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Original Article

The efficacy and safety of sulodexide in patients with diabetic nephropathy: a meta-analysis of randomized controlled trials

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Abstract: Background: Several studies reported that sulodexide might reduce proteinuria in patients with diabetic nephropathy (DN), and even investigated its possible mechanisms. However, the results were not consistent. This meta-analysis sought to assess the efficacy and safety of sulodexide in patients with DN. Methods: Literature reviews of PubMed, MEDLINE, The Cochrane Library, Embase, Sinomed, CNKI, Wanfang, VIP and clinical trial register centers in English and Chinese were conducted to identify randomized controlled trials comparing sulodexide with placebo in DN patients. Quality assessment was performed with Cochrane Handbook's tools for assessing risk of bias; meta-analysis was conducted by RevMan 5.3. Results: Up to April 2015, 442 articles were identified. After full-text checking and quality assessment, 22 articles were finally included involving 29 studies, 3681 patients with DN. Compared with the control group, sulodexide reduced the urinary albumin excretion rate (WMD -29.63, 95% *CI* -50.16 to -9.11, *P*=0.005), 24-hour proteinuria (WMD -0.72, 95% *CI* -1.14 to -0.31, *P*=0.0006) and systolic blood pressure (WMD -2.37, 95% *CI* -3.87 to -0.88, *P*=0.002) in DN patients. However, there was no significant improvement in diastolic blood pressure (*P=0.45*) and fasting blood glucose (*P=0.47*). There were slightly more adverse events of skin rash, diarrhea, back pain, muscle and joint symptoms in patients with sulodexide than that in control group, but without statistical significance. Conclusion: Sulodexide can improve kidney function in DN patients. Therefore it can be considered as a beneficial therapeutic regimen for patients with DN.

Keywords: Diabetic nephropathy, sulodexide, randomized controlled trials, meta-analysis

Introduction

Diabetic nephropathy (DN) is a microvascular complication of diabetes mellitus, and the dominating cause of end-stage renal disease (ESRD), accounting for more than 40% of patients treated with dialysis [1, 2]. Despite attempts at rigorous control of hyperglycemia and hypertension, some patients with DN still experience cardiovascular or renal events [3]. Proteinuria is an important risk factor in aggravating and promoting DN progression. Therefore, effective drug or method to reduce clinical proteinuria is a current focus of attention [4]. Many clinical studies have verified that renin angiotensin system (RAS) inhibitors (angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) played a positive role in preventing or delaying the progression of DN, but these agents could cause hyperkalemia and creatinine elevation, most continued to deteriorate, that could not be reversed, and, ultimately, occurred ESRD [5-7]. Sulodexide has been employed as a novel treatment option for patients with DN.

Sulodexide is an exogenous glycosaminoglycans (GAGs) that may reduce albuminuria in DN, favorably interfering with mechanisms responsible for the changed the glomerular basement membrane (GBM), constituent and function (permselectivity) of the mesangial extracellular matrix [8, 9]. A few researches suggested that the function of sulodexide in kidney was complicated, it could possibly modulate the expression of genes involved in renal remodeling. Solini *et al.* in 1997 initiated the study of sulodexide in the treatment of DN,

then, multiple clinical studies of sulodexide were conducted in DN [10]. Although some clinical studies have shown that sulodexide plays an active role in delaying the process of DN, Packham DK *et al.* reported sulodexide failed to demonstrate renoprotection in overt type 2 diabetic nephropathy [11]. Given the above background, we conducted a meta-analysis to evaluate its efficacy and safety, and the possibility mechanisms.

Methods

Literature search strategy

Relevant articles were conducted by a search of PubMed, MEDLINE, The Cochrane Library, Embase, Sinomed, CNKI, Wanfang and VIP, for randomized controlled trials (RCTs) of sulodexide in diabetic nephropathy from the earliest data to April 30, 2015. Additional papers were found through a manual search of reference lists of all eligible articles and correlative review articles. We also searched for additional titles at the clinical trial register centers (*http://www.clinicaltrials.gov*). The following search terms were entered as independent terms: (diabetic nephropath* OR diabetic kidney disease* OR diabetic kidney injury OR diabetic chronic complication*) AND (sulodexide OR glucuronyl glucosamine glycan sulfate OR glucuronyl glucosaminoglycan sulfate OR 3-glucosaminoglycan sulfate OR glucuronyl glucosaminoglycan sulfate) AND (randomized controlled trials OR RCT OR controlled clinical trial OR randomized).

Inclusion criteria and exclusion criteria

Eligible studies met the following criteria: (1) patients with diabetic nephropathy; (2) primary study comparing sulodexide with placebo or blank control; (3) published in English or Chinese language; (4) RCT design; (5) at least four-week follow-up; (6) reporting at least one of the following outcomes: 24-hour proteinuria, urinary albumin excretion rate (UAER), and/or safety outcome. Studies not designed as randomized control studies, no or incomplete data provided, and animal tests were excluded from this meta-analysis.

Study selection and data extraction

According to the inclusion criteria, two investigators independently screened all titles and abstracts and extracted data from included studies. Multiple publications reporting on the same research were accepted only when additional relevant outcomes were presented; they were regarded as one study. Disagreements or uncertainties were adjudicated by consensus. If an agreement could not be reached, a third reviewer would decide. The following information should be extracted: (1) characteristics of trial subjects (including age, sex ratio and duration of diabetes) and its inclusion criteria; (2) type of intervention (including dose of sulodexide and therapy duration); and (3) type of outcome and measurement.

Statistical analysis

The main outcome was the change of urinary albumin excretion rate (UAER), 24-hour proteinuria from the baseline. Other outcomes include: (1) change from baseline in adverse effects (AEs); (2) change from baseline in incidence of fasting blood glucose (FBG); (3) change from baseline in blood pressure. The meta-analysis with fixed model was performed by weighted mean difference (WMD) and 95% *CI* for outcome of continuous variables (change from baseline in FBG and blood pressure). Random model was performed by weighted mean difference (WMD) and 95% *CI* for outcome of continuous variables (change from baseline in UAER and 24-hour proteinuria). Random model was performed by computing odds ratio (*OR*) and 95% *CI* for outcomes of dichotomous variables (AEs). The I^2 was calculated as an index of heterogeneity between researches. If I^2 was higher than 50%, sensitivity analysis were performed to determine the source of heterogeneity and to assess whether the heterogeneity significantly impacted the results.

Quality assessment and risk of bias

To verify the eligibility of randomized trials, two authors independently determined the adequacy of randomization and allocation concealment, blind methods (participants and personnel, and outcome assessment), extent of loss to follow-up, and whether the analysis had followed the intention-to-treat principle. Sensitive analysis was performed in studies with low quality. The analyses were performed using Review Manager 5.2 (Cochrane Collaboration, United Kingdom).

Results

Search results and study characteristics

The initial search strategy found 442 abstracts, of these, 22 articles met the inclusion criteria. The main characteristics of the 22 trials were

Table 1. Characteristics of randomized controlled trials included in the meta-analysis

Author, year	Average duration of diabetes (years)		Number of participants (n)		Male (%)		Average age (years)		Intervention		Flollow up (months)	Adverse effect
	T	C	T	C	T	C	T	C	T	C		
Huo, 2014 (low dose)	7.6±2.7	7.5±2.6	16	5	No message		59±9	59±9	Sulodexide	Irbesartan	4	Yes
Huo, 2014 (middle dose)	7.4±2.9	7.5±2.6	14	5	No message		58±8	59±9	Sulodexide	Irbesartan	4	Yes
Huo, 2014 (high dose)	7.7±2.5	7.5±2.6	15	5	No message		59±9	59±9	Sulodexide	Irbesartan	4	No
He, 2012	Not mentioned		33	33	63.6	57.6	45±3	42±3	Sulodexide + Routine therapy	Routine therapy	2	Not mentioned
Zhang, 2011	0.5±1.5	0.67±1.3	26	26	Not mentioned		35±66	40±68	Sulodexide + Routine therapy	Routine therapy	8	No message
Ren, 2010	Not mentioned		23	18	No message		55.8±11.3	54.6±11.2	Sulodexide + Routine therapy	Routine therapy	1	Yes
Ma, 2011	7.0±2.6	7.7±2.9	22	20	63.6	60	52.5±5.8	52.7±6.3	Sulodexide + Routine therapy	Routine therapy	3	No
Wang, 2009 (1)	9.7	10.7	38	34	47.1	50	No message		Sulodexide + Routine therapy	Routine therapy	3	Not mentioned
Wang, 2009 (2)	10	9.2	30	42	56.7	52.4	No message		Sulodexide + Benazepril	Benazepril	3	Not mentioned
Kang, 2013	No message		33	29	Not mentioned		Not mentioned		Sulodexide + Routine therapy	Routine therapy	2	No message
Chen, 2013 (low dose)	11.0±2	13.0±3	23	10	61	62	53.0±6	54.0±7	Sulodexide + Routine therapy	Routine therapy	4	Yes
Chen, 2013 (high dose)	12.0±5	13.0±3	23	11	65	62	56.0±4	54.0±7	Sulodexide + Routine therapy	Routine therapy	4	Yes
Wang, 2010	Not mentioned		13	13	No message		No message		Sulodexide + Routine therapy	Routine therapy	1	Not mentioned
Xiong, 2014	7.7±4.3	7.5±4.7	35	30	60	60	50.0±11.0	51.7±10.5	Sulodexide + Losartan Potassium	Losartan Potassium	2	No message
Chen, 2008	12.1	12.9	30	10	60	30	52.5	49.9	Sulodexide + Routine therapy	Routine therapy	3	Not mentioned
Achour, 2005	12-20	2-21	30	30	53.3	56.7	21±58	31±53	Sulodexide + Routine therapy	Routine therapy	12	Yes
Gambaro, 2002 (low dose)	16.0±9.6	17.2±10.4	56	18	No message		49.0±12.4	47±12.8	Sulodexide + Routine therapy	Routine therapy	4	Yes
Gambaro, 2002 (middle dose)	15.8±8.4	17.2±10.4	56	18	No message		47.4±12.1	47±12.8	Sulodexide + Routine therapy	Routine therapy	4	Yes
Gambaro, 2002 (high dose)	16.2±10.3	17.2±10.4	56	19	No message		46.9±12.5	47±12.8	Sulodexide + Routine therapy	Routine therapy	4	Yes
Solini, 1997	No message		6	6	Not mentioned		Not mentioned		Sulodexide + Routine therapy	Routine therapy	8	No
Packham, 2012	Not mentioned		619	629	79	74	62.3±9.4	63.6±9.5	Sulodexide + Routine therapy	Routine therapy	18	Yes
Lewis, 2011	No message		524	532	75.2	76.7	62.0±9.7	62.3±9.9	Sulodexide + Routine therapy	Routine therapy	8.5	Yes
Sulikowska, 2006	17.8±1.6	18.0±2.4	30	13	23.3	23.0	34.6±2.1	36.8±2.8	Sulodexide	Routine therapy	1	No
Dedov, 1997 (Microalbuminuria)	Not mentioned		9	9	33.3	66.7	27.9±11.2	33.3±2.5	Sulodexide	Placebo	1.5	Not mentioned
Dedov, 1997 (Macroalbuminuria)	Not mentioned		9	9	33.3	33.3	29.9±7.4	35.3±3.95	Sulodexide	Placebo	1.5	Not mentioned
Heerspink, 2008 (low dose)	No message		50	23	72.0	70.2	64.1±9.2	60.3±12.1	Sulodexide	Placebo	6	Yes
Heerspink, 2008 (high dose)	No message		52	24	73.1	70.2	61.1±11.2	60.3±12.1	Sulodexide	Placebo	6	Yes
Hu, 2009	Not mentioned		33	32	63.6	59.4	80±3.6	82±3.4	Sulodexide + Routine therapy	Routine therapy + Irbesartan + Irbesartan	2	No message
Hu, 2010	Not mentioned		33	32	63.6	59.4	80±3.6	82±3.4	Sulodexide + Routine therapy	Routine therapy + Perindopril + Perindopril	2	No message
Mao, 2010	11.0±6.0	9.0±5.0	30	30	63.3	66.7	61±11	59±5	Sulodexide + Routine therapy	Routine therapy + Benazepril + Benazepril	6	Not mentioned

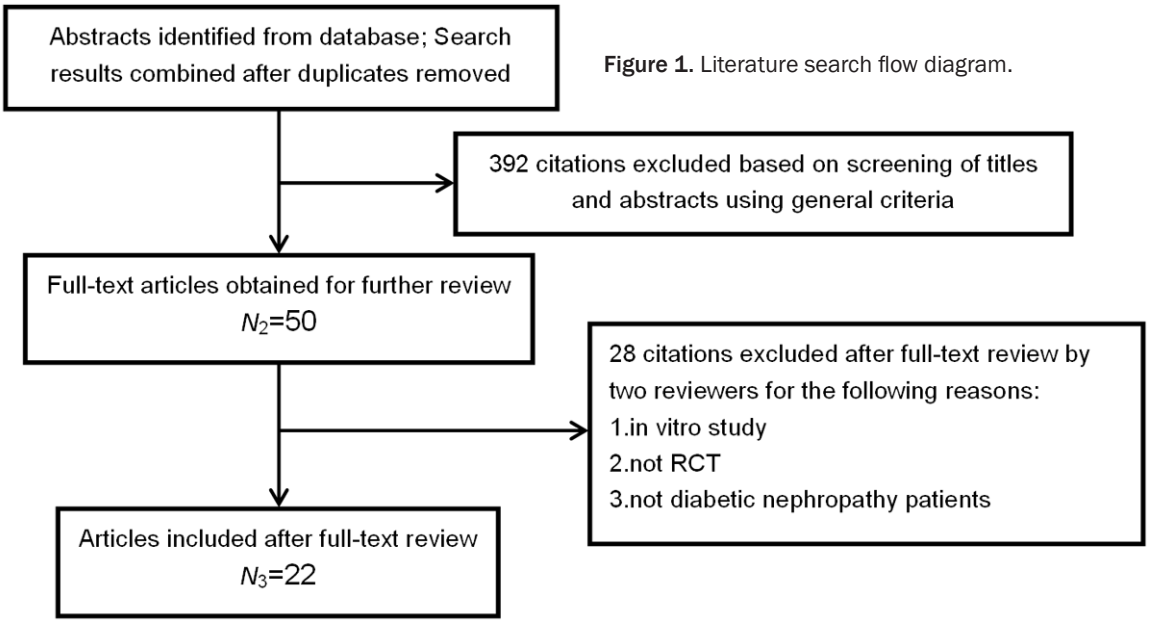

Figure 1. Literature search flow diagram.

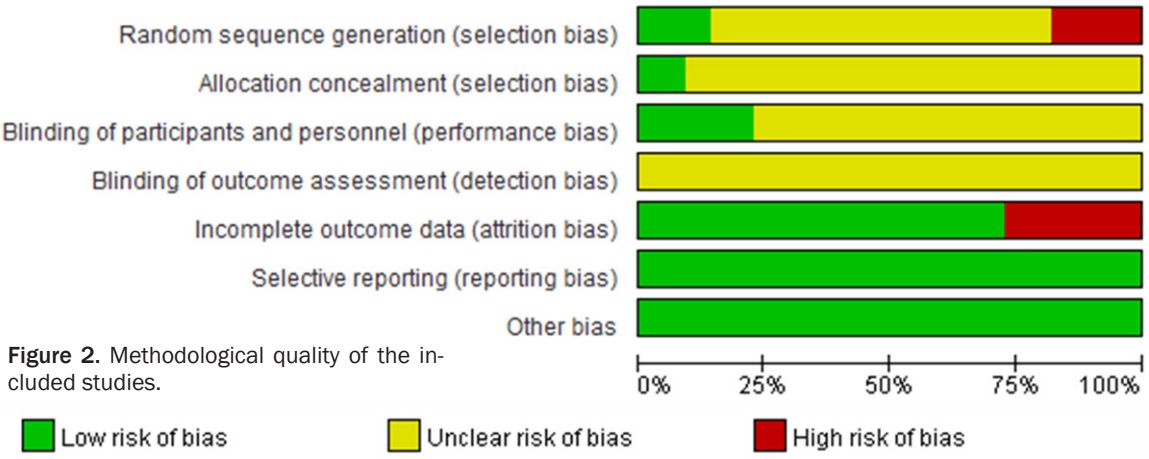

Figure 2. Methodological quality of the included studies.

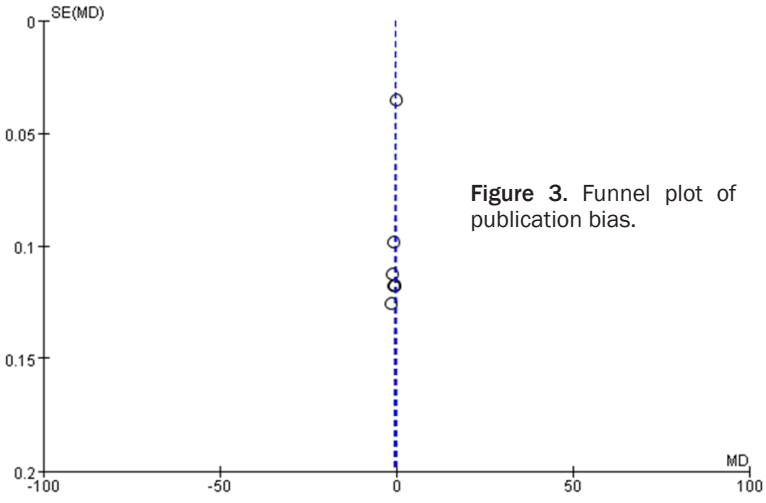

Figure 3. Funnel plot of publication bias.

shown in **Table 1**. Among the final 22 studies, 14 were conducted in China [12-25], eight in the USA [10, 11, 26-31] (searching progress was summarized in **Figure 1**). All the 22 studies included were randomized double-blinded trials, though none of them described blinding of outcome assessment nor expatiate allocation concealment. Detail information was shown in **Figure 2**. Funnel plot was used to analysis the publication bias, and a symmetrical

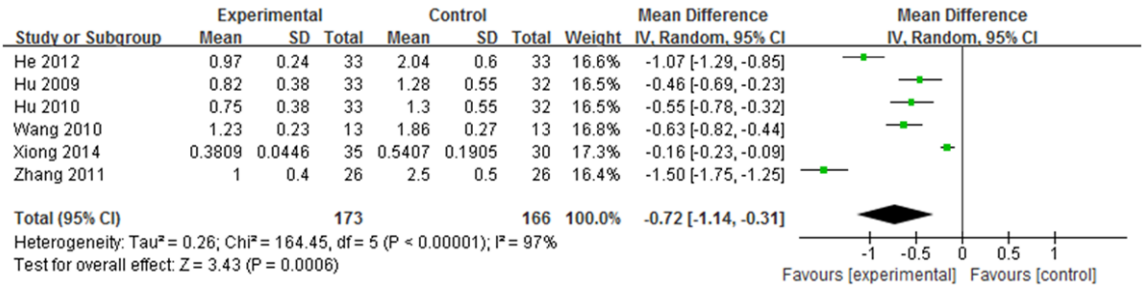

Figure 4. Forest plot of of 24-hour proteinuria from baseline.

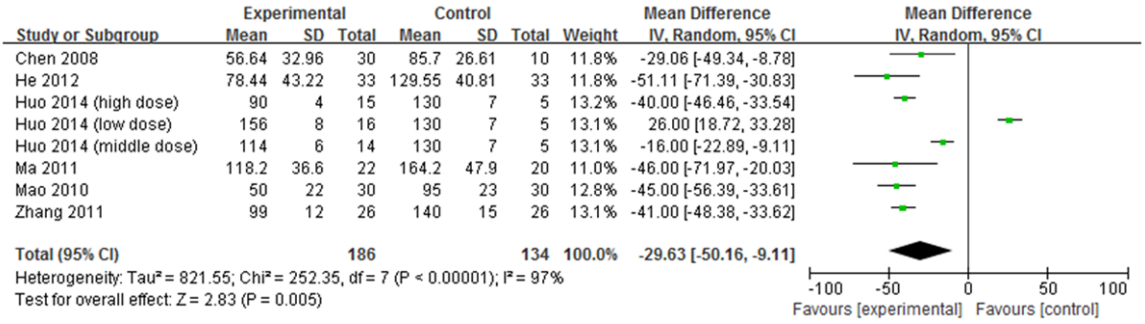

Figure 5. Forest plot of weighted mean difference in change of UAER from base line.

funnel plot was shown in **Figure 3** which indicated no publication bias existed.

Efficacy

Effect of sulodexide on 24-hour proteinuria: Six studies included 24-hour proteinuria with a total of 339 participants, 173 in sulodexide and 166 in control group. Random-effect model was used to merge SMD values (heterozygosity test, Chi^2=164.45, P<0.00001, I^2=97%). The heterozygosity may be caused by small samples or poor quality of the included studies. The pooled data was -0.72 (95% CI: -1.41 to -0.31, Z=343, P=0.0006; **Figure 4**) which suggested that there was statistically significant reduction in 24-hour proteinuria in sulodexide treated group.

Urinary albumin excretion rate (UAER)

Six studies reported UAER, 320 participants were evaluated, 186 in sulodexide treated group and 134 in control group. Random-effect model was used to merge SMD values (heterozygosity test, Chi^2=252.35, *P*<0.00001, I^2=97%). The heterozygosity may come from allocation concealment, unstrict implementation of randomization and double-blind and so on. The pooled data was -29.63 (95% *CI*: -50.16 to -9.11, Z=2.83, *P*=0.005; **Figure 5**) which indicated that there was statistically significant reduction in UAER in sulodexide treated group.

Fasting blood glucose (FBG)

Nine studies (ten groups) reported FBG and there was no significant heterozygosity among them. Sulodexide did not reduce FBG compared with control in these studies (**Figure 6**).

Blood pressure

The pooled data from all nine studies showed no statistically difference in DBP decline from baseline in sulodexide treatment compared with control group (WMD: -0.30; 95% *CI*: -1.08 to 0.48, Z=0.75, *P*=0.45). However, a statistically significant reduction in SBP was found (WMD: -2.37; 95% *CI*: -3.87 to -0.88, Z=3.11, *P*=0.002). The heterogeneity among trials were not significant (I^2=0%) (**Figures 7** and **8**).

Safety

Adverse events (AEs), although detailed data was not provided, including skin rash, diarrhea,

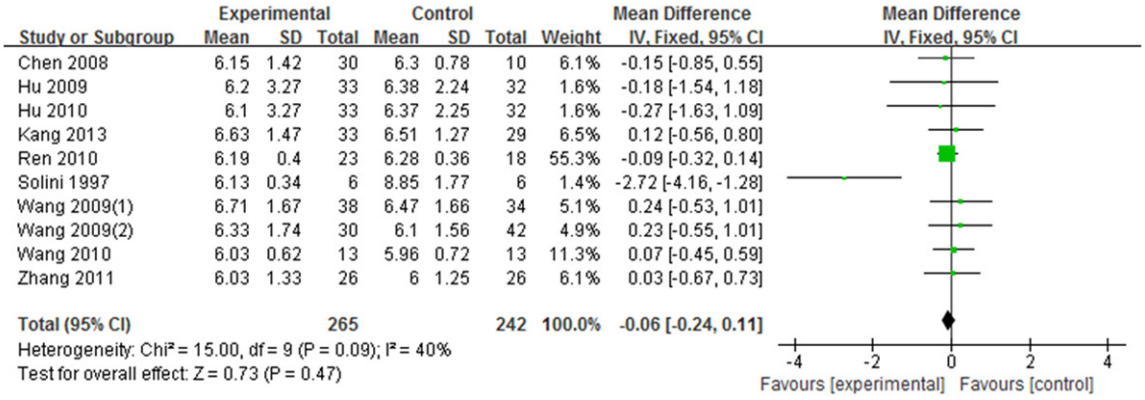

Figure 6. Forest plot of effects on fluctuation of FBG.

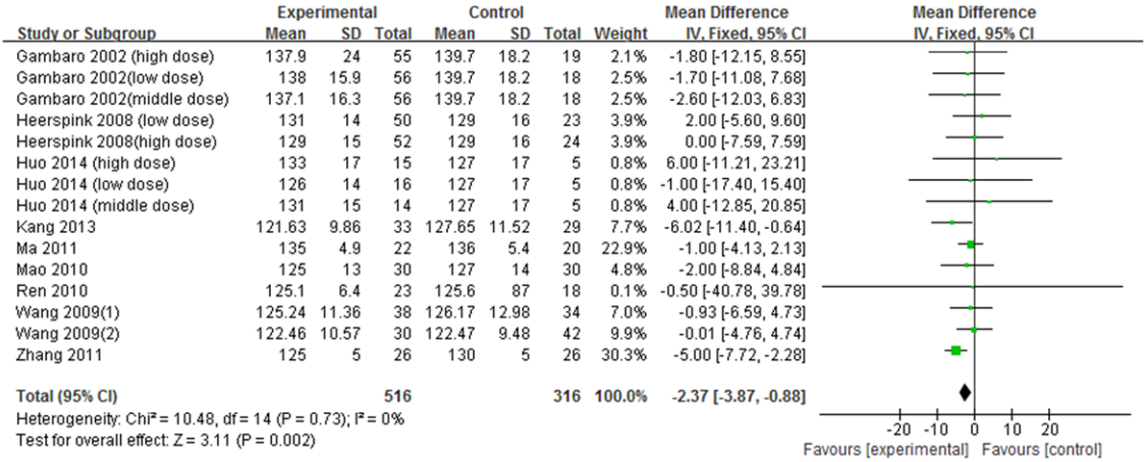

Figure 7. Forest plot of effects on SBP.

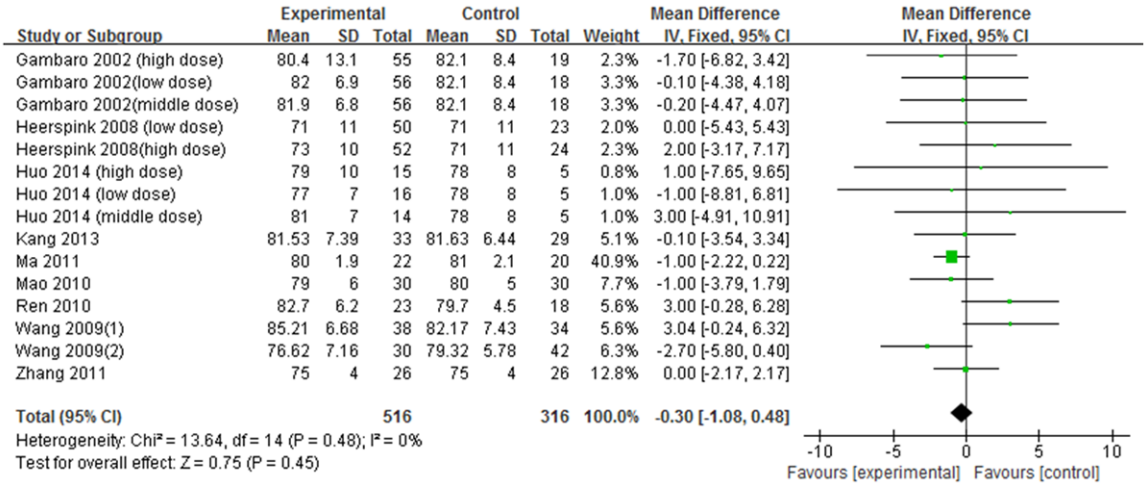

Figure 8. Forest plot of effects on DBP.

back pain, muscle and joint symptoms, were more in patients of the treatment group than that in control group, however, there was no statistically difference in the incidence of total

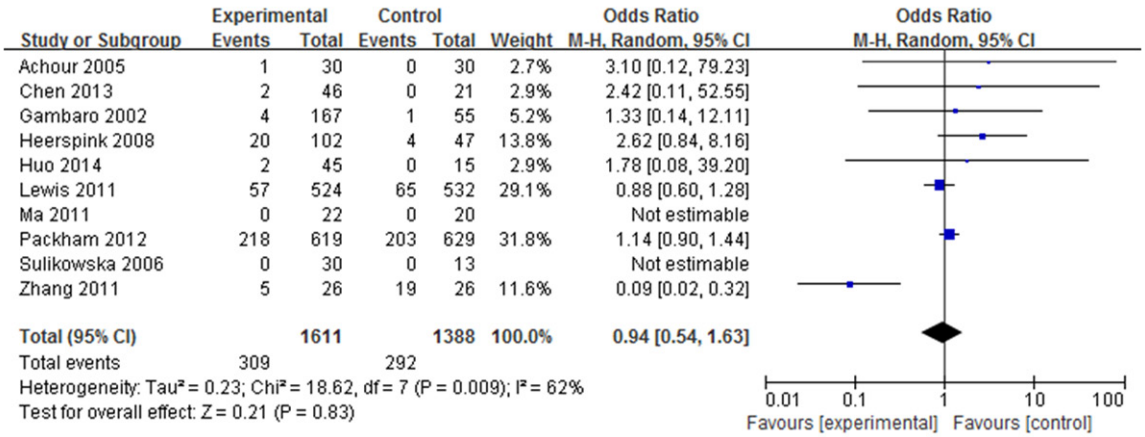

Figure 9. Forest plot of OR in incidence of the total AEs.

AEs (19.18% vs. 21.04%, respectively; *OR*: 0.94; 95% *CI*: 0.54-1.63; **Figure 9**).

Discussion

Diabetic nephropathy (DN) is a widely recognized microvascular complication of diabetes and the leading cause of end-stage kidney failure responsible for morbidity and mortality [32]. To delay the progression of DN, current guidelines recommend intensive treatment of hypertension with ACEIs and ARBs, optimization of glucose control and protein restriction [33]. Despite these interventions, some patients with DN either do not respond to or tolerate therapy, and consequently progress. In Irbesartan diabetic nephropathy trial (IDNT), only 40% of patients with overt proteinuria treated with irbesartan achieved a 50% reduction in proteinuria [34]. We long for new drugs to treat DN eagerly.

Sulodexide was benefit for nephropathy both in human and animal [35-37]. But there were some negative opinions [11, 17]. Our analysis suggested that sulodexide could reduce proteinuria and UAER significantly with few side effects. To get a better understanding of the underlying mechanism, we analyzed its effects on blood pressure, fasting blood glucose, triglycerides and cholesterol. It was found that sulodexide did not reduce the diastolic blood pressure and fasting blood glucose, suggesting that the renal protective of sulodexide was probably independent of blood pressure, fasting blood glucose and other pathways or mechanisms may exist.

Sulodexide is a preparation of low-molecular weight porcine glycosaminoglycan (GAG) polysaccharides comprised of fast-moving heparin (75-80%), and dermatan sulfate (20%) with a mean molecular weight of 11,000-15,000 Da [30]. It can be administrated orally, intramuscularly or intravenously [38]. Although it was first evaluated as an anti-thrombotic drug, it had no anticoagulant effect in oral administration [39], and had been proved to improve blood flow by lowering viscosity [40, 41], reduce cardiovascular events and vascular disease-associated skin ulcers [42-44]. Gambaro first observed the relationship between GAG and diabetic proteinuria in animal models and the suggested the administration of sulodexide in the treatment of DN [27, 45]. Then, several clinical studies demonstrated that sulodexide reduced albuminuria in patients with DN.

Sulodexide apparently reduces proteinuria by a non-blood pressure, non-RAAS related mechanism [46]. So, it increases a therapeutic option in those patients who failed to respond to RAAS inhibition. Moreover, it may add further reduction in patients' response to RAAS inhibition. Such additive effects were helpful. Some researchers suggested several mechanisms that may be involved in the protective of sulodexide.

Glomerular basement membranes (GBM) and sulodexide

Changes in GBM macromolecular composition are assumed to be the basis for its loss of size and charge selectivity [47, 48]. It is reported that sulodexide may alter the constituent and thickening of GBM, correct the anionic charge barrier depletion of GBM via direct deposition,

induction the synthesis and sulfation of heparin sulfate proteoglycan [49-51].

Extracellular matrix (ECM) and sulodexide

Changes in the ECM are notable characteristics in DN. The ECM plays an pivotal role in regulating the structure and function of adjacent cells, influencing cell anchorage and intercellular communication and accumulation of ECM can activate TGF-β1 [52, 53]. Data from animal and in vitro studies have demonstrated that sulodexide suppress high-glucose-induced overexpression of TGF-β1 and fibronectin in mesangial cells, meanwhile, suppress the enhanced expression of mesangial matrix and collagens TGF-β1 mediated [54-56]. It is notified that sulodexide alter the permeability of the mesangial ECM [8, 9].

Heparanase-1 and sulodexide

Heparanase-1 is upregulated in renal epithelial cells under high glucose conditions and has been implicated in the development of proteinuria in DN. Sulodexide may block the activity of heparanase-1 by recovering of heparan sulfate levels in podocytes [57, 58], completely blocking the albumin permeability in a glomerular basement membrane assay. Further experiments *in vitro* suggested that sulodexide restored the expression of cell surface heparin sulphate [59].

Inflammation, fibrosis and sulodexide

Hyperglycemia induces overexpression of all isoforms of TGFβ, which in turn play a vital role in inflammation and fibrosis that characterize DN. Sulodexide may inhibit synthesis of TGFβ, suppress production of inflammation factors, restrain albuminuria-induced and endothelin-mediated fibrosis in varieties of pathological conditions [60-62]. In addition, it can suppress the infiltration and activation of macrophage, decrease the apoptosis of glomerular cells and the pathological proliferation of mesangial cell, and modulate the expression of gene involved in renal remodeling [63-66].

Safety is a very important issue for a drug. In the light of our analysis, sulodexide did not increase the incidence of AEs significantly, including skin rash, diarrhea, back pain, muscle, and joint symptoms.

Due to the small sample size in the majority of studies, trials in large samples and long-term course of trial are needed to better illuminate the influence of sulodexide on DN.

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Disclosure of conflict of interest

None.

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