Effect of breviscapine injection on clinical parameters in diabetic nephropathy: A meta-analysis of randomized controlled trials

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Abstract. Diabetic nephropathy (DN) is currently a major public health problem worldwide. The objective of the present study was to evaluate the clinical effect of breviscapine injections in patients with DN. A meta-analysis was performed using the following databases to obtain published reports in any language: PubMed/MEDLINE, Embase, China National Knowledge Infrastructure, Chinese Evidence-Based Medicine, Wanfang Digital Periodicals, Chinese Academic Journals Full-text Database, Chinese Biological and Medical Database, China Doctoral and Masters Dissertations Full-text Database and the Chinese Proceedings of Conference Full-text Database. Two assessors independently reviewed each trial. A total of 35 randomized controlled trials, which performed studies on a total of 2,320 patients (1,188 in treatment groups and 1,132 in control groups), were included in the present meta-analysis. Data were analyzed using Stata version 11.0 for Windows. The results from the analysis demonstrated that breviscapine injections have greater therapeutic effects in patients with DN in comparison with the control group, including renal protective effects (reducing urine protein, serum creatinine and blood urea nitrogen) and adjustment for dyslipidemia (affecting levels of cholesterol, triglycerides and high density lipoproteins). These effects indicate that breviscapine injections are beneficial to patients with DN. Further studies are required to determine the mechanisms underlying the therapeutic effects of breviscapine.

Introduction

Diabetic nephropathy (DN) is a progressive disease with an increasing prevalence in developed and developing countries, and has a significant impact on morbidity and mortality from chronic kidney disease (CKD), end-stage renal disease (ESRD) and cardiovascular disease (1-3). Although significant progress has been made in understanding the pathogenesis of DN, the current treatments for diabetic kidney disease only provide partial therapeutic effects; more effective therapies for DN are required (4).

Erigeron breviscapus (Vant.) Hand.-Mazz. is a native plant species of Yunnan, China. Breviscapine, as a purified flavonoid extract from this species, was first isolated by Zhang *et al* (5). Breviscapine primarily contains two flavonoids, namely scutellarin and apigenin-7-O-β-glucoside. Scutellarin accounts for ~90% of the extract; apigenin-7-O-β-glucoside accounts for ~4% (6).

Breviscapine has a broad range of pharmacological effects, including dilation of micro-blood vessels, reduction of blood viscosity and improvement of the microcirculation; it also has an anti-platelet, anti-thrombotic action and can decrease plasma fibrin content and promote fibrinolytic activity (7,8). Since the 1970s, breviscapine injections have been extensively used in China for the treatment of ischemic cardiovascular and cerebrovascular diseases, such as angina pectoris, myocardial infarction and focal cerebral infarction (9,10).

Breviscapine has been demonstrated to possess a number of pharmacological functions in addition to its hemodynamic effects; it has been reported to serve as an anti-oxidative stress agent and a protein kinase C (PKC) inhibitor, and can improve renal function and reduce urinary micro-albuminuria, suggesting that this drug has great therapeutic potential for the treatment of DN (11,12). Although a number of clinical trials have investigated the renal protection provided by breviscapine in DN, uncertainties remain regarding the efficacy of breviscapine. This is primarily a result of the lack of high-quality, large-sample randomized clinical trials. The purpose of the present study was to systematically review randomized control trials (RCTs) and explore the effect of breviscapine in DN.

Materials and methods

Study design. All the RCTs that were identified to investigate the effect of breviscapine on DN were included. There was no restriction on the language or year of publication.

Subject criteria. Each patient included in the analysis fulfilled the definition of diabetic mellitus (13,14). Patients with DN in stages III-IV according to the DN diagnostic criteria of Mogensen *et al* (15) were included in the study. Patients with

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chronic diseases [chronic liver disease, chronic respiratory disease, heart failure, cerebrovascular disease, malignant tumors, serious hypertension, autoimmune disease, acute diabetic complications (for example, diabetic ketoacidosis), hyperglycemic hyperosmolar status], infectious diseases, organ transplants or a recent history of the application of nephrotoxic drugs, were excluded from the study.

Data extraction and appraisal of methodological quality. A standard data extraction method was performed independently by two authors, and the following information from each eligible study was recorded: Study design, participant characteristics [age, gender, history of diabetes mellitus (DM), number of patients in the breviscapine group and the control group], therapeutic intervention [basic treatment including diet control, the control of blood glucose, antihyperlipidemics, antihypertensives, angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB), and treatment duration]. Whether these parameters were comparable between the breviscapine treatment group and the control group was assessed.

An intravenous drip of breviscapine was administered to the patients in the treatment group. The commercial injection fluid (sourced from numerous companies across these studies) was produced from extracted flavonoids of *Erigeron breviscapus* (Vant) Hand.-Mazz., and was manufactured in accordance with the quality standards of the Chinese State Drug Administration. Each patient in the treatment groups received the same type of injection using the same standards; the dosage ranged from 20 to 100 mg/day, and the studies had a treatment duration of between 2 weeks and 1 month.

Therapeutic effect criteria included 24-h urine protein levels, urinary albumin excretion rate, renal function [serum creatinine (SCr) and blood urea nitrogen (BUN) levels], and levels of cholesterol, triglycerides, high density lipoproteins (HDL) and fibrinogen.

Search strategy. A systematic literature search was performed to identify studies concerning the treatment of patients with DN using breviscapine. MEDLINE/PubMed, Embase, the China National Knowledge Infrastructure (CNKI) Database, Chinese Evidence-Based Medicine Database (CEBM), Wanfang Digital Periodicals Database (WFDP), Chinese Journal Full-text Database (CJFD), Chinese Biological and Medical Database (CBM), China Doctoral and Masters Dissertations Full-text Database and the Chinese Proceedings of Conference Full-text Database were searched. Reference lists from the relevant studies were examined to identify further studies and previous reviews of the field. Articles citing the aforementioned studies were examined to identify additional relevant studies.

Assessment methodology. All articles that were identified in the database search were screened by two authors independently, and disagreements were resolved by consensus. Missing data from trials were obtained from the principal investigators of the relevant studies, if possible. The studies were graded for methodological quality according to the Jadad scale (16). A study was considered high quality if graded with ≥3 scores on the Jadad scale.

Statistical analysis. A meta-analysis was conducted using Stata version 11.0 for Windows (StataCorp LP, College Station, TX, USA). The principal measure of effect was the weighted mean difference (WMD) between the breviscapine and control groups, and the standardized mean difference (SMD) was used when analyzing 24-h urine protein as this is a continuous variable with large differences in mean. The confidence interval (CI) was 95%, as the outcome measurements were the same for each analysis. Heterogeneity was assessed using a χ^2 test ($P<0.1$ was considered to indicate a statistically significant difference) and an I^2 test ($I^2>50\%$, significant heterogeneity; $I^2<25\%$, insignificant heterogeneity). Begg's test was used to assess publication bias.

Results

Study characteristics. A total of 126 publications were initially identified; 64 were excluded as they were not relevant to the study question. A total of 62 clinical trials were retrieved for detailed evaluation. Of these, 28 were excluded for the following reasons: No measurement data (n=5), absence of a control group for comparison with the breviscapine group (n=1), patients were at clinical stage V of DN (n=2), supplementing the breviscapine treatment with other, similar drugs (n=11), breviscapine was administered as a control drug (n=5), oral administration (n=1) and duplicate publication (n=2). Thus, 34 studies comprising 34 RCTs were eligible for inclusion in the present analysis (11,17-50) These 34 RCTs are summarized in Tables I-III. A total of 2,260 patients were included (1,158 patients in treatment group and 1,102 patients in the control group). Each study was performed in China and all of the patients involved were Chinese.

24-h urine protein. A total of 25 clinical trials evaluated the 24-h urine protein in patients treated with breviscapine (n=858) and the control group (n=836). Fig. 1 presents a forest plot for the outcome measurements (SMD, -1.42; 95% CI, -1.83 to -1.02). In comparison with the control group, breviscapine significantly reduced 24-h urine protein in patients with DN ($P<0.001$).

Urinary albumin excretion rate. A total of 9 clinical trials evaluated the urinary albumin excretion rate in patients treated with breviscapine (n=291) and the control group (n=264). Fig. 2 presents a forest plot for the outcome measurements (WMD, -23.16; 95% CI, -37.20 to -9.12). In comparison with the control group, breviscapine significantly reduced the urinary albumin excretion rate in patients with DN ($P<0.001$).

SCr expression levels. A total of 21 clinical trials evaluated the expression level of SCr in patients treated with breviscapine (n=711) and the control group (n=689). Fig. 3 presents a forest plot for the outcome measurements (WMD, -12.50; 95% CI, -18.16 to -6.84). In comparison with the control group, breviscapine significantly reduced the expression level of SCr in patients with DN ($P<0.001$).

BUN expression levels. A total of 16 clinical trials evaluated the expression level of BUN in patients treated with breviscapine (n=594) and the control group (n=572). Fig. 4 presents

Table I. Study characteristics: Effect of breviscapine on renal function in patients with DN.

First author, year	Stage of DN	n	Age (years)	History of DM	Intervention (breviscapine)	Treatment duration	Blood urea nitrogen (mmol/l)		Serum creatinine (μmol/l)		Refs.
							Baseline	After intervention	Baseline	After intervention	
Chen, 2007			56.4	12 (y)							(17)
	III	T: 12			T: 100 mg i.v. drip. Qd-b	2 weeks	N	4.4±1.4	N	78±14	
		C: 12			C: -b			4.8±1.5		79±17	
	IV	T: 13			T: 100 mg i.v. drip. Qd-b	2 weeks	N	7.8±2.6	N	120±36	
		C: 13			C: -b			12.3±3.8		149±25	
Yu, 2010	III	T: 34	63.5±4.5	10.0±6.5 (y)	T: 50 mg i.v. drip. Qd-a	4 weeks	N	N	85±18	78±12	(18)
		C: 34	64.0±3.5	10.6±3.5 (y)	C: -a				91±15	85±16	
Wang, 2009	III	T: 20	68 (mean)	8 (y) (mean)	T: 50 mg i.v. drip. Qd-a	2 weeks	N	N	85±18	78±12	(19)
		C: 20	70 (mean)	10 (y) (mean)	C: -a				92±14	86±15	
Huang, 2011	III	T: 18	64 (mean)	8 (y) (mean)	T: 50 mg i.v. drip. Qd-a	4 weeks	N	N	85.0±18.0	78.0±12.0	(20)
		C: 18	66 (mean)	10 (y) (mean)	C: -a				92.1±13.9	86.0±15.0	
Shen, 2011	IV	T: 36	52.3±5.7	N	T: 50 mg i.v. drip. Qd-a	3 weeks	10.12±2.02	6.09±2.52	153.7±35.3	106.9±27.1	(21)
		C: 39	51.9±6.8	N	C: -a		9.35±1.87	6.93±2.65	150.1±39.5	125.2±30.5	
Wu, 2009	IV	T: 36	62±2	5.01±1.85 (y)	T: 50 mg i.v. drip. Qd-a	1 month	11.15±1.32	6.02±1.36	155.32±12.26	70.58±25.25	(22)
		C: 34	61±3	5.32±2.45 (y)	C: -a		12.31±2.54	9.86±1.55	153.25±15.74	132.36±23.21	
Huang, 2004	III	T: 34	66.5±8.4	4.8±2.5 (y)	T: 60 mg i.v. drip. Qd-u	3 weeks	5.48±1.26	5.46±1.35	85.59±20.12	84.34±19.89	(23)
		C: 28	65.3±6.5	4.58±2.10 (y)	C: -u		5.32±1.34	5.45±1.43	79.38±19.78	81.45±21.45	
Li, 2006	III-IV	T: 40	48-77 (mean 54.5)	4-18 (m)	T: 50 mg i.v. drip. Qd-a	4 weeks	12.06±1.84	5.28±1.57	218.63±18.84	132.53±17.32	(24)
		C: 36	50-75 (mean 53.5)	5-17 (m)	C: -a		11.63±2.25	9.04±1.35	218.54±19.20	180.60±20.1	
Fang, 2011	III	T: 58	43.76±11.92	2.36±0.97 (y)	T: 30 mg i.v. drip. Qd-a	3 weeks	13.45±3.02	7.76±1.69	139.41±10.13	117.05±6.94	(25)
		C: 58	42.67±10.42	2.69±1.05 (y)	C: -a		13.34±2.98	9.27±2.16	137.35±9.79	126.72±8.35	
Qiao, 2009			62.25±8.90	N							(26)
	IV	T: 52			T: 40 mg i.v. drip. Qd-a	4 weeks	16.1±10.1	10.2±9.0	310.9±156.4	220.1±66.4	
		C: 40			C: -a		14.7±9.2	11.5±9.3	289.1±123.1	210.2±49.8	
Zhong, 2011			41-65 (mean 54)	3-8 (y)							(27)
	III	T: 30			T: 30 mg i.v. drip. Qd-a	3 weeks	7.31±1.58	5.48±0.87	94.52±10.31	92.45±9.86	
		C: 29			C: -a		7.01±1.32	6.89±1.19	96.22±11.08	96.79±9.83	
Liu, 2011	III	T: 34	58.7±9.1	8.6±5.7 (y)	T: 50 mg i.v. drip. Qd-u	15 days	8.48±1.32	8.43±1.28	91.63±15.82	88.47±16.21	(28)
		C: 34	59.3±8.3	8.4±6.1 (y)	C: -u		8.39±1.29	8.41±1.33	89.85±14.78	90.45±15.58	
Xu, 2008	III-IV	T: 36	42-79	N	T: 100 mg i.v. drip. Qd-b	4 weeks	12.36±2.84	6.09±2.50	253.25±87.20	102.53±77.19	(29)
		C: 40	41-76	N	C: -b		11.04±1.62	9.96±1.55	239.40±101.17	196.68±88.24	
Wu, 2011	III	T: 30	58.3±7.4	7.1±4.5 (y)	T: 40 mg i.v. drip. Qd-a	2 weeks	4.98±1.76	5.01±1.64	75.64±15.23	73.68±12.45	(30)
		C: 30	55.9±8.1	6.8±5.1 (y)	C: -a		5.11±0.98	5.07±0.86	74.47±14.86	73.48±13.12	
Liu, 2007	III	T: 23	66±5	10±5 (y)	T: 50 mg i.v. drip. Qd-a	4 weeks	N	N	101.00±25.10	94.73±19.78	(31)
		C: 22	66±6	10±5 (y)	C: -a				85.00±18.50	78.00±11.53	

Table I. Continued.

First author, year	Stage of DN	n	Age (years)	History of DM	Intervention (breviscapine)	Treatment duration	Blood urea nitrogen (mmol/l)		Serum creatinine (μmol/l)		Refs.
							Baseline	After intervention	Baseline	After intervention	
Liu, 2007			66±5	10±4 (y)							(32)
	III	T: 22			T: 50 mg i.v. drip. Qd-a	2 weeks	N	N	85.0±18.5	78.0±11.5	
		C: 23			C: -a				91.6±13.8	85.6±15.4	
Jiang, 2010	III	T: 42	54.12±8.56	N	T: 40 mg i.v. drip. Qd-a	4 weeks	5.31±1.12	5.45±1.05	69.04±12.35	67.24±8.14	(33)
		C: 38	58.15±7.25	N	C: -a		5.35±1.21	5.26±0.95	69.25±9.20	68.15±10.15	
Zhang, 2006	III	T: 40	60±3	9.1±4.8 (y)	T: 20 mg i.v. drip. Qd-a	4 weeks	12.22±5.14	7.51±2.69	153.31±46.67	104.47±30.43	(34)
		C: 40	61±3	9.3±5.4 (y)	C: -a		12.32±5.26	8.54±3.26	152.24±50.14	123.78±35.67	
Qiao, 2010			66±3	9±3 (y)							(35)
	III	T: 30	49-72	6-21 (y)	T: 40 mg i.v. drip. Qd-a	1 month	16.3±2.8	10.0±0.9	121.03±24.90	72.82±11.48	
		C: 30	50-78	5-23 (y)	C: -a		15.9±3.1	12.5±2.8	123.02±18.40	87.02±12.83	
Lan, 2008			30-76 (mean 57.3)	5-28 (mean 1.9) (y)							(36)
	III	T: 13			T: 100 mg i.v. drip. Qd-b	2 weeks	N	4.1±1.2	N	75±13	
		C: 13			C: -b			4.6±1.5		78±14	
	IV	T: 15			T: 100 mg i.v. drip. Qd-b	2 weeks	N	7.6±2.3	N	122±36	
		C: 15			C: -b			12.0±3.5		150±25	
Huang, 2012			69.62±4.28	N							(37)
	III	T: 21			T: 100 mg i.v. drip. Qd-a	15 days	N	4.2±1.3	N	76±12	
		C: 21			C: -a			4.7±1.4		79±13	
	IV	T: 22			T: 100 mg i.v. drip. Qd-a	15 days	N	7.5±2.2	N	121±35	
		C: 22			C: -a			7.7±3.2		151±30	

n, patient number enrolled; DN, diabetic nephropathy; T, breviscapine treatment group; C, control group; DM, diabetes mellitus; y, year; m, month; N, not mentioned; a, ACEI and/or ARB used; b, ACEI or ARB not mentioned; u, ACEI or ARB not used; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Qd, once per day; i.v., intravenous.

Table II. Study characteristics: Effect of breviscapine on urine protein in patients with DN.

First author, year	Stage of DN	n	Age (year)	History of DM	Intervention (breviscapine)	Treatment duration	24-h urine protein (g)		Urine albumin excretion rate (μg/min)		Refs.
							Baseline	After intervention	Baseline	After intervention	
Chen, 2007			56.4	12 (y)							(17)
	III	T: 12			T: 100 mg i.v. drip. Qd-b	2 weeks	N	0.12±0.02	N	N	
		C: 12			C: -b			0.18±0.05			
	IV	T: 13			T: 100 mg i.v. drip. Qd-b	2 weeks	N	1.06±0.64	N	N	
		C: 13			C: -b			1.36±0.70			
Yu, 2010	III	T: 34	63.5±4.5	10.0±6.5 (y)	T: 50 mg i.v. drip. Qd-a	4 weeks	0.208±0.056	0.125±0.056	91.30±21.7	73.10±17.5	(18)
		C: 34	64.0±3.5	10.6±3.5 (y)	C: -a		0.216±0.055	0.175±0.055	119.2±24.5	87.80±22.3	
Wang, 2009	III	T: 20	68 (mean)	8 (y) (mean)	T: 50 mg i.v. drip. Qd-a	2 weeks	0.210±0.054	0.123±0.058	N	N	(19)
		C: 20	70 (mean)	10 (y) (mean)	C: -a		0.218±0.057	0.175±0.055			
Huang, 2011	III	T: 18	64 (mean)	8 (y) (mean)	T: 50 mg i.v. drip. Qd-a	4 weeks	N	N	140.0±36.0	82.0±38.7	(20)
		C: 18	66 (mean)	10 (y) (mean)	C: -a				145.3±38.0	116.7±36.7	
Shen, 2011	IV	T: 36	52.3±5.7	N	T: 50 mg i.v. drip. Qd-a	3 weeks	N	N	322.3±93.6	208.5±101.1	(21)
		C: 39	51.9±6.8		C: -a				306.5±78.3	253.9±85.7	
Wu, 2009	IV	T: 36	62±2	5.01±1.85 (y)	T: 50 mg i.v. drip. Qd-a	1 month	1.75±0.48	0.89±0.56	N	N	(22)
		C: 34	61±3	5.32±2.45 (y)	C: -a		1.89±0.56	1.15±0.36			
Huang, 2004	III	T: 34	66.5±8.4	4.8±2.5 (y)	T: 60 mg i.v. drip. Qd-u	3 weeks	0.146±0.040	0.066±0.050			(23)
		C: 28	65.3±6.5	4.58±2.1 (y)	C: -u		0.143±0.043	0.096±0.054			
Fang, 2011	III	T: 58	43.76±11.92	2.36±0.97 (y)	T: 30 mg i.v. drip. Qd-a	3 weeks	0.512±0.041	0.142±0.018	N	N	(25)
		C: 58	42.67±10.42	2.69±1.05 (y)	C: -a		0.505±0.039	0.315±0.026			
Qiao, 2009			62.25±8.9	N							(26)
	IV	T: 52			T: 40 mg i.v. drip. Qd-a	4 weeks	1.95±0.35	1.08±0.20	N	N	
		C: 40			C: -a		1.87±0.42	1.49±0.30			
Zhong, 2011			41-65 (mean 54)	3-8 (y)							(27)
	III	T: 30			T: 30 mg i.v. drip. Qd-a	3 weeks	0.151±0.051	0.092±0.027	N	N	
		C: 29			C: -a		0.149±0.048	0.124±0.037			
Zhai, 2000			37-72	5-20 (y)							(38)
	III-IV	T: 52			T: 100 mg i.v. drip. Qd-a	4 weeks	0.253±0.087	0.102±0.053	N	N	
		C: 52			C: -a		0.239±0.101	0.196±0.088			
Wang, 2011	III	T: 18	N	N	T: 40 mg i.v. drip. Qd-b	20 days	0.198±0.027	0.124±0.022	N	N	(39)
		C: 18			C: -b		0.198±0.028	0.198±0.023			
Qian, 2011			37.5±65.8	6.7 (y) (mean)							(40)
	III	T: 30			T: 60 mg i.v. drip. Qd-u	2 weeks	0.165±0.022	0.077±0.043	N	N	
		C: 30			C: -u		0.160±0.021	0.104±0.043			
Li, 2010	III	T: 30	62.8±5	7.6±2 (y)	T: 60 mg i.v. drip. Qd-a	15 days	N	N	56.43±42.86	22.13±15.89	(41)
		C: 28	61.5±5	7.2±2 (y)	C: -a				55.87±43.72	37.93±28.56	

Table II. Continued.

First author, year	Stage of DN	n	Age (year)	History of DM	Intervention (breviscapine)	Treatment duration	24-h urine protein (g)		Urine albumin excretion rate (μg/min)		Refs.
							Baseline	After intervention	Baseline	After intervention	
Liu, 2011	III	T: 34	58.7±9.1	8.6±5.7 (y)	T: 50 mg i.v. drip. Qd-u	15 days	0.155±0.020	0.075±0.041	N	N	(28)
		C: 34	59.3±8.3	8.4±6.1 (y)	C: -u		0.158±0.019	0.102±0.041			
Xu, 2008	III-IV	T: 36	42-79	N	T: 100 mg i.v. drip. Qd-b	4 weeks	3.13±0.51	2.04±0.43	N	N	(29)
		C: 40	41-76		C: -b		3.07±0.48	2.76±0.62			
Wu, 2011	III	T: 30	58.3±7.4	7.1±4.5 (y)	T: 40 mg i.v. drip. Qd-a	2 weeks	0.185±0.062	0.081±0.031	N	N	(30)
		C: 30	55.9±8.1	6.8±5.1 (y)	C: -a		0.181±0.071	0.102±0.048			
Liu, 2007	III	T: 23	66±5	10±5 (y)	T: 50 mg i.v. drip. Qd-a	4 weeks	0.85±0.38	0.25±0.27	83.19±38.98	56.63±33.64	(31)
		C: 22	66±6	10±5 (y)	C: -a		0.61±0.30	0.41±0.18	66.39±42.87	52.56±36.73	
Liu, 2007			66±5	10±4 (y)							(32)
	III	T: 22			T: 50 mg i.v. drip. Qd-a	2 weeks	N	N	95.4±52.6	43.5±23.4	
		C: 23			C: -a				94.1±54.2	88.5±36.7	
Jiang, 2010	III	T: 42	54.12±8.56	N	T: 40 mg i.v. drip. Qd-a	4 weeks	0.172±0.051	0.084±0.029	N	N	(33)
		C: 38	58.15±7.25		C: -a		0.175±0.073	0.098±0.056			
Zhang, 2006	III	T: 40	60±3	9.1±4.8 (y)	T: 20 mg i.v. drip. Qd-a	4 weeks	0.376±0.020	0.104±0.013	N	N	(34)
		C: 40	61±3	9.3±5.4 (y)	C: -a		0.377±0.020	0.182±0.013			
Qiao, 2010	III	T: 30	49-72	6-21 (y)	T: 40 mg i.v. drip. Qd-a	1 month	0.85±0.34	0.26±0.25	82.21±37.82	42.51±32.81	(35)
		C: 30	50-78	5-23 (y)	C: -a		0.60±0.31	0.41±0.09	85.36±42.45	54.54±35.68	
Lan, 2008			30-76 (mean 57.3)	5-28 (mean 1.9) (y)							(36)
	III	T: 13			T: 100 mg i.v. drip. Qd-b	2 weeks	N	0.13±0.03	N	N	
		C: 13			C: -b			0.17±0.04			
Wang, 2005	III	T: 32	56.43±17.13	N	T: 100 mg i.v. drip. Qd-a	15 days	2.93±0.62	2.07±0.49	N	N	(42)
		C: 32	61.58±15.36		C: -a		2.87±0.52	2.73±0.62			
Li, 2011	III	T: 50	41-72 (mean 52.5)	4-11 (mean 8.2) (y)	T: 60 mg i.v. drip. Qd-u	15 days	N	N	85.95±14.22	69.36±13.41	(43)
		C: 50	40-72 (mean 51.8)	4-10 (mean 7.8) (y)	C: -u				86.14±14.07	78.48±15.13	
Zhao, 2012	III	T: 30	45-70	6-30 (y)	T: 50 mg i.v. drip. Qd-u	4 weeks	2.54±1.48	1.27±0.98	N	N	(44)
		C: 30	46-71	5-32 (y)	C: -u		2.14±1.56	2.08±1.47			
Liu, 2008	III	T: 53	57.5±3.6	8.6±5.7 (y)	T: 40 mg i.v. drip. Qd-u	15 days	0.169±0.058	0.078±0.041	N	N	(45)
		C: 53	56.5±3.8	8.4±5.8 (y)	C: -u		0.168±0.059	0.166±0.058			
Liu, 2003	III-IV	T: 24	46.0±6.6	6.5±4.4 (y)	T: 100 mg i.v. drip. Qd-b	1 month	1.99±1.46	1.55±1.38	N	N	(46)
		C: 24	46.2±6.8	6.2±4.8 (y)	C: -b		2.03±1.34	1.66±1.42			
Yuan. 2005	III	T: 24	N	N	T: 40 mg i.v. drip. Qd-b	30 days	0.198±0.027	0.123±0.022	N	N	(47)
		C: 24			C: -b		0.198±0.029	0.197±0.023			

Table II. Continued.

First author, year	Stage of DN	n	Age (year)	History of DM	Intervention (breviscapine)	Treatment duration	24-h urine protein (g)		Urine albumin excretion rate (μg/min)		Refs.
							Baseline	After intervention	Baseline	After intervention	
	IV	T: 15 C: 15			T: 100 mg i.v. drip. Qd-b C: -b	2 weeks	N	1.09±0.68 1.32±0.70	N	N	
Kang, 2003	III	T: 48 C: 20	61.5±14.6 62.3±11.5	18.7±12.8 (y) 18.2±11.6 (y)	T: 100 mg i.v. drip. Qd-b C: -b	2 weeks	N	N	89.92±11.62 91.08±10.76	43.13±7.18 89.56±12.37	(11)
Huang, 2012			69.62±4.28	N							(37)
	III	T: 21 C: 21			T: 100 mg i.v. drip. Qd-a C: -a	15 days	N	0.13±0.02 0.18±0.02	N	N	
	IV	T: 22 C: 22			T: 100 mg i.v. drip. Qd-a C: -a	15 days	N	1.08±0.67 1.31±0.69	N	N	

n, patient number enrolled; DN, diabetic nephropathy; T, breviscapine treatment group; C, control group; DM, diabetes mellitus; y, year; m, month; N, not mentioned; a, ACEI and/or ARB used; b, ACEI or ARB not mentioned; u, ACEI or ARB not used; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Qd, once per day; i.v., intravenous.

a forest plot for the outcome measurements (WMD, -1.52; 95% CI, -2.25 to -0.78). In comparison with the control group, breviscapine significantly reduced the expression level of BUN in patients with DN (P<0.001).

Cholesterol expression levels. A total of 12 clinical trials evaluated the expression level of cholesterol in patients treated with breviscapine (n=394) and the control group (n=351). Fig. 5 presents a forest plot for the outcome measurements (WMD, -0.67; 95% CI, -1.12 to -0.22). In comparison with the control group, breviscapine significantly reduced the expression level of cholesterol in patients with DN (P<0.001).

Triglyceride expression levels. A total of 15 clinical trials evaluated the expression level of triglycerides in patients treated with breviscapine (n=472) and the control group (n=428). Fig. 6 presents a forest plot for the outcome measurements (WMD, -0.52; 95% CI, -0.72 to -0.33). In comparison with the control group, breviscapine significantly reduced the expression level of triglycerides in patients with DN (P<0.001).

HDL expression levels. A total of 5 clinical trials evaluated the expression level of HDL in patients treated with breviscapine (n=172) and the control group (n=132). Fig. 7 presents a forest plot for the outcome measurements (WMD, 1.57; 95% CI, 0.47 to 2.67). In comparison with the control group, breviscapine significantly increased the expression level of high density lipoproteins in patients with DN (P<0.001).

Fibrinogen expression levels. A total of 9 clinical trials evaluated the expression level of fibrinogen in patients treated with breviscapine (n=296) and the control group (n=261). Fig. 8 presents a forest plot for the outcome measurements (WMD, -1.25; 95% CI, -1.56 to -0.93). In comparison with the control group, breviscapine significantly reduced the expression level of fibrinogen in patients with DN (P<0.001).

Adverse effects. No systematic review on adverse effects was conducted as reporting of side effects was lacking in the clinical trials in this meta-analysis.

Publication bias assessment. The Begg's test determined that bias assessment was not significant in any of the RCTs analyzed (P>0.1).

Discussion

The prevalence of DM has markedly increased in recent years and is projected to affect 4.4% of the world's population by 2030 (51). DN is considered to be the most devastating complication associated with diabetes, with respect to a patients' quality of life and chances of survival (52). Current treatments are not adequate, and as the burden of DN continues to increase worldwide there is a requirement for the development of novel treatments (53).

Oxidative stress caused by increased free radical production is understood to serve a central role in the development of DN (54). The abnormal metabolism of glucose or free fatty acids via mitochondria pathways, and the activation of nicotinamide adenine dinucleotide phosphate oxidases

Table III. Study characteristics: Effect of breviscapine on blood fat and fibrinogen in patients with DN.

First author, year	Stage of DN	n	Age (years)	History of DM (years)	Intervention (breviscapine)	Treatment duration	Cholesterol (mmol/l)		Triglyceride (mmol/l)		HDL		Fg (g/l)		Refs.
							Baseline	After intervention	Baseline	After intervention	Baseline	After intervention	Baseline	After intervention	
Wang, 2009	III	T: 20	68 (mean)	8 (mean)	T: 50 mg i.v.drip. Qd-a,x	2 weeks	5.8±0.9	5.8±0.7	1.9±0.8	1.9±0.7	N	N	N	N	(19)
		C: 20	70 (mean)	10 (mean)	C: -a,x		5.9±0.8	5.9±0.8	1.9±0.7	1.9±0.7					
Huang, 2011	III	T: 18	64 (mean)	8 (mean)	T: 50 mg i.v.drip. Qd-a,x	4 weeks	5.8±0.9	5.8±0.7	1.9±0.8	1.9±0.7	N	N	N	N	(20)
		C: 18	66 (mean)	10 (mean)	C: -a,x		5.9±0.8	5.9±0.8	1.9±0.7	1.9±0.7					
Wu, 2009	IV	T: 36	62±2	5.01±1.8	T: 50 mg i.v.drip. Qd-a,x	1 month	6.36±0.33	4.21±0.42	3.85±0.26	2.21±0.39	N	N	5.48±0.35	4.01±0.38	(22)
		C: 34	61±3	5.32±2.45	C: -a,x		6.48±0.26	5.95±0.31	3.65±0.41	3.35±0.31			5.35±0.36	5.15±0.28	
Huang, 2004	III	T: 34	66.5±8.4	4.8±2.5	T: 60 mg i.v.drip. Qd-u,x	3 weeks	5.59±1.34	3.87±1.46	2.25±0.97	1.56±0.78	N	N	N	N	(23)
		C: 28	65.3±6.5	4.58±2.1	C: -u,x		5.79±1.56	3.99±1.65	2.19±0.89	1.67±0.67					
Qiao, 2009	IV	T: 52	62.25±8.9	N	T: 40 mg i.v.drip. Qd-a,w	4 weeks	4.95±0.90	4.41±0.52	1.70±0.80	1.60±0.56	0.93±0.17	1.24±0.35	N	N	(26)
		C: 40			C: -a,w		4.80±0.89	4.76±0.81	1.76±0.62	1.78±0.61	0.96±0.15	0.98±0.18			
Zhong, 2011	III	T: 30	41-65 (mean 54)	3-8	T: 30 mg i.v.drip. Qd-a,x	3 weeks	N	N	2.86±0.45	1.84±0.29	N	N	5.99±0.75	3.83±0.53	(27)
		C: 29			C: -a,x				2.73±0.35	2.25±0.27			5.86±0.75	4.62±0.31	
Wang, 2011	III	T: 18	N	N	T: 40 mg i.v.drip. Qd-b,x	20 days	N	N	2.90±0.31	1.74±0.16	1.26±0.12	4.52±0.08	N	N	(39)
		C: 18			C: -b,x				2.91±0.29	2.71±0.21	1.25±0.14	2.41±0.06			
Qian, 2011	III	T: 30	37.5±65.8	6.7 (mean)	T: 60 mg i.v.drip. Qd-u,x	2 weeks	N	N	2.80±0.31	1.93±0.33	1.45±0.43	4.85±0.49	N	N	(40)
		C: 30			C: -u,x				3.70±1.09	2.99±0.40	1.74±0.45	2.50±0.29			
Huang, 2006	IV	T: 22	18-76 (mean 56.8)	N	T: 40 mg i.v.drip. Qd-b,x	2 weeks	N	N	N	N	N	N	5.30±1.73	2.84±1.64	(49)
		C: 22	20-74 (mean 55.4)		C: -b,x								5.45±1.52	4.05±1.43	
Li, 2011	III	T: 50	41-72 (mean 52.5)	4-11 (mean 8.2)	T: 60 mg i.v.drip. Qd-u,w	15 days	5.24±0.98	5.13±0.94	2.18±0.89	1.94±0.92	N	N	N	N	(43)
		C: 50	40-72 (mean 51.8)	4-10 (mean 7.8)	C: -u,w		5.28±0.96	5.25±0.93	2.16±0.86	2.14±0.94					
Liu, 2003	III-IV	T: 24	46±6.6	6.5±4.4	T: 100 mg i.v.drip. Qd-b,x	1 month	9.33±3.22	4.12±1.45	2.69±1.53	2.06±1.61	N	N	5.18±0.61	3.13±1.03	(46)
		C: 24	46.2±6.8	6.2±4.8	C: -b,x		9.29±3.19	5.38±1.36	2.78±1.69	2.14±1.55			5.24±1.67	5.35±1.06	
Guo, 2008	IV	T: 34	54.2	9.8	T: 50 mg i.v.drip. Qd-a,x	20 days	N	N	N	N	N	N	5.40±0.95	4.00±0.44	(48)
		C: 30			C: -a,x								5.20±1.65	5.10±0.85	

Table III. Continued.

First author, year	Stage of DN	n	Age (year)	History of DM (years)	Intervention (breviscapine)	Treatment duration	Cholesterol (mmol/l)		Triglyceride (mmol/l)		HDL		Fg (g/l)		Refs.
							Baseline	After intervention	Baseline	After intervention	Baseline	After intervention	Baseline	After intervention	
Kang, 2003	III	T: 48	61.5±14.6	18.7±12.8	T: 100 mg i.v.drip. Qd-b,x	2 weeks	7.12±0.46	6.48±0.21	2.50±0.27	1.79±0.24	0.86±0.15	1.08±0.17	3.75±0.62	2.81±0.57	(11)
		C: 20	62.3±11.5	18.2±11.6	C: -b,x		7.08±0.42	6.98±0.40	2.51±0.26	2.47±0.28	0.89±0.13	0.90±0.12	3.64±0.82	3.71±0.48	
Xu, 2008	III-IV	T: 36	42-79	N	T: 100 mg i.v.drip. Qd-b,x	4 weeks	5.20±0.76	3.05±0.72	2.69±1.53	1.36±1.61	N	N	5.18±0.61	3.13±1.03	(29)
		C: 40	41-76		C: -b,x		5.18±0.73	4.98±0.68	2.78±1.61	2.64±1.55			5.35±1.67	5.24±1.06	
Liu, 2007	III	T: 22	66±5	10±4	T: 50 mg i.v.drip. Qd-a,x	2 weeks	5.79±0.88	5.85±0.74	1.94±0.83	1.90±0.72	N	N	N	N	(31)
		C: 23			C: -a,x		5.91±0.81	5.86±0.81	1.90±0.66	1.89±0.69					
Jiang, 2010	III	T: 42	54.12±8.56	N	T: 40 mg i.v.drip. Qd-a,x	4 weeks	N	N	N	N	N	N	4.72±2.01	2.53±1.65	(33)
		C: 38	58.15±7.25		C: -a,x								4.69±1.52	4.32±1.29	
Qiao, 2010	III	T: 30	66±3	9±3	T: 40 mg i.v.drip. Qd-a,y	1 month	4.93±0.81	4.29±0.50	1.73±0.71	1.40±0.40	N	N	N	N	(35)
		C: 30	49-72	6-21	C: -a,y		4.80±0.29	4.78±0.80	1.75±0.18	1.73±0.60					
Yuan, 2005	III	T: 24	50-78	5-23	T: 40 mg i.v. drip. Qd-b,x	30 days	8.17±1.04	6.49±1.30	2.89±0.33	1.75±0.15	1.25±0.13	4.95±0.09	3.96±0.08	3.28±0.02	(47)
		C: 24	N	N	C: -b,x		8.19±1.00	7.81±1.23	2.90±0.29	2.69±0.20	1.24±0.15	2.00±0.07	3.97±0.08	3.88±0.05	

n, patient number enrolled; DN, diabetic nephropathy; T, breviscapine treatment group; C, control group; DM, diabetes mellitus; y, year; m, month; N, not mentioned; a, ACEI and/or ARB used; b, ACEI or ARB not mentioned; u, ACEI or ARB not used; w, antihyperlipidemics used; x, antihyperlipidemics not mentioned; z, antihyperlipidemics not used; HDL, high density lipoproteins; Fg, fibrinogen; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Qd, once per day; i.v., intravenous.

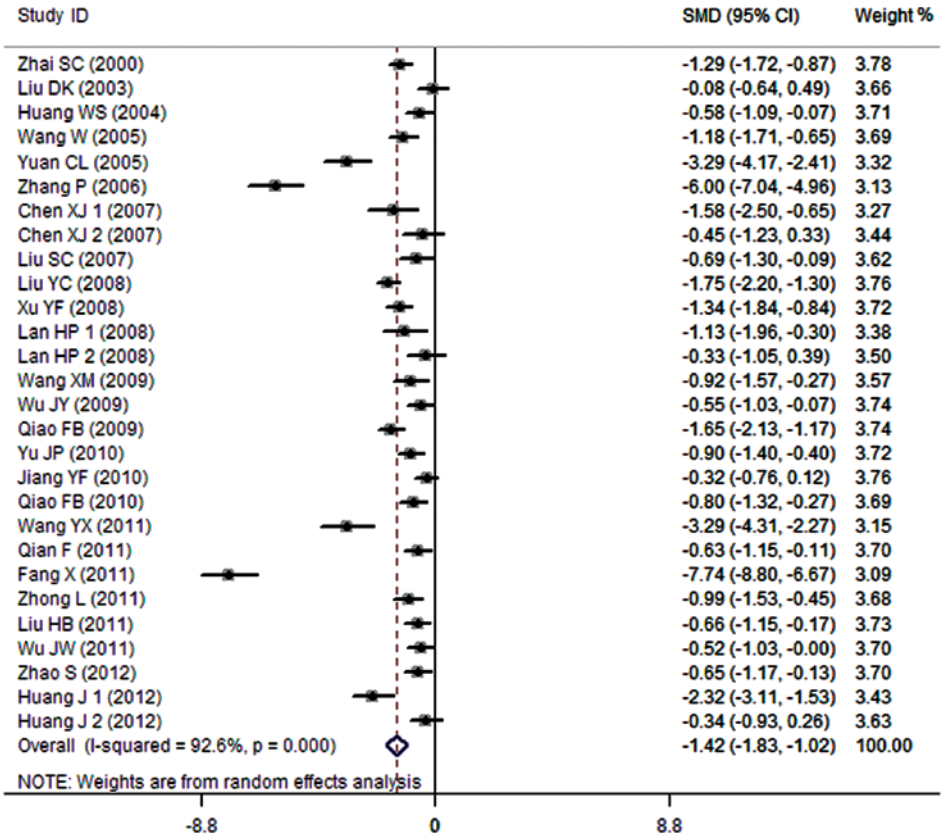

Figure 1. Effect of breviscapine on 24-h urine protein in patients with diabetic nephropathy. ID, identification; SMD, standardized mean difference; CI, confidence interval.

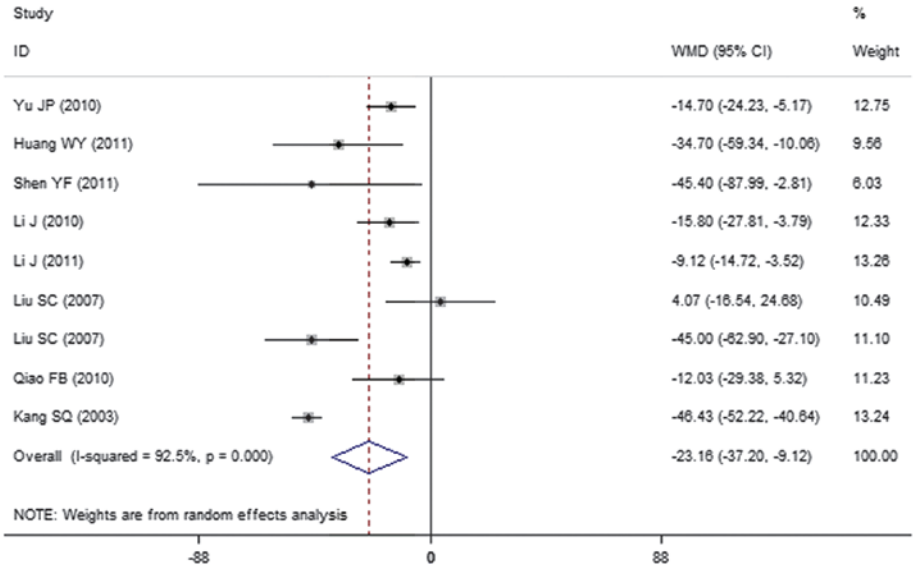

Figure 2. Effect of breviscapine on urine albumin excretion rate in patients with diabetic nephropathy. ID, identification; WMD, weighted mean difference; CI, confidence interval.

via PKC have been recognized as contributors towards the production of oxidants (55). Breviscapine possesses a variety of pharmacological functions other than hemodynamic effects, and can serve as an anti-oxidative stress agent and inhibitor of PKC (56,57). In addition, Zhao *et al* (58) and Wagener *et al* (59) observed in diabetic rat models that breviscapine can inhibit podocyte apoptosis by modulating the expression of B-cell lymphoma 2 (Bcl-2) and Bcl-2-Associated X Protein genes.

The present meta-analysis quantitatively evaluated the clinical effect of breviscapine in the treatment of patients with DN by integrating the outcomes of 35 RCTs that studied the effects of breviscapine on 1,188 patients with DN and 1,132 control subjects. The results demonstrated that the expression levels of

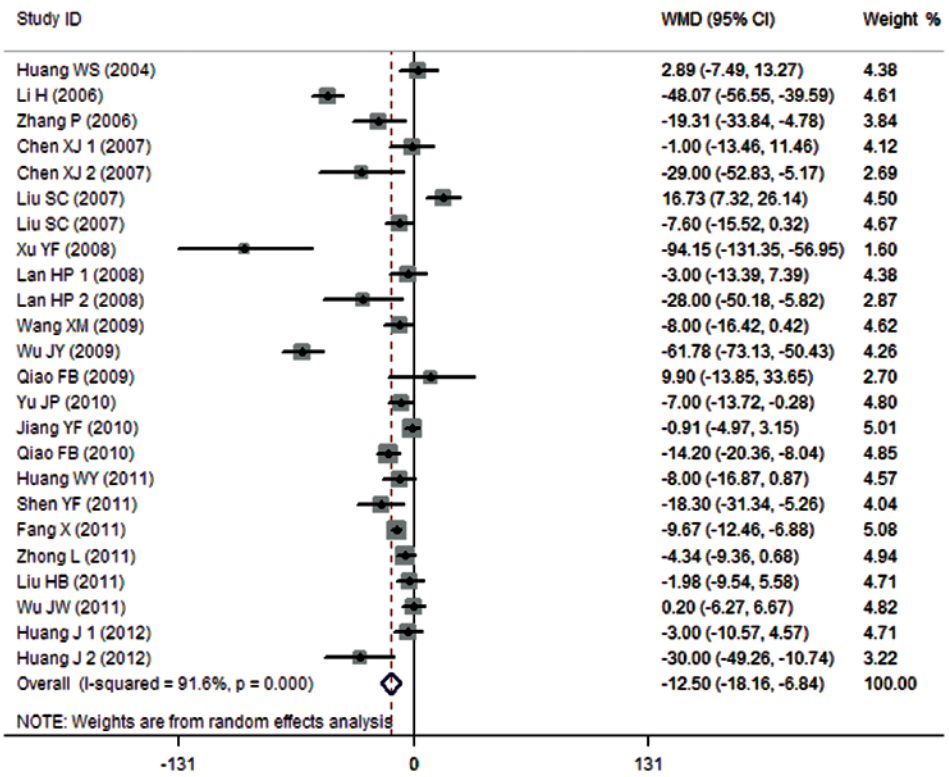

Figure 3. Effect of breviscapine on serum creatinine in patients with diabetic nephropathy. ID, identification; WMD, weighted mean difference; CI, confidence interval.

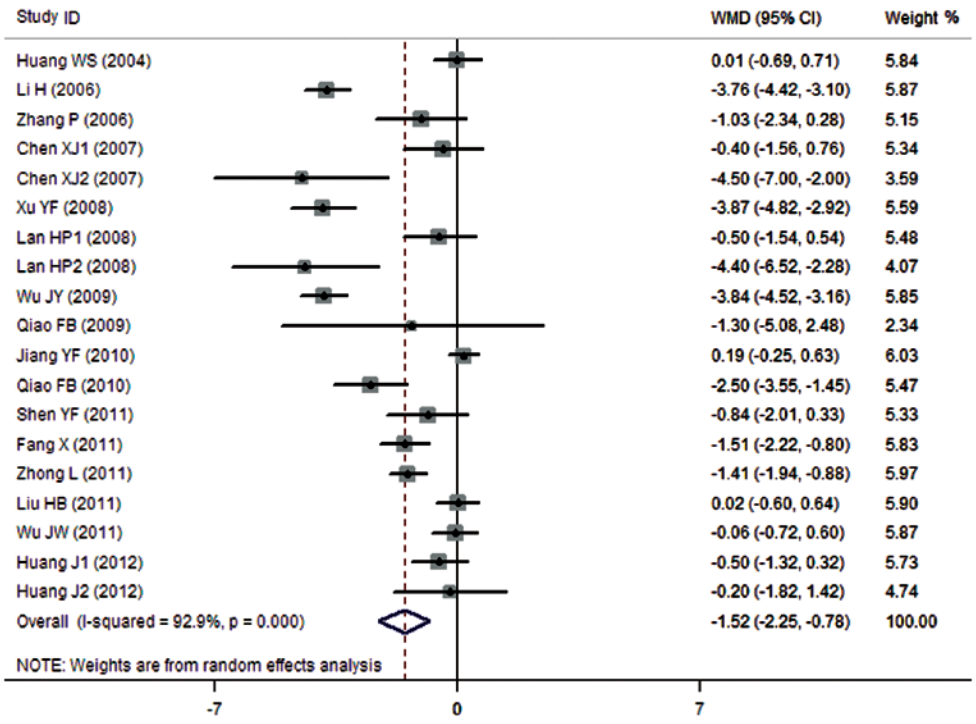

Figure 4. Effect of breviscapine on blood urea nitrogen in patients with diabetic nephropathy. ID, identification; WMD, weighted mean difference; CI, confidence interval.

SCr and BUN were significantly lower in patients treated with breviscapine in comparison with control subjects, suggesting that the drug serves a protective role in the renal system of patients with DN.

Microalbuminuria is regarded as the earliest clinical sign of DN. It is defined as a urinary albumin excretion rate ranging from 30-300 mg/day, and the definitive measurement is based on a timed urine collection during a 24-h period (60). The

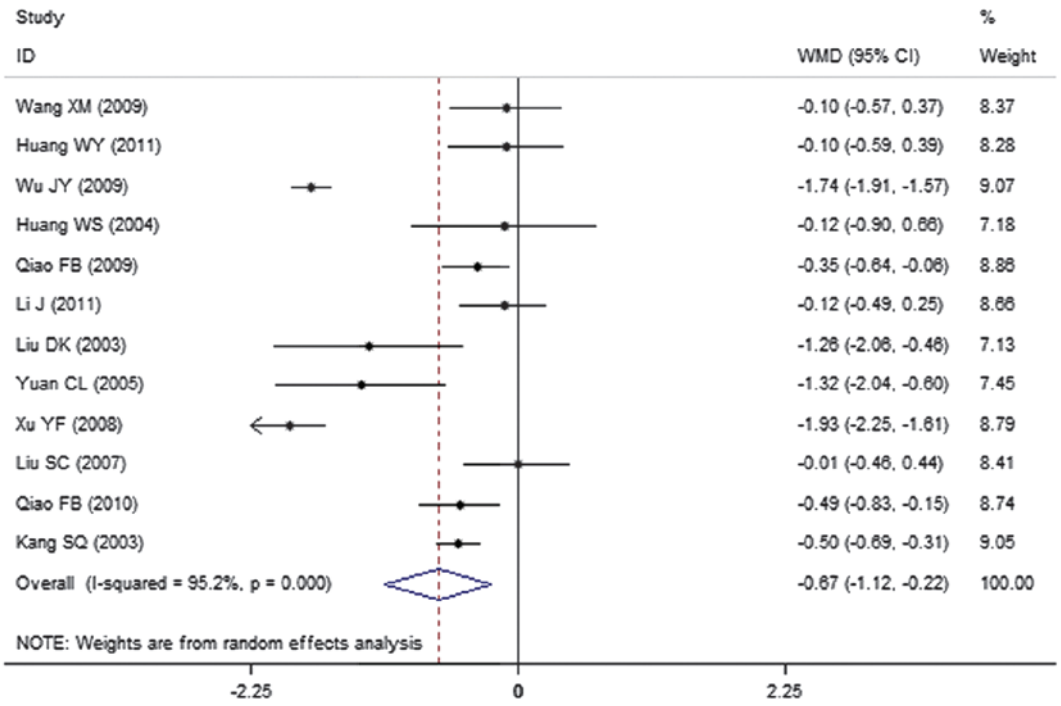

Figure 5. Effect of breviscapine on cholesterol in patients with diabetic nephropathy. ID, identification; WMD, weighted mean difference; CI, confidence interval.

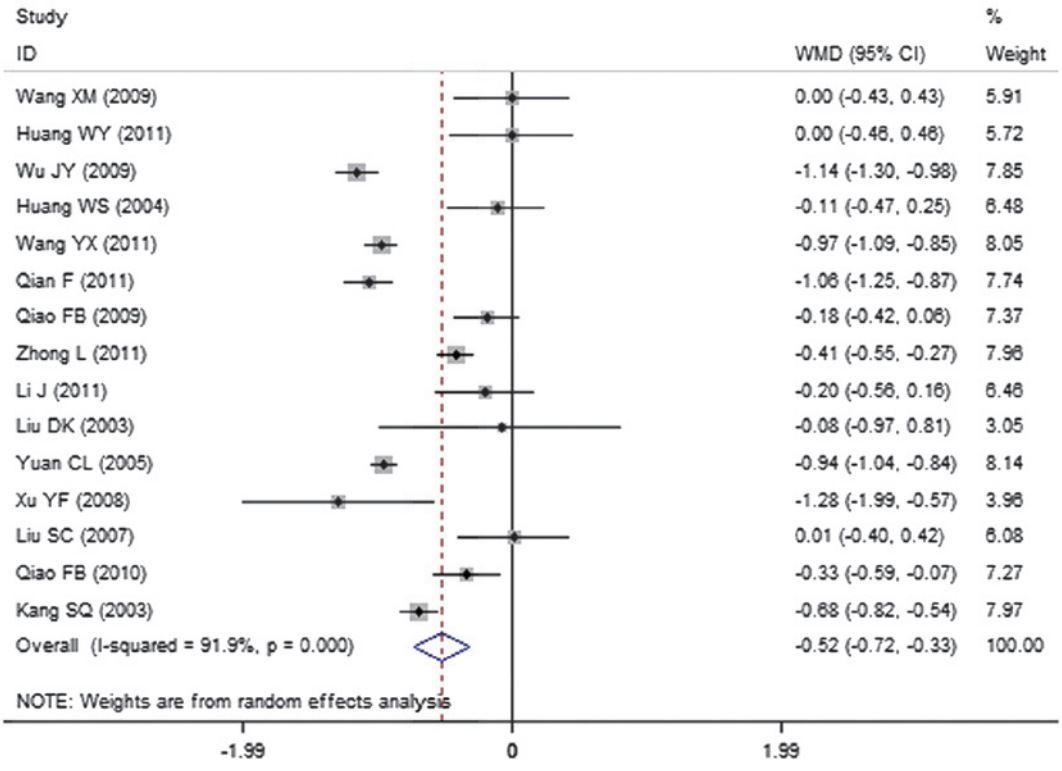

Figure 6. Effect of breviscapine on triglyceride in patients with diabetic nephropathy. ID, identification; WMD, weighted mean difference; CI, confidence interval.

present meta-analysis indicated that breviscapine can reduce urinary protein levels, with a reduction in 24-h urine protein values and the urinary albumin excretion rate; a reduction in urinary protein may contribute towards the renal protective effect of breviscapine in patients with DN.

There is evidence that dyslipidemia serves an important role in the progression of kidney disease in patients with diabetes (61). Dyslipidemia in diabetes is a condition that results in hypertriglyceridemia, low high-density lipoprotein levels, and increased small and low-density lipoprotein

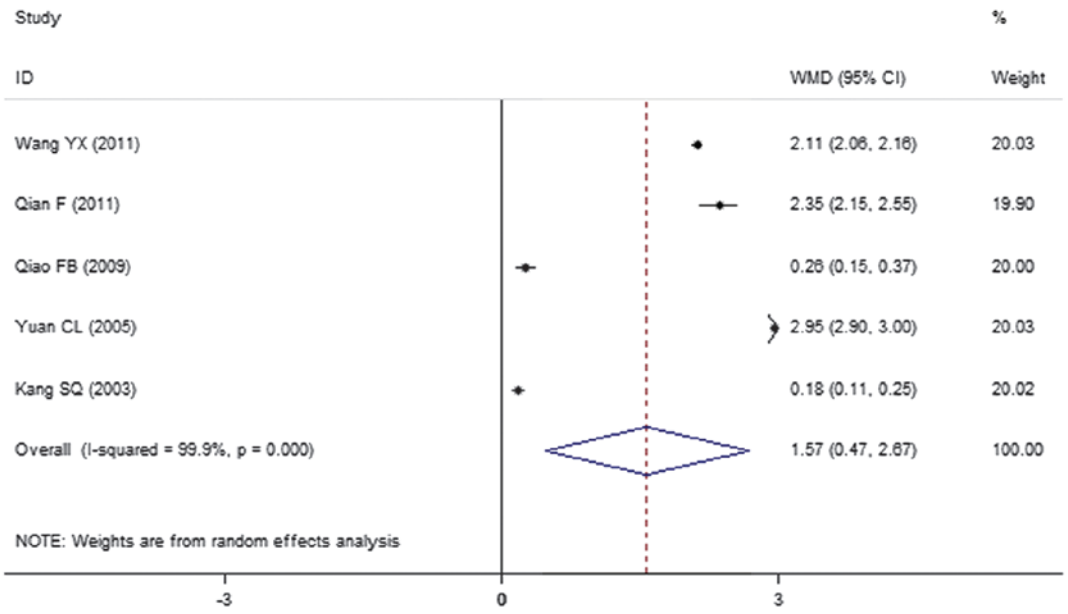

Figure 7. Effect of breviscapine on high density lipoproteins in patients with diabetic nephropathy. ID, identification; WMD, weighted mean difference; CI, confidence interval.

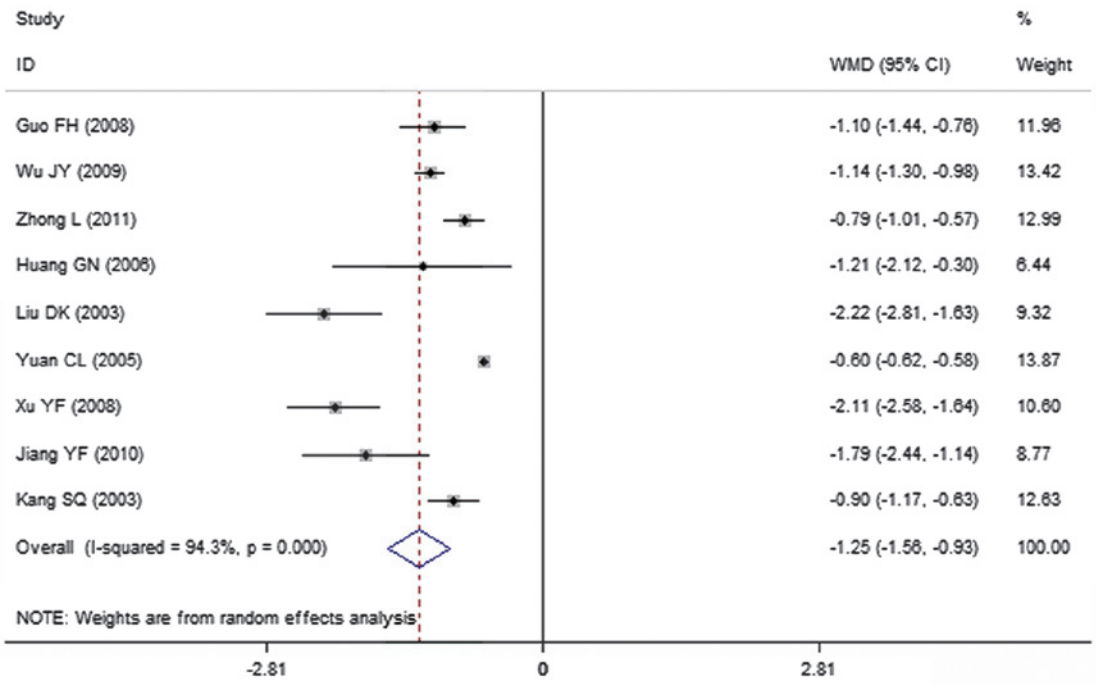

Figure 8. Effect of breviscapine on fibrinogen in patients with diabetic nephropathy. ID, identification; WMD, weighted mean difference; CI, confidence interval.

particles (62). Dyslipidemia is associated with the occurrence and progression of DN, and chronic kidney disease affects dyslipidemia (63). Lipids may cause glomerular and tubulointerstitial injury through mediators such as reactive oxygen species, cytokines and chemokines, and through hemodynamic changes (64). A number of trials have demonstrated that treating dyslipidemia not only decreased the risk of cardiovascular events, but also delayed the progression of DN (65). The present meta-analysis indicates that breviscapine reduces the levels of cholesterol and triglyceride, but increases the level of HDL, in patients with DN; breviscapine is, therefore, capable of reversing dyslipidemia and protecting the renal system.

The present meta-analysis also demonstrated that breviscapine can reduce fibrinogen levels in patients with DN, which is in accordance with its function of promoting fibrinolytic activity, or may be related associated indirectly with the reduction of urine protein levels by breviscapine.

The protective effect of breviscapine is important with regard to the treatment of patients with DN; breviscapine reduces urine protein, improves renal function and adjusts

dyslipidemia. However, the present study explores only the clinical effect of breviscapine, and further studies are required to identify its underlying mechanisms. It is important to note that the majority of the RCTs analyzed in the present study were not of the highest quality; the toxicity of the drug was not thoroughly investigated and in a number of RCTs the lack of liver and kidney toxicity was discussed, but the associated data was not presented in detail. Further research is required that will adopt high quality methodology, including double-blind, multi-centered RCTs with large samples, and conduct long-term follow ups of patients treated with breviscapine in order to investigate its long-term safety.

Acknowledgements

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