters of before interventions on urinary protein excretion

Parameters	Odd ratio	Confidence limit (95%)	p-value
Sex (female vs. male)	0.571	0.552-0.871	0.075
Age (<50 years vs. ≥50 years)	0.592	0.551-0.881	0.071
Ethnicity (China mainland residential Han Chinese vs. others)	0.413	0.562-0.821	0.098
Body mass index (<24 vs. ≥24 kg m^{2-1})	0.622	0.571-0.942	0.069
History of type-2 diabetes (<6 vs. ≥6 years)	0.711	0.512-0.952	0.066
Diastolic pressure (<90 vs. ≥90 mmHg)	0.551	0.552-0.832	0.087
Systolic pressure (<140 vs. ≥140 mmHg)	0.562	0.542-0.872	0.082
Glycosylated hemoglobin (<7 vs. ≥7%)	0.572	0.552-0.884	0.086
Total cholesterol (<240 vs. ≥240 mg dL^{-1})	0.583	0.532-0.892	0.085
Triglycerides (<200 vs. ≥200 mg dL^{-1})	0.592	0.521-0.921	0.084
Antidiabetic treatment (insulin vs. oral hypoglycemic agent(s))	0.89	0.492-0.985	0.052

Multivariate analysis. Odd ratio>1 with $p<0.05$ were considered significant

Table 4: Adverse effects reported during 24 weeks of interventions

Event/ Interventions	Cohorts: VS — Valsartan	Cohorts: TV — *Tripterygium wilfordii* polyglycosides+valsartan	Cohorts: TP — *Tripterygium wilfordii* polyglycosides	Comparisons: p-value	Comparisons: q-value VS vs. TV	Comparisons: q-value VS vs. TP	Comparisons: q-value TV vs. TP
Patients put on interventions	127	158	165				
Itchy skin	3 (2)	5 (3)	9 (5)	0.345	N/A	N/A	N/A
Rash	0 (0)	2 (1)	6 (4)	0.055	N/A	N/A	N/A
Nausea	1 (1)	4 (3)	7 (4)	0.191	N/A	N/A	N/A
Joint pain	5 (4)	4 (3)	1 (1)	0.152	N/A	N/A	N/A
Respiratory tract infection	2 (2)	2 (1)	0 (0)	0.301	N/A	N/A	N/A
Liver function abnormalities	2 (2)	12 (8)	18 (11)**	0.008	2.799	4.383	1.49
Leukopenia	5 (4)*	4 (3)*	0 (0)	0.049	1.195	3.379	2.305
Amenorrhea in female patients	0 (0)	3 (2)	7 (4)**	0.048	1.534	3.459	2.027
Hyperkalemia	1 (1)	11 (7)	29 (18)**	<0.0001	2.614	7.175	4.809
Dizziness	15 (12)*	14 (9)*	1 (1)	0.001	1.399	5.077	3.885
Vertigo	7 (6)*	5 (3)*	0 (0)	0.013	1.739	4.125	2.512
Headache	25 (20)*	27 (17)*	2 (1)	<0.0001	0.977	7.019	6.397
Diarrhea	7 (6)*	4 (3)*	1 (1)	0.034	2.204	3.663	1.525
Weakness	5 (4)*	4 (2)*	0 (0)	0.049	1.195	3.379	2.305
Fever	8 (6)*	9 (6)*	0 (0)	0.006	0.378	3.991	3.827

Variables are expressed as frequency (%). One-way ANOVA was used for statistical analysis. The Tukey test was used for post hoc analysis. All results were considered significant if $p<0.05$ and $q>3.32$. N/A: Not applicable. *Valsartan-emergent adverse effect. ** *Tripterygium wilfordii* polyglycosides-emergent adverse effect. VS cohort: Patients have received 160 mg/day valsartan for 24 weeks, TV cohort: Patients have received 20 mg *Tripterygium wilfordii* polyglycosides 3 times in a day plus 160 mg/day valsartan for 24 weeks, TP cohort: Patients have received 40 mg *Tripterygium wilfordii* polyglycosides 3 times in a day for 12 weeks followed by 20 mg *Tripterygium wilfordii* polyglycosides 3 times in a day for 12 weeks

Adverse effects: There were no deaths of patients who received 24 weeks of interventions. Patients of VS cohort reported joint pain, leukopenia, dizziness, vertigo, headache, diarrhoea, weakness and fewer during 24 weeks of interventions. Patients of the TV cohort reported itchy skin, liver function abnormalities, leukopenia, hyperkalemia, dizziness, vertigo, headache, diarrhoea, weakness and fever during 24 weeks of interventions. Patients of the TP cohort reported itchy skin, liver function abnormalities, amenorrhea and hyperkalemia during 24 weeks of interventions. The details of adverse effects during 24 weeks of interventions are reported in Table 4.

DISCUSSION

The study reported that after 24 weeks of interventions patients of VS, TV and TP cohorts have reported a reduction in urinary protein excretion and patients of the TP cohort had a significant percentage reduction of urinary protein excretion than those of VS cohort. The results of urinary protein excretion in the current study were consistent with those of randomized trials[6,10]. Both randomized trials[6,10] are performed with a small sample size. The podocyte-protective, anti-inflammatory, immunosuppressive and anti-oxidative stress effects of *Tripterygium wilfordii* polyglycosides reduce renal inflammation and damage of renal functions leads to reduces urinary protein excretion[10-12]. Valsartan monotherapy, valsartan plus *Tripterygium wilfordii* polyglycosides and a high dose of *Tripterygium wilfordii* polyglycosides are effective for the management of urinary protein excretion in diabetic nephropathic patients.

The study reported that after 24 weeks of interventions patients of the TV and TP cohort were recorded an elevation in serum albumin levels and patients of TP and TV cohorts had a significant percentage elevation in serum albumin levels than those of VS cohort. The results of the serum albumin levels of the current study were consistent with those of a randomized trial[6]. Valsartan monotherapy is required a longer period of interventions for the elevation of serum albumin levels[13]. *Tripterygium wilfordii* polyglycosides increases the synthesis of serum albumin[6] which shortens the time for the elevation of serum albumin levels. A total of 24 weeks of valsartan monotherapy (160 mg/day) is not enough to increase serum albumin levels of patients with diabetic nephropathy.

The study reported that during 24 weeks of valsartan interventions, patients were reported leukopenia, dizziness, vertigo, headache, diarrhoea, weakness and fever. The results of the valsartan-emergent adverse effect of the current study agreed with those of randomized trials[6,10]. These side effects are common side effects of valsartan interventions[14]. A total of 160 mg/day valsartan interventions for 24 weeks is not tolerated by most patients.

During 24 weeks of interventions, patients of the TV cohort reported valsartan-emergent adverse effects only and patients of the TP cohort reported liver function abnormalities, amenorrhea and hyperkalemia. The results of *Tripterygium wilfordii* polyglycosides-emergent adverse effect of the current study agreed with those of randomized trials[6,10]. A total of 60 mg/day of *Tripterygium wilfordii* polyglycosides for 24 weeks is well-tolerated by patients but 120 mg/day of *Tripterygium wilfordii* polyglycosides for 12 weeks is responsible for adverse effects. A high dose of *Tripterygium wilfordii* polyglycosides for a longer time is responsible for toxic effects[15]. *Tripterygium wilfordii* polyglycosides are affected by a large number of genes involved in metabolic pathways, which are responsible for multi-organ toxicities[16]. Although good results in reducing proteinuria, improvement in serum albumin values in the intervention groups with the new drug compared to valsartan, the adverse effects being very frequent hyperkalemia and liver enzyme abnormalities, it is recommended to perform a sub-analysis looking for reasons or causes of the presence of these adverse effects in these groups. To rule out the side effects of *Tripterygium wilfordii* polyglycosides, further study is needed.

The study reported that the demographics, clinical and laboratory parameters before interventions were not associated with the reduction of urinary protein excretion. The results of parameters responsible for the reduction of urinary protein excretion were not agreed with those of meta-analysis and systematic review[13] and a cross-sectional study[4]. The reasons for such contradictory results are the different inclusion criteria of the current study.

In the limitations of the study, for example, small retrospective analysis and lack of randomized trial. The controlled double-blind trial is not possible here because, in China, patients have legal rights for the selection of traditional Chinese medicine for the treatment of disease(s). The study is not generalized because *Tripterygium wilfordii* polyglycosides are not freely available in other countries. *Tripterygium wilfordii* polyglycosides are reported infertility[6] but the current study did not evaluate such effect. This is because most of the male patients included in the study were old-aged. The patients with mild to moderate proteinuria who account for a significant proportion of diabetic nephropathy were not included in the study. The participants were included

according to the level of serum creatinine but not according to an estimated glomerular filtration rate range. Too little evidence to extrapolate data. It is risky to recommend a drug with so little evidence and with such severe adverse effects such as hyperkalemia, even today where there is an important therapeutic arsenal with great evidence in the management of proteinuria in diabetics. There are no details of the active compounds present in traditional Chinese medicine, *Tripterygium wilfordii* and the dosing regimens are unclear. The diagnosis of diabetic nephropathy is unclear and no clinical guidelines have been followed. Safety and efficacy have not been evaluated according to clear guidelines. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers such as valsartan are the first-line approved agents for treating diabetic and non-diabetic proteinuria with clearly explained mechanisms of action and long-term safety records. The current study has not explained how diabetic patients with nephrotic range proteinuria can be ethically treated with only *Tripterygium wilfordii* polyglycosides without angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Distinct mechanisms of action of *Tripterygium wilfordii* polyglycosides at a cellular level are required to explain their antiproteinuric effects. It is worth noting the intention of the study to seek alternatives in the management of proteinuria in patients with diabetic nephropathy but the use of *Tripterygium wilfordii* polyglycosides is not left as it has so little scientific contribution.

CONCLUSION

A total of 160 mg/day valsartan monotherapy for 24 weeks is not enough for the management of diabetic nephropathy. The treatment with *Tripterygium Wilfordii* polyglycosides promotes an important decrease of urine protein excretion in Chinese diabetic nephropathy patients and it could improve the quality of life of these patients. However, 120 mg/day of *Tripterygium wilfordii* polyglycosides for 12 weeks had unwanted serious adverse effects.

SIGNIFICANCE STATEMENT

A retrospective study to investigate the effects of *Tripterygium wilfordii* polyglycosides and/or valsartan on diabetic nephropathy patients reported that valsartan monotherapy is not enough for the management of diabetic nephropathy. Also, *Tripterygium wilfordii* polyglycosides have multi-organ toxicity during the management of diabetic nephropathy. The study is provided insides of management of diabetic nephropathy that many physicians have not evaluated.

ACKNOWLEDGMENTS

The authors are thankful for the medical, non-medical and nursing staff of the Affiliated Hospital of Jiangnan University, Binhu District, Wuxi, China.

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