Research Article **Open Access**

Yan Hong, Zhihong Gui, Xiaoping Cai, Lejian lan*

Clinical efficacy and safety of tripterygium glycosides in treatment of stage IV diabetic nephropathy: A meta-analysis

DOI 10.1515/med-2016-0099
received October 29, 2016; accepted December 16, 2016

Abstract: The aim of this meta-analysis was to evaluate the clinical efficacy and safety of tripterygium glycosides in treatment of stage IV diabetic nephropathy. Methods Through searching the PubMed and CNKI databases, the open published clinically controlled trials related to efficacy and safety of tripterygium glycosides in the treatment of stage IV diabetic nephropathy were collected. The pooled total efficacy, 24h urinary protein, serum creatinine and tripterygium glycosides related toxicity were calculated using Stata 11.0 software. Results Fourteen publications including 992 subjects (512 in the experimental group and 480 in the control group) were included in this study. Eight studies reported the total clinical efficacy comparing the experiment and control groups. No significant statistical heterogeneity was found in total efficacy (I^2=24.9%, p>0.05). Thus, the combined odds ratio (OR) was pooled by fixed effect model. The pooled OR=4.16 with its 95% CI 2.71~6.37 (p<0.05), which indicated the total efficacy in the experiment group, was significant higher than that of control group (p<0.05); Thirteen studies reported the post-treatment 24h urinary protein value. Statistical heterogeneity analysis indicated significant heterogeneity across studies (I^2=91.1%, p<0.05); that data was pooled by a random effects model. The combined standardized mean difference (SMD) was -1.55 with its 95%CI -2.06~1.03, (p<0.05). The results indicated that post-treatment 24h urinary protein in the experiment group was significant lower than that in control group (p<0.05); Ten studies reported the post-treatment serum creatinine. Significant heterogeneity existed across those studies (I^2=82.3%, p<0.05). Thereafter, the data was pooled by a random effect model. The combined standardized mean difference (SMD) was -0.24 with its 95%CI -0.40~0.09, (p<0.05). The results indicated that the post-treatment serum creatinine in experiment group was significant lower than that of control group (p<0.05); Eight studies reported tripterygium glycoside-associated toxicity such as liver function damage, gastrointestinal reactions and menstrual disorders. With no statistical heterogeneity among the studies, the data was pooled by fixed effect model. The pooled OR=6.42 (95%CI 2.23~18.48, p<0.05). The pooled results showed the tripterygium glycoside- associated toxicity incidence rate was significant higher in the experiment group than that of the control group (p<0.05); There were no publication bias for effect size of total efficacy, 24h urinary protein, and serum creatinine. However, for tripterygium glycoside-related toxicity, the publication bias was significant (t=-3.55, p<0.05). Conclusion The present evidence shows that tripterygium glycosides can improve clinical efficacy, reduce the 24h urinary protein and serum creatinine, but that they increase the tripterygium glycoside-related toxicity in treatment of stage IV diabetic nephropathy.

Keywords: Tripterygium glycosides; Clinical efficacy; Safety; Diabetic nephropathy; Meta-analysis

***Corresponding author: Lejian lan,** Department of nephrology, The sixth Affiliated Hospital of Wenzhou Medical University, People's Hospital of Lishui City, Zhejiang Province 323000, PR China, Tel. +86-(0578)2780013, E-mail: lanlj101@126.com
Yan Hong, Department of clinical pharmacy, The fifth Affiliated Hospital of Wenzhou Medical University, Lishui Central Hospital, Zhejiang Province 323000, PR China
Zhihong Gui, Department of nephrology, The sixth Affiliated Hospital of Wenzhou Medical University, People's Hospital of Lishui City, Zhejiang Province 323000, PR China
Xiaoping Cai, Department of Respiratory, The sixth Affiliated Hospital of Wenzhou Medical University, People's Hospital of Lishui City, Zhejiang Province 323000, PR China

1 Introduction

Diabetic nephropathy (DN) is one of the most frequently diagnosed chronic complications in patients with diabetes mellitus. DN is characterized by nephrotic syndromes and diffuse scarring of the glomeruli due to longstanding diabetes mellitus and is a prime reason for dialysis in many developed countries. Published studies have confirmed that persistent proteinuria was an independent risk factor for the progression of diabetic nephropathy [1, 2] and that it was also one of the independent important prognostic factors. Therefor, reducing persistent proteinuria has become an important treatment purpose. Many clinical trials have confirmed that the renin angiotensin system and angiotensin II receptor blockers can reduce the levels of urinary protein in patients with DN, thereby delaying its progression. However, only use of angiotensin converting enzyme inhibitor/angiotensin receptor blockers (ARB/ACEI) for treatment of DN was not ideal [3,4]. Several studies [3-5] have achieved relatively go results for ARB/ACEI combined with tripterygium glycosides in the treatment of DN. However, because a small number of cases were included in each study, the statistical power was limited. Therefore, in this present meta-analysis, we included the openly available published studies and pooled the results to further evaluate the clinical efficacy and safety of tripterygium glycosides in treatment of stage IV diabetic nephropathy.

2 Methods

2.1 Publication searching

The associated publication searching procedure was performed by two reviewers independently. Clinical controlled trials comparing tripterygium glycosides plus ARB/ACEI vs. ARB/ACEI alone in the treatment of stage IV diabetic nephropathy were electronically searched in the PubMed and CNKI databases before July 2016. We used the following formula for PubMed and CNKI databases:: ("tripterygium glycosides" OR tripterygium*) AND ("diabetic nephropathy" OR DN) AND ("clinical efficacy" OR efficacy OR "urinary protein" OR "serum creatinine" OR "liver function damage" OR "gastrointestinal reaction" OR "menstrual disorders") Searches were limited to human trials, with the language restriction of English and Chinese. All references of relevant articles were scanned for additional analysis.

2.2 Inclusion and exclusion criteria

The patients' inclusion criteria, treatment process, and outcomes of the relevant studies were extracted by two reviewers and then checked by a third reviewer. The patients of the original studies were diagnosed of DN at clinical stage IV; the treatment drug was ACEI/ARB alone or ACEI/ARB plus tripterygium glycosides; The outcomes were restricted to total efficacy, 24h urinary protein, serum creatinine, and tripterygium glycoside-related toxicity. The exclusion criterias were: case report or review study type; duplicated publications; insufficient data for calculating OR and 95% CI; published in other languages (not Chinese or English).

2.3 Data extraction and quality assessment

Data of each included study was extracted by Lan Lejian and Hong Yan independently and cross checked. If disagreement was encountered, the third author (Zhihong Gui) was consulted for consensus. The general information such as journal where the paper was published, the authors of the paper, the year of publication and the treatment methods were extracted from each of the included papers. The results for total efficacy, 24h urinary protein, serum creatinine, and tripterygium glycoside- related toxicity were extracted by two reviewers independently and cross-checked. The methodological qualities of each included study were evaluated by two reviewers by the Cochrane Reviews Handbook standards.

2.4 Statistical analysis

We use Stata 11.0 (http://www.stata.com; Stata Corporation, College Station, TX) to do all statistical analyses. Dichotomous data was presented as odds ratio (OR) and its corresponding 95% confidence interval (CI). The measurement data was presented as standard mean difference (SMD). Statistical heterogeneity across the studies was evaluated by the chi-square (χ^2) test[6], and inconsistency was calculated by I^2[7]. If significant statistical heterogeneity existed among the studies ($p<0.05$), the random-effects method was used to pool the data. Otherwise, a fixed-effect method was used. The publication bias was evaluated by Egger's line regression tests and Begg's funnel plot [13].

3 Results

3.1 Publication characteristics

Two hundred and eleven publications were initially identified through searching the CNKI and PubMed databases. After reading the title, abstract, and full text, 197 studies were excluded from this meta-analysis for duplicated publication, without appropriate outcome data. or not being a clinically controlled trial. Finally, 14 studies with 992 subjects (512 in the experiment group and 480 in control group) were included in this study (Figure 1). The main characteristics of the included 14 publications [3-5, 8-17] are shown in Table 1.

3.2 Study quality assessment

The methodological quality of the included each study was evaluated by a six-question instrument. The general qualities of 14 studies were relative poor. Nine studies reported the adequate sequence generation. None of the included studies reported the allocation concealment, were free of selective reporting, of free of other bias. Only one study reported blindness. The outcome of methodological quality of the included 14 studies is shown in Figure 2.

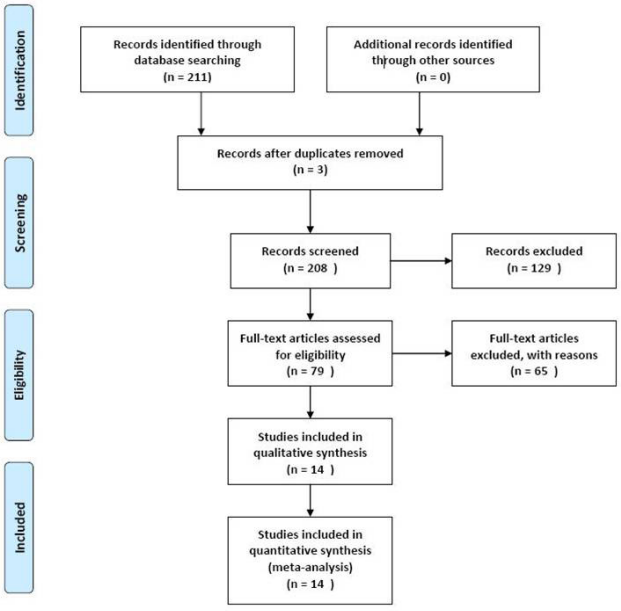

Figure 1: The publication searching flow chart.

3.3 Meta-analysis

3.3.1 Total efficacy

Eight studies reported the total clinical efficacy between the experiment and control groups. No significant statistical heterogeneity was found in total efficacy (I^2=24.9%, p>0.05). Thus, the combined odds ratio (OR) was pooled

Table 1: Main characteristics of the 14 studies

Study	no.		Treatment	Course (month)	Outcome	Urine protein
	Experiment	Control				
Cai 2012[8]	32	29	TG 20mg tid+Valsartan 40-80mg/d	3	(1), (3)	>3.5g
Huang 2010[9]	25	23	TG 20mg tid+ Irbesartan 75-150mg/d	6	(1), (2), (3)	>3.5g
Wang 2012[10]	38	19	TG 20mg tid+Valsartan 160mg/d	6	(1), (3)	>1.0g
Tan 2010[11]	25	23	TG 20mg tid+ Irbesartan 75-150mg/d	6	(1), (2), (3)	>3.5g
Song 2005[12]	35	32	TG1mg/kg/d+ Benazepril 5-10mg/d	6	(1), (3)	>1.0g
Li 2014[13]	26	27	TG1mg/kg/d+ Valsartan 80-160mg/d	3	(1), (3)	>3.5g
Yun 2014[14]	32	29	TG 20mg tid+Valsartan 80-160mg/d	3	(1), (3)	>3.5g
Li 2013[15]	43	43	TG 20mg tid+Valsartan 80mg/d	3	(3)	>0.5g
Li 2013[16]	30	30	TG1mg/kg/d+ Valsartan 100mg/d	3	(1), (2), (3)	>0.5g
Zhao 2011[17]	23	23	TG 20mg tid+Valsartan 160mg/d	1	(1), (3)	>1.5g
Chen 2013[3]	20	20	TG1mg/kg/d+ Benazepril 20mg/d	1	(1), (2)	>1.5g
Pu 2013[4]	98	98	TG 20mg tid+Valsartan 80-160mg/d	1	(1), (2)	>0.5g
Xu 2014[5]	25	25	TG1mg/kg/d+ Benazepril 20mg/d	1	(1), (2), (3)	>1.5g
Chen 2009[18]	60	59	TG1mg/kg/d	6	(1), (3)	>1.5g

(1) 24h urinary protein; (2) clinical efficacy; (3) Serum creatinine

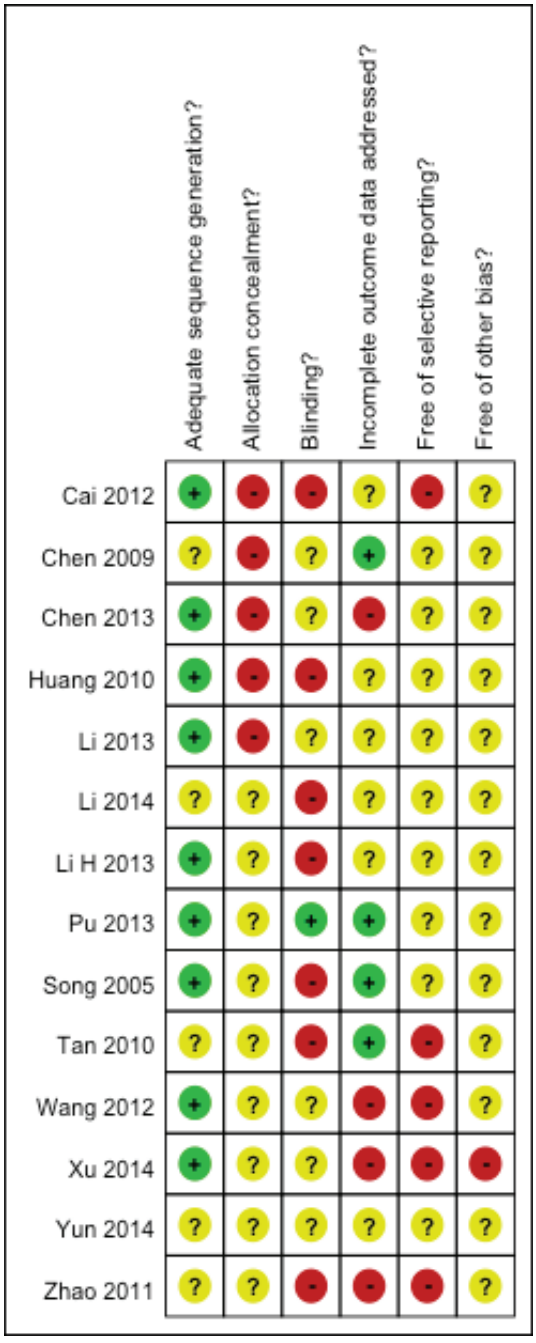

Figure 2: Quality assessment. (The authors' judgments for each risk of bias item. + indicates low risk, - high risk, ? moderate risk.

by a fixed effect model. The pooled OR=4.16 with its 95%CI 2.71~6.37 ($p < 0.05$), which indicated the total efficacy of the experiment group was significant higher than that of the control group ($p < 0.05$), Figure 3.

3.3.2 24h urinary protein

Thirteen studies reported the post-treatment 24h urinary protein quantity. Statistical heterogeneity analysis indicated significant heterogeneity across the studies (I^2=91.1%, $p<0.05$). The data was pooled by a random effect model. The combined standardized mean difference (SMD) was -1.55 with its 95%CI -2.06~1.03, ($p < 0.05$). The results indicated that the 24h urinary protein in the experiment group was significant lower than that of the control group ($p < 0.05$), Figure 4.

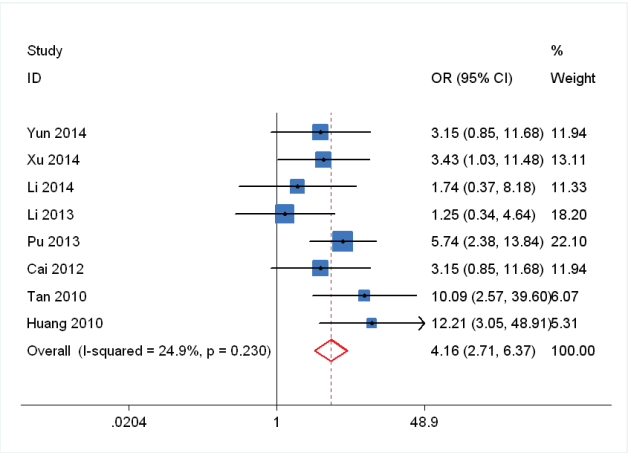

Figure 3: Forest plot of clinical efficacy for tripterygium glycosides in treatment of stage IV diabetic nephropathy. (The squares and horizontal lines demonstrate the study-specific OR and 95% CI. The area of the squares reflects the stud- specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI)

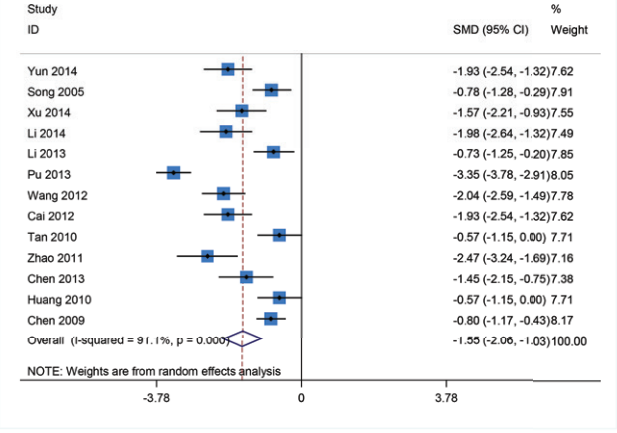

Figure 4: Forest plot of 24h urinary protein for tripterygium glycosides in treatment of stage IV diabetic nephropathy. (The squares and horizontal lines demonstrate the study-specific OR and 95% CI. The area of the squares reflects the study specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI).

3.3.3 Serum creatinine

Ten studies reported the post-treatment serum creatinine. Significant heterogeneity across the studies existed; it was evaluated by chi-square test (I^2=82.3%, p<0.05). Thereafter, the data was pooled by a random effect model. The combined standardized mean difference (SMD) was -0.24 with its 95%CI -0.40~0.09, (p<0.05). The results indicated that after the treatment, serum creatinine in that experiment group was significant lower than that of the control group (p<0.05), Figure 5.

3.4 Toxicity

Eight studies reported tripterygium glycoside-associated toxicity such liver function damage, gastrointestinal reaction, or menstrual disorders. Without statistical heterogeneity among the studies, the data was pooled by a fixed effect model. The pooled OR=6.42 (95%CI: 2.23~18.48, p<0.05). The pooled results showed the tripterygium glycoside-associated toxicity incidence was significant higher than that of the control group (p<0.05), Figure 6.

3.5 Publication bias

Publication bias was evaluated by Begg's funnel plot and Egger's line regression test for each effect size (total efficacy, 24h urinary protein, serum creatinine, and tripterygium glycoside-related toxicity). The Begg's funnel plot for the effect size appears asymmetric at the bottom (Figure 7). However, the Egger's line regression test indicated no publication bias for effect size of total efficacy, 24h urinary protein, and serum creatinine. However, for tripterygium glycoside-related toxicity, the publication bias was significant (t=-3.55, p<0.05).

4 Discussion

Diabetic nephropathy, also known as diabetic kidney disease, is a progressive kidney disease caused by damage to the capillaries in the kidneys' glomeruli [19]. The pathogenesis of diabetic nephropathy includes many factors such as hemodynamics, inflammation, oxidative stress, and immune reactions [20-22]. The clinical symptom of diabetic nephropathy is proteinuria, and renal function gradually decreases. The purposes for treatment for DN were to decrease the progression of kidney damage and control associated complications such as proteinuria, hypoproteinemia, and others. The major treatment modality was angiotensin converting enzyme inhibitor / angiotensin receptor blockers (ARB/ACEI)[23, 24]. This treatment can generally reduce proteinuria and retard the progression of DN. Other factors such as controlling high blood pressure, controlling blood sugar levels, and dietary salt intake are also important for the DN management.

Recently, several prospective clinical studies have discussed the clinical efficacy of tripterygium glycosides in treatment of stage IV diabetic nephropathy. Most of the studies showed that ARB/ACEI combined with tripterygium glycosides can improve clinical efficacy, decrease the 24h urinary protein, and serum creatinine. However,

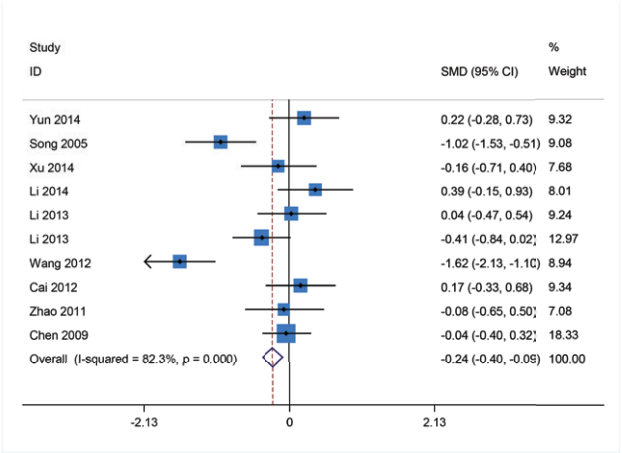

Figure 5: Forest plot of serum creatinine for tripterygium glycosides in treatment of stage IV diabetic nephropathy. (The squares and horizontal lines demonstrate the study-specific OR and 95% CI. The area of the squares reflects the study specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI).

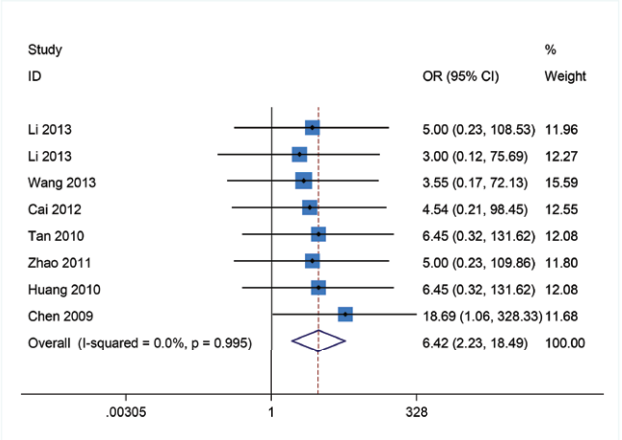

Figure 6: Forest plot of tripterygium glycoside-related toxicity for tripterygium glycosides in treatment of stage IV diabetic nephropathy. (The squares and horizontal lines demonstrate the study-specific OR and 95% CI. The area of the squares reflects the study specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI).

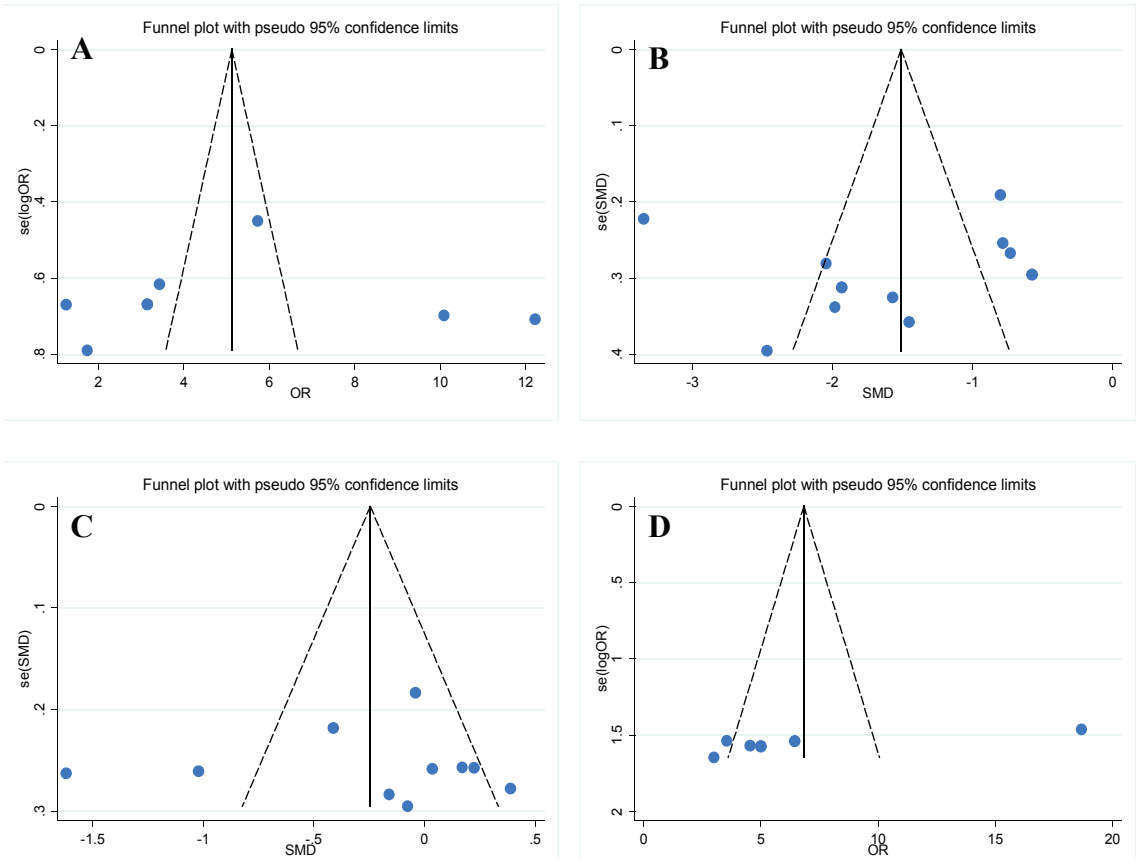

Figure 7: Funnel plot for evaluation the publication bias.(A: total efficacy; B: 24h urinary protein; C: serum creatinine; D: tripterygium glycosides related toxicity)

the indicators of tripterygium glycoside-associated toxicity, such as nausea and vomiting, anorexia, abdominal distension, and bone marrow suppression was also increased. However, because a small number of cases was included in each study, the statistical power was limited. To further investigate the clinical efficacy and safety of tripterygium glycosides in treatment of stage Ⅳ diabetic nephropathy, studies must be performed with larger study groups. In our present meta-analysis, 14 prospective clinical studies including 992 subjects (512 in experiment group and 480 in congrol group) were included. Eight studies reported the total clinical efficacy between experiment and control groups. The pooled results indicated the total efficacy of the experiment group was significant higher than that of the control group ($p<0.05$). This result demonstrated that ARB/ACEI combined with tripterygium glycosides can improve the clinical efficacy by about 4-fold. Thirteen studies reported the post-treatment 24h urinary protein quantity; the combined standardized mean difference (SMD) was -1.55. That result indicated that the after treatment, the 24h urinary protein in the experiment group was significant lower than that of the control group ($p<0.05$), showing that ARB/ACEI combined with tripterygium glycosides can significant decrease the 24h urinary protein compared with ARB/ACEI use alone. Ten studies reported the post-treatment serum creatinine. The results indicated that the after treatment, ARB/ACEI combined with tripterygium glycosides can significantly decrease the serum creatinine compared with ARB/ACEI only ($p<0.05$); Eight studies reported tripterygium glycoside-associated toxicity such as liver function damage, gastrointestinal reaction, and menstrual disorders. The pooled results showed the tripterygium glycoside-associated toxicity incidence was significant higher than that of the control group ($p<0.05$). Thus, the present evidence indicates that tripterygium glycosides combined with ARB/ACEI can improve clinical efficacy, reduce the 24h urinary protein, and serum creatinine as compared with ARB/ACEI treatment only.

Several limitations were also found in this meta-analysis: (1) The general quality of the included studies was poor; (2) Significant statistical heterogeneity existed across the included studies; (3) Only Chinese and English

studies were included in this meta-analysis; (4) Significant publication bias was found in this meta-analysis.

Conflict of interest statement: Authors state no conflict of interest.

References

[1] Tziomalos K, Athyros VG. Diabetic Nephropathy: New Risk Factors and Improvements in Diagnosis. Rev Diabet Stud 2015;12:110-118

[2] Svensson MK, Tyrberg M, Nystrom L, et al. The risk for diabetic nephropathy is low in young adults in a 17-year follow-up from the Diabetes Incidence Study in Sweden (DISS). Older age and higher BMI at diabetes onset can be important risk factors. Diabetes Metab Res Rev 2015;31:138-146

[3] Chen XY. Clinical observation of benazepril combined with tripterygium glycosides in the treatment of diabetic nephropathy. Shaanxi Journal of Traditional Chinese Medicine 2013;34:1016-1017

[4] Pu Y, Zou QM, Pu W. Analysis of the effect of Valsartan combined with tripterygium glycosides in the treatment of diabetic nephropathy. Jilin Medical Journal 2013;34:5789-5791

[5] Xu BX. Clinical analysis of tripterygium glycosides combined with benazepril in the treatment of diabetic nephropathy. Journal of Bethune Military Medical College 2014;12:90-91

[6] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-188

[7] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-560

[8] Cai XP. ARB combined with tripterygium glycosides in the treatment of diabetic nephropathy. Journal of Clinical Medicine in Practice 2012;16:112-114

[9] Huang NC. Clinical study of tripterygium glycosides and irbesartan in the treatment of diabetic nephropathy. Jilin Medical Journal 2010;31:5312-5313

[10] Wang ML. Clinical observation on the effect of valsartan combined with tripterygium glycosides in the treatment of diabetic nephropathy. Chinese Journal of Clinical Rational Drug Use 2012;5:84-85

[11] Tan YS, Wang M. Tripterygium glycosides combined irbesartan in the treatment of diabetic nephropathy. China Healthcare Innovation 2010:32-33

[12] Song HX Gong J, Chen W, et al. Effects of tripterygium glycosides on urinary monocyte chemotaxis protein -1 in diabetic nephropathy patients. Chinese Journal of Integrated Traditional and Western Medicine 2005;5:416-418

[13] Li D. Tripterygium glycosides adjuvant treatment of diabetic nephropathy: reported of 53 cases. Heilongjiang Medical Journal 2014;38:1029-1030

[14] Yu WF. A clincial study of tripterygium glycosides adjuvant treatment of diabetic nephropathy. Nei Mongol Journal of Traditional Chinese Medicine 2014;26:15

[15] Li MR. Clinical study of Tripterygium glycosides combined with valsartan capsule in treatment of diabetic nephropathy. 2013;9:138

[16] Li H. Efficacy and safety of tripterygium glycosides combined with losartan in the treatment of diabetic nephropathy. Chinese Remedies & Clinics 2013;13:649-650

[17] Zhao RY, Tang BS, Shi XL, et al. Clinical effect of tripterygium glycosides combined with observation in the treatment of diabetic nephropathy: reported of 46 cases. Chinese Journal of Integrated Traditional and Western Nephrology 2011;12:811-813

[18] Chen QN. Clinical observation of tripterygium glycosides int treatment of diabetic nephropathy. Chinese Journal of Integrated Traditional and Western Nephrology 2009;10:717-718

[19] Ringholm L, Damm JA, Vestgaard M, et al. Diabetic Nephropathy in Women With Preexisting Diabetes: From Pregnancy Planning to Breastfeeding. Curr Diab Rep 2016;16:12

[20] Marketou NP, AUID- Oho, Chrousos GP, et al. Diabetic Nephropathy in Type 1 Diabetes: A Review of Early Natural History, Pathogenesis and Diagnosis. Diabetes Metab Res Rev 2016

[21] Kume S, Koya D, Uzu T, et al. Role of nutrient-sensing signals in the pathogenesis of diabetic nephropathy. Biomed Res Int 2014;2014:315494

[22] Yamahara K, Yasuda M, Kume S, et al. The role of autophagy in the pathogenesis of diabetic nephropathy. Journal of diabetes research 2013;2013:193757

[23] Abdelhafiz AH, Nahas ME, de Oliveira JM. Management of diabetic nephropathy in older patients: a need for flexible guidelines. Postgrad Med 2014;126:171-177

[24] [24] Chan G, Tang SC. Current practices in the management of diabetic nephropathy. J R Coll Physicians Edinb 2013;43:330-332