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Review Article

Efficacy of sulodexide in treating idiopathic membranous nephropathy among Chinese patients: a meta-analysis

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Abstract: Objective: To evaluate the efficacy of Sulodexide in treating idiopathic membranous nephropathy (IMN) in the Chinese population. Methods: We systematically reviewed all eligible randomized clinical trials (RCTs) conducted in China that investigated the effects of Sulodexide on IMN. Three RCTs published between 2013 and 2022 were included, encompassing a total of 146 patients. The primary outcomes evaluated were changes in urine total protein (UTP), serum albumin (ALB), cholesterol (CHOL), and fibrinogen (FIB) levels. Results: Statistically significant differences were observed in the Sulodexide treatment group compared to the control group for the following parameters: reduction in UTP and CHOL, increase in ALB, and reduction in FIB levels. Conclusion: Sulodexide, when combined with conventional therapy, effectively reduces UTP and CHOL levels, decreases FIB levels, and increases ALB in Chinese patients with IMN.

Keywords: Sulodexide, idiopathic membranous nephropathy, systematic review, meta-analysis

Introduction

Membranous nephropathy (MN) is a group of diseases characterized by renal pathology, including subepithelial immune complex deposition and diffuse thickening of the glomerular basement membrane (GBM). It represents one of the most common pathological types of adult nephrotic syndrome (NS). MN is divided into idiopathic membranous nephropathy (IMN) and secondary membranous nephropathy, with IMN accounting for approximately 70% of adult MN cases [1] and 29% of primary glomerular diseases [2]. Approximately 30% of IMN patients recover spontaneously, another 30% progress to renal insufficiency, and about 40% advance to end-stage renal disease within 5-10 years [3].

Current IMN treatments primarily utilize hormones and immunosuppressive agents, including alkylating agents, calcium-modulated neurophosphatase inhibitors, mycophenolate, rituximab, and bortezomib. However, these treatments are often accompanied by significant drug-related toxicities, particularly in refractory IMN where increasing drug dosages may exacerbate side effects without enhancing efficacy, thus doing more harm than good. Consequently, multi-targeted therapy has been proposed as an effective approach for patients with refractory IMN that does not increase side effects, though its recurrence rate and long-term efficacy remain unconfirmed [4].

Clinically, IMN is particularly prone to hypercoagulation and thromboembolic complications

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[5]. This susceptibility is partly due to hypoproteinemia from massive protein loss, which triggers compensatory protein synthesis by the liver and increased fat production leading to hyperlipidemia [6]. Additionally, alterations in the body's coagulation, anticoagulation, and fibrinolytic systems, along with abnormal platelet activation and function, contribute to hypercoagulation [7, 8]. The production of neutrophil extracellular traps and the resulting hypercoagulable states further complicate the situation [9]. Factors such as hypoproteinemia causing extravasation of plasma components, reduced effective blood volume, and increased blood viscosity, along with long-term adrenal glucocorticoid use that stimulates procoagulant activity, exacerbate the risk of thrombotic and embolic complications [10]. Ultimately, these abnormal immune responses activate the body's coagulation system, leading to intrarenal coagulation and microthrombosis in glomerular capillaries, which adversely affects the prognosis of renal diseases.

As a result, anticoagulation therapy plays a critical role in IMN treatment. Commonly used agents include low molecular weight heparin, aspirin, warfarin, and dipyridamole, which are effective in managing hypercoagulable states but may cause side effects such as allergies, bleeding, and liver or kidney damage with long-term use.

Sulodexide, a glycosaminoglycan and widely used antithrombotic drug, effectively reduces thrombotic risk with a lower incidence of bleeding compared to traditional agents [11]. It exhibits multiple biological activities including hypolipidemic, anticoagulant, anti-factor Xa, and heparin cofactor II affinity. Glycosaminoglycans, fundamental components of blood vessels, help maintain the normal negative charge on vessel walls, inhibit cellular proliferation, and prevent the loss of basement membrane and extracellular matrix functionality, thus improving membrane permeability. Sulodexide also inhibits platelet adhesion and thrombus formation, enhances circulation by reducing high fibrinogen and very low-density lipoprotein levels, and decreases plasma fibrinogen activator inhibitor 1 concentrations. Notably, it inhibits the increase in the glomerular extracellular matrix while significantly reducing the risk of bleeding compared to heparin [12].

Recent studies have shown that long-term, low-dose sulodexide is as effective as anti-proteinuric and Raynaud protection therapy in patients with chronic kidney disease [13]. Additionally, sulodexide combined with telmisartan or leflunomide has been reported to significantly reduce urinary protein, increase plasma albumin levels, improve renal function, lower lipid levels, minimally impact liver function, and maintain a high safety profile [14, 15]. Despite these findings, a systematic evaluation of this treatment approach for IMN has not been conducted. Therefore, this study performs a meta-analysis of RCTs to assess the clinical efficacy of sulodexide in the treatment of IMN.

Materials and methods

Literature search

A comprehensive computer search was conducted across multiple databases including Embase, PubMed, the Cochrane Library Clinical Controlled Trials Register, Wanfang, CNKI, and VIPshop, covering all entries from the inception of each database through December 2022. Search terms used were "sulodexide", "membranous nephropathy", and "clinical studies" in both Chinese and English. References of retrieved articles were also reviewed for relevancy.

Inclusion and exclusion criteria

Inclusion criteria: (1) Published RCTs evaluating sulodexide for MN. (2) A minimum follow-up period of 6 months. (3) Studies involving Chinese patients with IMN. (4) Availability of complete data sets. (5) Studies published in either Chinese or English. Exclusion criteria: (1) Non-RCT studies. (2) Studies with incomplete data.

Data collection

Data from all included studies were extracted, detailing participant characteristics, study baseline, and intervention specifics for each group. Primary outcomes assessed were urine total protein (UTP), albumin (ALB), cholesterol (CHOL), and fibrinogen (FIB).

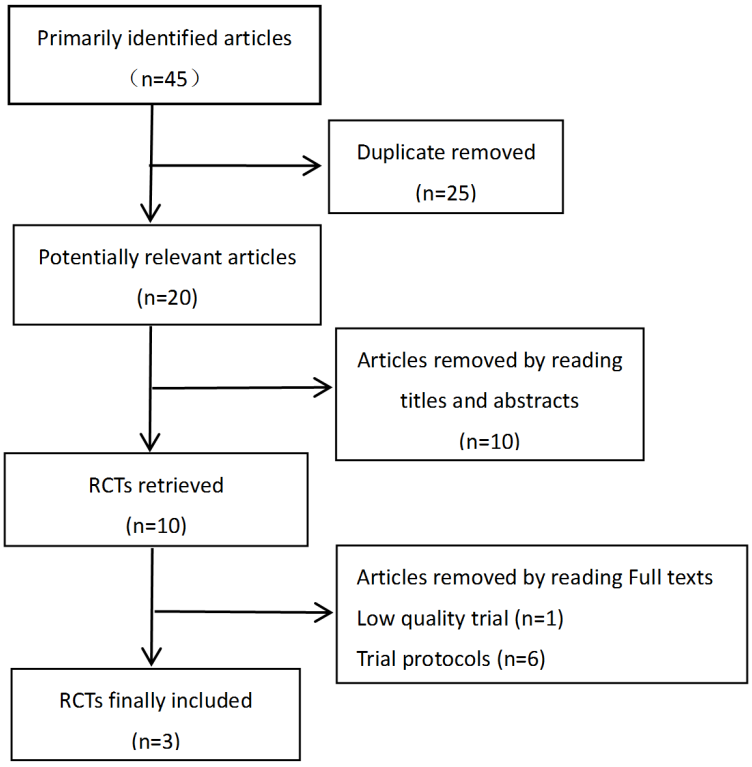

Figure 1. Flowchart of the process for selecting studies for the systematic review. RCTs, randomized clinical trials.

Quality assessment

The quality of included studies was assessed using the Cochrane risk of bias tool, considering selection, performance, detection, attrition, reporting biases, and other potential sources of bias. Two reviewers independently conducted the literature extraction and verification. Any disagreements were resolved through consultation with a third reviewer.

Statistical analysis

Statistical analysis was carried out using Cochrane Review Manager version 5.3. Heterogeneity was evaluated; studies exhibiting $P \geq 0.10$ and $I^2 \leq 50\%$ were considered to have good homogeneity and were analyzed using a fixed-effects model. Conversely, studies with poor homogeneity were analyzed using a random-effects model. The effect size for categorical variables was represented as odds ratios, and for continuous variables as mean differences (MD), with results displayed in forest plots. Differences were deemed statistically significant at $P<0.05$.

Results

Literature search and screening results

A comprehensive literature search was conducted across multiple databases including Embase, PubMed, the Cochrane Library, Wanfang, CNKI, and VIPshop, yielding a total of 45 articles, all in Chinese and none in English. Following the removal of 25 duplicate entries, an initial screening based on titles and abstracts excluded 10 articles. A further 7 were excluded after full-text reviews. Ultimately, three articles [16-18], encompassing 146 cases, met the inclusion criteria for this systematic review. The search process is illustrated in **Figure 1**, and clinical details from the included studies are summarized in **Table 1**.

Risk of bias assessment

The three studies included [16-18] utilized a randomized design and described allocation concealment, but did not specify any blinding measures. Detection bias was not discussed in these studies. Outcome data were complete and evaluated using the Cochrane Risk of Bias Assessment Tool (**Figures 2** and **3**).

UTP levels

The three studies [16-18] assessed changes in UTP after treatment in both the treatment and control groups. There was minimal statistical heterogeneity among the studies ($P=0.51$, $I^2=0\%$), warranting the use of a fixed-effects model for analysis. The results indicated a significant reduction in UTP in the treatment group compared to the control group, with an MD of -0.72 (95% CI: -1.13 to -0.31, $P=0.0006$) (**Figure 4**).

ALB levels

Three studies [16-18] evaluated changes in albumin levels after treatment for IMN in both

Table 1. Characteristics of the studies included in this systematic review

Studies	Baseline Characteristics	Interventions/Controls of Participants
Wu et al. 2013 [16]	I:N=30 Age: 42±11; Gender: M26 F4; Pathology: I:24 II:6. C:N=30; Age: 46±12; Gender: M24 F6; Pathology: I:22 II:8.	I: Basic therapy combined with Sulodexide (specifications: injection 600 LSU/PCS; 250 LSU/capsule), 600 LSU static point once/day, course of 20 days, changed to 500 LSU, oral, 2/day; Tripterygium wilfordii, 1 mg/kg.d, 3 times a day, orally. C: Basic treatment combined with Tripterygium wilfordii, 1 mg/kg.d, 3 times a day, oral. Follow-up period: 6 months.
Tang et al. 2013 [17]	I:N=17; Age: 42±14; Gender: M9 F8. C:N=17; Age: 38±16; Gender: M12 F5.	I: Sulodexide (specifications: 250 LSU/capsule), 250 LSU, oral, 2/day; Telmisartan, 80 mg, once a day, oral. C: Telmisartan, 80 mg, once a day, oral. Follow-up period: 6 months.
Cai et al. 2015 [18]	N=52; Gender: M34 F18; Age: I: 42.5±13.9; Pathology: I:32 II:20.	I (n=26): Conventional treatment combined with Sulodexide, 600 LSU once/day, treatment course 20 days, changed to 500 LSU, oral, 2/day; Tripterygium wilfordii, 1 mg/kg.d, 3 times a day, oral. C (n=26): Conventional treatment combined with Tripterygium wilfordii (1 mg/kg.d, 3 times a day, oral). Follow-up period: 6 months.

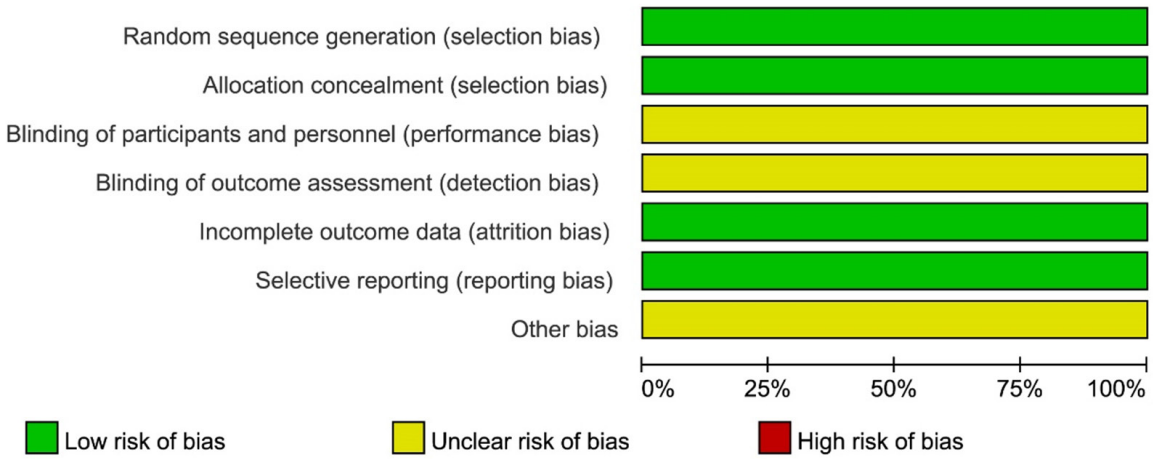

Figure 2. Risk of bias graph.

treatment and control groups, showing low statistical heterogeneity (P=0.21, I^2=35%). A fixed-effects model was employed for analysis. The results indicated a significant increase in albumin levels post-treatment in the treatment group compared to the control group, with an MD of 2.95 (95% CI: 1.61, 4.30, P<0.0001) (**Figure 5**).

CHOL levels

The same three studies [16-18] also assessed cholesterol levels post-treatment in IMN patients. With minimal heterogeneity observed (P=0.76, I^2=0%), a fixed-effects model was used. The analysis revealed a significant reduction in CHOL levels in the treatment group relative to the control group, with an MD of -0.93 (95% CI: -1.33, -0.54, P<0.00001) (**Figure 6**).

FIB levels

Two studies [16, 18] compared changes in FIB levels following IMN treatment, exhibiting low statistical heterogeneity (P=0.56, I^2=0%). A fixed-effects model was applied, demonstrat-

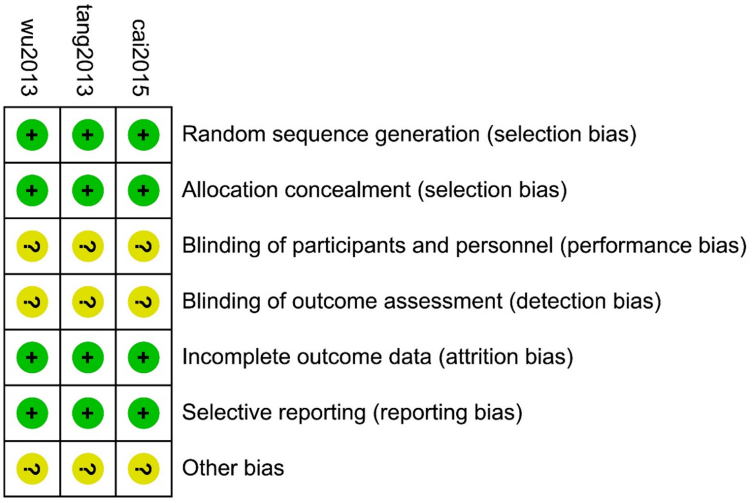

Figure 3. Risk of bias summary. "+" means low risk of bias, "-" means high risk of bias, "?" means unclear risk of bias.

ing a significant decrease in levels post-treatment in the treatment group compared to the control group, with an MD of -1.15 (95% CI: -1.52, -0.78, P<0.00001) (**Figure 7**).

Publication bias assessment

A funnel plot was constructed using UTP data to evaluate potential publication bias due to small sample sizes. The plot showed that studies were generally symmetrically distributed around the funnel plot's midline, indicating a slight asymmetric distribution but suggesting a low risk of publication bias (**Figure 8**).

Discussion

IMN is a prevalent cause of NS in adults, with incidence rates on the rise [19] and an emerging trend toward younger patients [20]. IMN markedly heightens the risk of secondary thrombotic and embolic diseases, particularly in cases with persistent, very low protein levels, with venous thromboembolism (VTE) occurrence ranging from 7% to 36% [21]. VTE is a severe complication of NS, associated with high morbidity and mortality [22]. Despite the efficacy of long-term anticoagulation therapy, it leads to increased healthcare costs and potential complications, some of which may be life-threatening [23]. Thus, optimizing anticoagulant drug selection and developing tailored anticoagulation treatment plans are crucial for enhancing patient outcomes, minimizing complications, and improving quality of life.

Warfarin therapy has been shown to reduce thrombosis in patients whose NS results from IMN [24]; however, its high bleeding risk raises concerns about its overall effectiveness [25]. Low-molecular-weight heparin may alleviate intra-glomerular hypercoagulation and mend the glomerular basement membrane, thereby preventing urinary protein leakage and subsequent renal damage, though its anticoagulant effect alone is not entirely satisfactory [26, 27]. Aspirin, often used in low doses as an antiplatelet to prevent thromboembolism, benefits only a limited number of NS patients when used prophylactically [28, 29]. Dipyridamole inhibits platelet cyclooxygenase activity and thromboxane synthesis, reducing platelet aggregation [30]. Reports suggest that combining dipyridamole with prednisolone can enhance renal function and decrease blood hypercoagulability in NS patients, proving more effective and less burdensome in terms of adverse effects [31]. Routinely used in clinical settings, dipyridamole is favored for its rapid onset, sustained effect, and potential to reduce costs [32]; however, robust evidence supporting its efficacy in preventing thromboembolic events in IMN patients is lacking.

New oral anticoagulants (DOACs), such as coagulation factor Xa inhibitors and thrombin inhibitors, offer convenient administration and quick action. Nevertheless, it remains uncertain whether DOACs match the efficacy and safety of traditional anticoagulants like heparin and warfarin in NS patients [33]. Their effectiveness in preventing arterial thrombotic events in this patient group is also yet to be determined.

Currently, no comprehensive and definitive anticoagulation treatment exists for IMN with significant proven efficacy. However, research on sulodexide has demonstrated that it can synergistically enhance the reduction of UPT levels, decrease CHOL and FIB levels, and

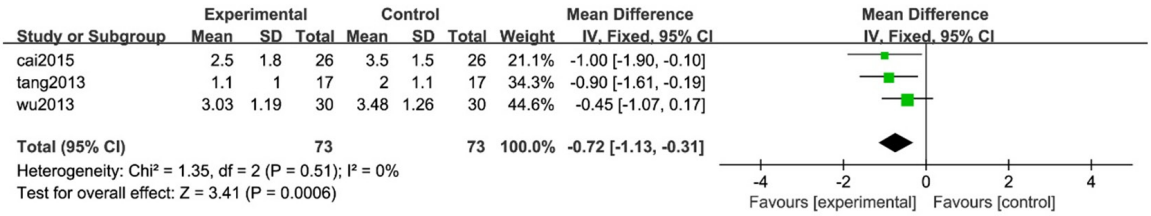

Figure 4. Meta-analysis of UTP after IMN treatment in sulodexide group and control group. UTP, Urine protein quantification; IMN, idiopathic membranous nephropathy.

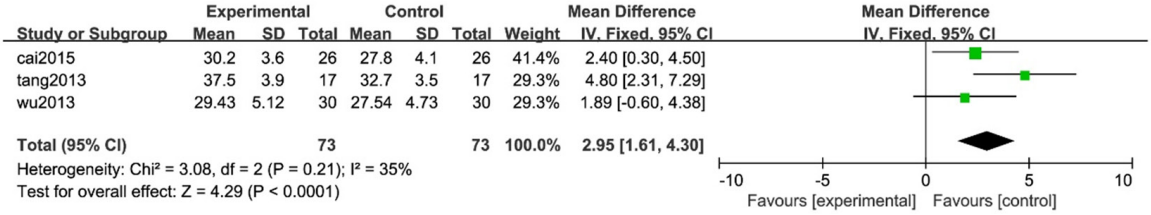

Figure 5. Meta-analysis of ALB after IMN treatment in sulodexide group and control group. ALB, Albumin; IMN, idiopathic membranous nephropathy.

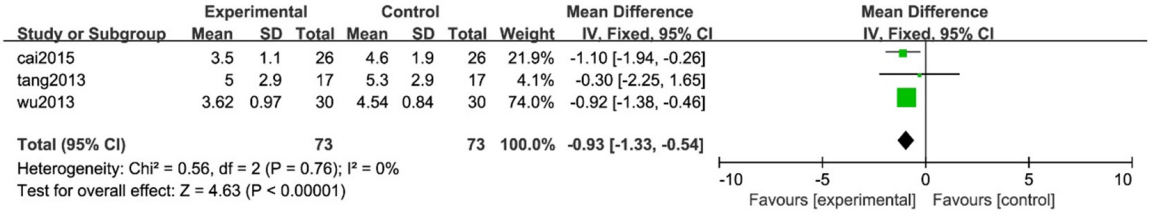

Figure 6. Meta-analysis of CHOL after IMN treatment in sulodexide group and control group. CHOL, Cholesterol; IMN, idiopathic membranous nephropathy.

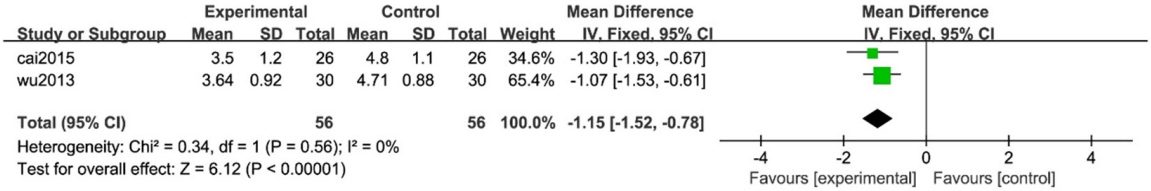

Figure 7. Meta-analysis of FIB after IMN treatment in sulodexide group and control group. FIB, Fibrinogen; IMN, idiopathic membranous nephropathy.

increase ALB levels when combined with conventional treatments, thus mitigating the risk of thrombosis.

Despite these promising findings, this meta-analysis has several limitations that warrant further investigation and improvement: (1) The limited number of included studies restricts comprehensive subgroup analysis and in-depth discussion of the effectiveness and safety of sulodexide in combination with conventional IMN treatments. (2) The quality of the included studies is suboptimal, with potential publication bias. (3) All included studies are in Chinese, excluding research from other countries and languages. (4) The overall follow-up duration was brief, which may not accurately reflect long-term outcomes.

In summary, the combination of sulodexide with conventional IMN treatment significantly reduces UPT levels, lowers CHOL and FIB, and

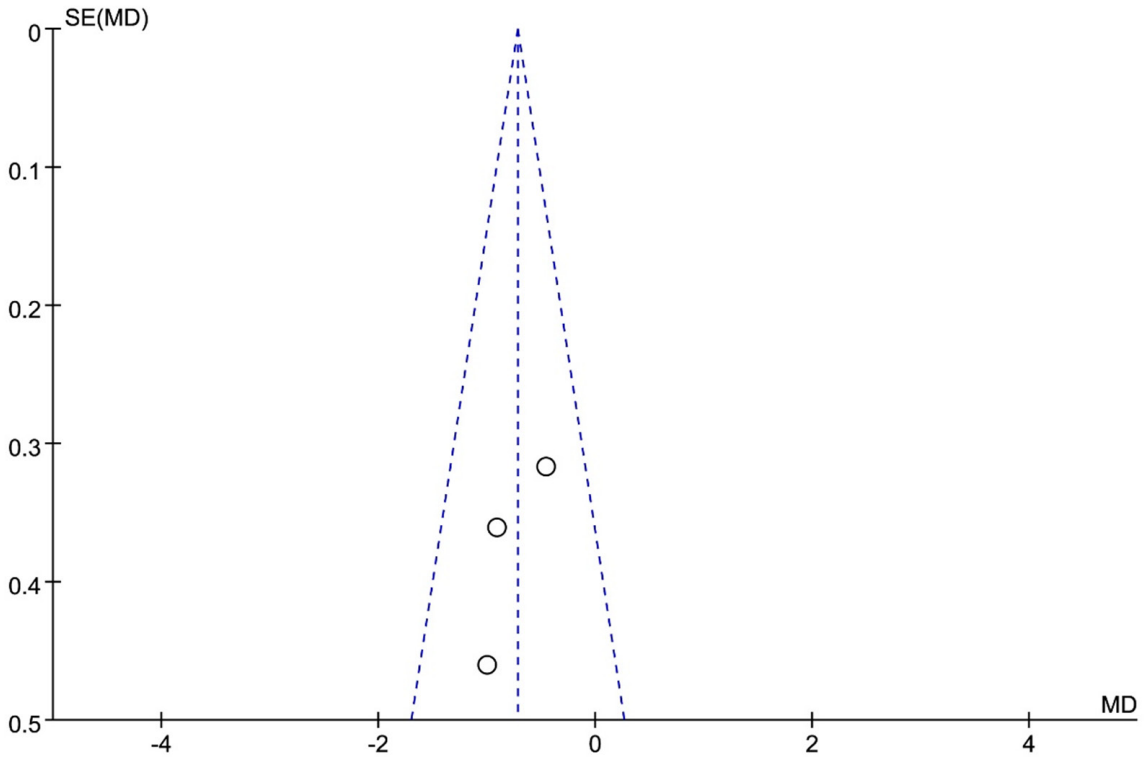

Figure 8. Funnel plots of UTP published bias. UTP, Urine protein quantification.

increases ALB levels, justifying its clinical application alongside standard treatments for enhanced efficacy and safety. However, its impact on the long-term prognosis of patients and reduction of thrombotic risk endpoints remains unclear. Therefore, to systematically explore the long-term efficacy of sulodexide for IMN and reduce thrombotic events, a larger-scale, multicenter, fully randomized controlled trial with extended follow-up is essential.

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Disclosure of conflict of interest

None.

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